Health Evidence Review Commission's Value-based Benefits Subcommittee

August 8, 2019

8:00 AM - 1:00 PM

Clackamas Community College
Wilsonville Training Center, Room 111-112
29373 SW Town Center Loop E, Wilsonville, Oregon, 97070

Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
8/8/2019
8:00am - 1:00pm
Clackamas Community College
29373 SW Town Center Loop E,
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
A working lunch will be served at approximately 12:00 PM
All times are approximate

Note: public testimony on specific agenda topics will be taken at the time that agenda item is discussed

I. Call to Order, Roll Call, Approval of Minutes – Kevin Olson **8:00 AM**

II. Staff report – Ariel Smits, Cat Livingston, Darren Coffman **8:05 AM**
- **A.** Errata

III. Straightforward/Consent agenda – Ariel Smits **8:10 AM**
- **A.** Consent table
- **B.** Genetic testing for siponimod

IV. 2019 ICD-10-CM code placement **8:15 AM**
- **A.** Code review table
- **B.** Code review issues

V. Previous discussion items **8:45 AM**
- **A.** Non-LANA certification for lymphedema providers

VI. New discussion items **9:00 AM**
- **A.** Repair of varicoceles in children and adolescents
- **B.** Incontinence procedures
    A. General incontinence procedure summary
    B. Sacral stimulation
    C. Artificial urinary sphincter
    D. Sling procedure for male urinary incontinence
    E. Urethral bulking injections for urinary incontinence
- **C.** Chronic lower extremity venous disease
- **D.** Lead screening and investigation
- **E.** Telephone and email visit guidelines
- **F.** Vestibular rehabilitation
- **G.** Prolotherapy
- **H.** Opportunistic salpingectomy guideline clarification

I. Surgical treatments and islet cell autotransplantation after pancreatectomy for chronic pancreatitis

J. Biologic matrix for breast reconstruction

VII. Coverage guidances **11:55 PM**

A. Temporary percutaneous mechanical circulatory support devices (IMPELLA)

VIII. Public comment for topics not on the agenda above **12:55 PM**

IX. Adjournment – Kevin Olson **1:00 PM**

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on May 16. 2019

For specific coding recommendations and guideline wording, please see the text of the 5/16/2019 VbBS minutes.

RECOMMENDED CODE MOVEMENT (effective 10/1/2019)

- Add the procedure code for injections for plantar fasciitis to an uncovered line
- Add the procedure code for radiofrequency ablation for knee osteoarthritis to an uncovered line
- Add the procedure code for pneumatic compression devices for lymphedema therapy to an uncovered line
- Move procedure codes for functional MRI (fMRI) from an unfunded line to the epilepsy surgery line
- Make various straightforward coding changes

ITEMS CONSIDERED BUT NO RECOMMENDATIONS FOR CHANGES MADE

- Reprioritization of the chronic pain syndrome/fibromyalgia line was considered, but not recommended
- Preventive treatment of women at high risk for lymphedema was considered, but not recommended

RECOMMENDED GUIDELINE CHANGES (effective 10/1/2019)

- Edit the guideline for opioids for conditions of the back and spine to remove the requirement for those on long-term opioid therapy to be tapered off completely over a specified period of time *[Note: see the 5/16/19 HERC minutes for further changes made to the guideline]*
- Make various straightforward guideline note changes

2020 BIENNIAL REVIEW (effective January 1, 2020)

- Create a new line for liver transplantation for hepatic malignancies in the funded region

VALUE-BASED BENEFITS SUBCOMMITTEE
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
May 16, 2019
8:00 AM – 1:00 PM

Members Present: Kevin Olson, MD, Chair; Holly Jo Hodges, MD, Vice-Chair; Mark Gibson; Vern Saboe, DC; Gary Allen, DMD; Adriane Irwin, PharmD.

Members Absent: none

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Daphne Peck; Jason Gingerich; Dana Hargunani, MD.

Also Attending: Renae Wentz, MD (Oregon Health Authority); Laura Ocker, LAc; Mary Kelly Rolf; Douglass Carr, MD (Umpqua Health); Jeanne Savage, MD (WVCH); Wendy Gordon; Larry Gordon; Rika Bierek (Oregon Medical Association); Kelly Howard; Len Ramey; Amara M; Kathy Spain; Noel Elliot; Joseph Elliot; Laura Dolph; Jay Hall.

Ø **Roll Call/Minutes Approval/Staff Report**

The meeting was called to order at 8:05 am and roll was called. Minutes from the 3/14/19 VbBS meeting were reviewed and approved unanimously as submitted. Smits reviewed the errata document; there were no questions.

Coffman announced that Kathryn Schabel, MD, was confirmed this week by the Oregon Senate to a HERC position; she already serves on HTAS.

Ø **Topic: Straightforward/Consent Agenda**

Discussion: There was no discussion about the consent agenda items.

Recommended Actions:

1) Add 11971 (Removal of tissue expander(s) without insertion of prosthesis) to lines 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER and 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
2) Add 96132 and 96133 (Neuropsychological testing evaluation services) to line 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS Treatment: SINGLE FOCAL SURGERY
3) Remove M54.0 family (Panniculitis affecting regions of neck and back) from line 401 CONDITIONS OF THE BACK AND SPINE
    a. Add M54.0 family to line 519 PANNICULITIS
4) Add 19370 (Open periprosthetic capsulotomy, breast), 19371 (Periprosthetic capsulectomy, breast), and 19380 (Revision of reconstructed breast) to line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER

5) Add G12.20 (Motor neuron disease, unspecified) to line 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
    a. Advise HSD to remove G12.20 from the Undefined Diagnosis File
6) The coding specification attached to line 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS was updated to include one additional CPT code (CPT 63650 Percutaneous implantation of neurostimulator electrode array, epidural):
    a. "Spinal cord stimulation (63650~~63655~~-63688) is not included on this line when paired with ICD-10-CM category G90.5 Complex regional pain syndrome/reflex sympathetic dystrophy…"
7) Add L8690, L8691, L8693, and L8694 (Auditory osseointegrated device) to lines 311 HEARING LOSS - AGE 5 OR UNDER and 444 HEARING LOSS - OVER AGE OF FIVE
8) Add HCPCS L8692 (Auditory osseointegrated device, external sound processor, used without osseointegration, body worn, includes headband or other means of external attachment) to line 311 HEARING LOSS - AGE 5 OR UNDER
9) Modify GN103 as shown in Appendix A
10) Modify GN173 as shown in Appendix A
11) Remove ICD-10 M47.01 family (Anterior spinal artery compression syndromes) and the M47.02 family (Vertebral artery compression syndromes) from lines 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS and 401 CONDITIONS OF THE BACK AND SPINE
12) Add ICD-10 M47.01 family (Anterior spinal artery compression syndromes) and the M47.02 family (Vertebral artery compression syndromes) to line 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
13) Recommend HSD add CPT 97033 (Application of a modality to 1 or more areas; iontophoresis, each 15 minutes) to the Ancillary File

MOTION: To approve the recommendations stated in the consent agenda. CARRIES 6-0.

Ø **Topic: 2020 Biennial Review: Reprioritization of certain chronic pain conditions**

Discussion: Dr. Dana Hargunani thanked the Commission for allowing a pause in their deliberations to allow for the third-party review. She has been pleased by the appraisal assessment by Aggregate Analytics Incorporated (AAI). She said her task to do a complete review of the conflict of interest policies is underway.

Hargunani thanked the staff and the members of the Chronic Pain Task Force (CPTF) who worked on this topic for +18 months. She thanked the public who have had tremendous engagement on this topic from near and far. This input, both from personal accounts and from professionals, has contributed significantly to the Commission's work.

She said the Commission was looking at opening the back-pain guideline, particularly around opioid prescribing. There is forthcoming evidence expected to be published later this year and expect to re-open the topic this coming winter.

Hargunani said OHA, separate from HERC, is developing a task force around opioid prescribing guidelines.

Dr. Andrea Skelly then gave a presentation on AAI's evidence appraisal and clarifying questions from the subcommittee were answered.

Smits gave a brief presentation of the history of the topic and summarized the three options included in the materials on the potential reprioritization of fibromyalgia and four additional chronic pain conditions.

Public testimony
Kelly Rolf, a fibromyalgia patient. Ms. Rolf testified about her various medical conditions, and how they responded well to opioid medications. These medications allowed her to function. She has had her opioid doses reduced, and now is having trouble functioning and is at times suicidal from the pain.

Douglas Carr, the CMO of Umpqua Health Alliance, testified about the sparse evidence to support the interventions being proposed for coverage for certain chronic pain conditions. He noted that high quality evidence will be available this winter on this topic. He noted that the non-pharmacologic interventions have slight or no long-term benefit. He recommended adoption of option 1 (no change from current coverage) and have the HERC review upcoming studies when they become available.

Larry Gordon, the husband of a chronic pain patient, testified about the unintended consequences and misinterpretations of the CDC opioid guidelines. His wife was forced tapered from opioids, and had negative consequences including suicidal ideation. He supports grandfathering in current chronic pain patients who are taking opioids appropriately. He also recommended considering coverage of opioids for patients not currently on them, as the CDC guidelines say that these types of patients can be treated with long-term opioids. He feels there is no evidence for forced tapers. He felt there should be no hard limits on opioid dosing as no evidence exists to support these limits. There are no studies finding that opioids don't work long term—there is just no study of long-term opioids at all. People have committed suicide and experienced other harms due to tapering. He recommended putting a hold on a decision and waiting for coming evidence.

Kelly Howard, a chronic pain patient, testified regarding coverage of additional opioids for pain flares. Breakthrough pain occurs 50-90% of the time for patients on opioids. Flares can increase stress and reduce a patient's medical status. Non-opioid treatments for flares may not be sufficient. She requested access to all tools to deal with breakthrough pain.

Amara M, the cofounder of the Oregon Pain Action Group, testified about being encouraged that the HERC was reopening guidelines on opioids for back conditions. She asked for an emergency halt/pause for opioid tapers for any conditions, including back and spine conditions. She noted that AAI found that evidence was missing for excluding fibromyalgia. She requested consideration of option 3C (allows opioid therapy for chronic pain consistent with national guidelines). She recommended not excluding any diagnosis (such as fibromyalgia) from opioid therapy based on diagnosis code. She also requested that the Commission not remove coverage of additional opioids for flares of chronic pain.

Kathy Spain, a chronic pain patient with fibromyalgia, testified that opioid pain medication was the only therapy that worked for her. Opioid therapy allowed her to function normally in daily life. With opioid therapy, she is able to work part time, do leisure activities and care for family. She has been

treated with opioids for 18 yrs. Without opioids, she would lose function and the ability to do things she enjoys. Pain medications are lifesaving. She feels that there is a stigma currently for being a chronic pain patient.

Laura Dolph, a chronic pain patient due to porphyria, testified in support of option 3c, but not in favor of removing coverage of flare for back pain opioid therapy. She feels that medications help flares, and that no evidence has been shown that treating flares is harmful. She testified against forced tapers. She has tried alternative pain therapies, which helped a bit mentally, but did not affect her pain. She attempted suicide twice due to pain. Pain management should be an exclusive arrangement between patient and provider.

Joseph Elliot, the husband of a chronic pain patient, testified about how opioid therapy has helped her for over 10 yrs. With opioid therapy, his wife is a normally functioning woman with some mobility limitations. If forced to taper off opioids, she would lose function, and has lost cognitive abilities when off opioids in the past. He urged the subcommittee to consider the impact on families and loved ones of removing opioid therapy.

Jeanne Savage, the CMO of Willamette Valley Community Health CCO and a family physician, testified. She noted that many conditions are not currently covered that we want to cover, like asymptomatic hernias, but OHP must balance what is not covered if you choose to cover these particular chronic pain conditions. CCOs have limits on what they can afford to pay for. She stressed the need for the subcommittee to consider fiscal responsibility.

VbBS Discussion:
Saboe requested information on the number of patients on OHP who have one of these 5 diagnoses under consideration. Gingerich replied that there appears to be about 7,000 OHP patients with one of these diagnoses and no other covered diagnosis. Coffman added that patients with only these diagnoses might or might not currently have medications covered, depending on comorbid conditions, lack of PA process in their CCO, etc. Gibson noted that the definition of some of these conditions are so poor that it is difficult to determine what we are treating. He also noted that the proposed interventions have low evidence of effectiveness.

VbBS then reviewed the line scoring for the proposed new line. They determined the most appropriate scores are a "4" for healthy life years, a "3" for suffering, a "0" for tertiary prevention (due to being unsure if treatment of chronic pain prevents development of any condition), a "1" for effectiveness and a "0.8" to need for service. These scores result in a line score of 112, which would keep any new line at about line 528, the current location of these conditions. Based on the fact that the rescoring did not move the line, the VbBS voted 6-0 in favor of option 1, which makes no change to coverage for these 5 specific chronic pain conditions.

The VbBS then discussed the proposed edits to Guideline Note 60, OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE. Hodges asked what evidence was used for the creation of GN60; the reply was expert opinion. Hodges suggested just deleting the dates in the previous taper wording that had already passed, rather than changing the entire taper language. Olson noted that the proposed wording resulted in no consequences for a patient who failed to taper off opioids. Hodges argued that the CCOs are using GN60 and having no issues with the current wording. She suggested waiting to make any changes to the GN60 wording until the global evaluation of the back line planned for this winter. Olson noted that we don't have evidence of how to safely taper patients, or whether

patients need to be tapered down to zero. Irwin was not comfortable leaving GN60 with the current wording. She noted that public comments have shown harms, and that it gives a bad message to leave tapering verbiage in our guideline. Irwin suggested simply deleting GN60. Hodges argued against the staff suggested wording changes, which included nothing about patient safety, harmful doses, or the need to taper patients to safer doses of opioids. Hargunani replied that the CDC guidelines do not actually recommend tapering a patient's opioid dose down if the patient is taking over a certain dose; rather the CDC guidelines just state that caution needs to be taken when considering increasing dose over a certain level. Olson expressed his concern for patient abandonment that might be an unintentional consequence of the current guideline. A recommendation was approved in favor of the staff suggested wording changes to the tapering paragraph in GN60.

Lastly, the VbBS discussed the proposed language regarding removal of additional opioids for treatment of flares of pain, as proposed by the CPTF. Irwin was concerned about the lack of evidence to support this change. Gibson noted that this type of change can be addressed when the VbBS looks at the entire guideline this coming winter. The decision was to make no change to flare language (continue to include in Guideline Note 60).

Note: further changes to Guideline Note 60 were made at the May 2019 HERC meeting. Please see the 5/16/19 HERC minutes for that discussion.

Recommended Actions:

1) No change to the current prioritization of chronic pain syndrome (ICD-10 G89.4), chronic pain due to trauma (ICD-10 G89.21), other chronic postprocedural pain (ICD-10 G89.28), other chronic pain (ICD-10 G89.29), and fibromyalgia (ICD-10 M79.7)
2) Modify guideline note 60 as shown in Appendix A

MOTION: To recommend the changes to Guideline Note 60 as presented. CARRIES 5-1 (Nay: Hodges)

Ø **Topic: 2020 Biennial Review: Reprioritization of liver transplant for hepatic malignancies**

Discussion: Smits reviewed the summary document. There were no questions or discussion.

Recommended Actions:

1) A new line for liver transplantation for hepatic malignancies was created as indicated below with the line scoring shown, effective January 2020

Line: XXX
Condition: CANCER OF LIVER OTHER THAN ANGIOSARCOMA (See Guideline Notes 64,65)
Treatment: LIVER TRANSPLANT
ICD-10: C22.0 [Liver cell carcinoma], C22.2 [Hepatoblastoma], C22.4 [Other sarcomas of liver], C22.7 [Other specified carcinomas of liver], C22.8 [Malignant neoplasm of liver, primary, unspecified as to type],T86.40-T86.49,Z48.23,Z51.11,Z52.6 [transplant rejection codes, post transplant care visit codes]
CPT: 47133-47147,86825-86835,93792,93793,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99451,99452,99468-99480, 99487-99491,99495-99498,99605-99607
HCPCS: G0068,G0071,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G2010-G2012

Line Scoring

	Line XXX
Category (Non-Fatal Condition)	6
Healthy Life Years (0-10)	7
Suffering (0-5)	4
Population effects (0-5)	0
Vulnerable population (0-5)	0
Tertiary prevention (0-5)	0
Effectiveness (0-5)	3
Need for service (0-1)	1
Net cost	0
Score	1320
Approximate line	264

2) The original line was modified as shown below, and kept at the current prioritization

Line: 560
Condition: ~~CANCER~~ ANGIOSARCOMA OF LIVER; ~~AND~~ INTRAHEPATIC BILE DUCT~~S~~ CARCINOMA
Treatment: LIVER TRANSPLANT
ICD-10: ~~C22.0 [Liver cell carcinoma],~~ C22.1 [Intrahepatic bile duct carcinoma], ~~C22.2 [Hepatoblastoma],~~ C22.3 [Angiosarcoma of liver], ~~C22.4 [Other sarcomas of liver], C22.7 [Other specified carcinomas of liver], C22.8 [Malignant neoplasm of liver, primary, unspecified as to type],~~T86.40-T86.49,Z48.23,Z51.11,Z52.6 [transplant care visit codes]
CPT: 47133-47147,86825-86835,93792,93793,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99449,99451,99452,99468-99480, 99487-99491,99495-99498,99605-99607
HCPCS: G0068,G0071,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467,G0490,G0508-G0511,G0513,G0514,G2010-G2012

MOTION: To recommend the new line and line scoring, and modifications of the old line as presented. CARRIES 6-0.

Ø **Topic: Functional MRI (fMRI) and epilepsy surgery**

Discussion: Livingston presented the issue summary.

Dr. David Spencer, from OHSU, was introduced on the phone. He declared no conflict of interest. He shared that the existing test, the Wada test, which is considered the gold standard, has some inherent difficulties. Limitations of the Wada test have also impaired developing a robust evidence base for fMRI. They have seen some adverse effects such as small strokes. fMRI can sometimes provide more specific localizing information than the Wada test.

Olson asked what percentage of time do you use fMRI instead of Wada? Spencer stated it is used to determine whether the language hemisphere is dominant. He is quite confident it does a good job or is equivalent to the Wada test. There is still evolving evidence. The Wada test used to be applied to every patient about to undergo epilepsy surgery, but now it is applied more selectively. There are some cases where neither fMRI or Wada is necessary. Sometimes fMRI is preferred, and other times the Wada test is preferred.

Attention turned to the proposed guideline limiting use to identify the eloquent cortex. Spencer clarified that eloquent cortex is about whichever part of the brain is primarily responsible and is not limited to language. They only have about 10 cases per year. Hodges clarified what exactly would be on the chart notes, whether information about identifying eloquent cortex would be documented and Spencer confirmed it would in the neurologist's notes. Spencer discussed that there is evidence for motor mapping as well. He recommended staying with the more general term of eloquent cortex rather than limiting to language. Subcommittee members debated the need for the guideline.

MOTION: To recommend the code and guideline note addition as presented. FAILED 1-4. (Nay: Allen, Hodges, Irwin, Saboe; Abstained: Olson)

MOTION: To recommend the code changes without the guideline. CARRIES 6-0.

Recommended Actions:

1) Add the following CPT codes to Line 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS Treatment: SINGLE FOCAL SURGERY
    a. CPT 70555 Magnetic resonance imaging, brain, functional MRI; requiring physician or psychologist administration of entire neurofunctional testing
    b. CPT 96020 Neurofunctional testing selection and administration during noninvasive imaging functional brain mapping, with test administered entirely by a physician or other qualified health care professional (ie, psychologist), with review of test results and report
2) Remove the Line 660 entries for CPT codes 70555 and 96020
3) Leave 70554 (Magnetic resonance imaging, brain, functional MRI; including test selection and administration of repetitive body part movement and/or visual stimulation, not requiring physician or psychologist administration) on Line 660, as it is not focused on language and does not involve physician or psychologist involvement

Ø **Topic: Injections for plantar fasciitis**

Discussion: Smits reviewed the summary document and noted that the podiatrists consulted on this topic agreed with the staff recommendation. There was no discussion.

Recommended Actions:

1) Add CPT 20550 (Injection(s); single tendon sheath, or ligament, aponeurosis (eg, plantar "fascia")) to line 537 LESION OF PLANTAR NERVE; PLANTAR FASCIAL FIBROMATOSIS, with the coding specification below:
    a. "CPT 20550 only appears on this line for corticosteroid injections."

MOTION: To recommend the code and coding specification changes as presented. CARRIES 6-0.

Ø **Topic: Radiofrequency ablation for knee osteoarthritis**

Discussion: Smits reviewed the summary document. There was no discussion.

Recommended Actions:

1) Add radiofrequency ablation (standard, cooled or cryoablation) for knee arthritis to line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
2) Add an entry to Guideline Note 173 as shown in Appendix A

MOTION: To recommend the code and guideline note changes as presented. CARRIES 6-0.

Ø **Topic: Non-LANA certification for lymphedema therapy**

Discussion: Smits introduced the topic. There was general agreement that the requirement for LANA certification for lymphedema therapists should be broadened to include other certifications if LANA certified providers were not available. However, the manner of the wording of the guideline was debated. The current guideline restricts coverage to providers who are LANA certified, or who have graduated from a certified program in the last 2 years. This second provision is to allow providers who are in the process of getting enough hours to become LANA certified to provide care to OHP patients. However, the wording was felt to be problematic, and various wording revisions were suggested. The decision was to table this topic and have HERC staff work on revising the wording and bring back to the August VbBS meeting.

Recommended Actions:

1) Staff to work on revised language to the lymphedema therapy guideline and bring back to a future VbBS meeting

Ø **Topic: Preventive lymphedema treatment for high risk women**

Discussion: Smits reviewed the summary document; there was no discussion.

Recommended Actions:

1) Make no change to the current coverage of lymphedema and the current limitation to lymphedema therapy to those patients with diagnosed lymphedema

Ø **Topic: Pneumatic compression devices**

Discussion: Smits reviewed the summary document; there was no discussion.

Recommended Actions:

1) Add HCPCS E0650-E0673 and E0676 (Pneumatic compressor; Segmental pneumatic appliance for use with pneumatic compressor) to line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS/GN173 as shown in Appendix A

MOTION: To recommend the code and guideline note changes as presented. CARRIES 6-0.

Ø **Public Comment:**

No additional public comment was received.

Ø **Issues for next meeting:**

- Non-LANA certification for lymphedema therapists

Ø **Next meeting:**

August 8, 2019 at Clackamas Community College, Wilsonville Training Center, Wilsonville Oregon, Rooms 111-112.

Ø **Adjournment:**

The meeting adjourned at 12:30 PM.

Appendix A

Revised Guideline Notes

GUIDELINE NOTE 60, OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE

Lines 346,361,401,527

Opioid medications are only included on these lines under the following criteria:

For acute injury, acute flare of chronic pain, or after surgery:

1) During the first 6 weeks opioid treatment is included on these lines ONLY:
   a) When each prescription is limited to 7 days of treatment, AND
   b) For short acting opioids only, AND
   c) When one or more alternative first line pharmacologic therapies such as NSAIDs, acetaminophen, and muscle relaxers have been tried and found not effective or are contraindicated, AND
   d) When prescribed with a plan to keep active (home or prescribed exercise regime) and with consideration of additional therapies such as spinal manipulation, physical therapy, yoga, or acupuncture, AND
   e) There is documented verification that the patient is not high risk for opioid misuse or abuse.
2) Treatment with opioids after 6 weeks, up to 90 days after the initial injury/flare/surgery is included on these lines ONLY:
   a) With documented evidence of improvement of function of at least thirty percent as compared to baseline based on a validated tools (e.g. Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale, Oswestry, Neck Disability Index, SF-MPQ, and MSPQ).
   b) When prescribed in conjunction with therapies such as spinal manipulation, physical therapy, yoga, or acupuncture.
   c) With verification that the patient is not high risk for opioid misuse or abuse. Such verification may involve
      i) Documented verification from the state's prescription monitoring program database that the controlled substance history is consistent with the prescribing record
      ii) Use of a validated screening instrument to verify the absence of a current substance use disorder (excluding nicotine) or a history of prior opioid misuse or abuse
      iii) Administration of a baseline urine drug test to verify the absence of illicit drugs and non-prescribed opioids.
   d) Each prescription must be limited to 7 days of treatment and for short acting opioids only
3) Long-term opioid treatment (>90 days) after the initial injury/flare/surgery is not included on these lines except for the taper process described below.

~~Transitional coverage for patients on long-term opioid therapy as of July 1, 2016:~~
~~For patients on covered chronic opioid therapy as of July 1, 2016, opioid medication is included on these lines only from July 1, 2016 to December 31, 2016. During the period from January 1, 2017 to December 31, 2017, continued coverage of opioid medications requires an individual treatment plan developed by January 1, 2017 which includes a taper with an end to opioid therapy no later than January 1, 2018 and include a taper goal to zero. Tapering should be unidirectional, generally with a 5-10% decrease monthly and can be paused or slowed if the prescriber believes this is medically appropriate. Taper plans must include nonpharmacological treatment strategies for managing the patient's pain based on Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE. If a~~

~~patient has developed dependence and/or addiction related to their opioids, treatment is available on Line 4 SUBSTANCE USE DISORDER.~~

Transitional coverage for patients on long-term opioid therapy:
For patients receiving long-term opioid therapy (>90 days) for conditions of the back and spine, continued coverage of opioid medications requires an individual treatment plan which includes a taper plan *[when clinically indicated]*. Opioid tapering should be done on an individualized basis with a shared goal set by the patient and provider based on the patient's overall status. Taper plans should include nonpharmacological treatment strategies for managing the patient's pain. During the taper, behavioral health conditions need to be regularly assessed and appropriately managed. In some situations (e.g., in the setting of active substance use disorder, history of opioid overdose, aberrant behavior), more rapid tapering or transition to medication assisted treatment may be appropriate and should be directed by the prescribing provider. If a patient has developed *[an]* opioid use disorder, treatment is included on Line 4 SUBSTANCE USE DISORDER.

NOTE: Additional changes made at the May 16, 2019 HERC meeting are noted above in *[italics]*

GUIDELINE NOTE 103, BONE ANCHORED HEARING AIDS

Lines 311,444

Bone anchored hearing aids (BAHA, CPT 69714, 69715; HCPCS L8690-8694) are included on these lines when the following criteria are met:

A) The patient is aged 5-20 years for implanted bone anchored hearing aids; headband mounted BAHA devices may be used for children under age 5
B) Treatment is for unilateral severe to profound hearing loss when the contralateral ear has normal hearing with or without a hearing aid
C) Traditional air amplification hearing aids and contralateral routing of signal (CROS) hearing aid systems are not indicated or have been tried and are found to be not effective
D) Implantation is unilateral.

Use of BAHA for treatment of tinnitus is not covered

GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 500

The following interventions are prioritized on Line 500 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

69710 ~~HCPCS L8690-L8693~~	Implantation or replacement of electromagnetic bone conduction hearing device in temporal bone ~~Auditory osseointegrated device~~	Less effective than other therapies	June, 2014, Aug. 2015

Appendix A

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
E0650-E0673 and E0676	Pneumatic compressor Segmental pneumatic appliance for use with pneumatic compressor	Insufficient evidence of effectiveness	May, 2019
64640	Destruction by neurolytic agent; other peripheral nerve or branch	Insufficient evidence of effectiveness	May, 2019 (knee osteoarthritis)

Section 2.0

Staff Report

Errata
August 2019

1) Two HCPCS codes were mistakenly added to the new liver transplant for hepatic malignancies line at the May, 2019 VbBS/HERC meetings. These codes were determined to belong only on line 3 at the January, 2019 VbBS/HERC meetings. These codes will be removed from the new liver transplant line when effective January 1, 2020.
    a. G0513 Prolonged preventive service(s) (beyond the typical service time of the primary procedure), in the office or other outpatient setting requiring direct patient contact beyond the usual service; first 30 minutes (list separately in addition to code for prev
    b. G0514 Prolonged preventive service(s) (beyond the typical service time of the primary procedure), in the office or other outpatient setting requiring direct patient contact beyond the usual service; each additional 30 minutes (list separately in addition to cod
2) The CPT codes representing applied behavioral analysis (ABA) in GN75 were not updated when these codes were replaced with new codes for 2019
    a. Excerpt of GN75 showing updated codes

GUIDELINE NOTE 75, APPLIED BEHAVIOR ANALYSIS FOR AUTISM SPECTRUM DISORDER

Line 193

Applied behavioral analysis (ABA), including early intensive behavioral intervention (EIBI), represented by CPT codes 97151-97158 ~~0359T-0374T~~, is included on Line 193 AUTISM SPECTRUM DISORDERS for the treatment of autism spectrum disorders.

ABA services are provided in addition to any rehabilitative services (e.g. physical therapy, occupational therapy, speech therapy) included in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES that are indicated for other acute qualifying conditions.

Section 4.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—August 2019

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
58541-58544	Supracervical hysterectomy	464 UTERINE PROLAPSE; CYSTOCELE	Line 464 contains all hysterectomy CPT codes except for the supracervical hysterectomy codes	Add 58541-58544 to line 464
68720	Dacryocystorhinostomy (fistulization of lacrimal sac to nasal cavity)	393 STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN	Claims reconsideration for pairing of CPT 68720 with congenital lacrimal duct deformity diagnoses, which appear on line. 68720 is currently on line 508 DYSFUNCTION OF NASOLACRIMAL SYSTEM IN ADULTS; LACRIMAL SYSTEM LACERATION	Add 68720 to line 393
95012	Nitric oxide expired gas determination	9 ASTHMA	In March, 2018, HERC added 95012 to line 9 to allow use in asthma management. However, the January, 2018 HERC decision was to also allow use in diagnosis of asthma. To best accomplish both of these objectives, 95012 should be placed on the Diagnostic Procedures File.	Remove 95012 from line 9 Advise HSD to add 95012 to the Diagnostic Procedures File
97535	Self-care/home management training (eg, activities of daily living (ADL) and compensatory training, meal preparation, safety procedures, and instructions in use of assistive technology devices/adaptive equipment) direct one-on-one contact, each 15 minutes	421 LYMPHEDEMA	HSD requested addition of CPT 97535 to line 421 as self-management is standard of care in this population. 97535 is on 50+ lines.	Add 97535 to line 421

Consent Agenda Issues—August 2019

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
99091	Collection and interpretation of physiologic data (eg, ECG, blood pressure, glucose monitoring) digitally stored and/or transmitted by the patient and/or caregiver to the physician or other qualified health care professional, qualified by education, training, licensure/regulation (when applicable) requiring a minimum of 30 minutes of time, each 30 days	Ancillary	CPT 99453-99454 and 99457 were added to the Ancillary List as new codes for 2019. These codes are all for remote monitoring of physiologic data. These codes are all highly similar to CPT 99091, which has been a code for 20 years. 99091 has never previously been reviewed by the HSC/HERC.	Advise HSD to add 99091 to the Ancillary List
D48.7	Neoplasm of uncertain behavior of other specified sites • Neoplasm of uncertain behavior or eye • Neoplasm of uncertain behavior of heart • Neoplasm of uncertain behavior of peripheral nerves of orbit	113 CANCER OF EYE AND ORBIT	This code includes neoplasm of uncertain behavior of heart but does not pair with appropriate codes.	Add D48.7 to • Line 372 BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS • Line 200 CANCER OF SOFT TISSUE (has malignant neoplasms of the heart)

Genetic Testing Prior to Siponimod Prescribing

Question: Should testing for the CYP2C9*3/*3 genetic variant be paired with multiple sclerosis diagnoses for siponimod prescribing?

Question source: CareOregon

Issue: Siponimod (brand name Mayzent) is a new medication for multiple sclerosis (MS) that has recently been FDA approved, and the FDA requires CYP2C9*3/*3 genetic testing prior to prescribing. If a patient is positive for the CYP2C9*3/*3 genetic variant, the drug is contraindicated. CYP2C9*3/*3 is a variant in cytochrome P450 family 2, subfamily C, polypeptide 9

Testing is billed with CPT 81227 (CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)), which is currently on line 660/GN173. CPT 81227 was placed on line 660 as a new 2012 CPT code. At the time of the 2011 Genetics Advisory Panel review, this code was being used for testing for determining anticoagulant therapy, for which there is no evidence of effectiveness.

From the FDA label for siponimod:
Before initiation of treatment with MAYZENT, test patients to determine CYP2C9 genotype. MAYZENT is contraindicated in patients homozygous for CYP2C9*3 (i.e., CYP2C9*3/*3 genotype), which is approximately 0.4%-0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. MAYZENT dosage adjustment is recommended in patients with CYP2C9*1/*3 or *2/*3 genotype because of an increase in exposure to siponimod.

From CareOregon

> I believe 81227 can be covered under the comorbid rule, since it is medically necessary for patients with MS being considered for Mayzent treatment. However, it may be more expedient to run it past the Genetics Advisory Panel, and if they agree, move 81227 only to the MS line, 252, with possible mention in GN D1.

HERC staff recommendations:

1) Add CPT 81227 (CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)) to line 252 MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM
2) Add CPT 81227 to the GAP agenda for the fall to determine if there are any other evidence-based or regulatory required uses of this test
3) Remove CPT 81227 from line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
4) Modify GN173 as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

81225~~-81227~~, 81226, 81230-81231	Cytochrome P450 gene analysis	Insufficient evidence of effectiveness	December, 2011 November, 2017

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MAYZENT safely and effectively. See full prescribing information for MAYZENT.

MAYZENT® (siponimod) tablets, for oral use
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------

MAYZENT is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

- Assessments are required prior to initiating MAYZENT (2.1)
- Titration is required for treatment initiation (2.2, 2.3)
- The recommended maintenance dosage is 2 mg (2.2)
- The recommended maintenance dosage in patients with a CYP2C9*1/*3 or *2/*3 genotype is 1 mg (2.3)
- First-dose monitoring is recommended for patients with sinus bradycardia, first- or second-degree [Mobitz type I] atrioventricular (AV) block, or a history of myocardial infarction or heart failure (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 0.25 mg and 2 mg (3)

----------CONTRAINDICATIONS----------

- Patients with a CYP2C9*3/*3 genotype (4)
- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure (4)
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: MAYZENT may increase the risk. Obtain a complete blood count (CBC) before initiating treatment. Monitor for infection during treatment. Do not start in patients with active infection. (5.1)
- Macular Edema: An ophthalmic evaluation is recommended before starting treatment and if there is any change in vision while taking MAYZENT. Diabetes mellitus and uveitis increase the risk. (5.2)
- Bradyarrhythmia and Atrioventricular Conduction Delays: MAYZENT may result in a transient decrease in heart rate; titration is required for treatment initiation. Consider resting heart rate with concomitant beta-blocker use; obtain cardiologist consultation before concomitant use with other drugs that decrease heart rate (5.3, 7.2, 7.3)
- Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated. (5.4)
- Liver Injury: Obtain liver enzyme results before initiation. Closely monitor patients with severe hepatic impairment. Discontinue if significant liver injury occurs. (5.5)
- Increased Blood Pressure (BP): Monitor BP during treatment. (5.6)
- Fetal Risk: Women of childbearing potential should use effective contraception during and for 10 days after stopping MAYZENT. (5.7)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence greater than 10%) are headache, hypertension, and transaminase increases. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Vaccines: Avoid live attenuated vaccines during and for up to 4 weeks after treatment with MAYZENT (7.4)
- CYP2C9 and CYP3A4 Inhibitors: Increase in siponimod exposure; concomitant use of MAYZENT with moderate CYP2C9 and moderate or strong CYP3A4 inhibitors is not recommended (7.5)
- CYP2C9 and CYP3A4 Inducers: Decrease in siponimod exposure; concomitant use of MAYZENT with moderate CYP2C9 and strong CYP3A4 inducers is not recommended (7.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Assessments Prior to First Dose of MAYZENT
2.2 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*1, *1/*2, or *2/*2
2.3 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*3 or *2/*3
2.4 First Dose Monitoring in Patients With Certain Preexisting Cardiac Conditions
2.5 Reinitiation of MAYZENT After Treatment Interruption
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Infections
5.2 Macular Edema
5.3 Bradyarrhythmia and Atrioventricular Conduction Delays
5.4 Respiratory Effects
5.5 Liver Injury
5.6 Increased Blood Pressure
5.7 Fetal Risk
5.8 Posterior Reversible Encephalopathy Syndrome
5.9 Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies
5.10 Severe Increase in Disability After Stopping MAYZENT
5.11 Immune System Effects After Stopping MAYZENT
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies
7.2 Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate
7.3 Beta-Blockers
7.4 Vaccination
7.5 CYP2C9 and CYP3A4 Inhibitors
7.6 CYP2C9 and CYP3A4 Inducers
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 CYP2C9 Genotype
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MAYZENT is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to First Dose of MAYZENT

Before initiation of treatment with MAYZENT, assess the following:

CYP2C9 Genotype Determination

Test patients for CYP2C9 variants to determine CYP2C9 genotype *[see Dosage and Administration (2.2, 2.3), Contraindications (4), and Use in Specific Populations (8.6)]*. An FDA-cleared or -approved test for the detection of CYP2C9 variants to direct the use of siponimod is not currently available.

Complete Blood Count

Review results of a recent complete blood count (CBC) *[see Warnings and Precautions (5.1)]*.

Ophthalmic Evaluation

Obtain an evaluation of the fundus, including the macula *[see Warnings and Precautions (5.2)]*.

Cardiac Evaluation

Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist and first-dose monitoring is recommended *[see Dosage and Administration (2.4) and Warnings and Precautions (5.3)]*.

Determine whether patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction *[see Drug Interactions (7.2, 7.3)]*.

Current or Prior Medications

If patients are taking anti-neoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with MAYZENT *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

Vaccinations

Test patients for antibodies to varicella zoster virus (VZV) before initiating MAYZENT; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with MAYZENT *[see Warnings and Precautions (5.1)]*.

Liver Function Tests

Obtain recent (i.e., within last 6 months) transaminase and bilirubin levels *[see Warnings and Precautions (5.5)]*.

2.2 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*1, *1/*2, or *2/*2

Maintenance Dosage

After treatment titration *(see Treatment Initiation)*, the recommended maintenance dosage of MAYZENT is 2 mg taken orally once daily starting on Day 6. Dosage adjustment is required in patients with a CYP2C9*1/*3 or *2/*3 genotype *[see Dosage and Administration (2.3)]*.

Treatment Initiation

Initiate MAYZENT with a 5-day titration, as shown in Table 1 *[see Warnings and Precautions (5.3)]*. A starter pack should be used for patients who will be titrated to the 2-mg maintenance dosage *[see How Supplied/Storage and Handling (16.1, 16.2)]*.

Table 1 Dose Titration Regimen to Reach MAYZENT 2 mg Maintenance Dosage

Titration	Titration Dose	Titration Regimen
Day 1	0.25 mg	1 x 0.25 mg
Day 2	0.25 mg	1 x 0.25 mg
Day 3	0.50 mg	2 x 0.25 mg
Day 4	0.75 mg	3 x 0.25 mg
Day 5	1.25 mg	5 x 0.25 mg

If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.

2.3 Recommended Dosage in Patients With CYP2C9 Genotypes *1/*3 or *2/*3

Maintenance Dosage

In patients with a CYP2C9*1/*3 or *2/*3 genotype, after treatment titration *(see Treatment Initiation)*, the recommended maintenance dosage of MAYZENT is 1 mg taken orally once daily starting on Day 5.

Treatment Initiation

Initiate MAYZENT with a 4-day titration, as shown in Table 2 *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*. Do not use the starter pack for patients who will be titrated to the 1-mg maintenance dosage.

Table 2 Dose Titration Regimen to Reach MAYZENT 1 mg Maintenance Dosage

Titration	Titration Dose	Titration Regimen
Day 1	0.25 mg	1 x 0.25 mg
Day 2	0.25 mg	1 x 0.25 mg
Day 3	0.50 mg	2 x 0.25 mg
Day 4	0.75 mg	3 x 0.25 mg

If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.

2.4 First Dose Monitoring in Patients With Certain Preexisting Cardiac Conditions

Because initiation of MAYZENT treatment results in a decrease in heart rate (HR), first-dose 6 hour monitoring is recommended for patients with sinus bradycardia [HR less than 55 beats per minute (bpm)], first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.2)]*.

First Dose 6-Hour Monitoring

Administer the first dose of MAYZENT in a setting where resources to appropriately manage symptomatic bradycardia are available. Monitor patients for 6 hours after the first dose for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. Obtain an ECG in these patients at the end of the Day 1 observation period.

Additional Monitoring After 6-Hour Monitoring

If any of the following abnormalities are present after 6 hours (even in the absence of symptoms), continue monitoring until the abnormality resolves:

- The heart rate 6 hours postdose is less than 45 bpm
- The heart rate 6 hours postdose is at the lowest value postdose, suggesting that the maximum pharmacodynamic effect on the heart may not have occurred
- The ECG 6 hours postdose shows new onset second-degree or higher AV block

If postdose symptomatic bradycardia, bradyarrhythmia, or conduction related symptoms occur, or if ECG 6 hours post-dose shows new onset second degree or higher AV block or QTc greater than or equal to 500 msec, initiate appropriate management, begin continuous ECG monitoring, and continue monitoring until the symptoms have resolved if no pharmacological treatment is required. If pharmacological treatment is required, continue monitoring overnight and repeat 6-hour monitoring after the second dose.

Advice from a cardiologist should be sought to determine the most appropriate monitoring strategy (which may include overnight monitoring) during treatment initiation, if treatment with MAYZENT is considered in patients:

- With some preexisting heart and cerebrovascular conditions *[see Warnings and Precautions (5.3)]*
- With a prolonged QTc interval before dosing or during the 6-hour observation, or at additional risk for QT prolongation, or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes *[see Warnings and Precautions (5.3) and Drug Interactions (7.2)]*
- Receiving concurrent therapy with drugs that slow heart rate or AV conduction *[see Drug Interactions (7.2, 7.3)]*

2.5 Reinitiation of MAYZENT After Treatment Interruption

After the initial titration is complete, if MAYZENT treatment is interrupted for 4 or more consecutive daily doses, reinitiate treatment with Day 1 of the titration regimen *[see Dosage and Administration (2.2, 2.3)]*; also complete first-dose monitoring in patients for whom it is recommended *[see Dosage and Administration (2.4)]*.

3 DOSAGE FORMS AND STRENGTHS

0.25 mg tablet: Pale red, unscored, round biconvex film-coated tablet with beveled edges, debossed with ⏻ on one side & 'T' on other side.

2 mg tablet: Pale yellow, unscored, round biconvex film-coated tablet with beveled edges, debossed with ⏻ on one side & 'II' on other side.

4 CONTRAINDICATIONS

MAYZENT is contraindicated in patients who have:

- A CYP2C9*3/*3 genotype *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.5)]*
- In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III or IV heart failure
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker *[see Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Risk of Infections

MAYZENT causes a dose-dependent reduction in peripheral lymphocyte count to 20%-30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. MAYZENT may therefore increase the risk of infections, some serious in nature *[see Clinical Pharmacology (12.2)]*. Life-threatening and rare fatal infections have occurred in association with MAYZENT.

In Study 1 *[see Clinical Studies (14)]*, the overall rate of infections was comparable between the MAYZENT-treated patients and those on placebo (49.0% vs. 49.1% respectively). However, herpes zoster, herpes infection, bronchitis, sinusitis, upper respiratory infection, and fungal skin infection were more common in MAYZENT-treated patients. In Study 1, serious infections occurred at a rate of 2.9% in MAYZENT-treated patients compared to 2.5% of patients receiving placebo.

Before initiating treatment with MAYZENT, results from a recent complete blood count (i.e., within 6 months or after discontinuation of prior therapy) should be reviewed.

Initiation of treatment with MAYZENT should be delayed in patients with severe active infection until resolution. Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3-4 weeks after discontinuation of MAYZENT, vigilance for infection should be continued throughout this period *[see Warnings and Precautions (5.11)]*.

Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Suspension of treatment with MAYZENT should be considered if a patient develops a serious infection.

Cryptococcal Infections

Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with another sphingosine 1-phosphate (S1P) receptor modulator. Rare cases of CM have also occurred with MAYZENT. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. MAYZENT treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Herpes Viral Infections

Cases of herpes viral infection, including one case of reactivation of VZV infection leading to varicella zoster meningitis, have been reported in the development program of MAYZENT. In Study 1, the rate of herpetic infections was 4.6% in MAYZENT-treated patients compared to 3.0% of patients receiving placebo. In Study 1, an increase in the rate of herpes zoster infections was reported in 2.5% of MAYZENT-treated patients compared to 0.7% of patients receiving placebo. Patients without a healthcare professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT *(see Vaccinations below).*

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No cases of PML have been reported in MAYZENT-treated patients in the development program; however, PML has been reported in patients treated with a S1P receptor modulator and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, treatment with MAYZENT should be suspended until PML has been excluded.

Prior and Concomitant Treatment with Anti-neoplastic, Immune-Modulating, or Immunosuppressive Therapies

Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be coadministered with caution because of the risk of additive immune system effects during such therapy *[see Drug Interactions (7.1)]*.

Vaccinations

Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating MAYZENT treatment. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with MAYZENT, following which initiation of treatment with MAYZENT should be postponed for 4 weeks to allow the full effect of vaccination to occur.

The use of live attenuated vaccines should be avoided while patients are taking MAYZENT and for 4 weeks after stopping treatment *[see Drug Interactions (7.1)]*.

Vaccinations may be less effective if administered during MAYZENT treatment. MAYZENT treatment discontinuation 1 week prior to and until 4 weeks after a planned vaccination is recommended.

5.2 Macular Edema

Macular edema was reported in 1.8% of MAYZENT-treated patients compared to 0.2% of patients receiving placebo. The majority of cases occurred within the first four months of therapy.

An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients before starting treatment and at any time if there is any change in vision while taking MAYZENT.

Continuation of MAYZENT therapy in patients with macular edema has not been evaluated. A decision on whether or not MAYZENT should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Macular Edema in Patients with a History of Uveitis or Diabetes Mellitus

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during MAYZENT therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In the clinical trial experience in adult patients with all doses of MAYZENT, the rate of macular edema was approximately 10% in MS patients with a history of uveitis or diabetes mellitus versus 2% in those without a history of these diseases. In addition to the examination of the fundus, including the macula, prior to treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

5.3 Bradyarrhythmia and Atrioventricular Conduction Delays

Since initiation of MAYZENT treatment results in a transient decrease in heart rate and atrioventricular conduction delays, an up-titration scheme should be used to reach the maintenance dosage of MAYZENT *[see Dosage and Administration (2.2, 2.3) and Clinical Pharmacology (12.2)]*.

MAYZENT was not studied in patients who had:

- In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, or decompensated heart failure requiring hospitalization
- New York Heart Association Class II-IV heart failure
- Cardiac conduction or rhythm disorders, including complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia, sick sinus syndrome, Mobitz type II second degree AV-block or higher grade AV-block (either history or observed at screening), unless patient has a functioning pacemaker
- Significant QT prolongation (QTc greater than 500 msec)
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs *[see Drug Interactions (7.2)]*

Reduction in Heart Rate

After the first titration dose of MAYZENT, the heart rate decrease starts within an hour, and the Day 1 decline is maximal at approximately 3-4 hours. With continued up-titration, further heart rate decreases are seen on subsequent days, with maximal decrease from Day 1-baseline reached on Day 5-6. The highest daily post-dose decrease in absolute hourly mean heart rate is observed on Day 1, with the pulse declining on average 5-6 bpm. Post-dose declines on the following days are less pronounced. With continued dosing, heart rate starts increasing after Day 6 and reaches placebo levels within 10 days after treatment initiation.

In Study 1, bradycardia occurred in 4.4% of MAYZENT-treated patients compared to 2.9% of patients receiving placebo. Patients who experienced bradycardia were generally asymptomatic. Few patients experienced symptoms, including dizziness or fatigue, and these symptoms resolved within 24 hours without intervention *[see Adverse Reactions (6.1)]*. Heart rates below 40 bpm were rarely observed.

Atrioventricular Conduction Delays

Initiation of MAYZENT treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. The AV conduction delays manifested in most of the cases as first-degree AV block (prolonged PR interval on ECG), which occurred in 5.1% of MAYZENT-treated patients and in 1.9% of patients receiving placebo in Study 1. Second-degree AV blocks, usually Mobitz type I (Wenckebach), have been observed at the time of treatment initiation with MAYZENT in less than 1.7% of patients in clinical trials. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours, rarely required treatment with atropine, and did not require discontinuation of MAYZENT treatment.

If treatment with MAYZENT is considered, advice from a cardiologist should be sought:

- In patients with significant QT prolongation (QTc greater than 500 msec)
- In patients with arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs *[see Drug Interactions (7.2)]*
- In patients with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension

- In patients with a history of second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block *[see Contraindications (4)]*

Treatment-Initiation Recommendations

- Obtain an ECG in all patients to determine whether preexisting conduction abnormalities are present.
- In all patients, a dose titration is recommended for initiation of MAYZENT treatment to help reduce cardiac effects *[see Dosage and Administration (2.2, 2.3)]*.
- In patients with sinus bradycardia (HR less than 55 bpm), first- or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure with onset > 6 months prior to initiation, ECG testing and first-dose monitoring is recommended *[see Dosage and Administration (2.1, 2.4)]*.
- Since significant bradycardia may be poorly tolerated in patients with history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, or severe untreated sleep apnea, MAYZENT is not recommended in these patients. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.
- Use of MAYZENT in patients with a history of recurrent syncope or symptomatic bradycardia should be based on an overall benefit-risk assessment. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring.
- Experience with MAYZENT is limited in patients receiving concurrent therapy with drugs that decrease heart-rate (e.g., beta-blockers, calcium channel blockers - diltiazem and verapamil, and other drugs that may decrease heart rate, such as ivabradine and digoxin). Concomitant use of these drugs during MAYZENT initiation may be associated with severe bradycardia and heart block.
    - For patients receiving a stable dose of a beta-blocker, the resting heart rate should be considered before introducing MAYZENT treatment. If the resting heart rate is greater than 50 bpm under chronic beta-blocker treatment, MAYZENT can be introduced. If resting heart rate is less than or equal to 50 bpm, beta-blocker treatment should be interrupted until the baseline heart-rate is greater than 50 bpm. Treatment with MAYZENT can then be initiated and treatment with a beta-blocker can be reinitiated after MAYZENT has been up-titrated to the target maintenance dosage *[see Drug Interactions (7.3)]*.
    - For patients taking other drugs that decrease heart rate, treatment with MAYZENT should generally not be initiated without consultation from a cardiologist because of the potential additive effect on heart rate *[see Dosage and Administration (2.4) and Drug Interactions (7.2)]*.

Missed Dose During Treatment Initiation and Reinitiation of Therapy Following Interruption

If a titration dose is missed or if 4 or more consecutive daily doses are missed during maintenance treatment, reinitiate Day 1 of the dose titration and follow titration monitoring recommendations *[see Dosage and Administration (2.2, 2.3)]*.

5.4 Respiratory Effects

Dose-dependent reductions in absolute forced expiratory volume over 1 second (FEV_1) were observed in MAYZENT-treated patients as early as 3 months after treatment initiation. In a placebo-controlled trial in adult patients, the decline in absolute FEV_1 from baseline compared to placebo was 88 mL [95% confidence interval (CI): 139, 37] at 2 years. The mean difference between MAYZENT-treated patients and patients receiving placebo in percent predicted FEV_1 at 2 years was 2.8% (95% CI: -4.5, -1.0). There is insufficient information to determine the reversibility of the decrease in FEV_1 after drug discontinuation. In Study 1, five patients discontinued MAYZENT because of decreases in pulmonary function testing. MAYZENT has been tested in MS patients with mild to moderate asthma and chronic obstructive pulmonary disease. The changes in FEV_1 were similar in this subgroup compared with the overall population. Spirometric evaluation of respiratory function should be performed during therapy with MAYZENT if clinically indicated.

5.5 Liver Injury

Elevations of transaminases may occur in MAYZENT-treated patients. Recent (i.e., within last 6 months) transaminase and bilirubin levels should be reviewed before initiation of MAYZENT therapy.

In Study 1, elevations in transaminases and bilirubin were observed in 10.1% of MAYZENT-treated patients compared to 3.7% of patients receiving placebo, mainly because of transaminase [alanine aminotransferase/aspartate aminotransferase/gamma-glutamyltransferase (ALT/AST/GGT)] elevations.

In Study 1, ALT or AST increased to three and five times the upper limit of normal (ULN) in 5.6% and 1.4% of MAYZENT-treated patients, respectively, compared to 1.5% and 0.5% of patients receiving placebo, respectively. ALT or AST increased eight and ten times ULN in MAYZENT-treated patients (0.5% and 0.2%, respectively) compared to no patients receiving placebo. The majority of elevations occurred within 6 months of starting treatment. ALT levels returned to normal within approximately 1 month after discontinuation of MAYZENT. In clinical trials, MAYZENT was discontinued if the elevation exceeded a 3-fold increase and the patient showed symptoms related to hepatic dysfunction.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia, or jaundice and/or dark urine during treatment, should have liver enzymes checked. MAYZENT should be discontinued if significant liver injury is confirmed.

Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test values when taking MAYZENT, caution should be exercised when using MAYZENT in patients with a history of significant liver disease.

5.6 Increased Blood Pressure

In Study 1, MAYZENT-treated patients had an average increase over placebo of approximately 3 mmHg in systolic pressure and 1.2 mmHg in diastolic pressure, which was first detected after approximately 1 month of treatment initiation and persisted with continued treatment. Hypertension was reported as an adverse reaction in 12.5% of MAYZENT-treated patients and in 9.2% of patients receiving placebo. Blood pressure should be monitored during treatment with MAYZENT and managed appropriately.

5.7 Fetal Risk

Based on animal studies, MAYZENT may cause fetal harm *[see Use in Specific Populations (8.1)]*. Because it takes approximately 10 days to eliminate MAYZENT from the body, women of childbearing potential should use effective contraception to avoid pregnancy during and for 10 days after stopping MAYZENT treatment.

5.8 Posterior Reversible Encephalopathy Syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving a sphingosine 1-phosphate (S1P) receptor modulator. Such events have not been reported for MAYZENT-treated patients in the development program. However, should a MAYZENT-treated patient develop any unexpected neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider a MRI. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, MAYZENT should be discontinued.

5.9 Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation, when initiating MAYZENT.

Initiating treatment with MAYZENT after treatment with alemtuzumab is not recommended *[see Drug Interactions (7.1)]*.

5.10 Severe Increase in Disability After Stopping MAYZENT

Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping MAYZENT treatment. Patients should be observed for a severe increase in disability upon MAYZENT discontinuation and appropriate treatment should be instituted, as required.

5.11 Immune System Effects After Stopping MAYZENT

After stopping MAYZENT therapy, siponimod remains in the blood for up to 10 days. Starting other therapies during this interval will result in concomitant exposure to siponimod.

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy *[see Clinical Pharmacology (12.2)]*. However, residual pharmacodynamics effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3-4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore caution should be applied 3-4 weeks after the last dose of MAYZENT *[see Drug Interactions (7.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Macular Edema *[see Warnings and Precautions (5.2)]*
- Bradyarrhytmia and Atrioventricular (AV) Conduction Delays *[see Warnings and Precautions (5.3)]*
- Respiratory Effects *[see Warnings and Precautions (5.4)]*
- Liver Injury *[see Warnings and Precautions (5.5)]*
- Increased Blood Pressure *[see Warnings and Precautions (5.6)]*
- Fetal Risk *[see Warnings and Precautions (5.7)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.8)]*
- Unintended Additive Immunosuppressive Effects From Prior Treatment With Immunosuppressive or Immune-Modulating Therapies *[see Warnings and Precautions (5.9)]*
- Severe Increase in Disability After Stopping MAYZENT *[see Warnings and Precautions (5.10)]*
- Immune System Effects After Stopping MAYZENT *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1737 MS patients have received MAYZENT at doses of at least 2 mg daily. These patients were included in Study 1 *[see Clinical Studies (14)]* and in a Phase 2 placebo-controlled study in patients with MS. In Study 1, 67% of MAYZENT-treated patients completed the double-blind part of the study, compared to 59.0% of patients receiving placebo. Adverse events led to discontinuation of treatment in 8.5% of MAYZENT-treated patients, compared to 5.1% of patients receiving placebo. The most common adverse reactions (incidence at least 10%) in MAYZENT-treated patients in Study 1 were headache, hypertension, and transaminase increases.

Table 3 lists adverse reactions that occurred in at least 5% of MAYZENT-treated patients and at a rate at least 1% higher than in patients receiving placebo.

Table 3 Adverse Reactions Reported in Study 1 (Occurring in at Least 5% of MAYZENT-Treated Patients and at a Rate at Least 1% Higher Than in Patients Receiving Placebo)

Adverse Reaction	MAYZENT 2 mg (N = 1099) %	Placebo (N = 546) %
Headache[a]	15	14
Hypertension[b]	13	9
Transaminase increased[c]	11	3
Falls	11	10
Edema peripheral[d]	8	4
Nausea	7	4
Dizziness	7	5
Diarrhea	6	4
Bradycardia[e]	6	3
Pain in extremity[f]	6	4

Terms were combined as follows:
[a]headache, tension headache, sinus headache, cervicogenic headache, drug withdrawal headache, and procedural headache.
[b]hypertension, blood pressure increased, blood pressure systolic increased, essential hypertension, blood pressure diastolic increased.
[c]alanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, liver function test increased, hepatic function abnormal, liver function test abnormal, transaminases increased.
[d]edema peripheral, joint swelling, fluid retention, swelling face.
[e]bradycardia, sinus bradycardia, heart rate decreased.
[f]pain in extremity and limb discomfort.

The following adverse reactions have occurred in less than 5% of MAYZENT-treated patients but at a rate at least 1% higher than in patients receiving placebo: herpes zoster, lymphopenia, seizure, tremor, macular edema, AV block (1st and 2nd degree), asthenia, and pulmonary function test decreased *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.4)]*.

Seizures

In Study 1, cases of seizures were reported in 1.7% of MAYZENT-treated patients, compared to 0.4% in patients receiving placebo. It is not known whether these events were related to the effects of MS, to MAYZENT, or to a combination of both.

Respiratory Effects

Dose-dependent reductions in forced expiratory volume over 1 second (FEV_1) were observed in patients treated with MAYZENT *[see Warnings and Precautions (5.4)]*.

Vascular Events

Vascular events, including ischemic strokes, pulmonary embolisms, and myocardial infarctions, were reported in 3.0% of MAYZENT-treated patients compared to 2.6% of patients receiving placebo. Some of these events were fatal. Physicians and patients should remain alert for the development of vascular events throughout treatment, even in the absence of previous vascular symptoms. Patients should be informed about the symptoms of cardiac or cerebral ischemia caused by vascular events and the steps to take if they occur.

Malignancies

Malignancies such as malignant melanoma *in situ* and seminoma were reported in MAYZENT-treated patients in Study 1. An increased risk of cutaneous malignancies has been reported in association with another S1P modulator.

7 DRUG INTERACTIONS

7.1 Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies

MAYZENT has not been studied in combination with anti-neoplastic, immune-modulating, or immunosuppressive therapies. Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration *[see Warnings and Precautions (5.1)]*.

When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered in order to avoid unintended additive immunosuppressive effects *[see Warnings and Precautions (5.9)]*.

Because of the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with MAYZENT after alemtuzumab is not recommended.

MAYZENT can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

7.2 Anti-Arrhythmic Drugs, QT Prolonging Drugs, Drugs That May Decrease Heart Rate

MAYZENT has not been studied in patients taking QT prolonging drugs.

Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. If treatment with MAYZENT is considered, advice from a cardiologist should be sought.

Because of the potential additive effects on heart rate, treatment with MAYZENT should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazem), or other drugs that may decrease heart rate (e.g., ivabradine, digoxin) *[see Warnings and Precautions (5.3) and Drug Interactions (7.3)]*. If treatment with MAYZENT is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation.

7.3 Beta-Blockers

Caution should be applied when MAYZENT is initiated in patients receiving treatment with a beta-blocker because of the additive effects on lowering heart rate; temporary interruption of the beta-blocker treatment may be needed prior to initiation of MAYZENT *[see Warnings and Precautions (5.3)]*. Beta-blocker treatment can be initiated in patients receiving stable doses of MAYZENT *[see Clinical Pharmacology (12.2)]*.

7.4 Vaccination

During and for up to one month after discontinuation of treatment with MAYZENT, vaccinations may be less effective; therefore MAYZENT treatment should be paused 1 week prior and for 4 weeks after vaccination *[see Warnings and Precautions (5.1)]*.

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during MAYZENT treatment and for up to 4 weeks after discontinuation of treatment with MAYZENT *[see Warnings and Precautions (5.1)]*.

7.5 CYP2C9 and CYP3A4 Inhibitors

Because of a significant increase in exposure to siponimod, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g., fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate - moderate or strong CYP3A4 inhibitor.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inhibitors.

7.6 CYP2C9 and CYP3A4 Inducers

Because of a significant decrease in siponimod exposure, concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP3A4 induction is not recommended for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducer (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer.

Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inducers.

Concomitant use of MAYZENT and moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended for patients with CYP2C9*1/*3 and*2/*3 genotype *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of MAYZENT in pregnant women. Based on animal data and its mechanism of action, MAYZENT can cause fetal harm when administered to a pregnant woman

(see Data). Reproductive and developmental studies in pregnant rats and rabbits have demonstrated MAYZENT-induced embryotoxicity and fetotoxicity in rats and rabbits and teratogenicity in rats. Increased incidences of post-implantation loss and fetal abnormalities (external, urogenital and skeletal) in rat and of embryo-fetal deaths, abortions and fetal variations (skeletal and visceral) in rabbit were observed following prenatal exposure to siponimod starting at a dose 2 times the exposure in humans at the highest recommended dose of 2 mg/day.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

When siponimod (0, 1, 5, or 40 mg/kg) was orally administered to pregnant rats during the period of organogenesis, post implantation loss and fetal malformations (visceral and skeletal) were increased at the lowest dose tested, the only dose with fetuses available for evaluation. A no-effect dose for adverse effects on embryo-fetal development in rats was not identified. Plasma exposure AUC at the lowest dose tested was approximately 18 times that in humans at the recommended human dose (RHD) of 2 mg/day.

When siponimod (0, 0.1, 1, or 5 mg/kg) was orally administered to pregnant rabbits during the period of organogenesis, embryolethality and increased incidences of fetal skeletal variations were observed at all but the lowest dose tested. Plasma exposure (AUC) at the no-effect dose (0.1 mg/kg) for adverse effects on embryo-fetal development in rabbits is less that than in humans at the RHD.

When siponimod (0, 0.05, 0.15, or 0.5 mg/kg) was orally administered to female rats throughout pregnancy and lactation, increased mortality, decreased body weight, and delayed sexual maturation were observed in the offspring at all but the lowest dose tested. An increase in malformations was observed at all doses. A no-effect dose for adverse effects on pre- and postnatal development in rats was not identified. The lowest dose tested (0.05 mg/kg) is less than the RHD, on a mg/m^2 basis.

8.2 Lactation

Risk Summary

There are no data on the presence of siponimod in human milk, the effects of MAYZENT on the breastfed infant, or the effects of the drug on milk production. A study in lactating rats has shown excretion of siponimod and/or its metabolites in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MAYZENT and any potential adverse effects on the breastfed infant from MAYZENT or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Before initiation of MAYZENT treatment, women of childbearing potential should be counselled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with MAYZENT *[see Use in Specific Populations (8.1)]*. Since it takes approximately 10 days to eliminate the compound from the body after stopping treatment, the potential risk to the fetus may persist and women should use effective contraception during this period *[see Warnings and Precautions (5.7)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of MAYZENT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 CYP2C9 Genotype

Before initiation of treatment with MAYZENT, test patients to determine CYP2C9 genotype. MAYZENT is contraindicated in patients homozygous for CYP2C9*3 (i.e., CYP2C9*3/*3 genotype), which is approximately 0.4%-0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. MAYZENT dosage adjustment is recommended in patients with CYP2C9*1/*3 or *2/*3 genotype because of an increase in exposure to siponimod *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.5)]*.

10 OVERDOSAGE

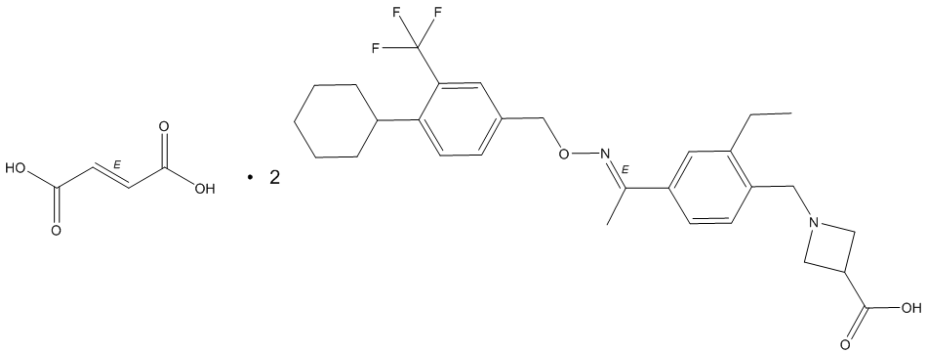
In patients with overdosage of MAYZENT, it is important to observe for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of pulse rate and blood pressure are required, and ECGs should be performed *[see Warnings and Precautions (5.3, 5.6) and Clinical Pharmacology (12.2)]*.

There is no specific antidote to siponimod available. Neither dialysis nor plasma exchange would result in meaningful removal of siponimod from the body. The decrease in heart rate induced by MAYZENT can be reversed by atropine or isoprenaline.

11 DESCRIPTION

MAYZENT tablets contains siponimod, a sphingosine 1-phosphate receptor modulator, as 2:1 co-crystal of siponimod and fumaric acid and has the following chemical name:
1-[[4-[(1*E*)-1-[[[4-Cyclohexyl-3-(trifluoromethyl)phenyl]methoxy]imino]ethyl]-2-ethylphenyl]methyl]-3-azetidinecarboxylic acid (2*E*)-2-butenedioate (2:1). Its molecular formula is $C_4H_4O_4 \cdot 2C_{29}H_{35}F_3N_2O_3$, and its molecular weight is 1149.29 g/mol.

Its structure is shown below:



It is a white to almost white powder.

MAYZENT is provided as 0.25 mg and 2 mg film-coated tablets for oral use. Each tablet contains 0.25 mg or 2 mg siponimod, equivalent to 0.28 mg or 2.22 mg as 2:1 co-crystal of siponimod and fumaric acid, respectively.

MAYZENT tablets contain the following inactive ingredients: colloidal silicon dioxide, crospovidone, glyceryl behenate, lactose monohydrate, microcrystalline cellulose, with a film coating containing iron oxides (black and red iron oxides for the 0.25 mg strength and red and yellow iron oxides for the 2 mg strength), lecithin (soy), polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator. Siponimod binds with high affinity to S1P receptors 1 and 5. Siponimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which siponimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

12.2 Pharmacodynamics

Immune System

MAYZENT induces a dose-dependent reduction of the peripheral blood lymphocyte count within 6 hours of the first dose, caused by the reversible sequestration of lymphocytes in lymphoid tissues.

With continued daily dosing, the lymphocyte count continues to decrease, reaching a nadir median (90% CI) lymphocyte count of approximately 0.560 (0.271-1.08) cells/nL in a typical CYP2C9*1/*1 or *1/*2, non-Japanese patient, corresponding to 20% to 30% of baseline. Low lymphocyte counts are maintained with chronic daily dosing *[see Warnings and Precautions (5.1)]*.

Lymphocyte counts returned to the normal range in 90% of patients within 10 days of stopping therapy. After stopping MAYZENT treatment, residual lowering effects on peripheral lymphocyte count may persist for up to 3-4 weeks after the last dose *[see Warnings and Precautions (5.1)]*.

Heart Rate and Rhythm

MAYZENT causes a transient reduction in heart rate and atrioventricular conduction upon treatment initiation *[see Warnings and Precautions (5.3)]*. The maximum decline in heart rate is seen in the first 6 hours post dose. Autonomic responses of the heart, including diurnal variation of heart rate and response to exercise, are not affected by siponimod treatment.

A transient, dose-dependent decrease in heart rate was observed during the initial dosing phase of MAYZENT, which plateaued at doses greater than or equal to 5 mg, and bradyarrhythmic events (AV blocks and sinus pauses) were detected at a higher incidence under MAYZENT treatment, compared to placebo.

No second-degree AV blocks of Mobitz type II or higher degree were observed. Most AV blocks and sinus pauses occurred above the recommended dose of 2 mg, with notably higher incidence under non-titrated conditions compared to dose titration conditions *[see Dosage and Administration (2.2, 2.3)]*.

The decrease in heart rate induced by MAYZENT can be reversed by atropine or isoprenaline.

Beta-Blockers

The negative chronotropic effect of coadministration of siponimod and propranolol was evaluated in a dedicated pharmacodynamics (PD)/safety study. The addition of propranolol on top of siponimod at steady-state had less pronounced negative chronotropic effects (less than additive effect) than the addition of siponimod to propranolol at steady state (additive HR effect) *[see Drug Interactions (7.3)]*.

Cardiac Electrophysiology

In a thorough QT study with doses of 2 mg (recommended dose) and 10 mg (five times the recommended dose) siponimod at steady-state, siponimod treatment resulted in a prolongation of QT_c, with the maximum mean (upper bound of the two-sided 90% CI) of 7.8 (9.93) ms at 2 mg dose and 7.2 (9.72) ms at 10 mg dose. There was an absence of dose- and exposure-response relationship for QTc effects with the 5-fold dose and exposures achieved by the supratherapeutic dose. No subject had absolute QTcF greater than 480 ms or ΔQTcF greater than 60 ms for siponimod treatment.

Pulmonary Function

Dose-dependent reductions in absolute forced expiratory volume over 1 second were observed in MAYZENT-treated patients and were greater than in patients taking placebo *[see Warnings and Precautions (5.4)]*.

12.3 Pharmacokinetics

Siponimod concentration increases in an apparent dose-proportional manner after multiple once-daily doses of siponimod 0.3 mg to 20 mg. Steady-state plasma concentrations are reached after approximately 6 days of once-daily dosing, and steady-state levels are approximately 2-3-fold greater than the initial dose. An up-titration regimen is used to reach the clinical therapeutic dose of siponimod of 2 mg after 6 days, and 4 additional days of dosing are required to reach the steady-state-plasma concentrations.

Absorption

The time (T_{max}) to reach maximum plasma concentrations (C_{max}) after oral administration of immediate release oral dosage forms of siponimod was about 4 hours (range 3-8 hours). Siponimod absorption is extensive (greater than or equal

to 70%, based on the amount of radioactivity excreted in urine and the amount of metabolites in feces extrapolated to infinity). The absolute oral bioavailability of siponimod is approximately 84%. After administration of siponimod 2 mg once-daily over 10 days, a mean C_{max} of 30.4 ng/mL and mean area under plasma concentration-time curve over dosing interval (AUC_{tau}) of 558 h*ng/mL were observed on day 10. Steady-state was reached after approximately 6 days of once-daily administration of siponimod.

Food Effect

Food intake resulted in delayed absorption (the median Tmax increased by approximately 2-3 hours). Food intake had no effect on the systemic exposure of siponimod (C_{max} and AUC). Therefore, MAYZENT may be taken without regard to meals.

Distribution

Siponimod distributes to body tissues with a moderate mean volume of distribution of 124 L. Siponimod fraction found in plasma is 68% in humans. Animal studies show that siponimod readily crosses the blood-brain-barrier. Protein binding of siponimod is greater than 99.9% in healthy subjects and in hepatic and renal impaired patients.

Elimination

Metabolism

Siponimod is extensively metabolized, mainly via CYP2C9 (79.3%), followed by CYP3A4 (18.5%). The pharmacological activity of the main metabolites M3 and M17 is not expected to contribute to the clinical effect and the safety of siponimod in humans.

Excretion

An apparent systemic clearance (CL/F) of 3.11 L/h was estimated in MS patients. The apparent elimination half-life is approximately 30 hours.

Siponimod is eliminated from the systemic circulation mainly due to metabolism, and subsequent biliary/fecal excretion. Unchanged siponimod was not detected in urine.

Specific Populations

Male and Female Patients

Gender has no influence on siponimod pharmacokinetics (PK).

Racial or Ethnic Groups

The single-dose PK parameters were not different between Japanese and Caucasians healthy subjects, indicating absence of ethnic sensitivity on the PK of siponimod.

Patients with Renal Impairment

No dose adjustments are needed in patients with renal impairment. Mean siponimod half-life and C_{max} (total and unbound) were comparable between subjects with severe renal impairment and healthy subjects. Unbound AUCs were only slightly increased (by 33%), compared to healthy subjects, and it is not expected to be clinically significant. The effects of end-stage renal disease or hemodialysis on the PK of siponimod has not been studied. Due to the high plasma protein binding (greater than 99.9%) of siponimod, hemodialysis is not expected to alter the total and unbound siponimod concentration and no dose adjustments are anticipated based on these considerations.

Patients with Hepatic Impairment

No dose adjustments for siponimod are needed in patients with hepatic impairment. The unbound siponimod AUC parameters are 15% and 50% higher in subjects with moderate and severe hepatic impairment, respectively, in comparison with healthy subjects for the 0.25 mg single dose studied. The increased unbound siponimod AUC in subjects with moderate and severe hepatic impairment is not expected to be clinically significant. The mean half-life of siponimod was unchanged in hepatic impairment.

Drug Interaction Studies

Siponimod (and Metabolites M3, M17) as a Causative Agent of Interaction

In vitro investigations indicated that siponimod and its major systemic metabolites M3 and M17 do not show any clinically relevant drug-drug interaction potential at the therapeutic dose of 2 mg once-daily for all investigated CYP enzymes and transporters.

Siponimod as an Object of Interaction

CYP2C9 is polymorphic and the genotype influences the fractional contributions of the two oxidative metabolism pathways to overall elimination. Physiologically based PK modeling indicates a differential CYP2C9 genotype-dependent inhibition and induction of CYP3A4 pathways. With decreased CYP2C9 metabolic activity in the respective genotypes, a larger effect of the CYP3A4 perpetrators on siponimod exposure is anticipated.

Coadministration of Siponimod with CYP2C9 and CYP3A4 Inhibitors

The coadministration of fluconazole (moderate CYP2C9 and CYP3A4 dual inhibitor) 200 mg daily at steady-state and a single dose of siponimod 4 mg in CYP2C9*1/*1 healthy volunteers led to a 2-fold increase in the AUC of siponimod. Mean siponimod terminal half-life was increased by 50%. Fluconazole led to a 2- to 4-fold increase in the $AUC_{tau,ss}$ of siponimod across different CYP2C9 genotypes, according to in silico evaluation *[see Drug Interactions (7.5)]*.

Coadministration of Siponimod with CYP2C9 and CYP3A4 Inducers

The coadministration of siponimod 2 mg daily in the presence of 600 mg daily doses of rifampin (strong CYP3A4 and moderate CYP2C9 dual inducer) decreased siponimod $AUC_{tau,ss}$ and $C_{max,ss}$ by 57% and 45%, respectively in CY2C9*1/*1 subjects. Rifampin and efavirenz (moderate CYP3A4 inducer) reduced the $AUC_{tau,ss}$ of siponimod by up to 78% and up to 52%, respectively, across CYP2C9 genotypes, according to in silico evaluation *[see Drug Interactions (7.6)]*.

Oral Contraceptives

The effects of coadministration of siponimod 2 mg and 4 mg (twice the recommended dosage) once daily with a monophasic oral contraceptive (OC) containing 30 mcg ethinyl estradiol and 150 mcg levonorgestrel were assessed in 24 healthy female subjects (18 to 40 years of age; CYP2C9*1/*1 genotype). There were no clinically relevant effects on the PK or PD of the OC. No interaction studies have been performed with OCs containing other progestagens; however, an effect of siponimod on their exposure is not expected.

12.5 Pharmacogenomics

The CYP2C9 genotype has a significant impact on siponimod metabolism. After a single dose of 0.25 mg siponimod, AUC_{inf} and AUC_{last} was approximately 2- and 4-fold higher in subjects with the CYP2C9*2/*3 and CYP2C9*3/*3 genotypes, respectively, while there was only a minor increase of C_{max} by 21% and 16%, respectively, compared to extensive metabolizers (CYP2C9*1/*1). Mean half-life is prolonged in CYP2C9*2/*3 and CYP2C9*3/*3 carriers (51 hours and 126 hours, respectively).

An apparent systemic clearance (CL/F) of about 3.11 L/h was estimated in CYP2C9 extensive metabolizer (CYP2C9*1/*1 and CYP2C9*1/*2) MS patients after multiple oral administrations of siponimod. Cl/F is 2.5, 1.9, 1.6, and 0.9 L/h in subjects with the CYP2C9*2/*2, CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3 genotypes respectively. The resultant increase in siponimod AUC was approximatively 25, 61, 91, and 285% higher in CYP2C9*2/*2, CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3 subjects, respectively, as compared to CYP2C9*1/*1 subjects *[see Dosage and Administration (2.1, 2.3) and Contraindications (4)]*. As the apparent clearance estimated for CYP2C9*1*2 subjects is comparable to that of CYP2C9*1/*1 subjects, similar siponimod exposure is expected for both genotypes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Oral carcinogenicity studies of spinomod were conducted in mice and rats. In mice administered siponimod (0, 2, 8, or 25 mg/kg/day) for up to 104 weeks, there was an increase in malignant lymphoma in females at all doses and in hemangiosarcoma and combined hemangioma and hemangiosarcoma at all doses in males and females. The lowest dose tested is approximately 5 times the recommended human dose (RHD) of 2 mg/day, on a body surface area (mg/m^2) basis.

In rats, administration of siponimod (0, 10, 30, or 90 mg/kg/day in males; 0, 3, 10, or 30 mg/kg/day in females) for up to 104 weeks, there was an increase in thyroid follicular cell adenoma and combined thyroid follicular cell adenoma and carcinoma in males at the highest dose tested. These findings are considered secondary to liver enzyme induction in rats

and are not considered relevant to humans. Plasma siponimod exposure (AUC) at the highest dose tested is approximately 200 times that in humans at the RHD.

Mutagenesis

Siponimod was negative in a battery of *in vitro* (Ames, chromosomal aberration in mammalian cells) and *in vivo* (micronucleus in mouse and rat) assays.

Impairment of Fertility

When siponimod was administered orally (0, 2, 20, or 200 mg/kg) to male rats (mated with untreated females) prior to and throughout the mating period, there was a dose-related increase in precoital interval at all doses. A decrease in implantation sites, an increase in preimplantation loss, and a decrease in the number of viable fetuses were observed at the highest dose tested. The higher no-effect dose for adverse effects on fertility (20 mg/kg) is approximately 100 times the RHD on a mg/m^2 basis.

When siponimod was administered orally (0, 0.1, 0.3, or 1 mg/kg) to female rats (mated with untreated males) prior to and during mating, and continuing to Day 6 of gestation, no effects on fertility were observed up to the highest dose tested (1 mg/kg). Plasma siponimod exposure (AUC) at the highest dose tested is approximately 16 times that in humans at the RHD.

14 CLINICAL STUDIES

The efficacy of MAYZENT was demonstrated in Study 1, a randomized, double-blind, parallel-group, placebo-controlled, time-to-event study in patients with secondary progressive multiple sclerosis (SPMS) who had evidence of disability progression in the prior 2 years, no evidence of relapse in 3 months prior to study enrollment, and an Expanded Disability Status Scale (EDSS) score of 3.0-6.5 at study entry (NCT 01665144).

Patients were randomized to receive either once daily MAYZENT 2 mg or placebo, beginning with a dose titration *[see Dosage and Administration (2.2)]*. Evaluations were performed at screening, every 3 months during the study, and at the time of a suspected relapse. MRI evaluations were performed at screening and every 12 months.

The primary endpoint of the study was the time to 3-month confirmed disability progression (CDP), defined as at least a 1-point increase from baseline in EDSS (0.5-point increase for patients with baseline EDSS of 5.5 or higher) sustained for 3 months. A prespecified hierarchical analysis consisted of the primary endpoint and 2 secondary endpoints, the time to 3-month confirmed worsening of at least 20% from baseline on the timed 25-foot walk test and the change from baseline in T2 lesion volume. Additional endpoints included annualized relapse rate (relapses/year) and MRI measures of inflammatory disease activity.

Study duration was variable for individual patients (median study duration was 21 months, range 1 day-37 months).

Study 1 randomized 1651 patients to either MAYZENT 2 mg (N = 1105) or placebo (N = 546); 82% of MAYZENT-treated patients and 78% of placebo-treated patients completed the study. Median age was 49.0 years, 95% of patients were white, and 60% female. The median disease duration was 16.0 years, and median EDSS score at baseline was 6.0 (56% of patients had ≥ 6.0 EDSS at baseline); 36% of patients had one or more relapses in the 2 years prior to study entry; 22% of those patients with available imaging had one or more gadolinium-enhancing lesions on their baseline MRI scan; 78% of patients had been previously treated with an MS therapy.

Results are presented in Table 4. MAYZENT was superior to placebo in reducing the risk of confirmed disability progression, based on a time-to-event analysis (hazard ratio 0.79, $p < 0.0134$; see Figure 1). MAYZENT did not significantly delay the time to 20% deterioration in the timed 25-foot walk, compared to placebo. Patients treated with MAYZENT had a 55% relative reduction in annualized relapse rate, compared to patients on placebo (nominal p-value < 0.0001). The absolute reduction in the annualized relapse rate was 0.089. Although MAYZENT had a significant effect on disability progression compared to placebo in patients with active SPMS (e.g., SPMS patients with an MS relapse in the 2 years prior to the study), the effect of MAYZENT in patients with non-active SPMS was not statistically significant (see Figure 2).

Table 4 Clinical and MRI Results From Study 1

	MAYZENT	PLACEBO
Clinical Outcomes		
Proportion of patients with confirmed disability progression[1]	26%	32%
Relative risk reduction	21% (p = 0.0134)*	
Absolute risk Reduction	6%	
Proportion of patients with confirmed worsening in timed 25-foot walk	40%	41%
	p = NS	
Annualized relapse rate[2]	0.071	0.160
Relative reduction (%)	55% ($p < 0.01$)^	
Absolute reduction	0.089	
	$p < 0.01$^	
MRI Endpoints		
Change from baseline in T2 lesion volume (mm^3) (95% CI)[3]	184 (54; 314)	879 (712; 1047)
	$p < 0.01$^	

All analyses are based on the full analysis set (FAS), which includes all randomized subjects who took at least one dose of study medication. p-values are two-sided.

(1) Defined as an increase of 1.0 point or more from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline score of 5.5 or less, or 0.5 or more when the baseline score is greater than 5.5. Progression confirmed at 3 months. Cox proportional hazard model.

(2) Defined as the average number of confirmed relapses per year (estimated from negative binomial regression model for recurrent events).

(3) Adjusted mean averaged over Months 12 and 24.

* Statistically significant.

NS, Not statistically significant.

^ Nominal p value, not corrected for multiple comparisons.

Figure 1 Time to Confirmed Disability Progression Based on EDSS (Study 1)

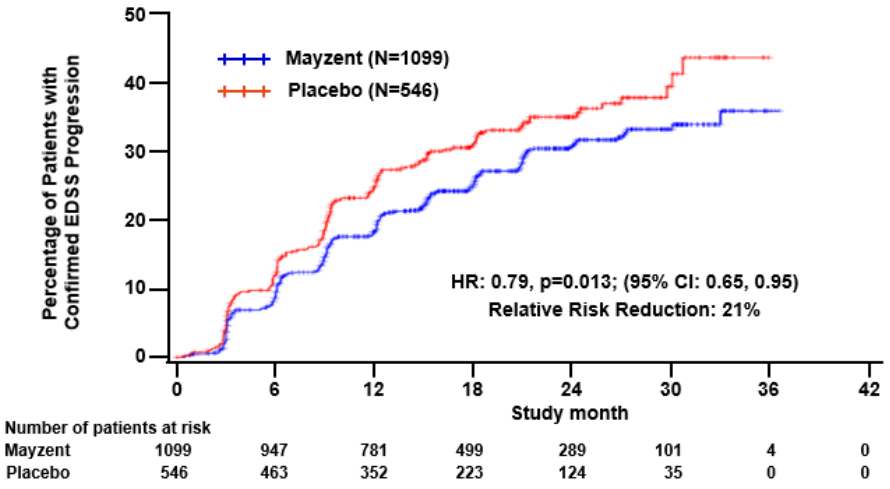
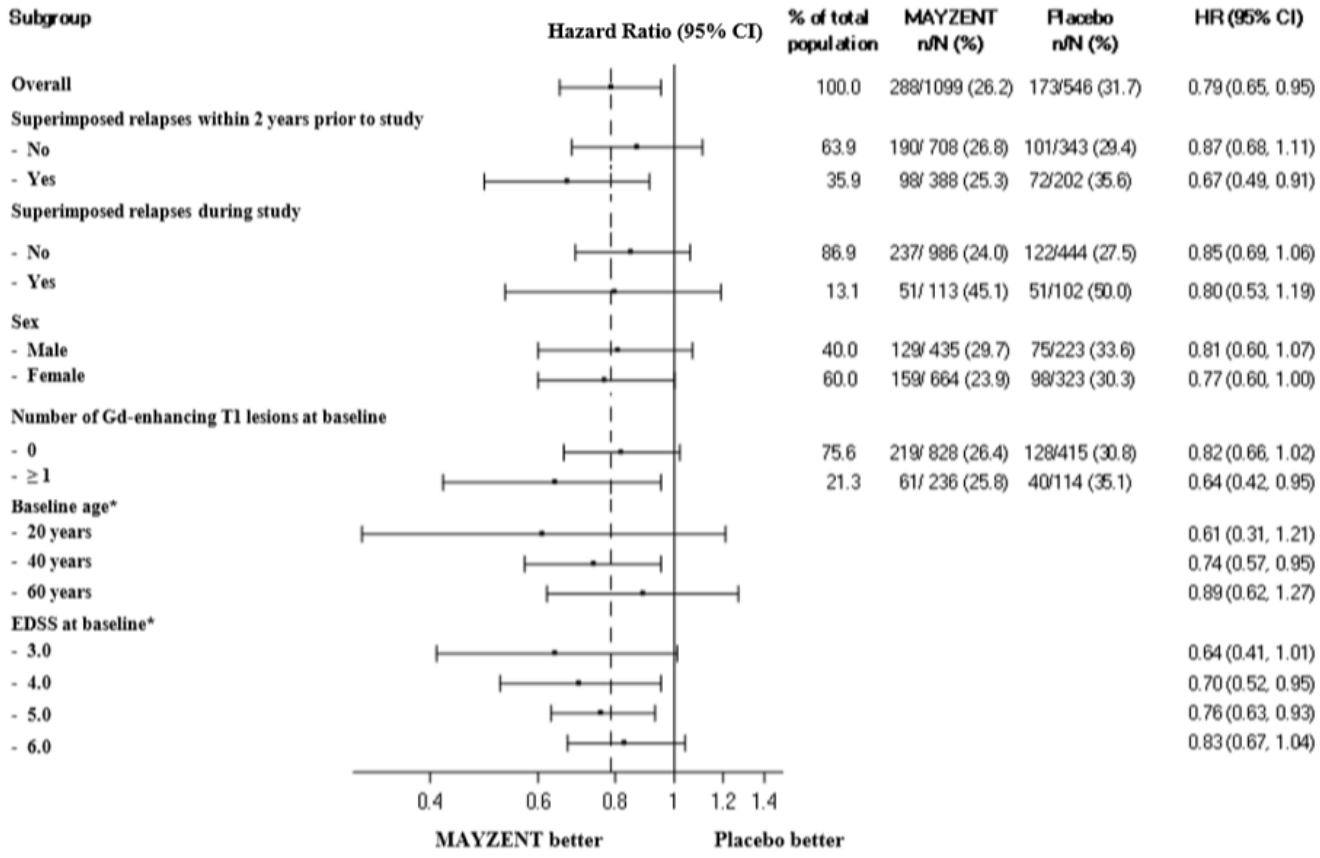


Figure 2 Time to Confirmed Disability Progression Based on EDSS (Study 1), Subgroup Analysis



*HR and 95% CI presented are model-based estimates for a range of values of age and EDSS.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MAYZENT film-coated tablets are supplied as follows:

0.25 mg tablet: Pale red, unscored, round biconvex film-coated tablet with beveled edges, debossed with on one side and 'T' on other side.

Starter Pack* – blister card of twelve 0.25 mg tablets in a calendarized blister wallet.....NDC 0078-0979-12

*This starter pack is only intended for patients who will receive the 2 mg maintenance dosage.

Bottle of 28 tablets.....NDC 0078-0979-50

2 mg tablet: Pale yellow, unscored, round biconvex film-coated tablet with beveled edges, debossed with on one side and 'II' on other side.

Bottle of 30 tablets.....NDC 0078-0986-15

16.2 Storage and Handling

Unopened Containers

Store unopened containers of MAYZENT 0.25 mg and 2 mg film-coated tablets in a refrigerator between 2°C to 8°C (36°F to 46°F).

Opened Containers

Store opened containers of MAYZENT as follows:

Starter Pack/Blister Card

MAYZENT 0.25 mg film-coated tablets in the Starter Pack may be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] for up to 1 week after opening the blister. Store in original container.

Bottles

MAYZENT 0.25 mg and 2 mg film-coated tablets in bottles may be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] for up to 1 month after opening the bottles.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Tell patients not to discontinue MAYZENT without first discussing this with the prescribing physician. Advise patients to contact their physician if they accidently take more MAYZENT than prescribed.

Risk of Infections

Inform patients that they may have an increased risk of infections, some of which could be life-threatening, when taking MAYZENT, and that they should contact their physician if they develop symptoms of infection *[see Warnings and Precautions (5.1)]*. Advise patients that the use of some vaccines containing live virus (live attenuated vaccines) should be avoided during treatment with MAYZENT and MAYZENT should be paused 1 week prior and until 4 weeks after a planned vaccination. Recommend that patients postpone treatment with MAYZENT for at least 1 month after VZV vaccination. Inform patients that prior or concomitant use of drugs that suppress the immune system may increase the risk of infection.

Macular Edema

Advise patients that MAYZENT may cause macular edema, and that they should contact their physician if they experience any changes in their vision while taking MAYZENT *[see Warnings and Precautions (5.2)]*. Inform patients with diabetes mellitus or a history of uveitis that their risk of macular edema is increased.

Cardiac Effects

Advise patients that initiation of MAYZENT treatment results in transient decrease in heart rate *[see Warnings and Precautions (5.3)]*. Inform patients that to reduce this effect, dosage titration is required. Advise patients that dosage titration is also required if a dose is missed for more than 24 hours during the titration or if 4 or more consecutive daily maintenance doses are missed *[see Dosage and Administration (2.2, 2.3, 2.5) and Warnings and Precautions (5.3)]*. Inform certain patients with certain pre-existing cardiac conditions that they will need to be observed in the doctor's office or other facility for at least 6 hours after the first dose and after reinitiation if treatment is interrupted or discontinued for certain periods *[see Dosage and Administration (2.4)]*.

Respiratory Effects

Advise patients that they should contact their physician if they experience new onset or worsening of dyspnea *[see Warnings and Precautions (5.4)]*.

Liver Injury

Inform patients that MAYZENT may increase liver enzymes. Advise patient that they should contact their physician if they experience any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine during treatment *[see Warnings and Precautions (5.5)]*.

Pregnancy and Fetal Risk

Inform patients that, based on animal studies MAYZENT may cause fetal harm *[see Warnings and Precautions (5.7)]*. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Advise women of childbearing potential of the need for effective contraception during treatment with MAYZENT and for 10 days after stopping MAYZENT. Advise a female patient to immediately inform that prescriber if she is pregnant or planning to become pregnant *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1, 8.3)]*.

Posterior Reversible Encephalopathy Syndrome

Advise patients to immediately report to their healthcare provider any symptoms involving sudden onset of severe headache, altered mental status, visual disturbances, or seizure. Inform patients that delayed treatment could lead to permanent neurological sequelae *[see Warnings and Precautions (5.8)]*.

Severe Increase in Disability After Stopping MAYZENT

Inform patients that severe increase in disability has been reported after discontinuation of another sphingosine 1-phosphate (S1P) receptor modulator like MAYZENT. Advise patients to contact their physician if they develop worsening symptoms of MS following discontinuation of MAYZENT *[see Warnings and Precautions (5.10)]*.

Immune System Effects After Stopping MAYZENT

Advise patients that MAYZENT continues to have effects, such as lowering effects on peripheral lymphocyte count, for up to 3-4 weeks after the last dose *[see Warnings and Precautions (5.11)]*.

Storage and Handling

Instruct patients to store any unopened containers of MAYZENT in a refrigerator. Inform patients that opened starter packs may be stored at room temperature for 1 week and opened bottles may be stored at room temperature for 1 month *[see How Supplied/Storage and Handling (16.2)]*.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2019-45

MEDICATION GUIDE
MAYZENT (Mā'zĕnt)
(siponimod)
tablets, for oral use

What is the most important information I should know about MAYZENT?

1. **MAYZENT may cause serious side effects, including: Slow heart rate (bradycardia or bradyarrhythmia) when you start taking MAYZENT.** MAYZENT can cause your heart rate to slow down, especially after you take your first dose. You should have a test to check the electrical activity of your heart called an electrocardiogram (ECG) before you take your first dose of MAYZENT.

   During the initial updosing period (4 days for the 1 mg daily dose or 5 days for the 2 mg daily dose), if you miss 1 or more doses of MAYZENT, you need to restart the updosing. Call your healthcare provider if you miss a dose of MAYZENT. See **"How should I take MAYZENT?"**

2. **Infections.** MAYZENT can increase your risk of serious infections that can be life-threatening and cause death. MAYZENT lowers the number of white blood cells (lymphocytes) in your blood. This will usually go back to normal within 3 to 4 weeks of stopping treatment. Your healthcare provider should review a recent blood test of your white blood cells before you start taking MAYZENT.

   Call your healthcare provider right away if you have any of these symptoms of an infection during treatment with MAYZENT and for 3 to 4 weeks after your last dose of MAYZENT:

   - fever
   - tiredness
   - body aches
   - chills
   - nausea
   - vomiting
   - headache with fever, neck stiffness, sensitivity to light, nausea, confusion (these may be symptoms of meningitis, an infection of the lining around your brain and spine)

3. A problem with your vision called macular edema. Macular edema can cause some of the same vision symptoms as a multiple sclerosis (MS) attack (optic neuritis). You may not notice any symptoms with macular edema. If macular edema happens, it usually starts in the first 1 to 4 months after your start taking MAYZENT. Your healthcare provider should test your vision before you start taking MAYZENT and any time you notice vision changes during treatment with MAYZENT. Your risk of macular edema is higher if you have diabetes or have had an inflammation of your eye called uveitis.

   Call your healthcare provider right away if you have any of the following:

   - blurriness or shadows in the center of your vision
   - a blind spot in the center of your vision
   - sensitivity to light
   - unusually colored (tinted) vision

See "What are possible side effects of MAYZENT?" for more information about side effects.

What is MAYZENT?

MAYZENT is a prescription medicine that is used to treat relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

It is not known if MAYZENT is safe and effective in children.

Who should not take MAYZENT?

Do not take MAYZENT if you:

- have a CYP2C9*3/*3 genotype. Before starting treatment with MAYZENT, your CYP2C9 genotype should be determined by your healthcare provider. Ask your healthcare provider if you are not sure.
- have had a heart attack, chest pain called unstable angina, stroke or mini-stroke (transient ischemic attack or TIA), or certain types of heart failure in the last 6 months
- have certain types of heart block or irregular or abnormal heartbeat (arrhythmia), unless you have a pacemaker

What should I tell my healthcare provider before taking MAYZENT?

Before taking MAYZENT, tell your healthcare provider about all of your medical conditions, including if you:

- have an irregular or abnormal heartbeat
- a history of stroke or other diseases related to blood vessels in the brain
- breathing problems, including during your sleep
- a fever or infection, or you are unable to fight infections due to a disease or taking medicines that lower your immune system. Tell your healthcare provider if you have had chicken pox or have received the vaccine for chicken pox. Your

healthcare provider may do a blood test for chicken pox virus. You may need to get the full course of vaccine for chicken pox and then wait 1 month before you start taking MAYZENT**.**

- have slow heart rate
- have liver problems
- have diabetes
- have eye problems, especially an inflammation of the eye called uveitis
- have high blood pressure
- are pregnant or plan to become pregnant. MAYZENT may harm your unborn baby. Talk to your healthcare provider right away if you become pregnant while taking MAYZENT or if you become pregnant within 10 days after you stop taking MAYZENT.
  - If you are a woman who can become pregnant, you should use effective birth control during your treatment with MAYZENT and for at least 10 days after you stop taking MAYZENT.
- are breastfeeding or plan to breastfeed. It is not known if MAYZENT passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take MAYZENT.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you:

- take medicines to control your heart rhythm (antiarrhythmics), or blood pressure (antihypertensives), or heart beat (such as calcium channel blockers or beta-blockers)
- take medicines that affect your immune system, such as beta-interferon or glatiramer acetate, or any of these medicines that you took in the past
- have recently received a live vaccine. You should avoid receiving **live** vaccines during treatment with MAYZENT. MAYZENT should be stopped 1 week before and for 4 weeks after receiving a live vaccine. If you receive a live vaccine, you may get the infection the vaccine was meant to prevent. Vaccines may not work as well when given during treatment with MAYZENT.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist when you get a new medicine.

Using MAYZENT and other medicines together may affect each other causing serious side effects.

How should I take MAYZENT?

The daily maintenance dose of MAYZENT is either 1 mg or 2 mg, depending on your CYP2C9 genotype. Ask your healthcare provider if you are not sure about your daily maintenance dose.

Start your treatment with MAYZENT using the following titration schedule:

For the 1 mg daily maintenance dose:	**Tablets a day**
Day 1	1 x 0.25 mg tablet
Day 2	1 x 0.25 mg tablet
Day 3	2 x 0.25 mg tablet
Day 4	3 x 0.25 mg tablet
Day 5 and every day after	4 x 0.25 mg tablet

For the 2 mg daily maintenance dose, use the starter pack:	**Tablets a day**
Day 1	1 x 0.25 mg tablet
Day 2	1 x 0.25 mg tablet
Day 3	2 x 0.25 mg tablet
Day 4	3 x 0.25 mg tablet
Day 5	5 x 0.25 mg tablet
Day 6 and every day after	1 x 2 mg tablet

- Take MAYZENT exactly as your healthcare provider tells you. Do not change your dose or stop taking MAYZENT unless your healthcare provider tells you to.
- Take MAYZENT 1 time each day.
- Take MAYZENT with or without food.
- If you miss 1 or more doses of MAYZENT **during** the initial dose titration, you need to restart the medication.
- If you miss a dose of MAYZENT **after** the initial dose-titration, take it as soon as you remember.
- If MAYZENT treatment is stopped for 4 days in a row, treatment has to be restarted with the titration.
- **Do not stop taking MAYZENT without talking with your healthcare provider first.**

What are the possible side effects of MAYZENT?

MAYZENT may cause serious side effects, including:

- **See "What is the most important information I should know about MAYZENT?"**
- **increased blood pressure.** Your healthcare provider should check your blood pressure during treatment with MAYZENT.
- **liver problems.** MAYZENT may cause liver problems. Your healthcare provider should do blood tests to check your liver before you start taking MAYZENT. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - nausea
  - vomiting
  - stomach pain
  - tiredness
  - loss of appetite
  - your skin or the whites of your eyes turn yellow
  - dark urine
- **breathing problems.** Some people who take MAYZENT have shortness of breath. Call your healthcare provider right away if you have new or worsening breathing problems.
- **swelling and narrowing of the blood vessels in your brain.** A condition called PRES (Posterior Reversible Encephalopathy Syndrome) has happened with drugs in the same class. Symptoms of PRES usually get better when you stop taking MAYZENT. However, if left untreated, it may lead to a stroke. Call your healthcare provider right away if you have any of the following symptoms:
  - sudden severe headache
  - sudden confusion
  - sudden loss of vision or other changes in your vision
  - seizure
- **severe worsening of multiple sclerosis after stopping MAYZENT.** When MAYZENT is stopped, symptoms of MS may return and become worse compared to before or during treatment. Always talk to your doctor before you stop taking MAYZENT for any reason. Tell your healthcare provider if you have worsening symptoms of MS after stopping MAYZENT.

The most common side effects of MAYZENT include:

- headache
- high blood pressure (hypertension)
- abnormal liver tests

Tell your healthcare provider if you have any side effects that bother you or that do not go away.

These are not all of the possible side effects of MAYZENT. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MAYZENT?

Before opening:

- MAYZENT 0.25 mg and 2 mg tablets should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C).

After opening:

- MAYZENT 0.25 mg tablets **in the Starter Pack** may be stored at room temperature, 68°F to 77°F (20°C to 25°C), for up to 1 week after opening.
- MAYZENT 0.25 mg and 2 mg tablets **in bottles** may be stored at room temperature, 68°F to 77°F (20°C to 25°C), for up to 1 month after opening.

Keep MAYZENT and all medicines out of the reach of children.

General information about the safe and effective use of MAYZENT

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use MAYZENT for a condition for which it was not prescribed. Do not give MAYZENT to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for more information about MAYZENT that is written for health professionals.

What are the ingredients in MAYZENT?

Active ingredient: siponimod

Inactive ingredients: colloidal silicon dioxide, crospovidone, glyceryl behenate, lactose monohydrate, microcrystalline cellulose, with a film coating containing iron oxides (black and red iron oxides for the 0.25 mg strength and red and yellow iron oxides for the 2 mg strength), lecithin (soy), polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

Distributed by: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936
For more information, go to www.pharma.us.novartis.com or call 1-888-669-6682.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: March 2019

T2019-46

Section 5.0

New Codes

2019 New ICD-10-CM Codes

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
D75.A	Glucose-6-phosphate dehydrogenase (G6PD) deficiency without anemia	D55 (Anemia due to glucose-6-phosphate dehydrogenase [G6PD] deficiency) is on line 194	194 HEREDITARY ANEMIAS, HEMOGLOBINOPATHIES, AND DISORDERS OF THE SPLEEN	Patients may have normal hematocrit between episodes, but may still require hematology care
D81.30	Adenosine deaminase deficiency, unspecified	D81.3 (Adenosine deaminase [ADA] deficiency) was on lines 71,95,292,313,345,377	Dysfunction lines (71,292,345,377) 95 HEREDITARY IMMUNE DEFICIENCIES Tx Bone marrow transplant 313 DISORDERS INVOLVING THE IMMUNE SYSTEM	All adenosine deaminase deficiency variations can cause developmental delays, growth issues, and some degree of immune deficiency
D81.31	Severe combined immunodeficiency due to adenosine deaminase deficiency		71,95,292,313,345,377	See above
D81.32	Adenosine deaminase 2 deficiency		71,95,292,313,345,377	See above
D81.39	Other adenosine deaminase deficiency		71,95,292,313,345,377	See above
H81.4	Vertigo of central origin	H81.41-H81.49 (Vertigo of central origin, left, right, bilateral, or unspecied ear) are on line 510	510 VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM	
I26.93	Single subsegmental pulmonary embolism without acute cor pulmonale	Other PE diagnoses are on line 214	214 ACUTE PULMONARY HEART DISEASE AND PULMONARY EMBOLI	
I26.94	Multiple subsegmental pulmonary emboli without acute cor pulmonale		214 ACUTE PULMONARY HEART DISEASE AND PULMONARY EMBOLI	
I48.11	Longstanding persistent atrial fibrillation	I48.1 (Persistent atrial fibrillation) was on line 347	347 CARDIAC ARRHYTHMIAS	
I48.19	Other persistent atrial fibrillation		347 CARDIAC ARRHYTHMIAS	
I48.20	Chronic atrial fibrillation, unspecified	I48.2 (Chronic atrial fibrillation) was on line 347	347 CARDIAC ARRHYTHMIAS	
I48.21	Permanent atrial fibrillation		347 CARDIAC ARRHYTHMIAS	

2019 New ICD-10-CM Codes

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
I80.241	Phlebitis and thrombophlebitis of right peroneal vein	Other deep vein phlebitis and thrombophlebitis diagnoses are on line 79	79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	Peroneal veins are considered deep veins (not superficial) and therefore should be placed on line 79
I80.242	Phlebitis and thrombophlebitis of left peroneal vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	
I80.243	Phlebitis and thrombophlebitis of peroneal vein, bilateral		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	
I80.249	Phlebitis and thrombophlebitis of unspecified peroneal vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	
I80.251	Phlebitis and thrombophlebitis of right calf muscular vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues
I80.252	Phlebitis and thrombophlebitis of left calf muscular vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues
I80.253	Phlebitis and thrombophlebitis of calf muscular vein, bilateral		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues
I80.259	Phlebitis and thrombophlebitis of unspecified calf muscular vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues
I82.451	Acute embolism and thrombosis of right peroneal vein	Other acute embolism and thrombosis of deep calf veins are on line 79	79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	Peroneal veins are considered deep veins (not superficial) and therefore should be placed on line 79
I82.452	Acute embolism and thrombosis of left peroneal vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	
I82.453	Acute embolism and thrombosis of peroneal vein, bilateral		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	
I82.459	Acute embolism and thrombosis of unspecified peroneal vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	
I82.461	Acute embolism and thrombosis of right calf muscular vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues
I82.462	Acute embolism and thrombosis of left calf muscular vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues
I82.463	Acute embolism and thrombosis of calf muscular vein, bilateral		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues

2019 New ICD-10-CM Codes

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
I82.469	Acute embolism and thrombosis of unspecified calf muscular vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues
I82.551	Chronic embolism and thrombosis of right peroneal vein	Other acute embolism and thrombosis of deep calf veins are on line 79	79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	Peroneal veins are considered deep veins (not superficial) and therefore should be placed on line 79
I82.552	Chronic embolism and thrombosis of left peroneal vein	Other acute embolism and thrombosis of deep calf veins are on line 79	79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	Peroneal veins are considered deep veins (not superficial) and therefore should be placed on line 79
I82.553	Chronic embolism and thrombosis of peroneal vein, bilateral	Other acute embolism and thrombosis of deep calf veins are on line 79	79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	Peroneal veins are considered deep veins (not superficial) and therefore should be placed on line 79
I82.559	Chronic embolism and thrombosis of unspecified peroneal vein	Other acute embolism and thrombosis of deep calf veins are on line 79	79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	Peroneal veins are considered deep veins (not superficial) and therefore should be placed on line 79
I82.561	Chronic embolism and thrombosis of right calf muscular vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues
I82.562	Chronic embolism and thrombosis of left calf muscular vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues
I82.563	Chronic embolism and thrombosis of calf muscular vein, bilateral		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues
I82.569	Chronic embolism and thrombosis of unspecified calf muscular vein		79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP	See issues
L89.006	Pressure-induced deep tissue damage of unspecified elbow	Other L89 series codes are on line 379	379 CHRONIC ULCER OF SKIN	
L89.016	Pressure-induced deep tissue damage of right elbow		379 CHRONIC ULCER OF SKIN	
L89.026	Pressure-induced deep tissue damage of left elbow		379 CHRONIC ULCER OF SKIN	
L89.106	Pressure-induced deep tissue damage of unspecified part of back		379 CHRONIC ULCER OF SKIN	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
L89.116	Pressure-induced deep tissue damage of right upper back		379 CHRONIC ULCER OF SKIN	
L89.126	Pressure-induced deep tissue damage of left upper back		379 CHRONIC ULCER OF SKIN	
L89.136	Pressure-induced deep tissue damage of right lower back		379 CHRONIC ULCER OF SKIN	
L89.146	Pressure-induced deep tissue damage of left lower back		379 CHRONIC ULCER OF SKIN	
L89.156	Pressure-induced deep tissue damage of sacral region		379 CHRONIC ULCER OF SKIN	
L89.206	Pressure-induced deep tissue damage of unspecified hip		379 CHRONIC ULCER OF SKIN	
L89.216	Pressure-induced deep tissue damage of right hip		379 CHRONIC ULCER OF SKIN	
L89.226	Pressure-induced deep tissue damage of left hip		379 CHRONIC ULCER OF SKIN	
L89.306	Pressure-induced deep tissue damage of unspecified buttock		379 CHRONIC ULCER OF SKIN	
L89.316	Pressure-induced deep tissue damage of right buttock		379 CHRONIC ULCER OF SKIN	
L89.326	Pressure-induced deep tissue damage of left buttock		379 CHRONIC ULCER OF SKIN	
L89.46	Pressure-induced deep tissue damage of contiguous site of back, buttock and hip		379 CHRONIC ULCER OF SKIN	
L89.506	Pressure-induced deep tissue damage of unspecified ankle		379 CHRONIC ULCER OF SKIN	
L89.516	Pressure-induced deep tissue damage of right ankle		379 CHRONIC ULCER OF SKIN	
L89.526	Pressure-induced deep tissue damage of left ankle		379 CHRONIC ULCER OF SKIN	
L89.606	Pressure-induced deep tissue damage of unspecified heel		379 CHRONIC ULCER OF SKIN	
L89.616	Pressure-induced deep tissue damage of right heel		379 CHRONIC ULCER OF SKIN	

2019 New ICD-10-CM Codes

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
L89.626	Pressure-induced deep tissue damage of left heel		379 CHRONIC ULCER OF SKIN	
L89.816	Pressure-induced deep tissue damage of head		379 CHRONIC ULCER OF SKIN	
L89.896	Pressure-induced deep tissue damage of other site		379 CHRONIC ULCER OF SKIN	
L89.96	Pressure-induced deep tissue damage of unspecified site		379 CHRONIC ULCER OF SKIN	
N63.15	Unspecified lump in the right breast, overlapping quadrants	Other breast lump diagnoses are DWF	Diagnostic Workup File (DWF)	
N63.25	Unspecified lump in the left breast, overlapping quadrants		Diagnostic Workup File (DWF)	
N99.85	Post endometrial ablation syndrome		529 CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA	See issues
Q66.00	Congenital talipes equinovarus, unspecified foot	Q66.0 (Congenital talipes equinovarus) is on line 359	359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.01	Congenital talipes equinovarus, right foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.02	Congenital talipes equinovarus, left foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.10	Congenital talipes calcaneovarus, unspecified foot	Q66.1 (Congenital talipes calcaneovarus) is on line 359	359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.11	Congenital talipes calcaneovarus, right foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.12	Congenital talipes calcaneovarus, left foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
Q66.211	Congenital metatarsus primus varus, right foot	Q66.21 (Congenital metatarsus primus varus) is on line 540	540 DEFORMITIES OF FOOT	
Q66.212	Congenital metatarsus primus varus, left foot		540 DEFORMITIES OF FOOT	
Q66.219	Congenital metatarsus primus varus, unspecified foot		540 DEFORMITIES OF FOOT	
Q66.221	Congenital metatarsus adductus, right foot	Q66.22 (Congenital metatarsus adductus) is on line 359	359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.222	Congenital metatarsus adductus, left foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.229	Congenital metatarsus adductus, unspecified foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.30	Other congenital varus deformities of feet, unspecified foot	Q66.3 (Other congenital varus deformities of feet) is on line 359	359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.31	Other congenital varus deformities of feet, right foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.32	Other congenital varus deformities of feet, left foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.40	Congenital talipes calcaneovalgus, unspecified foot	Q66.4 (Congenital talipes calcaneovalgus) is on line 359	359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.41	Congenital talipes calcaneovalgus, right foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.42	Congenital talipes calcaneovalgus, left foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
Q66.70	Congenital pes cavus, unspecified foot	Q66.7 (Congenital pes cavus) is on line 359	359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.71	Congenital pes cavus, right foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.72	Congenital pes cavus, left foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.90	Congenital deformity of feet, unspecified, unspecified foot	Q66.9 (Congenital deformity of feet, unspecified) is on line 359	359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.91	Congenital deformity of feet, unspecified, right foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q66.92	Congenital deformity of feet, unspecified, left foot		359 DEFORMITY/CLOSED DISLOCATION OF JOINT AND RECURRENT JOINT DISLOCATIONS	
Q79.60	Ehlers-Danlos syndrome, unspecified	Q79.6 (Ehlers-Danlos syndrome) is on line 525	525 DEFORMITIES OF UPPER BODY AND ALL LIMBS	
Q79.61	Classical Ehlers-Danlos syndrome		525 DEFORMITIES OF UPPER BODY AND ALL LIMBS	
Q79.62	Hypermobile Ehlers-Danlos syndrome		525 DEFORMITIES OF UPPER BODY AND ALL LIMBS	
Q79.63	Vascular Ehlers-Danlos syndrome		525 DEFORMITIES OF UPPER BODY AND ALL LIMBS	Considered to be severe Ehlers-Danlos syndrome
Q79.69	Other Ehlers-Danlos syndromes		525 DEFORMITIES OF UPPER BODY AND ALL LIMBS	
Q87.11	Prader-Willi syndrome		Dysfunction lines: 71,292,345,377	see issues
Q87.19	Other congenital malformation syndromes predominantly associated with short stature	Q87.1 (Congenital malformation syndromes predominantly associated with short stature) is on the dysfunction lines	Dysfunction lines: 71,292,345,377	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
R11.15	Cyclical vomiting syndrome unrelated to migraine		526 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS	See issues
R82.81	Pyuria	Similar abnormal urine findings are DWF	Diagnostic Workup File (DWF)	
R82.89	Other abnormal findings on cytological and histological examination of urine	Similar abnormal urine findings are DWF	Diagnostic Workup File (DWF)	
S02.121A	Fracture of orbital roof, right side, initial encounter for closed fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.121B	Fracture of orbital roof, right side, initial encounter for open fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.121D	Fracture of orbital roof, right side, subsequent encounter for fracture with routine healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.121G	Fracture of orbital roof, right side, subsequent encounter for fracture with delayed healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.121K	Fracture of orbital roof, right side, subsequent encounter for fracture with nonunion		441 MALUNION AND NONUNION OF FRACTURE	
S02.121S	Fracture of orbital roof, right side, sequela		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.122A	Fracture of orbital roof, left side, initial encounter for closed fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.122B	Fracture of orbital roof, left side, initial encounter for open fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.122D	Fracture of orbital roof, left side, subsequent encounter for fracture with routine healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.122G	Fracture of orbital roof, left side, subsequent encounter for fracture with delayed healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
S02.122K	Fracture of orbital roof, left side, subsequent encounter for fracture with nonunion		441 MALUNION AND NONUNION OF FRACTURE	
S02.122S	Fracture of orbital roof, left side, sequela		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.129A	Fracture of orbital roof, unspecified side, initial encounter for closed fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.129B	Fracture of orbital roof, unspecified side, initial encounter for open fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.129D	Fracture of orbital roof, unspecified side, subsequent encounter for fracture with routine healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.129G	Fracture of orbital roof, unspecified side, subsequent encounter for fracture with delayed healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.129K	Fracture of orbital roof, unspecified side, subsequent encounter for fracture with nonunion		441 MALUNION AND NONUNION OF FRACTURE	
S02.129S	Fracture of orbital roof, unspecified side, sequela		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.831A	Fracture of medial orbital wall, right side, initial encounter for closed fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.831B	Fracture of medial orbital wall, right side, initial encounter for open fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.831D	Fracture of medial orbital wall, right side, subsequent encounter for fracture with routine healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.831G	Fracture of medial orbital wall, right side, subsequent encounter for fracture with delayed healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
S02.831K	Fracture of medial orbital wall, right side, subsequent encounter for fracture with nonunion		441 MALUNION AND NONUNION OF FRACTURE	
S02.831S	Fracture of medial orbital wall, right side, sequela		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.832A	Fracture of medial orbital wall, left side, initial encounter for closed fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.832B	Fracture of medial orbital wall, left side, initial encounter for open fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.832D	Fracture of medial orbital wall, left side, subsequent encounter for fracture with routine healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.832G	Fracture of medial orbital wall, left side, subsequent encounter for fracture with delayed healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.832K	Fracture of medial orbital wall, left side, subsequent encounter for fracture with nonunion		441 MALUNION AND NONUNION OF FRACTURE	
S02.832S	Fracture of medial orbital wall, left side, sequela		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.839A	Fracture of medial orbital wall, unspecified side, initial encounter for closed fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.839B	Fracture of medial orbital wall, unspecified side, initial encounter for open fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.839D	Fracture of medial orbital wall, unspecified side, subsequent encounter for fracture with routine healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
S02.839G	Fracture of medial orbital wall, unspecified side, subsequent encounter for fracture with delayed healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.839K	Fracture of medial orbital wall, unspecified side, subsequent encounter for fracture with nonunion		441 MALUNION AND NONUNION OF FRACTURE	
S02.839S	Fracture of medial orbital wall, unspecified side, sequela		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.841A	Fracture of lateral orbital wall, right side, initial encounter for closed fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.841B	Fracture of lateral orbital wall, right side, initial encounter for open fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.841D	Fracture of lateral orbital wall, right side, subsequent encounter for fracture with routine healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.841G	Fracture of lateral orbital wall, right side, subsequent encounter for fracture with delayed healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.841K	Fracture of lateral orbital wall, right side, subsequent encounter for fracture with nonunion		441 MALUNION AND NONUNION OF FRACTURE	
S02.841S	Fracture of lateral orbital wall, right side, sequela		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.842A	Fracture of lateral orbital wall, left side, initial encounter for closed fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.842B	Fracture of lateral orbital wall, left side, initial encounter for open fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
S02.842D	Fracture of lateral orbital wall, left side, subsequent encounter for fracture with routine healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.842G	Fracture of lateral orbital wall, left side, subsequent encounter for fracture with delayed healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.842K	Fracture of lateral orbital wall, left side, subsequent encounter for fracture with nonunion		441 MALUNION AND NONUNION OF FRACTURE	
S02.842S	Fracture of lateral orbital wall, left side, sequela		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.849A	Fracture of lateral orbital wall, unspecified side, initial encounter for closed fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.849B	Fracture of lateral orbital wall, unspecified side, initial encounter for open fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.849D	Fracture of lateral orbital wall, unspecified side, subsequent encounter for fracture with routine healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.849G	Fracture of lateral orbital wall, unspecified side, subsequent encounter for fracture with delayed healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.849K	Fracture of lateral orbital wall, unspecified side, subsequent encounter for fracture with nonunion		441 MALUNION AND NONUNION OF FRACTURE	
S02.849S	Fracture of lateral orbital wall, unspecified side, sequela		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.85XA	Fracture of orbit, unspecified, initial encounter for closed fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.85XB	Fracture of orbit, unspecified, initial encounter for open fracture		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
S02.85XD	Fracture of orbit, unspecified, subsequent encounter for fracture with routine healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.85XG	Fracture of orbit, unspecified, subsequent encounter for fracture with delayed healing		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
S02.85XK	Fracture of orbit, unspecified, subsequent encounter for fracture with nonunion		441 MALUNION AND NONUNION OF FRACTURE	
S02.85XS	Fracture of orbit, unspecified, sequela		229 FRACTURE OF FACE BONES; INJURY TO OPTIC AND OTHER CRANIAL NERVES	
T50.911A	Poisoning by multiple unspecified drugs, medicaments and biological substances, accidental (unintentional), initial encounter		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.911D	Poisoning by multiple unspecified drugs, medicaments and biological substances, accidental (unintentional), subsequent encounter		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.911S	Poisoning by multiple unspecified drugs, medicaments and biological substances, accidental (unintentional), sequela		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.912A	Poisoning by multiple unspecified drugs, medicaments and biological substances, intentional self-harm, initial encounter		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.912D	Poisoning by multiple unspecified drugs, medicaments and biological substances, intentional self-harm, subsequent encounter		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
T50.912S	Poisoning by multiple unspecified drugs, medicaments and biological substances, intentional self-harm, sequela		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.913A	Poisoning by multiple unspecified drugs, medicaments and biological substances, assault, initial encounter		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.913D	Poisoning by multiple unspecified drugs, medicaments and biological substances, assault, subsequent encounter		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.913S	Poisoning by multiple unspecified drugs, medicaments and biological substances, assault, sequela		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.914A	Poisoning by multiple unspecified drugs, medicaments and biological substances, undetermined, initial encounter		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.914D	Poisoning by multiple unspecified drugs, medicaments and biological substances, undetermined, subsequent encounter		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.914S	Poisoning by multiple unspecified drugs, medicaments and biological substances, undetermined, sequela		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.915A	Adverse effect of multiple unspecified drugs, medicaments and biological substances, initial encounter	T50.995 (Adverse effect of other drugs, medicaments and biological substances, initial encounter) is on line 103	103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.915D	Adverse effect of multiple unspecified drugs, medicaments and biological substances, subsequent encounter		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
T50.915S	Adverse effect of multiple unspecified drugs, medicaments and biological substances, sequela		103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS	
T50.916A	Underdosing of multiple unspecified drugs, medicaments and biological substances, initial encounter	T50.996 (Underdosing of other drugs, medicaments and biological substances, initial encounter) is in the Diagnostic Workup File (DWF)	Diagnostic Workup File (DWF)	
T50.916D	Underdosing of multiple unspecified drugs, medicaments and biological substances, subsequent encounter		Diagnostic Workup File (DWF)	
T50.916S	Underdosing of multiple unspecified drugs, medicaments and biological substances, sequela		Diagnostic Workup File (DWF)	
T67.01XA	Heatstroke and sunstroke, initial encounter	T67.0XX (Heatstroke and sunstroke) is on line 181	181 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE)	
T67.01XD	Heatstroke and sunstroke, subsequent encounter		181 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE)	
T67.01XS	Heatstroke and sunstroke, sequela		181 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE)	
T67.02XA	Exertional heatstroke, initial encounter		181 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE)	
T67.02XD	Exertional heatstroke, subsequent encounter		181 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE)	
T67.02XS	Exertional heatstroke, sequela		181 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE)	
T67.09XA	Other heatstroke and sunstroke, initial encounter		181 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE)	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
T67.09XD	Other heatstroke and sunstroke, subsequent encounter		181 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE)	
T67.09XS	Other heatstroke and sunstroke, sequela		181 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE)	
Y35.009A	Legal intervention involving unspecified firearm discharge, unspecified person injured, initial encounter	Other legal intervention codes are in the Informational Diagnosis File	Informational Diagnosis File	
Y35.009D	Legal intervention involving unspecified firearm discharge, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.009S	Legal intervention involving unspecified firearm discharge, unspecified person injured, sequela		Informational Diagnosis File	
Y35.019A	Legal intervention involving injury by machine gun, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.019D	Legal intervention involving injury by machine gun, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.019S	Legal intervention involving injury by machine gun, unspecified person injured, sequela		Informational Diagnosis File	
Y35.029A	Legal intervention involving injury by handgun, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.029D	Legal intervention involving injury by handgun, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.029S	Legal intervention involving injury by handgun, unspecified person injured, sequela		Informational Diagnosis File	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
Y35.039A	Legal intervention involving injury by rifle pellet, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.039D	Legal intervention involving injury by rifle pellet, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.039S	Legal intervention involving injury by rifle pellet, unspecified person injured, sequela		Informational Diagnosis File	
Y35.049A	Legal intervention involving injury by rubber bullet, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.049D	Legal intervention involving injury by rubber bullet, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.049S	Legal intervention involving injury by rubber bullet, unspecified person injured, sequela		Informational Diagnosis File	
Y35.099A	Legal intervention involving other firearm discharge, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.099D	Legal intervention involving other firearm discharge, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.099S	Legal intervention involving other firearm discharge, unspecified person injured, sequela		Informational Diagnosis File	
Y35.109A	Legal intervention involving unspecified explosives, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.109D	Legal intervention involving unspecified explosives, unspecified person injured, subsequent encounter		Informational Diagnosis File	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
Y35.109S	Legal intervention involving unspecified explosives, unspecified person injured, sequela		Informational Diagnosis File	
Y35.119A	Legal intervention involving injury by dynamite, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.119D	Legal intervention involving injury by dynamite, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.119S	Legal intervention involving injury by dynamite, unspecified person injured, sequela		Informational Diagnosis File	
Y35.129A	Legal intervention involving injury by explosive shell, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.129D	Legal intervention involving injury by explosive shell, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.129S	Legal intervention involving injury by explosive shell, unspecified person injured, sequela		Informational Diagnosis File	
Y35.199A	Legal intervention involving other explosives, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.199D	Legal intervention involving other explosives, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.199S	Legal intervention involving other explosives, unspecified person injured, sequela		Informational Diagnosis File	
Y35.209A	Legal intervention involving unspecified gas, unspecified person injured, initial encounter		Informational Diagnosis File	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
Y35.209D	Legal intervention involving unspecified gas, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.209S	Legal intervention involving unspecified gas, unspecified person injured, sequela		Informational Diagnosis File	
Y35.219A	Legal intervention involving injury by tear gas, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.219D	Legal intervention involving injury by tear gas, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.219S	Legal intervention involving injury by tear gas, unspecified person injured, sequela		Informational Diagnosis File	
Y35.299A	Legal intervention involving other gas, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.299D	Legal intervention involving other gas, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.299S	Legal intervention involving other gas, unspecified person injured, sequela		Informational Diagnosis File	
Y35.309A	Legal intervention involving unspecified blunt objects, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.309D	Legal intervention involving unspecified blunt objects, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.309S	Legal intervention involving unspecified blunt objects, unspecified person injured, sequela		Informational Diagnosis File	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
Y35.319A	Legal intervention involving baton, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.319D	Legal intervention involving baton, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.319S	Legal intervention involving baton, unspecified person injured, sequela		Informational Diagnosis File	
Y35.399A	Legal intervention involving other blunt objects, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.399D	Legal intervention involving other blunt objects, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.399S	Legal intervention involving other blunt objects, unspecified person injured, sequela		Informational Diagnosis File	
Y35.409A	Legal intervention involving unspecified sharp objects, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.409D	Legal intervention involving unspecified sharp objects, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.409S	Legal intervention involving unspecified sharp objects, unspecified person injured, sequela		Informational Diagnosis File	
Y35.419A	Legal intervention involving bayonet, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.419D	Legal intervention involving bayonet, unspecified person injured, subsequent encounter		Informational Diagnosis File	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
Y35.419S	Legal intervention involving bayonet, unspecified person injured, sequela		Informational Diagnosis File	
Y35.499A	Legal intervention involving other sharp objects, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.499D	Legal intervention involving other sharp objects, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.499S	Legal intervention involving other sharp objects, unspecified person injured, sequela		Informational Diagnosis File	
Y35.819A	Legal intervention involving manhandling, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.819D	Legal intervention involving manhandling, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.819S	Legal intervention involving manhandling, unspecified person injured, sequela		Informational Diagnosis File	
Y35.831A	Legal intervention involving a conducted energy device, law enforcement official injured, initial encounter		Informational Diagnosis File	
Y35.831D	Legal intervention involving a conducted energy device, law enforcement official injured, subsequent encounter		Informational Diagnosis File	
Y35.831S	Legal intervention involving a conducted energy device, law enforcement official injured, sequela		Informational Diagnosis File	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
Y35.832A	Legal intervention involving a conducted energy device, bystander injured, initial encounter		Informational Diagnosis File	
Y35.832D	Legal intervention involving a conducted energy device, bystander injured, subsequent encounter		Informational Diagnosis File	
Y35.832S	Legal intervention involving a conducted energy device, bystander injured, sequela		Informational Diagnosis File	
Y35.833A	Legal intervention involving a conducted energy device, suspect injured, initial encounter		Informational Diagnosis File	
Y35.833D	Legal intervention involving a conducted energy device, suspect injured, subsequent encounter		Informational Diagnosis File	
Y35.833S	Legal intervention involving a conducted energy device, suspect injured, sequela		Informational Diagnosis File	
Y35.839A	Legal intervention involving a conducted energy device, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.839D	Legal intervention involving a conducted energy device, unspecified person injured, subsequent encounter		Informational Diagnosis File	
Y35.839S	Legal intervention involving a conducted energy device, unspecified person injured, sequela		Informational Diagnosis File	
Y35.99XA	Legal intervention, means unspecified, unspecified person injured, initial encounter		Informational Diagnosis File	
Y35.99XD	Legal intervention, means unspecified, unspecified person injured, subsequent encounter		Informational Diagnosis File	

ICD10 Code	Description	Similar Code(s)	Recommended Placement	Notes
Y35.99XS	Legal intervention, means unspecified, unspecified person injured, sequela		Informational Diagnosis File	
Z01.020	Encounter for examination of eyes and vision following failed vision screening without abnormal findings	Similar code Z01.110 (Encounter for hearing examination following failed hearing screening) is on line 3	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	
Z01.021	Encounter for examination of eyes and vision following failed vision screening with abnormal findings		3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	
Z11.7	Encounter for testing for latent tuberculosis infection	Similar code Z11.1 (Encounter for screening for respiratory tuberculosis) is on line 3	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS	
Z22.7	Latent tuberculosis		50 PULMONARY TUBERCULOSIS	See issues
Z71.84	Encounter for health counseling related to travel		Excluded file (Travel Vaccines Etc.)	OHP is unable to pay for travel related medical care
Z86.002	Personal history of in-situ neoplasm of other and unspecified genital organs	Other Z86.00 codes are in the Informational Diagnosis File	Informational Diagnosis File	
Z86.003	Personal history of in-situ neoplasm of oral cavity, esophagus and stomach		314 CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA	See issues
Z86.004	Personal history of in-situ neoplasm of other and unspecified digestive organs		166 ANAL, RECTAL AND COLONIC POLYP	See issues
Z86.005	Personal history of in-situ neoplasm of middle ear and respiratory system		Informational Diagnosis File	
Z86.006	Personal history of melanoma in-situ		Informational Diagnosis File	
Z86.007	Personal history of in-situ neoplasm of skin		Informational Diagnosis File	
Z86.15	Personal history of latent tuberculosis infection		Informational Diagnosis File	
Z96.82	Presence of neurostimulator		Informational Diagnosis File	

2019 ICD-10 Code Review Issues

1) Embolism of calf veins
    a. Issue: Phlebitis, thrombophlebitis, and embolisms of the deep veins (eg. popliteal, tibial) are on line 79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP, whereas embolisms of superficial veins are on line 514 PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL. Peroneal veins are considered deep veins and therefore the new ICD-10 codes related to peroneal veins should be on line 79. Calf muscular veins are not generally considered deep veins, but are also not superficial veins. Controversy exists regarding whether calf muscular vein thrombosis requires treatment
    b. New ICD-10 codes
        i. I80.241-I80.249 (Phlebitis and thrombophlebitis of peroneal vein)
        ii. I80.251-I80.259 (Phlebitis and thrombophlebitis of calf muscular vein)
        iii. I82.451-I82.459 (Acute embolism and thrombosis of peroneal vein)
        iv. I82.461-I82.469 (Acute embolism and thrombosis of calf muscular vein)
        v. I82.551-I82.559 (Chronic embolism and thrombosis of peroneal vein)
        vi. I82.561-I82.569 (Chronic embolism and thrombosis of calf muscular vein)
    c. Evidence
        i. **De Martino 2012**, Systematic review and meta-analysis of treatment of deep calf venous thrombosis
            1. 2 RCTs and 6 cohort studies (454 patients)
                a. Adults with isolated calf vein deep venous thrombosis (DVT).
                b. The methodologic quality of most studies was poor.
            2. Pulmonary embolism (PE; odds ratio, 0.12; 95% confidence interval, 0.02-0.77; P = .03) and thrombus propagation (odds ratio, 0.29; 95% confidence interval, 0.14-0.62; P = .04) were significantly less frequent in those who received anticoagulation.
            3. Conclusions: Our review suggests that anticoagulation therapy for calf vein DVT may decrease the incidence of PE and thrombus propagation.
        ii. **Kearon 2016**, CHEST guideline for treatment of DVT
            1. isolated distal DVT
                a. two management options: (1) treat patients with anticoagulant therapy or (2) do not treat patients with anticoagulant therapy unless extension of their DVT is detected on a follow-up US examination (eg, after 1 and 2 weeks, or sooner if there is concern; there is no widely accepted protocol for surveillance US testing)
                b. Because about 15% of untreated isolated distal DVT are expected to subsequently extend into the popliteal vein and may cause PE, it is not acceptable to neither anticoagulate nor do surveillance to detect thrombus extension
    d. HERC staff summary: It is difficult to differentiate calf muscle veins from deep veins of the calf in the medical literature. It appears that calf muscle veins are generally included with peroneal veins in studies. While controversy exists about the need to treat calf vein thromboses, particularly the muscular calf veins, it appears that at a minimum follow up ultrasound is required and therefore these diagnoses should be on a covered line

   e. HERC staff recommendation:
      i. Place all new I80/I82 ICD-10 codes on line 79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP

2) Post endometrial ablation syndrome
   a. New ICD-10 Code: N99.85 Post endometrial ablation syndrome
   b. Definition: There appears to be no clear definition in the medical literature for "post endometrial ablation syndrome" and MEDLINE does not include any literature with that wording as a key word/phrase. **Sharp (2012)** outlines complications of endometrial ablation including pelvic pain and dysmenorrhea, failure to control menses, infection, pregnancy complications, and obstructed menses. Treatment generally involves hysterectomy, although specific treatment might include antibiotics or repeat endometrial ablation.
   c. Similar diagnoses
      i. N94.6 Dysmenorrhea: 555 DYSMENORRHEA
      ii. R10.2 Pelvic pain: 529 CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA
   d. Expert input: Dr. Michael Adler recommends prioritizing post endometrial ablation syndrome with other pelvic pain syndrome type diagnoses
   e. HERC staff recommendation
      i. Place ICD-10 N99.85 (Post endometrial ablation syndrome) on line 529 CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA
         1. Unclear what this diagnosis refers to, but appears to generally include pelvic pain

3) Prader Willi Syndrome
   a. New ICD-10 code: Q87.11 Prader-Willi syndrome
   b. Definition: Prader-Willi syndrome is a complex genetic condition that affects many parts of the body. Symptoms include hypotonia, poor growth, hyperphagia and obesity. People with Prader-Willi syndrome typically have mild to moderate intellectual impairment and learning disabilities. Behavioral problems are common. Puberty is delayed or incomplete.
   c. HERC staff recommendation:
      i. Place Q87.11 on the dysfunction lines (71,292,345,377) to allow for supportive therapies

4) Cyclical vomiting syndrome unrelated to migraine
   a. New ICD-10 code: R11.15 Cyclical vomiting syndrome unrelated to migraine
   b. Definition: Cyclic vomiting syndrome is a disorder that causes recurrent episodes of nausea, vomiting, and lethargy. This condition is diagnosed most often in young children, but it can affect people of any age. The episodes of nausea, vomiting, and lethargy last anywhere from an hour to 10 days. An affected person may vomit several times per hour, potentially leading to a dangerous loss of fluids (dehydration). Additional symptoms can include abdominal pain, diarrhea, headache, fever, and an increased sensitivity to light (photophobia) or to sound (phonophobia). Episodes of nausea, vomiting, and lethargy can occur regularly or apparently at random, or can be triggered by a variety of factors. If the condition is not treated, episodes usually occur four to 12 times per year. Between attacks, vomiting is absent, and nausea is either

absent or much reduced. However, many affected people experience other symptoms during and between episodes, including pain, lethargy, digestive disorders such as gastroesophageal reflux and irritable bowel syndrome, and fainting spells (syncope). Cyclic vomiting syndrome is often considered to be a variant of migraines, which are severe headaches often associated with pain, nausea, vomiting, and extreme sensitivity to light and sound. Cyclic vomiting syndrome is likely the same as or closely related to a condition called abdominal migraine, which is characterized by attacks of stomach pain and cramping.

c. Similar ICD-10 code: G43.D Abdominal migraine, which is on line 526 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
d. HERC staff recommendation:
    i. Place R11.15 on line 526 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS

5) Latent TB
    a. New ICD-10 code: Z22.7 Latent tuberculosis
    b. Definition: Persons with latent TB infection do not feel sick and do not have any symptoms. They are infected with *M. tuberculosis*, but do not have TB disease. The only sign of TB infection is a positive reaction to the tuberculin skin test or TB blood test. Persons with latent TB infection are not infectious and cannot spread TB infection to others. Treatment of latent TB infection is indicated if the patient meets criteria outlined by the CDC.
    c. In November, 2018, the HERC placed ICD-10 R76.1 (positive reaction to TB test) on line 50. Previously, this code series had been on the Diagnostic Workup File, which did not allow treatment for the positive test. Positive skin or blood tests for TB without active TB on chest xray is the definition of latent TB.
    d. Current Prioritized List status:
        i. There are 2 current TB lines:
            1. 50 PULMONARY TUBERCULOSIS
            2. 152 NON-PULMONARY TUBERCULOSIS
    e. HERC staff recommendation:
        i. Place Z22.7 on line 50 PULMONARY TUBERCULOSIS to be consistent with November 2018 placement of codes potentially associated with latent TB.

6) Personal history of in-situ neoplasm of gastrointestinal organs
    a. New ICD-10 Codes:
        i. Z86.003 Personal history of in-situ neoplasm of oral cavity, esophagus and stomach
        ii. Z86.004 Personal history of in-situ neoplasm of other and unspecified digestive organs
    b. Patients with a history of an in-situ neoplasm of the esophagus need regular EGDs for surveillance. A similar diagnosis would be K22.711 (Barrett's esophagus with high grade dysplasia), which is on line 314 CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA. Similarly, a stomach neoplasm diagnosis may require regular EGDs as a follow up.
    c. Patients with a history of a colon in-situ neoplasm would need surveillance with colonoscopies. A similar diagnosis would be K63.5 (Polyp of colon) which is on line 166 ANAL, RECTAL AND COLONIC POLYPS.

d. HERC staff recommendations
    i. Place Z86.003 on line 314 CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA
    ii. Place Z86.004 on line 166 ANAL, RECTAL AND COLONIC POLYP

Richard P. Cambria, MD, Section Editor
From the Society for Vascular Surgery

A meta-analysis of anticoagulation for calf deep venous thrombosis

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Objective: **This meta-analysis was initiated to assess the efficacy and safety of anticoagulation therapy for adult patients with isolated calf vein deep venous thrombosis (DVT).**
Methods: **We searched MEDLINE (1950-October 2010), the Cochrane Library (1993-October 2010), trial registries, meeting abstracts, and selected references, using no limits. Included studies compared the results of anticoagulation (vitamin K antagonist or therapeutic heparin) for a minimum of 30 days vs the results of no anticoagulation in adults with calf vein DVT proved by ultrasound imaging or venograph who were monitored for at least 30 days. Two independent reviewers extracted data using a piloted standardized form. Methodologic quality was assessed using the Cochrane Risk of Bias tool for randomized controlled trials (RCTs) and the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies. Discrepancies were resolved by consensus or by a third reviewer. Authors were contacted for additional information if necessary. Outcomes were pooled using Peto fixed-effects models.**
Results: **Of 2328 studies identified, two RCTs and six cohorts (126 patients treated with anticoagulation and 328 controls) met selection criteria. The methodologic quality of most studies was poor. Pulmonary embolism (PE; odds ratio, 0.12; 95% confidence interval, 0.02-0.77; $P = .03$) and thrombus propagation (odds ratio, 0.29; 95% confidence interval, 0.14-0.62; $P = .04$) were significantly less frequent in those who received anticoagulation. Significant heterogeneity existed in studies reporting mortality rates, but these demonstrated a trend toward fewer deaths with anticoagulation. When limited to randomized trials, the protective effect of anticoagulation for PE was no longer statistically significant, but the benefit for preventing thrombus progression persisted. Adverse events such as bleeding were sparsely reported but favored controls ($P = .65$).**
Conclusions: **Our review suggests that anticoagulation therapy for calf vein DVT may decrease the incidence of PE and thrombus propagation. However, due to poor methodologic quality and few events among included studies for PE, this finding is not robust. Thrombus propagation appears reduced with anticoagulation treatment. A rigorous RCT will assist in treatment decisions for calf vein DVT. (J Vasc Surg 2012;56:228-37.)**

Extensive evidence supports anticoagulation for patients with proximal deep venous thrombosis (DVT) to reduce death from pulmonary embolus (PE).[1] No similar consensus exists for thrombosis of the deep veins of the calf (cDVT).[2] Proponents of anticoagulation for cDVT cite the only randomized trial of anticoagulation for cDVT by Lagerstedt et al.[3] This study demonstrated a 3.5% nonfatal PE rate and 17% proximal thrombus extension rate in patients who did not receive anticoagulation. Others eschew anticoagulation for cDVT, citing a low venous thrombotic event rate during surveillance of cDVTs.[2]

To date, published observational studies of cDVT are inconsistent in their reporting of the risks associated with untreated cDVT: rates of PE and proximal extension range from 0% to 31%[4-6] and 0% to 20%, respectively.[5-8] Many of these studies report uncontrolled, single-center analyses of few patients. Risks associated with anticoagulation therapy in these series are infrequently examined. Therefore, we performed a systematic review and meta-analysis of anticoagulation vs no anticoagulation for cDVT to inform evidence-based guidelines.

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CHEST

Antithrombotic Therapy for VTE Disease
CHEST Guideline and Expert Panel Report

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PODCAST

BACKGROUND: We update recommendations on 12 topics that were in the 9th edition of these guidelines, and address 3 new topics.

METHODS: We generate strong (Grade 1) and weak (Grade 2) recommendations based on high- (Grade A), moderate- (Grade B), and low- (Grade C) quality evidence.

RESULTS: For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B), or edoxaban (Grade 2B) over vitamin K antagonist (VKA) therapy, and suggest VKA therapy over low-molecular-weight heparin (LMWH; Grade 2C). For VTE and cancer, we suggest LMWH over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C). We have not changed recommendations for who should stop anticoagulation at 3 months or receive extended therapy. For VTE treated with anticoagulants, we recommend against an inferior vena cava filter (Grade 1B). For DVT, we suggest not using compression stockings routinely to prevent PTS (Grade 2B). For subsegmental pulmonary embolism and no proximal DVT, we suggest clinical surveillance over anticoagulation with a low risk of recurrent VTE (Grade 2C), and anticoagulation over clinical surveillance with a high risk (Grade 2C). We suggest thrombolytic therapy for pulmonary embolism with hypotension (Grade 2B), and systemic therapy over catheter-directed thrombolysis (Grade 2C). For recurrent VTE on a non-LMWH anticoagulant, we suggest LMWH (Grade 2C); for recurrent VTE on LMWH, we suggest increasing the LMWH dose (Grade 2C).

CONCLUSIONS: Of 54 recommendations included in the 30 statements, 20 were strong and none was based on high-quality evidence, highlighting the need for further research.

CHEST 2016; 149(2):315-352

KEY WORDS: antithrombotic therapy; evidence-based medicine; GRADE approach; venous thromboembolism

FOR EDITORIAL COMMENT SEE PAGE 293

ABBREVIATIONS: AT9 = 9th Edition of the Antithrombotic Guideline; AT10 = 10th Edition of the Antithrombotic Guideline; CHEST = American College of Chest Physicians; CDT = catheter-directed thrombolysis; COI = conflict of interest; CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = CT pulmonary angiogram; GOC = Guidelines Oversight Committee; INR = International Normalized Ratio; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K oral anticoagulant; PE = pulmonary embolism; PTS = postthrombotic syndrome; RCT = randomized controlled trial; UEDVT = upper extremity deep vein thrombosis; US = ultrasound; VKA = vitamin K antagonist

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GENERAL GYNECOLOGY

Endometrial ablation: postoperative complications

Howard T. Sharp

Endometrial ablation as a treatment for abnormal uterine bleeding has evolved considerably over the past several decades. Postoperative complications include the following: (1) pregnancy after endometrial ablation; (2) pain-related obstructed menses (hematometra, postablation tubal sterilization syndrome); (3) failure to control menses (repeat ablation, hysterectomy); (4) risk from preexisting conditions (endometrial neoplasia, cesarean section); and (5) infection. Physicians performing endometrial ablation should be aware of postoperative complications and be able to diagnose and provide treatment for these conditions.

Key words: complications, endometrial ablation, hysteroscopy, infection

Endometrial ablation as a treatment for abnormal uterine bleeding has evolved considerably over the past several decades. In the early era of manual resectoscopic endometrial ablation (REA), the energy source options were laser fiber or rollerball/rollerbarrel electrodes to desiccate the endometrium or a loop electrode to resect the endometrium. Inherent in the evolutionary process are unintended consequences. Unfortunately, the use of energy sources and intrauterine distending media resulted in intraoperative complications that were in some cases life threatening and, in rare cases, life ending.[1]

As technology advanced, automated systems were designed and termed nonresectoscopic endometrial ablation (NREA) devices, global endometrial ablation devices, or second-generation endometrial ablation devices. Although these systems obviated the need for manual resectoscopic skills and fluid management systems, intraoperative complications still occurred but of differing types. These newer technologies include 5 ablative methods including a thermal balloon, circulated hot fluid, cryotherapy, radiofrequency electrosurgery, and microwave energy. All 5 methods have been compared with rollerball endometrial ablation by way of randomized clinical trials and are in general associated with similarly high patient satisfaction rates (86–99%), regardless of the method, but with wide ranges of amenorrhea rates (13.9–55.3%).[2]

Although these 2 categories of ablation methods (REA and NREA) may have different types of intraoperative complications, they have fairly similar postoperative complications. As is common with all forms of endometrial ablation, the entirety of the endometrium is rarely destroyed. As a result, complications can occur because the residual endometrium may allow implantation of an embryo, cause continued bleeding that may become obstructed, unobstructed but enough to be considered a failure, or may develop neoplasia. Therefore, the goal of this review was to focus on 5 categories of postsurgical complications including the following: (1) pregnancy after endometrial ablation, (2) pain-related obstructed menses (hematometra, postablation tubal sterilization syndrome), (3) failure to control menses (repeat ablation, hysterectomy), (4) risk from preexisting conditions (endometrial neoplasia, cesarean section), and (5) infection. Intraoperative complications such as fluid overload, uterine perforation, and hemorrhage will not be addressed in this article.

Pregnancy-related complications

The issue of contraception is one of the most significant issues that should be addressed in patients considering endometrial ablation. Endometrial ablation is not considered a form of contraception. Unfortunately, although pregnancy after endometrial ablation is associated with significant maternal and fetal morbidity and mortality, the performance tubal sterilization also carries a risk for complications such as post blation tubal sterilization syndrome (see section in the following text).

Pregnancy has been reported to occur in 0.7% of women who have undergone endometrial ablation.[3] Pregnancy has been reported as early as 5 weeks after ablation[4] and as late as 12 years postoperatively (with subsequent tubal reanastamosis in a planned pregnancy).[5] The chance of pregnancy occurring after endometrial ablation and tubal sterilization is estimated to be 0.002%, or 1 in 50,000.[6] Pregnancy has also been reported in an amenorrheic woman.[7] Successful pregnancies have been reported; however, there appears to be a greater risk of complications in pregnancies that follow endometrial ablation including preterm birth, intrauterine scarring/uterine chambering (creating separate uterine compartments), and postpartum hemorrhage.[8,9] The authors have hypothesized that the preterm labor is in part because of narrowing or sometimes chambering of the endometrial cavity resulting in a smaller area for gestation.

There are several reviews of pregnancy occurring after endometrial ablation, evaluating many of the same cases from the available literature and also adding information from their own case series while updating the cumulative number of pregnancies after endometrial ablation (n = 134).[10-12] This type of data

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Section 6.0

Previously Discussed Items

Certification for Lymphedema Providers

Question: How should the lymphedema therapy guideline be best modified to allow coverage if therapy is done by non-LANA certified therapists?

Question sources: several CCOs and providers; coverage guidance nomination process

Issue: This topic was discussed at the May, 2019 VBBS meeting. The initial concern of the CCOs was that there is a shortage of LANA-certified therapists in some areas of the state. At the May meeting, the VBBS was in favor of adding coverage for lymphedema therapy provided by non-LANA certified therapists, but had concerns with the proposed guideline wording changes proposed by HERC staff. Staff was directed to revise the guideline further and bring back for approval. Staff has reviewed the recommended new guideline changes with the CCO medical directors, who agree with the staff recommended changes.

Subsequently, the LANA executive director, Ms. Katina Kirby, and president, Dr. Paula Stewart, contacted HERC staff with concerns regarding the proposed changes. Specifically, they felt that usual NALEA was too limited (it includes only 4 schools) and did not ensure quality.

From Ms. Kirby:

> NALEA is too limited – only 4 schools comprise NALEA. This still would not achieve the availability of specialists to the patients. NALEA has no guidelines or policy/procedure for schools to join and has to date not included any of lymphedema program. By saying LANA eligible graduates from programs meeting the LANA educational eligibility requirement (which does include the NALEA schools but is not limited to just 4 programs) will be authorized to treat.

The LANA staff suggested changing the guideline to include

> "CLT-LANA eligible (graduates from a minimum 135-hour lymphedema program that meet the LANA eligibility requirements). http://www.clt-lana.org"

Per LANA, eligible training programs

> Provide proof of successful completion of qualified instructional course in Complete Decongestive Therapy (CDT) course work (consisting of 1/3 theoretical instruction and 2/3 practical lab work and documentation of 135-classroom hours) from no more than four consecutive or cumulative courses from one training program. Practical lab work is defined as real-time instruction with an instructor present. An instructional video that a student watches during home study would NOT be counted as part of the expected 2/3 practical lab work. Proof is accepted in the form of a computer certificate or letter from the school director.

Per LANA staff, their suggested edit would include Vodder trained therapists, but not likely Chickley (they have had no applications for certification from Chickley trained therapists).

Current guideline

GUIDELINE NOTE 43, LYMPHEDEMA

Line 421

Lymphedema treatments are included on this line when medically appropriate. These services are to be provided by a licensed practitioner who is certified by one of the accepted lymphedema training certifying organizations or a graduate of one of the National Lymphedema Network accepted training courses within the past two years. The only accepted certifying organization at this time is LANA (Lymphology Association of North America; http://www.clt-lana.org). Treatments for lymphedema are not subject to the visit number restrictions found in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.

It is the intent of the HERC that compression dressings/garments and other medical equipment needed for the treatment of lymphedema be covered even in the absence of ulcers or other complications.

HERC staff recommendation:

1) Modify GN 43 to remove the limitation to only LANA certified providers
    a. The version for entry #2 proposed by LANA is in purple

GUIDELINE NOTE 43, LYMPHEDEMA

Line 421

Lymphedema treatments are included on this line when medically appropriate. These services are to be provided by a licensed practitioner who is:

1) Certified by Lymphology Association of North America (LANA, http://www.clt-lana.org), OR
2) A graduate of one of the National Lymphedema Network or North American Lymphedema Education Association (NALEA) accepted training courses
2) CLT-LANA eligible (graduates from a minimum 135-hour lymphedema program that meet the LANA eligibility requirements). http://www.clt-lana.org

Services should be provided by a LANA certified therapist if available.
~~certified by one of the accepted lymphedema training certifying organizations or a graduate of one of the National Lymphedema Network accepted training courses within the past two years. The only accepted certifying organization at this time is LANA (Lymphology Association of North America; http://www.clt-lana.org).~~ Treatments for lymphedema are not subject to the visit number restrictions found in Guideline Note 6 REHABILITATIVE AND HABILITATIVE THERAPIES.

It is the intent of the HERC that compression dressings/garments and other medical equipment needed for the treatment of lymphedema be covered even in the absence of ulcers or other complications.

Section 7.0

New Discussion Items

Varicocele Repair in Pediatric Patients

Question: Should coverage for varicocele repair in certain pediatric populations be moved to a higher priority line on the Prioritized List?

Question source: Casey A Seideman MD, OHSU Pediatric Urology

Issue: Varicoceles are currently on a low priority line below the funding line. Dr. Seideman has requested consideration for coverage for varicoceles in children which meet certain criteria.

A varicocele is an enlargement of the veins within the scrotum. The prevalence of varicoceles is as high as 15% in children and adolescents. The main effect of varicocele is its potential role in male infertility. In about 20% of adolescents with varicocele, fertility problems will arise. Management options include monitoring, radiographic intervention, or surgical varicocelectomy. Current guidelines recommend testicular volume loss or growth lag as the main indication for intervention to preserve or improve fertility. Other indications include pain, co-existing testicular anomalies, and abnormal semen analysis.

From Dr. Seideman:

> Most of the time, varicoceles in kids are asymptomatic – and do not require surgical intervention. Sometimes, however, they can cause significant pain/discomfort and impact daily living, or they can stunt testicular growth. In these rare instances, I would say that a varicocelectomy is the gold standard of treatment.

Varicoceles in adult men are only recommended for treatment if they are causing infertility issues.

Current Prioritized List status
ICD10 I86.1 (Scrotal varices) is on line 545 SUBLINGUAL, SCROTAL, AND PELVIC VARICES.

Similar diagnoses:
ICD10 N43.3 (Hydrocele, unspecified) is on line 542 HYDROCELE
ICD10 N43.4 (Spermatocele of epididymis) in on line 542 HYDROCELE
ICD10 N50.0 (Atrophy of testis) is on line 467 GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT (no surgical CPT codes pair)
ICD10 N50.81 (testicular pain) is on the Diagnostic Work Up File

Fertility surgery/issues cannot be covered as part of a Medicaid program by federal rules.

Varicocele Repair in Pediatric Patients

Evidence:

1) **Locke 2017**, systematic review and meta-analysis of RCTS of treatment for varicoceles in children and adolescents
    a. N=9 studies (N=1266 patients) total included
        i. N=5 studies (N=385 patients) included in quantitative analysis
    b. In the nine studies included, some of the authors reported indications for treatment as pain, discrepancy in testicular volume >20% from the contralateral side and varicocele grade II or higher
    a. Meta-analysis based on available outcomes data demonstrated an improvement in testicular volume (mean difference 3.18 mL, 95% CI 1.94-4.42) and in sperm count (mean difference 25.54 x 10^6/mL, 95% CI 12.84-38.25) in patients who underwent radiological or surgical treatment compared with conservative management.
    b. Surgical outcomes and adverse events are not reported consistently.
    a. Conclusions: Based on current available randomized controlled trials, there is low to moderate level of evidence that radiological or surgical treatment of adolescent varicocele is associated with improved testicular size/growth and sperm concentration. The ultimate effects on fertility and paternity rates are not known.

Expert guidelines

1) **American Urological Association 2001** (archived): Report on varicocele and infertility
    a. Adolescents who have a varicocele and objective evidence of reduced ipsilateral testicular size should be offered varicocele repair. Adolescents who have a varicocele but normal ipsilateral testicular size should be offered follow-up monitoring with annual objective measurements of testicular size and/or semen analyses.
1) **Tekgul 2015** European Society for Pediatric Urology guidelines
    a. There is no evidence that treatment of varicocele at pediatric age will offer a better andrological outcome than an operation performed later.
    b. The recommended indication criteria for varicocelectomy in children and adolescents are:
        i. varicocele associated with a small testis;
        ii. additional testicular condition affecting fertility;
        iii. bilateral palpable varicocele;
        iv. pathological sperm quality (in older adolescents);
        v. symptomatic varicocele (pain).

    Level of evidence: 2; Grade of Recommendation: B

HERC staff summary

Repair of varicoceles in children and adolescents is recommended by expert opinion when there is pain and/or a reduction in testicular volume by 20% compared to the contralateral side. Repair of varicocele has limited evidence of improving fertility; no reports on improvement in gonadal function were found.

HERC staff recommendation:

1) Consider moving varicoceles in children and adolescents to a covered line on the Prioritized List with a guideline
    a. Add ICD-10 I86.1 (Scrotal varices) to line 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
    b. Add the following treatment CPT codes to line 327
        i. CPT 36470 (Injection of sclerosant; single incompetent vein (other than telangiectasia))
        ii. CPT 37241-37242 (Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; venous, other than hemorrhage (eg, congenital or acquired venous malformations, venous and capillary hemangiomas, varices, varicoceles))
        iii. CPT 55530-55550 (Excision of varicocele or ligation of spermatic veins for varicocele)
    c. Add a new guideline as shown below to lines 327 and 545 SUBLINGUAL, SCROTAL, AND PELVIC VARICES

GUIDELINE NOTE XXX REPAIR OF VARICOCELES IN CHILDREN AND ADOLESCENTS

Lines 327,545

Varicocele repair is only included on line 327 for children and adolescents (up through age 18) with:

1) Pain affecting activities of daily living from the varicocele; OR
2) Objective evidence of reduced ipsilateral testicular size of 20% of more compared to the contralateral testicle; OR
3) Varicocele in a patient with a solitary testicle.

All other varicocele repair is included on line 545.

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Review Article

Treatment of varicocele in children and adolescents: A systematic review and meta-analysis of randomized controlled trials

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Keywords
Adolescent; Varicocele; Surgical intervention; Radiological intervention; Hydrocele; Varicocele recurrence

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Summary

Background
The prevalence of varicoceles is as high as 15% in children and adolescents. Optimal management of varicoceles has not been consolidated. Options include observation, radiological intervention, or surgical varicocelectomy.

Objective
Herein, we aim to assess the outcomes of radiological and surgical interventions for varicocele in children and adolescents evaluated by RCTs.

Study design
The study subjects were children and adolescents up to 21 years old, diagnosed with varicocele and allocated to receive either "surgical or radiological intervention" or "no treatment".

Materials and methods
We searched MEDLINE and EMBASE (Ovid platform), Web of Science, CINAHL, Cochrane Central Register of Controlled Trials, Google Scholar, Clinical-Trials.gov, and the World Health Organization International Clinical Trials Registry Platform for RCTs reporting on varicocele treatment in children and adolescents up to June 23, 2016. Only RCTs with patients aged under 21 years were included. Main outcomes of interest included changes in testicular size, semen analysis parameters, surgical adverse events and failures.

Results
Nine eligible studies were included in the systematic review. Meta-analysis based on available outcomes data demonstrated an improvement in testicular volume (mean difference 3.18 mL, 95% CI 1.94–4.42) and in sperm count (mean difference 25.54 $\times$ 10^6/mL, 95% CI 12.84–38.25) in patients who underwent radiological or surgical treatment compared with conservative management.

Conclusions
Based on current available randomized controlled trials, there is low to moderate level of evidence that radiological or surgical treatment of adolescent varicocele is associated with improved testicular size/growth and sperm concentration. The ultimate effects on fertility and paternity rates are not known.

Introduction

The prevalence of varicoceles is as high as 15% in children and adolescents [1,2]. Varicocele is the result of an abnormal enlargement of the pampiniform venous plexus, the structure responsible for venous drainage to the testicular, pudendal, and cremasteric veins [3]. The grading system for detection of a varicocele consists of grade 1: palpable only on Valsalva maneuver, grade 2: palpable with no Valsalva maneuver, and grade 3: visible with no need for palpation. Management options include monitoring, radiographic intervention, or surgical varicocelectomy. The main effect of varicocele is its potential role in male infertility. Current guidelines recommend testicular volume loss or growth lag as the main indication for intervention to preserve or improve fertility. Other indications include pain, co-existing testicular anomalies, and abnormal semen analysis [4]. However, evidence supporting best treatment practices is lacking. Our literature search found several reviews on the optimal management strategy in children and adolescents with varicoceles [5–10]. Nevertheless, the authors of these reviews included several various types of studies not as rigorous as randomized controlled trials (RCTs). It is well known that uncontrolled and non-randomized studies can overestimate the effect of interventions [11]. Furthermore, because of the variable inclusion criteria and different outcome measurements reported in these reviews there was significant

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Report on Varicocele and Infertility

An **AUA**
Best Practice Policy
and
ASRM
Practice Committee Report

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How This Document Was Created

This document was written by the Male Infertility Best Practice Policy Committee of the American Urological Association, Inc.® (AUA) and the Practice Committee of the American Society for Reproductive Medicine (ASRM). The two organizations agreed to collaborate to prepare documents of importance in the field of male infertility. The Male Infertility Best Practice Policy Committee was created in 1999 by the Board of Directors of the American Urological Association, Inc.® The Committee co-chairmen and members were selected by the Practice Parameters, Guidelines and Standards Committee (PPGSC) of the AUA. The membership of the Committee included nine urologists, one reproductive endocrinologist, one family physician and one research andrologist. The mission of the Committee was to develop recommendations, based on expert opinion, for optimal clinical practices in the diagnosis and treatment of male infertility. It was not the intention of the committee to produce a comprehensive treatise on male infertility. This document was submitted for peer review by 125 physicians and researchers from the disciplines of urology, gynecology, reproductive endocrinology, primary care and family medicine, andrology and reproductive laboratory medicine. Modifications were made by the Practice Committee of the ASRM. After the final revisions were made based upon the peer review process and the Practice Committee of the ASRM, the documents were submitted to, and approved by the Board of Directors of the AUA and the Board of Directors of the ASRM. These "Best Practice Policies" are intended to assist urologists, gynecologists, reproductive endocrinologists, primary care practitioners and reproductive researchers. Funding of the Committee was provided by the AUA. Committee members received no remuneration for their work. Each member of the Committee provided a conflict of interest disclosure to the AUA.

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CONTENTS

Introduction 1

Detection of varicoceles 2

Indications for treatment of a varicocele 2

Varicocele treatment, IUI and assisted reproduction 3

Treatment of varicoceles 3
- Surgical repair
- Percutaneous embolization treatment
- Complications

Results of varicocele treatment

Follow-up

References 5

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Introduction

Varicoceles are present in 15 percent of the normal male population and in approximately 40 percent of men presenting with infertility (1). The preponderance of experimental data from clinical and animal models demonstrates a deleterious effect of varicoceles on spermatogenesis. Testicular temperature elevation and venous reflux appear to play an important role in varicocele-induced testicular dysfunction, although the exact pathophysiology of varicocele-induced damage is not yet completely understood. This review offers recommendations regarding best practice policies for evaluation and treatment of varicoceles.

Detection of varicoceles

Evaluation of a patient with a varicocele should include a careful medical and reproductive history, a physical examination and at least two semen analyses. The physical examination should be performed with the patient in both the recumbent and upright positions. A palpable varicocele feels like a "bag of worms" and disappears or is very significantly reduced when the patient is recumbent. When a suspected varicocele is not clearly palpable, the scrotum should be examined while the patient performs a Valsalva maneuver in a standing position.

Only palpable varicoceles have been documented to be associated with infertility. Therefore, ancillary diagnostic measures, such as scrotal ultrasonography, thermography, Doppler examination, radionuclide scanning and spermatic venography, should not be used for the detection of subclinical varicoceles in patients without a palpable abnormality. Scrotal ultrasonography, however, may be indicated for clarification of an inconclusive physical examination of the scrotum. Spermatic venography may be useful to demonstrate the anatomic position of refluxing spermatic veins that recur or persist after varicocele repair.

Recommendation: *Routine evaluation of infertile men with varicoceles should include a medical and reproductive history, physical examination and a minimum of two semen analyses. Imaging studies are not indicated for the standard evaluation unless physical exam is inconclusive.*

Indications for treatment of a varicocele

When the male partner of a couple attempting to conceive has a varicocele, treatment of the varicocele should be considered when all of the following conditions are met: 1) the varicocele is palpable on physical examination of the scrotum; 2) the couple has known infertility; 3) the female partner has normal fertility or a potentially treatable cause of infertility; and 4) the male partner has abnormal semen parameters or abnormal results from sperm function tests. Varicocele treatment for infertility is not indicated in patients with either normal semen quality or a subclinical varicocele.

An adult male who is not currently attempting to achieve conception, but has a palpable varicocele, abnormal semen analyses and a desire for future fertility, is also a candidate for varicocele repair. Young adult males with varicoceles, who have normal semen parameters, may be at risk for progressive testicular dysfunction and should be offered monitoring with semen analyses every one to two years, in order to detect the earliest sign of reduced spermatogenesis.

Adolescent males who have unilateral or bilateral varicoceles and objective evidence of reduced testicular size ipsilateral to the varicocele should also be considered candidates for varicocele repair (2, 3, 4, 5). If objective evidence of reduced testis size is not present, adolescents with varicoceles should be followed with annual objective measurements of testis size and/or semen analyses in order to detect the earliest sign of varicocele-related testicular injury. Varicocele repair should be offered at the first detection of testicular or semen abnormality.

Recommendations: *Varicocele treatment should be offered to the male partner of a couple attempting to conceive, when all of the following are present: 1) a varicocele is palpable; 2) the couple has documented infertility; 3) the female has normal fertility or potentially correctable infertility; and 4) the male partner has one or more abnormal semen parameters or sperm function test results.*

Adult men who have a palpable varicocele and abnormal semen analyses but are not currently attempting to conceive should also be offered varicocele repair.

Young men who have a varicocele and normal semen analyses should be followed with semen analyses every one to two years.

Adolescents who have a varicocele and objective evidence of reduced ipsilateral testicular size should be offered varicocele repair. Adolescents who have a varicocele but normal ipsilateral testicular size should be offered follow-up monitoring with annual objective measurements of testicular size and/or semen analyses.

Varicocele treatment, IUI, and assisted reproduction

Varicocele repair, intrauterine insemination (IUI) and in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) are options for the management of couples with male factor infertility associated with a varicocele. The decision as to which method of management to use is influenced by many factors. Most importantly, varicocele repair has the potential to reverse a pathological condition and effect a permanent cure for infertility, as opposed to IUI or ART, which is required for each attempt at pregnancy. Other factors to be considered are the age of the female partner (See ASRM Committee Opinion on Age-Related Infertility), the unknown long-term health effects of IVF and ICSI on the offspring resulting from these techniques, and the possibly greater cost effectiveness of varicocele treatment than of IVF with or without ICSI (6). Finally, failure to treat a varicocele may result in a progressive decline in semen parameters, further compromising a man's chances for future fertility (7, 8, 9).

Varicocele repair usually is not indicated as the primary treatment for couples when IVF is necessary for treatment of a female factor. Nevertheless, there are certain circumstances in which treatment of a varicocele should be considered before initiating ART even when there is a female factor present. Specifically, varicocele repair has been shown to restore at least low numbers of sperm to the ejaculate in some men with non-obstructive azoospermia due to either hypospermatogenesis or late maturation arrest (10, 11). In these cases, varicocele repair may restore sperm to the ejaculate, thus making it possible to perform IVF/ICSI without testicular sperm aspiration or extraction. Therefore, testicular biopsy and varicocele repair may be offered to these men.

Recommendations: *Varicocele repair may be considered as the primary treatment option when a man with a varicocele has suboptimal semen quality and a normal female partner. IVF with or without ICSI may be considered the primary treatment option when there is an independent need for such techniques to treat a female factor, regardless of the presence of varicocele and suboptimal semen quality.*

Treatment of varicoceles

There are two approaches to varicocele repair: surgery and percutaneous embolization. Surgical repair of a varicocele may be accomplished by various open surgical methods, including retroperitoneal, inguinal and subinguinal approaches, or by laparoscopy. Percutaneous embolization treatment of a varicocele is accomplished by percutaneous embolization of the refluxing internal spermatic vein(s). None of these methods has been proven to be superior to the others in its ability to improve fertility.

Surgical repair

Most experts perform inguinal or subinguinal surgical repair employing loupes or an operating microscope for optical magnification. Techniques using optical magnification maximize preservation of arterial and lymphatic vessels while reducing the risk of persistence or recurrence of varicocele (12). Laparoscopy has been used for varicocele repair but this approach carries the risk of major intraperitoneal complications, such as injury to bowel, bladder and major blood vessels. Although uncommon, intraperitoneal complications may be serious and require laparotomy for correction.

Percutaneous embolization treatment

Percutaneous embolization to repair varicoceles may be associated with less pain than occurs after the standard inguinal surgical approach, but availability of physicians with experience in interventional radiologic techniques is required. Moreover, in some patients, interventional access to the internal spermatic veins cannot be achieved because of technical problems.

Complications

The potential complications of varicocele repair occur infrequently and are usually mild. All approaches to varicocele surgery are associated with a small risk of wound infection, hydrocele, persistence or recurrence of varicocele and, rarely, testicular atrophy. Potential complications from an inguinal incision for varicocele

repair include scrotal numbness and prolonged pain.

Recommendation: *The treating physician's experience and expertise, together with the options available, should determine the choice of varicocele treatment.*

Results of varicocele treatment

Surgical treatment successfully eliminates over 90 percent of varicoceles. The results of percutaneous embolization are variable and depend on the experience and skill of the interventional radiologist performing the procedure. Most studies have reported that semen quality improves in a majority of patients following varicocele repair (13).

The fertility outcomes of varicocele repair have been described in numerous published studies. Most of these studies lack adequate numbers of patients, randomization and/or controls, and, therefore, it is not possible to reach a clear conclusion on the fertility outcome of varicocele repair. Of the published controlled studies, the majority have failed to use randomization, men with palpable varicoceles, men with abnormal semen analyses and/or men with normal female partners. Most of these trials, however, show improvement in fertility after varicocele treatment, with only a few indicating that varicocele treatment has little or no effect on fertility. A review of twelve controlled studies found a pregnancy rate of 33 percent (95% confidence interval, 28-39 percent) in couples in which the male received varicocele treatment, as compared with 16 percent (95% confidence interval, 13-20 percent) in untreated couples over one year (6).

There are only two well-designed, randomized, controlled studies using men with palpable varicoceles, abnormal semen parameters and normal spouses (14, 15). While one of the studies showed no greater likelihood of pregnancy following varicocele repair, it did demonstrate significant improvement in testis volume and semen parameters compared to controls (15). The other study, using a crossover design, showed a statistically significant improvement in fertility following varicocele repair (14). The conception rate in couples in which the male had undergone varicocele repair was 60 percent within one year following surgery as compared to only 10 percent in the untreated control group.

Despite the absence of definitive studies on the fertility outcome of varicocele repair, varicocele treatment should be considered as a choice for appropriate infertile couples because: 1) varicocele repair has been proven to improve semen parameters in most men; 2) varicocele treatment may possibly improve fertility; and 3) the risks of varicocele treatment are small.

Follow-up

Patients should be evaluated after varicocele treatment for persistence or recurrence of the varicocele. If the varicocele persists or recurs, internal spermatic venography may be performed to identify the site of persistent venous reflux. Either surgical ligation or percutaneous embolization of the refluxing veins may be used. Semen analyses should be performed after varicocele treatment at about three-month intervals for at least one year or until pregnancy is achieved. IUI and ART should be considered for couples in which infertility persists after anatomically successful varicocele repair.

Recommendations: *Persistence or recurrence of a varicocele may be treated by either surgical ligation or percutaneous embolization of the refluxing veins.*

After treatment of a varicocele, semen analysis should be done at approximately three-month intervals for at least one year or until pregnancy occurs.

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This report is intended to provide medical practitioners with a consensus of principles and strategies for the care of couples with male infertility problems. The report is based on current professional literature, clinical experience and expert opinion. It does not establish a fixed set of rules or define the legal standard of care and it does not pre-empt physician judgment in individual cases. Physician judgment must take into account variations in resources and in patient needs and preferences.

Conformance with this best practice policy cannot ensure a successful result.

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These reports can be viewed online at http://www.auanet.org
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Guidelines on Paediatric Urology

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3F.3 Disease management

The treatment is surgical. An artificial erection is used to determine the degree of curvature and to check symmetry after the repair [191].

In hypospadias, chordee related to the tethering of the ventral skin and to the spongiosal pillars is first released. Only in a few cases, the penile curvature is caused by a short urethral plate, which should be cut. To repair the corporeal angulation in the isolated curvature, or curvature associated with hypospadias, different techniques of plication of corpora cavernosa (orthoplasty) are used [190].

In exstrophy/epispadias complex, a combination of complete release of the urethral body from the corpora and a different kind of corporoplasty with or without corporotomy is usually necessary to achieve a straight penis [192, 193].

3G VARICOCELE IN CHILDREN AND ADOLESCENTS

3G.1 Epidemiology, aetiology and pathophysiology

Varicocele is defined as an abnormal dilatation of testicular veins in the pampiniformis plexus caused by venous reflux. It is unusual in boys under 10 years of age and becomes more frequent at the beginning of puberty. It is found in 14-20% of adolescents, with a similar incidence during adulthood. It appears mostly on the left side (78-93% of cases). Right-sided varicoceles are less common; they are usually noted only when bilateral varicoceles are present and seldom occur as an isolated finding [194-196].

Varicocele develops during accelerated body growth and increased blood flow to the testes, by a mechanism that is not clearly understood. Genetic factors may be present. An anatomic abnormality leading to impaired venous drainage is expressed by the considerable prevalence of the left side condition where the internal spermatic vein drains into the renal vein. Varicocele can induce apoptotic pathways because of heat stress, androgen deprivation and accumulation of toxic materials. Severe damage is found in 20% of adolescents affected, with abnormal findings in 46% of affected adolescents. Histological findings are similar in children or adolescents and in infertile men. In 70% of patients with grade II and III varicocele, left testicular volume loss was found.

Several authors reported on reversal of testicular growth after varicocelectomy in adolescents [197, 198]. The average proportion of catch-up growth of 76.4% (range: 52.6-93.8%) has been found according to a recent meta-analysis [199] (LE: 2a). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels [200] (LE: 2).

In about 20% of adolescents with varicocele, fertility problems will arise [201]. The adverse influence of varicocele increases with time. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy [202-204] (LE: 1).

3G.2 Classification systems

Varicocele is classified into 3 grades:

- Grade I - Valsalva positive (palpable at Valsalva manoeuvre only);
- Grade II - palpable (palpable without the Valsalva manoeuvre);
- Grade III - visible (visible at distance) [205].

3G.3 Diagnostic evaluation

Varicocele is mostly asymptomatic, rarely causing pain at this age. It may be noticed by the patient or parents, or discovered by the paediatrician at a routine visit. The diagnosis depends upon the clinical finding of a collection of dilated and tortuous veins in the upright posture; the veins are more pronounced when the patient performs the Valsalva manoeuvre. The size of both testicles should be evaluated during palpation to detect a smaller testis.

Venous reflux into the plexus pampiniformis is diagnosed using Doppler colour flow mapping in the supine and upright position [206]. Venous reflux detected on ultrasound only is classified as subclinical varicocele. To discriminate testicular hypoplasia, the testicular volume is measured by ultrasound examination or by orchidometer. In adolescents, a testis that is smaller by > 2 mL or 20% compared to the other testis is considered to be hypoplastic [207] (LE: 2).

Extension of Wilms tumour into the renal vein and inferior vena cava can cause a secondary varicocele. A renal ultrasound should be routinely added in prepubertal boys and in isolated right varicocele (LE: 4).

In order to assess testicular injury in adolescents with varicocele, supranormal FSH and LH responses to the luteinising hormone-releasing hormone (LHRH) stimulation test are considered reliable, because histopathological testicular changes have been found in these patients [203, 208].

3G.4 Disease management

There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later. Beneficial effect of pubertal screening and treatment for varicocele regarding chance of paternity has been questioned according to a corresponding questionnaire in adult patients [209] (LE: 4).

The recommended indication criteria for varicocelectomy in children and adolescents are [195]:

- varicocele associated with a small testis;
- additional testicular condition affecting fertility;
- bilateral palpable varicocele;
- pathological sperm quality (in older adolescents);
- symptomatic varicocele.

Testicular (left + right) volume loss in comparison with normal testes is a promising indication criterion, once the normal values are available [210]. Repair of a large varicocele, causing physical or psychological discomfort, may also be considered. Other varicoceles should be followed-up until a reliable sperm analysis can be performed (LE: 4).

Surgical intervention is based on ligation or occlusion of the internal spermatic veins. Ligation is performed at different levels:

- inguinal (or subinguinal) microsurgical ligation;
- suprainguinal ligation, using open or laparoscopic techniques [211-214].

The advantage of the former is the lower invasiveness of the procedure, while the advantage of the latter is a considerably lower number of veins to be ligated and safety of the incidental division of the internal spermatic at the suprainguinal level.

For surgical ligation, some form of optical magnification (microscopic or laparoscopic) should be used because the internal spermatic artery is 0.5 mm in diameter at the level of the internal ring [211, 213]. The recurrence rate is usually < 10%.

Lymphatic-sparing varicocelectomy is preferred to prevent hydrocele formation and testicular hypertrophy development and to achieve a better testicular function according to the LHRH stimulation test [200, 211, 212, 215] (LE: 2). The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs [211, 213, 216, 217]. Angiographic occlusion of the internal spermatic veins also meets these requirements. It is based on retrograde or antegrade sclerotisation of the internal spermatic veins [218, 219]. However, although this method is less invasive and may not require general anaesthesia, it is associated with radiation burden, which is less controllable in the antegrade technique. Available data on failure rates combine anatomical inaccessibility and recurrence [195, 218, 219] (LE: 2).

3G.5 Conclusions and recommendations

Varicocele becomes more frequent at the beginning of puberty and is found in 14-20% of adolescents. Fertility problems are expected in 20% of them.

Varicocele is examined in the standing position and classified into three grades. Venous reflux is diagnosed using Doppler colour flow mapping in the supine and upright position. In up to 70% of patients with grade II and III varicocele, left testicular volume loss is reported; in late adolescence the contralateral right testis may also become smaller.

Recommendations	LE	GR
There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later.		
Surgery is recommended for: - varicocele associated with a small testis; - additional testicular condition affecting fertility; - pathological sperm quality (in older adolescents); - bilateral palpable varicocele; - symptomatic varicocele.	2	B

Treatments for Urinary Incontinence

Question: Which procedures should be paired with urinary incontinence on the Prioritized List?

Question source: HSD claims reconsideration

Issue: Multiple procedure codes that do not pair with urinary incontinence have been identified by HSD claims reconsideration. There has not been a comprehensive review of treatments covered for urinary incontinence in many years.

Stress incontinence (N39.3), mixed incontinence (N39.46) and intrinsic sphincter deficiency (ISD) (N36.42) are on line 453 URINARY INCONTINENCE and pair with a variety of treatments. There is a guideline note applied to line 453 outlining when surgical treatments are covered.

Treatments for urinary incontinence include pelvic muscle exercises (Kegel exercise), behavioral therapies such as bladder training and/or biofeedback, pharmacotherapies (e.g., anti-cholinergic agents, musculotropic relaxants, calcium channel blockers, tricyclic anti-depressants, or a combination of anti-cholinergic, anti-spasmodic medications and tricyclic anti-depressants), and a variety of surgical procedures including intra-urethral injection of collagen, and implantation of an artificial urinary sphincter. Surgical procedures can also include bladder suspension and sling procedures.

Additionally, sacral nerve stimulation for treatment of urinary incontinence was suggested for review by the coverage guidance process. HERC approved the review of this procedure by VBBS at their May, 2019 meeting.

Treatments for Urinary Incontinence

Procedure codes identified in claims reconsideration as not pairing with urinary incontinence:

CPT code	Code description	Current Placement	HERC staff recommendation
51700	Bladder irrigation, simple, lavage and/or instillation	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES, 215,271,275, 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION 329,352	Do not add to line 453 No mention of bladder irrigation found in NICE or Aetna coverage documents
51715	Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck	87 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM 327 432 HYPOSPADIAS AND EPISPADIAS	See separate review
53440	Sling operation for correction of male urinary incontinence (eg, fascia or synthetic)	71,87,327	See separate review
53445	Insertion of inflatable urethral/bladder neck sphincter, including placement of pump, reservoir, and cuff	71,87,327	See separate review
97112	Therapeutic procedure, 1 or more areas, each 15 minutes; neuromuscular reeducation of movement, balance, coordination, kinesthetic sense, posture, and/or proprioception for sitting and/or standing activities	60+ lines	Do not add to line 453 Multiple appropriate PT codes already are on line 453

Sacral Nerve Stimulation

Question: What, if any, conditions should sacral nerve stimulation be paired with on the Prioritized List?

Question source: Healthshare CCO; HTAS; HERC staff

Issue: Sacral nerve stimulation for non-obstructive urinary retention was nominated as an HTAS topic in 2016 but has not yet been reviewed by HTAS. The CPT codes for this treatment are listed as "Never Reviewed" in the HERC database and do not currently appear on the Prioritized List. A CCO recently requested guidance on what conditions this treatment should be covered for.

Sacral nerve stimulation (also known as sacral neuromodulation therapy) is a reversible treatment that uses a small device to send electrical impulses to the sacral nerves. These electrical impulses alter muscles and organs (the bladder, sphincter, and pelvic floor muscles) that contribute to bladder control. The electrical stimulation can often successfully eliminate or reduce certain bladder-control problems in some people. This treatment is used for non-obstructive urinary retention, overactive bladder, and urinary incontinence. It has also been used to treat fecal incontinence.

Currently, urinary incontinence, overactive bladder, and non-obstructive urinary retention are on a covered line paired with a variety of therapies. These therapies include surgical treatments like bladder sling procedures, as well as Botox injections, pelvic physical therapy, various oral medications, and DME such as catheters. Fecal incontinence is on a dysfunction line for pairing with DME such as adult sanitary garments, and on an uncovered line for surgical and other therapies according to Guideline Note 129.

Sacral Nerve Stimulation

Current Prioritized List status

CPT Code	Code Description	Current Placement
64561	Percutaneous implantation of neurostimulator electrode array; sacral nerve (transforaminal placement) including image guidance, if performed	Never Reviewed
64581	Incision for implantation of neurostimulator electrode array; sacral nerve (transforaminal placement)	Never Reviewed
64590	Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling	Never Reviewed
64595	Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver	285/422 COMPLICATIONS OF A PROCEDURE ALWAYS/USUALLY REQUIRING TREATMENT
HCPCS		
A4290	Sacral nerve stimulation test lead, each	Never reviewed
C1767	Generator, neurostimulator (implantable), non-rechargeable	174,250,292,346,361,440,527,660
C1778	Lead, neurostimulator (implantable)	174,250,292,346,361,440,527,660
C1787	Patient programmer, neurostimulator	Never reviewed
C1897	Lead, neurostimulator test kit (implantable)	174,250,292,346,361,440,527,660
L8679	Implantable neurostimulator, pulse generator, any type	Never reviewed
L8680	Implantable neurostimulator electrode, each	Never reviewed
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only	Never reviewed
L8682	Implantable neurostimulator radiofrequency receiver	Never reviewed
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver	Never reviewed
L8684	Radiofrequency transmitter (external) for use with implantable sacral root neurostimulator receiver for bowel and bladder management, replacement	Never reviewed
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension	Never reviewed
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension	Never reviewed
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension	Never reviewed
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension	Never reviewed

L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only	Never reviewed
ICD-10		
R15.9	Full incontinence of feces	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 526 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
N32.81	Overactive bladder	327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
N39.3-N39.9	Urinary incontinence	453 URINARY INCONTINENCE
R32	Unspecified urinary incontinence	Diagnostic Workup File
R33.8	Other retention of urine	327; DWF
R33.9	Retention of urine, unspecified	Diagnostic Workup File

GUIDELINE NOTE 129, FECAL INCONTINENCE

Lines 71,526

ICD-10-CM R15.9 (Full incontinence of feces) is included on Line 71 only for supportive equipment (e.g. diapers, gloves). Surgical treatment for fecal incontinence is included on Line 526 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS

Evidence

1) **NICE 2015** Sacral nerve stimulation for idiopathic chronic non-obstructive urinary retention
    a. Overall recommendation: Current evidence on the safety and efficacy of sacral nerve stimulation for idiopathic chronic non-obstructive urinary retention is adequate to support the use of this procedure
    b. First line therapies are medications (men) and urethral dilation and self-catheterization (men and women)
    c. Sacral nerve stimulation involves an evaluation phase to help the patient and clinician decide if long-term therapy will be beneficial
    d. Efficacy:
        i. A randomized controlled trial of 51 patients treated by sacral nerve stimulation or standard medical treatment
            1. the mean catheter volume per catheterization decreased from 339 ml to 49 ml at 6-month follow-up in the treatment group and from 350 ml to 319 ml in the control group ($p<0.0001$ comparing the mean differences).
            2. the mean total voided volume per day increased from 722 ml to 1808 ml at 6-month follow-up in the treatment group and decreased from 560 ml to 488 ml in the control group ($p<0.0001$ comparing the mean differences).
            3. the mean number of catheterizations per day decreased from 5.7 to 1.4 at 6-month follow-up in the treatment group and from 4.0 to 3.9 in the control group ($p<0.0001$) comparing the mean differences). At 18-month follow-up 58% (14/24) of patients treated by sacral nerve stimulation did not need catheterization.
        ii. A case series of 60 patients reported that 72% (43/60) of patients were voiding spontaneously and 50% (30/60) of patients no longer needed to use catheterization after a mean follow-up of 4 years. A case series of 40 patients reported that the mean number of catheterizations per day decreased from 4.3 to 1.0 after a mean follow-up of 41 months ($p<0.001$) and 55% (11/20) of patients with complete retention were able to stop catheterization completely.
    e. Safety
        i. The neurostimulator device was removed in 14% (4/28) of patients in a case series of 40 patients: 2 because of infection, 1 because of pain and 1 because of the need for MRI. In the same study, neurostimulator revision was necessary in 21% (6/28) of patients because of battery expiry or device malfunction in 4 patients and infection in 2 patients.
        ii. In a systematic review of 14 articles (1239 patients)
            1. Infection was reported in 4% of patients
            2. Lead migration was reported in 5% of patients
            3. Pain at the implant site, pain at the lead site and new pain (unspecified) were reported in 10% (128/1239), 2% and 4% of patients respectively
            4. Sensation of electric shock was reported in 2% of patients
        iii. In a case series of 60 patients
            1. Lead migration was reported in 28% (17/60) of patients
            2. Pain at the implant site was reported in 32% (19/60) of patients

3. Leg pain, pelvic pain and urethral pain were reported in 30% (18/60), 3% (2/60) and 3% (2/60) of patients respectively

2) **NICE 2019** Urinary Incontinence in Women
    a. Transcutaneous sacral nerve stimulation
        i. Do not offer transcutaneous sacral nerve stimulation to treat overactive (OAB) in women
    b. Percutaneous sacral nerve stimulation
        i. Offer percutaneous sacral nerve stimulation to women after review if:
            1. their OAB has not responded to conservative management including medicines, and
            2. their symptoms have not responded to botulinum toxin type A or
            3. they are not prepared to accept the risks of needing catheterisation associated with botulinum toxin type A.
        i. Discuss the long-term implications of percutaneous sacral nerve stimulation with women including:
            a. the need for test stimulation and probability of the test's success
            b. the risk of failure
            c. the long-term commitment
            d. the need for surgical revision
            e. the adverse effects.
3) **NICE 2004** Sacral nerve stimulation for fecal incontinence
    a. Overall recommendation:
        i. Current evidence on the safety and efficacy of sacral nerve stimulation for fecal incontinence appears adequate to support the use of this procedure
    b. Efficacy
        i. This procedure was subject to a systematic review commissioned by the Institute. The systematic review included six case series studies reporting on 266 patients in total. In patients who had permanent implants, complete continence was achieved in 41–75% (19/46–12/16) of patients, whereas 75–100% (3/4–16/16) of patients experienced a decrease of 50% or more in the number of incontinence episodes. There was also evidence to suggest an improvement in the ability to defer defecation after permanent implantation. Patients also reported improvements in both disease-specific and general quality-of-life scores after the procedure.
    c. Safety
        i. Complications were reported both during the test peripheral nerve evaluation phase and after implantation. Evidence from the systematic review indicated that of the 266 patients receiving test evaluation, 4% (10/266) experienced an adverse event. Fifty-six per cent (149/266) went on to receive permanent implantation. Of the patients who had permanent implants, 13% (19/149) reported adverse events. These included three patients who developed infections requiring device removal, seven patients who had lead migration requiring either relocation (five cases) or removal of the device, and six patient who experienced pain after implantation.
4) **AHRQ 2009** Treatment of Overactive Bladder in Women
    a. N= 1 RCT (98 patients) comparing sacral neuromodulation to medical therapy.
        i. This study, which randomized after successful test stimulation, found a reduction in daily urge incontinence episodes from 9.7 to 2.6 in the sacral

neuromodulation group, compared to an increase of 9.3 to 11.3 in the medical management group at 6 months ($p<0.01$) for patients with refractory OAB.124 At 18 months, 76 percent of participants receiving sacral neuromodulation reported that they were completely dry or had experienced a reduction in symptoms of 50 percent or greater. Note that the comparison is not ideal, as subjects continuing to receive medical therapy had already failed medical management.

ii. Reported an 82 percent decrease in pad use from 6.2 to 1.1 pads daily, six months following initiation of sacral neuromodulation

b. N=6 case series
   i. Decreases in mean incontinence episodes per day of 51 percent to 80 percent and from a median of five down to zero incontinence episodes a day. Length of follow-up in these studies ranged for six months to five years.
   ii. Three case series evaluating sacral neuromodulation also found significant decreases in pad use ranging from 49 to 84 percent fewer mean pads and a 75 percent decrease in median pad use.
c. Reduction in urinary frequency of between 31 and 45 percent is seen consistently across studies of sacral neuromodulation, regardless of study design
d. One cohort study and two case series found that sacral neuromodulation increased the mean voided volume between 1.7 to 1.9 fold, an increase of 78 mL to 108 mL per void
e. Peripheral neuromodulation and electromagnetic stimulation were clinically ineffective in changing voiding frequency

1) **NICE 2004** Sacral nerve stimulation for urge incontinence and urgency-frequency
   a. Overall recommendation
      i. Current evidence on the safety and efficacy of sacral nerve stimulation for urge incontinence and urgency-frequency appears adequate to support the use of this procedure
   b. Efficacy
      i. This procedure was subject to a systematic review commissioned by the Institute in November 2003. Evidence from two randomized controlled trials (RCTs), including a total of 50 patients with urge incontinence, showed that complete continence (completely dry with no incontinent episodes) or improvement of more than 50% in incontinence symptoms was observed in 50% and 80% of patients, respectively, following the procedure. This compared with 5% of patients in the control groups, who were receiving conservative treatments while waiting for an implant. In the one RCT that reported on patients with urgency-frequency, an improvement of more than 50% in incontinence symptoms was observed in 56% (14/25) of patients, compared with 4% (1/25) in the control group.
   a. Safety
      a. The results of the systematic review showed that, overall, the re-operation rate for patients with implants was 33% (283/860). The most common reasons for surgical revision were to replace or reposition implants due to pain or infection at the implant site, or to adjust and modify the lead system to correct breakage or migration.
      b. Pain at the site of the pulse generator or at the site of stimulation was reported in 24% (162/663) of patients, sometimes requiring replacement and repositioning of the pulse generator. Other complications included lead-related

problems such as migration (16%), wound problems (7%), adverse effects on bowel function (6%), and infection (5%). No cases of long-lasting neurological complications were identified.

Other payer policies

1) **Noridian 2019** LCD on Sacral Nerve Stimulation for Urinary and Fecal Incontinence
    1. Sacral nerve stimulation is covered for the treatment of urinary urge incontinence, urgency-frequency syndrome, and urinary retention. Sacral nerve stimulation involves both a temporary test stimulation to determine if an implantable stimulator would be effective and a permanent implantation in appropriate candidates. Both the test and the permanent implantation are covered. The NCD describes the following limitations for coverage to all three conditions:
        1) Patient must be refractory to conventional therapy (documented behavioral, pharmacologic and/or surgical corrective therapy) and be an appropriate surgical candidate such that implantation with anesthesia can occur.
        2) Patients with stress incontinence, urinary obstruction, and specific neurologic diseases (e.g., diabetes with peripheral nerve involvement) which are associated with secondary manifestations of the above three indications are excluded.
        3) Patient must have had a successful test stimulation in order to support subsequent implantation. Before a patient is eligible for permanent implantation, he/she must demonstrate a 50% or greater improvement through test stimulation. Improvement is measured through voiding diaries. Patient must be able to demonstrate adequate ability to record voiding diary data such that clinical results of the implant procedure can be properly evaluated.
    b. Fecal Incontinence: Noridian will cover sacral nerve modulation/stimulation for fecal incontinence when all of the following criteria are met:
        a. Chronic fecal incontinence with greater than two incontinent episodes on average per week and duration of incontinence greater than six months or for more than twelve months after vaginal childbirth; AND
        b. Documented failure or intolerance to conventional therapy (e.g., dietary modification, the addition of bulking and pharmacologic treatment); AND
        c. A successful percutaneous test stimulation, defined as at least 50% sustained (more than one week) improvement in symptoms; AND
        d. Condition is not related to anorectal malformation (e.g., congenital anorectal malformation; defects of the external anal sphincter over 60 degrees; visible sequelae of pelvic radiation; active anal abscesses and fistulae) and/or chronic inflammatory bowel disease; AND
        e. Incontinence is not related to another neurologic condition such as peripheral neuropathy or complete spinal cord injury.
    c. Sacral nerve modulation/stimulation is considered experimental, investigational and unproven for the treatment of chronic constipation or chronic pelvic pain**.**
2) **Aetna 2018** Urinary Incontinence
    a. Aetna considers implantation of the InterStim (Medtronic Inc., Minneapolis, MN), a device for unilateral stimulation of the sacral nerve, medically necessary for the

treatment of urge UI or symptoms of urge-frequency when all of the following criteria are met:

i. The member has experienced urge UI or symptoms of urge-frequency for at least 12 months and the condition has resulted in significant disability (the frequency and/or severity of symptoms are limiting the member's ability to participate in daily activities); *and*
ii. Pharmacotherapies (i.e., at least 2 different anti-cholinergic drugs or an anti-cholinergic and a beta-3 adrenergic receptor agonist (mirabregon)) as well as behavioral treatments (e.g., pelvic floor exercise, biofeedback, timed voids, and fluid management) have failed; *and*
iii. Test stimulation provides at least 50 % decrease in symptoms.

b. Aetna also considers implantation of the InterStim medically necessary for the treatment of non-obstructive urinary retention when all of the following criteria are met:

i. The member has experienced urinary retention for at least 12 months and the condition has resulted in significant disability (the frequency and/or severity of symptoms are limiting the member's ability to participate in daily activities); *and*
ii. Pharmacotherapies (e.g., alpha blockers and cholinergics, and antibiotics for urinary tract infections) as well as intermittent catheterization have failed or are not well-tolerated; *and*
iii. A test stimulation of the device has provided at least 50 % decrease in residual urine volume.

c. *Exclusions*: InterStim therapy has no proven value for individuals with mechanical obstruction such as benign prostatic hypertrophy, cancer, or urethral stricture; persons with stress incontinence; and individuals with neurologic disease origins, such as multiple sclerosis or diabetes with peripheral nerve involvement. InterStim has not been shown to be effective for urinary retention due to these causes.

3) **CIGNA 2018** Sacral Nerve and Tibial Nerve Stimulation for Urinary Voiding Dysfunction, Fecal Incontinence and Constipation

a. Urinary Voiding Dysfunction

i. A percutaneous screening trial of sacral nerve stimulation (SNS) with an external stimulator is considered medically necessary for the treatment of any of the following urinary voiding dysfunctions when there is failure, intolerance or contraindication to conservative medical management:
    1. urinary urge incontinence
    2. nonobstructive urinary retention
    3. urinary urgency/frequency syndrome
ii. Permanent SNS implantation for the treatment of urinary voiding dysfunction is considered medically necessary when BOTH of the following criteria are met:
    1. the individual has met the criteria for a percutaneous screening trial of SNS
    2. the individual experienced a beneficial clinical response to a percutaneous screening trial of SNS as evidenced by at least a 50% improvement in reported symptoms

b. Fecal Incontinence

i. A percutaneous screening trial of SNS with an external stimulator for fecal incontinence is considered medically necessary when ALL of the following criteria are met:
    1. failure, intolerance, or contraindication to conservative medical management
    2. sphincter surgery is either not indicated or is contraindicated
    3. absence of a significant anorectal malformation or chronic inflammatory bowel disease involving the anus
    4. fecal incontinence is not secondary to another neurological condition such as peripheral neuropathy or complete spinal cord injury
ii. Permanent SNS implantation for fecal incontinence is considered medically necessary when BOTH of the following criteria are met:
    1. the individual has met the criteria for a percutaneous screening trial of SNS
    2. the individual experienced a beneficial clinical response to a percutaneous screening trial of SNS as evidenced by at least a 50% improvement in reported symptoms
iii. SNS for the treatment of any other indication, including constipation is considered experimental, investigational or unproven.

HERC staff summary

Based on a limited number of small studies, a trusted source (NICE) recommends the use of sacral nerve stimulation for treatment of urinary incontinence, non-obstructive urinary retention, and overactive bladder, as well as fecal incontinence. AHRQ, in a review that is over 10 years old, did not find sufficient evidence to reach a conclusion on the use of sacral nerve stimulation for urinary incontinence. However, the limited number of studies included in the AHRQ review were all positive. All major insurers reviewed cover sacral nerve stimulation for urinary and fecal incontinence when patients meet certain criteria.

HERC staff recommendations

1) Add Sacral nerve stimulation to lines 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION, 453 URINARY INCONTINENCE and 526 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS
    1. CPT 64561 Percutaneous implantation of neurostimulator electrode array; sacral nerve (transforaminal placement) including image guidance, if performed
    2. CPT 64581 Incision for implantation of neurostimulator electrode array; sacral nerve (transforaminal placement)
    3. CPT 64590 (Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling)
    4. HCPCS A4290, C1767, C1778, C1787, C1897, L8679-L8689 (Implantable pulse generator, implantable electrodes, patient programmer, transmitter)
2) Modify GN129 as shown below

GUIDELINE NOTE 129, FECAL INCONTINENCE

Lines 71,526

ICD-10-CM R15.9 (Full incontinence of feces) is included on Line 71 only for supportive equipment (e.g. diapers, gloves). Surgical treatment for fecal incontinence is included on Line 526 DISORDERS OF FUNCTION OF STOMACH AND OTHER FUNCTIONAL DIGESTIVE DISORDERS.

Sacral nerve stimulation is included on line 526 only for fecal incontinence and only when all of the following criteria are met:

1) Documented failure or intolerance to conventional therapy (e.g., dietary modification, the addition of bulking and pharmacologic treatment); AND
2) A successful percutaneous test stimulation, defined as at least 50% sustained (more than one week) improvement in symptoms; AND
3) Condition is not related to anorectal malformation and/or chronic inflammatory bowel disease; AND
4) Incontinence is not related to another neurologic condition such as peripheral neuropathy or complete spinal cord injury.

3) Adopt a new guideline note for lines 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION and 453 URINARY INCONTINENCE as shown below:

GUIDELINE NOTE XXX SACRAL NERVE STIMULATION FOR URINARY CONDITIONS

Lines 327, 453

Sacral nerve stimulation is included on these lines only for urinary incontinence, non-obstructive urinary retention, and overactive bladder AND only when all of the following criteria are met:

1) The patient has had symptoms for at least 12 months and the condition has resulted in significant disability (the frequency and/or severity of symptoms are limiting the member's ability to participate in daily activities); AND
2) Documented failure or intolerance to pharmacotherapies and behavioral treatments (e.g., pelvic floor exercise, biofeedback, timed voids, and fluid management) and, for non-obstructive urinary retention, intermittent catheterization; AND

3) The patient must be an appropriate surgical candidate such that implantation with anesthesia can occur; AND
4) The patient does not have stress incontinence, urinary obstruction, and specific neurologic diseases (e.g., diabetes with peripheral nerve involvement, spinal cord injury, or multiple sclerosis); AND
5) Patient must have had a successful test stimulation, defined as a 50% or greater improvement in symptoms.

4) Consider reprioritization of surgical treatment of fecal incontinence as part of the 2022 Biennial Review

NICE guidance

Sacral nerve stimulation for idiopathic chronic non-obstructive urinary retention

Interventional procedures guidance
Published: 25 November 2015
nice.org.uk/guidance/ipg536

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

1 Recommendations

1.1 Current evidence on the safety and efficacy of sacral nerve stimulation for idiopathic chronic non-obstructive urinary retention is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit.

1.2 During the consent process, clinicians should ensure that patients understand the risk of complications, the likely need for further surgery and the possible need for device removal, and provide them with clear written information. In addition, the use of NICE's information for the public is recommended.

1.3 Patient selection and treatment should be done in specialist units by clinical teams who are experienced in the assessment, treatment and long-term care of patients with bladder dysfunction, and in the use of sacral nerve stimulation.

1.4 NICE encourages audit and reporting of long-term safety outcomes.

2 Indications and current treatments

2.1 Non-obstructive urinary retention is the inability to empty the bladder with no physical obstruction to the urine flow. It can occur as a result of neurological disorders, such as multiple sclerosis or spinal cord disease, or it can be idiopathic. In younger women, it may be caused by Fowler's syndrome, which is a rare disorder in which the urethral sphincter fails to relax to allow urine to be passed normally. This guidance covers idiopathic chronic non-obstructive urinary retention only (including Fowler's syndrome). Chronic non-obstructive urinary retention can cause complications such as recurrent urinary tract infections and chronic kidney disease.

2.2 Initial management in men is usually with drug therapy, such as alpha blockers, and urethral dilatation; whereas in women it is usually urethral dilatation only. The efficacy of these options is limited and most patients need to do clean intermittent self-catheterisation or have an indwelling catheter. If these measures are unacceptable to the patient or do not work well enough, then surgical urinary diversion procedures may be considered. Sacral nerve stimulation has been introduced as another option for patients with chronic non-obstructive urinary retention.

3 The procedure

3.1 Sacral nerve stimulation for idiopathic chronic non-obstructive urinary retention involves applying an electric current to one of the sacral nerves by an electrode placed through the corresponding sacral foramen. It aims to restore

the ability to empty the bladder voluntarily and to remove the need for catheterisation.

3.2 Sacral nerve stimulation involves an evaluation phase to help the patient and clinician decide if long-term therapy will be beneficial. Evaluation also includes assessing the integrity of the sacral nerves and identifying the optimal lead location. Two main techniques are used for this evaluation, both of which are initiated by an implantation procedure done using fluoroscopic guidance, with the patient under general or local anaesthesia. The conventional technique involves percutaneously placing a temporary lead, with a unipolar electrode, alongside a sacral nerve (usually S3) and taping it to the skin surface. A newer 2-stage technique involves implanting a permanent tined lead, with a quadripolar electrode, on the sacral nerve usually through the third sacral foramen. When the lead is correctly positioned, an extension cable is tunnelled to the proposed site for the neurostimulator, usually in the upper buttock. The lead is then tunnelled to the other buttock to provide a remote exit site through the skin.

3.3 In both techniques, the leads are attached to a small, external neurostimulator and the level of stimulation is adjusted to achieve normal voiding of urine while avoiding discomfort for the patient. The length of the evaluation phase varies but is generally around 3–7 days with the temporary lead method and approximately 2–4 weeks if a permanent lead is used.

3.4 When the evaluation phase is complete, the sacral nerve neurostimulator is implanted, usually with the patient under general anaesthesia. The neurostimulator is inserted into a subcutaneous pocket through a small incision in the upper buttock. If a permanent lead was used in the evaluation phase, it is connected to the neurostimulator. If a temporary lead was used, it is replaced by a permanent lead placed in approximately the same position and connected to the neurostimulator. The electrical current, generated by the neurostimulator and delivered by the lead, modifies sacral nerve activity. The patient can control the neurostimulator with a hand-held programmer, increasing or decreasing the level of stimulation or turning it on and off.

4 Efficacy

This section describes efficacy outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

4.1 A systematic review of 14 articles reported post-void residual volume from 7 of the articles (n=478). The mean difference in post-void residual volume decreased by 236 ml (95% confidence interval [CI] 219 to 253, p<0.0001, I^2=83%) after sacral nerve stimulation. A randomised controlled trial of 51 patients treated by sacral nerve stimulation or standard medical treatment, which was also included in the systematic review, reported that the mean catheter volume per catheterisation decreased from 339 ml to 49 ml at 6-month follow-up in the treatment group and from 350 ml to 319 ml in the control group (p<0.0001 comparing the mean differences).

4.2 The systematic review of 14 articles reported voided volume from 7 of the articles (n=478). The mean voided volume increased by 344 ml (95% CI 322 to 365, p<0.0001, I^2=97%) after sacral nerve stimulation. The randomised controlled trial of 51 patients reported that the mean total voided volume per day increased from 722 ml to 1808 ml at 6-month follow-up in the treatment group and decreased from 560 ml to 488 ml in the control group (p<0.0001 comparing the mean differences).

4.3 The randomised controlled trial of 51 patients reported that the mean number of catheterisations per day decreased from 5.7 to 1.4 at 6-month follow-up in the treatment group and from 4.0 to 3.9 in the control group (p<0.0001 comparing the mean differences). At 18-month follow-up 58% (14/24) of patients treated by sacral nerve stimulation did not need catheterisation. A case series of 60 patients reported that 72% (43/60) of patients were voiding spontaneously and 50% (30/60) of patients no longer needed to use catheterisation after a mean follow-up of 4 years. A case series of 40 patients reported that the mean number of catheterisations per day decreased from 4.3 to 1.0 after a mean follow-up of 41 months (p<0.001) and 55% (11/20) of patients with complete retention were able to stop catheterisation completely.

4.4 The case series of 40 patients reported that 69% (20/29) of patients with complete retention and 73% (8/11) of patients with incomplete retention had a

successful response to sacral nerve stimulation (defined by a reduction in the number of daily catheterisations by 50% and a decrease in the mean post-void residual urine volume by 50%). A case series of 93 patients with idiopathic urinary retention reported a success rate of 73%; the cure rate (100% success) was 63% for patients with Fowler's syndrome and 54% for patients with non-Fowler's idiopathic urinary retention.

4.5 The specialist advisers listed key efficacy outcomes as ability to void spontaneously, lower residual volume, reduced need for intermittent catheterisation, a 50% reduction in catheter volume per catheterisation, patient perception of cure or improvement, perception of improved flow rate, frequency of micturition or nocturia, pain relief, urodynamic measurements, pad tests or number of leaks per day (if overflow incontinence is present), quality of life, general health status, psychosocial measures, impact of self-catheterisation or incontinence.

5 Safety

This section describes safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

5.1 The neurostimulator device was removed in 14% (4/28) of patients in a case series of 40 patients: 2 because of infection, 1 because of pain and 1 because of the need for MRI. In the same study, neurostimulator revision was necessary in 21% (6/28) of patients because of battery expiry or device malfunction in 4 patients and infection in 2 patients. Device removal because of infection was reported in 2% (2/93) of patients in a case series of 93 patients. There were 63 surgical revisions in a case series of 60 patients during a total of 2878 months of sacral nerve stimulation. Device removal was reported in 4% of patients (actual numbers not reported) treated by sacral nerve stimulation at 18-month follow-up in a randomised controlled trial of 51 patients.

5.2 Infection was reported in 4% of patients in a systematic review of 14 articles, including a total of 1239 patients (actual numbers not reported). Infection was reported in 2% (2/93) of patients in the case series of 93 patients: both were successfully treated with antibiotics.

5.3 Lead migration was reported in 5% of patients in the systematic review of 14 articles, including a total of 1239 patients (actual numbers not reported). Lead migration was reported in 28% (17/60) of patients in the case series of 60 patients, 15 of whom were in the group of 30 patients who had a 1-stage procedure for implanting the neurostimulator.

5.4 Pain at the implant site, pain at the lead site and new pain (unspecified) were reported in 10% (128/1239), 2% and 4% of patients respectively, in the systematic review of 14 articles, including a total of 1239 patients. Pain at the implant site was reported in 32% (19/60) of patients in the case series of 60 patients. Leg pain, pelvic pain and urethral pain were reported in 30% (18/60), 3% (2/60) and 3% (2/60) of patients respectively, in the same study.

5.5 Sensation of electric shock was reported in 2% of patients in the systematic review of 14 articles, including a total of 1239 patients (actual numbers not reported).

5.6 Wound seroma was reported in 1 patient in the case series of 93 patients.

5.7 In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never done so). For this procedure, specialist advisers listed the following anecdotal adverse events: change in bowel function, and decubitus ulceration. They did not describe any theoretical adverse events.

6 Committee comments

6.1 This guidance covers idiopathic chronic non-obstructive urinary retention and not retention caused by neurological conditions such as multiple sclerosis or spinal cord injury. The Committee was advised that studies are in progress on sacral nerve stimulation for treating chronic non-obstructive urinary retention caused by neurological conditions, and NICE may produce guidance when the results have been published.

6.2 The Committee noted that there has been a move from using a 1-stage to a 2-stage technique for the evaluation phase of the procedure. It was advised that the latter is associated with better outcomes.

6.3 The Committee noted that patient commentaries reported consistent benefits from the procedure and described substantial improvements in quality of life.

7 Further information

7.1 For related NICE guidance, see the NICE website.

Information for patients

NICE has produced information on this procedure for patients and carers (information for the public). It explains the nature of the procedure and the guidance issued by NICE, and has been written with patient consent in mind.

About this guidance

NICE interventional procedures guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS.

This guidance was developed using the NICE interventional procedures guidance process.

We have produced information for the public explaining this guidance. Information about the evidence the guidance is based on is also available.

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual

responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

ISBN: 978-1-4731-1541-5

Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

Accreditation

Structured Abstract

Objectives: The Vanderbilt Evidence-based Practice Center systematically reviewed evidence on treatment of overactive bladder (OAB), urge urinary incontinence, and related symptoms. We focused on prevalence and incidence, treatment outcomes, comparisons of treatments, modifiers of outcomes, and costs.

Data: We searched PubMed, MEDLINE®, EMBASE, and CINAHL.

Review Methods: We included studies published in English from January 1966 to October 2008. We excluded studies with fewer than 50 participants, fewer than 75 percent women, or lack of relevance to OAB. Of 232 included publications, 20 were good quality, 145 were fair, and 67 poor. We calculated weighted averages of outcome effects and conducted a mixed-effects meta-analysis to investigate outcomes of pharmacologic treatments across studies.

Results: OAB affects more than 10 to 15 percent of adult women, with 5 to 10 percent experiencing urge urinary incontinence (UUI) monthly or more often. Six available medications are effective in short term studies: estimates from meta-analysis models suggest extended release forms (taken once a day) reduce UUI by 1.78 (95 percent confidence interval (CI): 1.61, 1.94) episodes per day, and voids by 2.24 (95 percent CI: 2.03, 2.46) per day. Immediate release forms (taken twice or more a day) reduce UUI by 1.46 (95 percent CI: 1.28, 1.64), and voids by 2.17 (95 percent CI: 1.81, 2.54). As context, placebo reduces UUI episodes by 1.08 (95 percent CI: 0.86, 1.30), and voids by 1.48 (95 percent CI: 1.19, 1.71) per day. No one drug was definitively superior to others, including comparison of newer more selective agents to older antimuscarinics.

Current evidence is insufficient to guide choice of other therapies including sacral neuromodulation, instillation of oxybutynin, and injections of botulinum toxin. Acupuncture was the sole complementary and alternative medicine treatment, among reflexology and hypnosis, with early evidence of benefit. The strength of the evidence is insufficient to fully inform choice of these treatments. Select behavioral interventions were associated with symptom improvements comparable to medications. Limited evidence suggests no clear benefit from adding behavioral interventions at the time of initiation of pharmacologic treatment.

Conclusions: OAB and associated symptoms are common. Treatment effects are modest. Quality of life and treatment satisfaction measures suggest such improvements can be important to women. The amount of high quality literature available is meager for helping guide women's choices. Gaps include weak or absent data about long-term followup, poorly characterized and potentially concerning harms, information about best choices to minimize side effects, and study of how combinations of approaches may best be used. This is problematic since the condition is chronic and a single treatment modality is unlikely to fully resolve symptoms for most women.

NICE guidance

Sacral nerve stimulation for faecal incontinence

Interventional procedures guidance
Published: 24 November 2004
nice.org.uk/guidance/ipg99

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

This guidance replaces IPG5.

1 Guidance

This document replaces previous guidance on sacral nerve stimulation for faecal incontinence (interventional procedure guidance 5).

1.1 Current evidence on the safety and efficacy of sacral nerve stimulation for faecal incontinence appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance.

1.2 The procedure should only be performed in specialist units by clinicians with a particular interest in the assessment and treatment of faecal incontinence.

2 The procedure

2.1 Indications

2.1.1 Faecal incontinence occurs when a person loses control of their bowel and is unable to retain faeces in the rectum. Faecal incontinence may result from dysfunction of the anal sphincter, which may be due to sphincter damage, spinal injury or a neurological disorder.

2.1.2 Faecal incontinence is associated with a high level of physical and social disability.

2.1.3 Typically, first-line treatment for faecal incontinence is conservative, such as anti-diarrhoeal medication and pelvic floor muscle training (including biofeedback therapy). In patients for whom conservative treatments have been unsuccessful, surgical alternatives include tightening the sphincter (overlapping sphincteroplasty), creating a new sphincter from the patient's own muscle (for example, dynamic graciloplasty) or implanting an artificial sphincter. Some patients may require colostomy. Sacral nerve stimulation is a surgical treatment option for patients with faecal incontinence.

2.2 Outline of the procedure

2.2.1 In patients with a weak but structurally intact sphincter, it may be possible to alter sphincter and bowel behaviour using the surrounding nerves and muscles. It involves applying an electric current to one of the sacral nerves via an electrode placed through the corresponding sacral foramen. Commonly, the procedure is tested in each patient over a 2- to 3-week period, with a temporary percutaneous peripheral nerve electrode attached to an external stimulator. If

significant benefit is achieved, then the permanent implantable pulse generator can be implanted.

2.3 Efficacy

2.3.1 This procedure was subject to a systematic review commissioned by the Institute. The systematic review included six case series studies reporting on 266 patients in total. In patients who had permanent implants, complete continence was achieved in 41–75% (19/46–12/16) of patients, whereas 75–100% (3/4–16/16) of patients experienced a decrease of 50% or more in the number of incontinence episodes. There was also evidence to suggest an improvement in the ability to defer defecation after permanent implantation. Patients also reported improvements in both disease-specific and general quality-of-life scores after the procedure. For more details, refer to the Sources of evidence section.

2.4 Safety

2.4.1 Complications were reported both during the test peripheral nerve evaluation phase and after implantation. Evidence from the systematic review indicated that of the 266 patients receiving test evaluation, 4% (10/266) experienced an adverse event. Fifty-six per cent (149/266) went on to receive permanent implantation. Of the patients who had permanent implants, 13% (19/149) reported adverse events. These included three patients who developed infections requiring device removal, seven patients who had lead migration requiring either relocation (five cases) or removal of the device, and six patients who experienced pain after implantation.

2.4.2 Implantation techniques have been modified in recent years, with a view to reducing the occurrence of complications.

Andrew Dillon
Chief Executive
November 2004

3 Further information

Sources of evidence

The evidence considered by the Interventional Procedures Advisory Committee is described in the following document.

Fraser C, Glazener C, Grant A et al. Systematic review of the efficacy and safety of sacral nerve stimulation for faecal incontinence. Aberdeen: Review Body for Interventional Procedures; 2004. Commissioned by the National Institute for Clinical Excellence.

Information for patients

NICE has produced information on this procedure for patients and carers ('Understanding NICE guidance'). It explains the nature of the procedure and the guidance issued by NICE, and has been written with patient consent in mind.

4 About this guidance

NICE interventional procedure guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS. It is for healthcare professionals and people using the NHS in England, Wales, Scotland and Northern Ireland, and is endorsed by Healthcare Improvement Scotland for implementation by NHSScotland.

This guidance was developed using the NICE interventional procedure guidance process.

It updates and replaces NICE interventional procedure guidance 5.

We have produced a summary of this guidance for patients and carers. Information about the evidence it is based on is also available.

Changes since publication

26 January 2012: minor maintenance.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

NICE guidance

Sacral nerve stimulation for urge incontinence and urgency-frequency

Interventional procedures guidance
Published: 23 June 2004
nice.org.uk/guidance/ipg64

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

This guidance replaces IPG4.

1 Guidance

This document replaced previous guidance on sacral nerve stimulation for 'Urge incontinence' (NICE Interventional Procedures Guidance no. 4) after the Interventional Procedures Advisory Committee reconsidered the procedure based on the results of a systematic review commissioned by NICE.

1.1 Current evidence on the safety and efficacy of sacral nerve stimulation for urge incontinence and urgency-frequency appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.

1.2 Patient selection is important. The diagnosis should be defined as clearly as possible and the procedure limited to patients who have not responded to conservative treatments such as lifestyle modifications, behavioural techniques and drug therapy. Patients should be selected on the basis of their response to peripheral nerve evaluation.

2 The procedure

2.1 Indications

2.1.1 Sacral nerve stimulation is used to treat the symptoms of an overactive bladder, including urinary urge incontinence and/or urgency frequency in patients who have failed or cannot tolerate conventional treatments.

2.1.2 In patients for whom conservative treatments have been unsuccessful, the standard alternatives include bladder reconstruction (such as augmentation and cystoplasty) and urinary diversion.

2.2 Outline of the procedure

2.2.1 Sacral nerve stimulation involves applying an electric current to one of the sacral nerves via an electrode placed through the corresponding sacral foramen. The electrode leads are attached to an implantable pulse generator, which stimulates nerves associated with the lower urinary tract.

2.3 Efficacy

2.3.1 This procedure was subject to a systematic review commissioned by the Institute in November 2003. Evidence from two randomised controlled trials (RCTs), including a total of 50 patients with urge incontinence, showed that complete continence (completely dry with no incontinent episodes) or improvement of more than 50% in incontinence symptoms was observed in 50% and 80% of patients, respectively, following the procedure. This compared with 5% of patients in the control groups, who were receiving conservative treatments while waiting for an implant. In the one RCT that reported on patients with urgency-frequency, an improvement of more than 50% in incontinence symptoms was observed in 56% (14/25) of patients, compared with 4% (1/25) in the control group. More evidence is available for patients with urge incontinence than for those with urgency-frequency. For more details, refer to the Sources of evidence section.

2.3.2 The results of the case series studies included in the systematic review showed similar results, with complete continence and improvement in symptoms being reported in 39% (139/361) and 67% (338/501) of patients with urge incontinence, respectively, and 41% (22/54) and 65% (75/116) of patients with urgency-frequency, respectively. The benefits of sacral nerve stimulation were reported to persist for at least 3–5 years after implantation. For more details, refer to the Sources of evidence section.

2.4 Safety

2.4.1 In general, evidence on the safety of this procedure was not well reported. Most complications observed in the studies were the result of technical problems related to implantation of the device. The results of the systematic review showed that, overall, the re-operation rate for patients with implants was 33% (283/860). The most common reasons for surgical revision were to replace or reposition implants due to pain or infection at the implant site, or to adjust and modify the lead system to correct breakage or migration. For more details, refer to the Sources of evidence section.

2.4.2 Pain at the site of the pulse generator or at the site of stimulation was reported in 24% (162/663) of patients, sometimes requiring replacement and repositioning of the pulse generator. Other complications included lead-related

problems such as migration (16%), wound problems (7%), adverse effects on bowel function (6%), and infection (5%). No cases of long-lasting neurological complications were identified. For more details, refer to the Sources of evidence section.

2.5 Other comments

2.5.1 There is a lack of long-term quality of life data.

2.5.2 There is limited evidence relating to the use of this procedure in older patients.

Andrew Dillon
Chief Executive
June 2004

3 Further information

Sources of evidence

The evidence considered by the Interventional Procedures Advisory Committee is described in the following document.

'Brazzelli M, Murray A, Fraser C, Grant A. Systematic review of the efficacy and safety of sacral nerve stimulation for urinary urge incontinence and urgency-frequency. Aberdeen: Review Body for Interventional Procedures; 2003'. Commissioned by the National Institute for Clinical Excellence.

Information for patients

NICE has produced information on this procedure for patients and carers ('Understanding NICE guidance'). It explains the nature of the procedure and the guidance issued by NICE, and has been written with patient consent in mind.

4 Other NICE recommendations on sacral nerve stimulation

Further recommendations have been made as part of the clinical guideline on lower urinary tract symptoms published in May 2010, as follows:

- Consider offering implanted sacral nerve stimulation to manage detrusor overactivity only to men whose symptoms have not responded to conservative management and drug treatments.

Clinical and cost-effectiveness evidence was reviewed in the development of this guideline which has led to this more specific recommendation. More information is available.

The IP guidance on sacral nerve stimulation for urge incontinence and urgency-frequency remains current, and should be read in conjunction with the clinical guideline.

5 About this guidance

NICE interventional procedure guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS. It is for healthcare professionals and people using the NHS in England, Wales, Scotland and Northern Ireland, and is endorsed by Healthcare Improvement Scotland for implementation by NHSScotland.

This guidance was developed using the NICE interventional procedure guidance process.

It updates and replaces NICE interventional procedure guidance 4.

We have produced a summary of this guidance for patients and carers. Information about the evidence it is based on is also available.

Changes since publication

27 January 2012: minor maintenance.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the

guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

Local Coverage Article:
Sacral Nerve Stimulation for Urinary and Fecal Incontinence (A53359)

Please Note: This view is an approximation of the CMS MCD Article Detail page.

Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	01111 - MAC A	J - E	California - Entire State
Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
Noridian Healthcare Solutions, LLC	A and B MAC	01182 - MAC B	J - E	California - Southern
Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01312 - MAC B	J - E	Nevada

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	01911 - MAC A	J - E	American Samoa California - Entire State Guam Hawaii Nevada Northern Mariana Islands

Article Information

General Information

Article ID Number
A53359

Original ICD-9 Article ID
A51543

Article Title
Sacral Nerve Stimulation for Urinary and Fecal Incontinence

Original Effective Date
10/01/2015

Revision Effective Date
02/28/2019

Revision Ending Date
N/A

Retirement Date
N/A

Article Guidance

Article Text:

Background
Sacral Nerve Stimulation for urinary incontinence is covered for the treatment of urinary urge incontinence, urge-frequency syndrome, and urinary retention by the CMS National Coverage Determination (NCD) 230.18, http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/ncd103c1_Part4.pdf. Direct stimulation of the sacral nerve(s) via an electrode array implanted at the level of the sacrum is the only treatment modality covered by the NCD. In addition, Noridian will cover sacral nerve stimulation by the same modality for the treatment of fecal incontinence, effective March 1, 2012.

Indications and Limitations

Urinary Incontinence
Sacral nerve stimulation is covered for the treatment of urinary urge incontinence, urgency-frequency syndrome, and urinary retention. Sacral nerve stimulation involves both a temporary test stimulation to determine if an implantable stimulator would be effective and a permanent implantation in appropriate candidates. Both the test and the permanent implantation are covered.

The NCD describes the following limitations for coverage to all three conditions:
• Patient must be refractory to conventional therapy (documented behavioral, pharmacologic and/or surgical corrective therapy) and be an appropriate surgical candidate such that implantation with anesthesia can occur.
• Patients with stress incontinence, urinary obstruction, and specific neurologic diseases (e.g., diabetes with peripheral nerve involvement) which are associated with secondary manifestations of the above three indications are excluded.
• Patient must have had a successful test stimulation in order to support subsequent implantation. Before a patient is eligible for permanent implantation, he/she must demonstrate a 50% or greater improvement through test stimulation. Improvement is measured through voiding diaries.

Patient must be able to demonstrate adequate ability to record voiding diary data such that clinical results of the implant procedure can be properly evaluated.

Fecal Incontinence
Noridian will cover sacral nerve modulation/stimulation for fecal incontinence effective March 1, 2012, when all of the following criteria are met:

• Chronic fecal incontinence with greater than two incontinent episodes on average per week and duration of incontinence greater than six months or for more than twelve months after vaginal childbirth; AND
• Documented failure or intolerance to conventional therapy (e.g., dietary modification, the addition of bulking and pharmacologic treatment); AND
• A successful percutaneous test stimulation, defined as at least 50% sustained (more than one week) improvement in symptoms; AND
• Condition is not related to anorectal malformation (e.g., congenital anorectal malformation; defects of the external anal sphincter over 60 degrees; visible sequelae of pelvic radiation; active anal abscesses and fistulae) and/or chronic inflammatory bowel disease; AND
• Incontinence is not related to another neurologic condition such as peripheral neuropathy or complete spinal cord injury.

Sacral nerve modulation/stimulation is considered **experimental, investigational and unproven for the treatment of chronic constipation or chronic pelvic pain.**

Sources:
•Internet Only Manual (IOM) *Medicare National Coverage Determination Manual*, Publication 100-03, Section 230.18 *Sacral Nerve Stimulation for Urinary Incontinence*;

•Abrams P et al. Fourth International Consultation on Incontinence recommendations of the International Scientific Committee: evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence;
• *Neurourol Urodyn*. 2010; 29(1):213-40;
• *Annals of Surgery*, March 2010, Vol 251, Number 3. *Sacral Nerve Stimulation for Fecal Incontinence, Results of a 120-Patient Prospective Multicenter Study*;
•Michelsen H, Thompson-Fawcett M, Lundy L, Krogh K, Laurberg S, Buntzen S;
•Six Year Experience with Sacral Nerve Stimulation for Fecal Incontinence;
• *Dis Colon Rectum*. 2010; 53(4)414-421; Mowatt G, Glazener CMA, Jarrett M. Sacral nerve stimulation for fecal incontinence and constipation in adults (Review);
• *The Cochrane Library*. 2009, Issue 1; National Institute for Health and Clinical Excellence. Fecal incontinence: the management of fecal incontinence in adults. NICE Clinical Guideline 49, June 2007;
•Trailblazer Health Enterprises, Local Coverage Determination for *Sacral Nerve Stimulation* – 4S-154AB-R9, Effective March 01, 2008

Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the article does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the article should be assumed to apply equally to all claims.

BILL TYPE CODE	BILL TYPE DESCRIPTION
011x	Hospital Inpatient (Including Medicare Part A)
013x	Hospital Outpatient
071x	Clinic - Rural Health
073x	Clinic - Freestanding
085x	Critical Access Hospital

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the article, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the article should be assumed to apply equally to all

Revenue Codes.

REVENUE CODE	REVENUE CODE DESCRIPTION
0272	Medical/Surgical Supplies and Devices - Sterile Supply
0274	Medical/Surgical Supplies and Devices - Prosthetic/Orthotic Devices
0275	Medical/Surgical Supplies and Devices - Pacemaker
0276	Medical/Surgical Supplies and Devices - Intraocular Lens
0278	Medical/Surgical Supplies and Devices - Other Implant
0279	Medical/Surgical Supplies and Devices - Other Supplies/Devices
0280	Oncology - General Classification
0289	Oncology - Other Oncology
0290	Durable Medical Equipment (other than renal) - General Classification
0360	Operating Room Services - General Classification
0510	Clinic - General Classification
0521	Freestanding Clinic - Clinic Visit by Member to RHC/FQHC
0624	Medical/Surgical Supplies and Devices - FDA Investigational Devices
0920	Other Diagnostic Services - General Classification

CPT/HCPCS Codes
Group 1 Paragraph: Covered CPT/HCPCS Codes:
Group 1 Codes:

CODE	DESCRIPTION
64561	PERCUTANEOUS IMPLANTATION OF NEUROSTIMULATOR ELECTRODE ARRAY; SACRAL NERVE (TRANSFORAMINAL PLACEMENT) INCLUDING IMAGE GUIDANCE, IF PERFORMED
64581	INCISION FOR IMPLANTATION OF NEUROSTIMULATOR ELECTRODE ARRAY; SACRAL NERVE (TRANSFORAMINAL PLACEMENT)

Group 2 Paragraph:

Ancillary Coding

Group 2 Codes:

CODE	DESCRIPTION
64585	REVISION OR REMOVAL OF PERIPHERAL NEUROSTIMULATOR ELECTRODE ARRAY
64590	INSERTION OR REPLACEMENT OF PERIPHERAL OR GASTRIC NEUROSTIMULATOR PULSE GENERATOR OR RECEIVER, DIRECT OR INDUCTIVE COUPLING
64595	REVISION OR REMOVAL OF PERIPHERAL OR GASTRIC NEUROSTIMULATOR PULSE GENERATOR OR RECEIVER
A4290	SACRAL NERVE STIMULATION TEST LEAD, EACH
C1767	GENERATOR, NEUROSTIMULATOR (IMPLANTABLE), NON-RECHARGEABLE
C1778	LEAD, NEUROSTIMULATOR (IMPLANTABLE)
C1883	ADAPTER/EXTENSION, PACING LEAD OR NEUROSTIMULATOR LEAD (IMPLANTABLE)
C1897	LEAD, NEUROSTIMULATOR TEST KIT (IMPLANTABLE)
L8680	IMPLANTABLE NEUROSTIMULATOR ELECTRODE, EACH

ICD-10 Codes that are Covered
Group 1 Paragraph:

Note: The “C” codes listed above are only applicable when billed under the hospital outpatient prospective payment system (OPPS) and they should be submitted in place of codes A4290.

Covered ICD-10-CM diagnosis codes for CPT/HCPCS codes 64561 and 64581

Group 1 Codes:

CODE	DESCRIPTION
N30.10	Interstitial cystitis (chronic) without hematuria
N30.11	Interstitial cystitis (chronic) with hematuria

CODE	DESCRIPTION
N36.44	Muscular disorders of urethra
N39.41	Urge incontinence
N39.42	Incontinence without sensory awareness
N39.46	Mixed incontinence
N39.490	Overflow incontinence
N39.492	Postural (urinary) incontinence
N39.498	Other specified urinary incontinence
R15.9	Full incontinence of feces
R32	Unspecified urinary incontinence
R33.0	Drug induced retention of urine
R33.8	Other retention of urine
R33.9	Retention of urine, unspecified
R35.0	Frequency of micturition
R39.11	Hesitancy of micturition
R39.14	Feeling of incomplete bladder emptying
R39.15	Urgency of urination
R39.191	Need to immediately re-void
R39.192	Position dependent micturition

ICD-10 Codes that are Not Covered
N/A

Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION
02/28/2019	R2	This article is revised to add Type of Bill (TOB) and Revenue codes in the Bill Type Codes and Revenue Codes fields and CPT codes 64585 and 64595 to the Ancillary Codes in the Group 2 Codes as indicated in the Internet Only Manual (IOM) *Claims Processing Manual*,, Publication 100-4 Chapter 32, Section 40.2-40.5.
10/01/2016	R1	The article was revised to add the following diagnoses effective 10/1/2016: N39.492, R39.191 and R39.192. R39.11 is added effective 10/1/2015. The JEA article A53358 is retired and JEA contract numbers are added to this JEB coverage article.

Associated Documents

Related Local Coverage Document(s)
N/A

Related National Coverage Document(s)
N/A

Statutory Requirements URL(s)
N/A

Rules and Regulations URL(s)
N/A

CMS Manual Explanations URL(s)
Medicare National Coverage Determinations Manual

Other URL(s)
N/A

Public Version(s)
Updated on 02/19/19 with effective dates 02/28/2019 - N/A
Updated on 09/21/16 with effective dates 10/01/2016 - 02/27/2019
Updated on 10/10/15 with effective dates 10/01/2015 - N/A

Keywords

- Sacral Nerve
- Stimulation
- Incontinence
- constipation

- 64561
- 64581
- 64585
- 64590
- 64595
- A4290
- C1767
- C1778
- C1883
- C1897
- L8680

Sling Procedure for Treatment of Male Urinary Incontinence

Question: Should the sling procedure be paired with male urinary incontinence?

Question source: HSD claims reconsideration

Issue: The male sling procedure helps men with urinary incontinence due to sphincter weakness or insufficiency caused by prior pelvic surgery including TURP (transurthethral resection of the prostate) and radical prostatectomy. In the male sling procedure, synthetic mesh-like tape is positioned around part of the urethral bulb, slightly compressing the urethra and moving it into a new position. Complications of this type of procedure are rare but may occur. They include bleeding and infection (of the mesh or the bone area or public bone), erosion, inability to urinate, or recurrent leakage.

Currently, the male sling procedure (CPT 53440 Sling operation for correction of male urinary incontinence (eg, fascia or synthetic)) does not pair with urinary incontinence. However, the more generic CPT codes generally used for female sling procedures (e.g. CPT 51990 and 51992, 57288) are paired with urinary incontinence on line 453 URINARY INCONTINENCE. There is currently a guideline associated with line 453 which outlines when surgical procedures are covered for treatment of urinary incontinence.

GUIDELINE NOTE 47, URINARY INCONTINENCE

Line 453

Surgery for genuine stress urinary incontinence may be indicated when all of the following are documented (A-G):

A) Patient history of (1, 2, and 3):
   1) Involuntary loss of urine with exertion
   2) Identification and treatment of transient causes of urinary incontinence, if present (e.g., delirium, infection, pharmaceutical causes, psychological causes, excessive urine production, restricted mobility, and stool impaction)
   3) Involuntary loss of urine on examination during stress (provocative test with direct visualization of urine loss) and low or absent post void residual
B) Patient's voiding habits
C) Physical or laboratory examination evidence of either (1 or 2):
   1) Urethral hypermobility
   2) Intrinsic sphincter deficiency
D) Diagnostic workup to rule out urgency incontinence
E) Negative preoperative pregnancy test result unless patient is postmenopausal or has been previously sterilized
F) Nonmalignant cervical cytology, if cervix is present
G) Patient required to have 3 months of alternative therapy (e.g., pessaries or physical therapy, including bladder training, pelvic floor exercises and/or biofeedback, as available). If limited coverage of physical therapy is available, patients should be taught pelvic floor exercises by their treating provider, physical therapist or trained staff, and have documented consistent practice of these techniques over the 3 month period.

Current Prioritized List status

CPT code	Code description	Current Lines
51990	Laparoscopy, surgical; urethral suspension for stress incontinence	453 URINARY INCONTINENCE
51992	Laparoscopy, surgical; sling operation for stress incontinence (eg, fascia or synthetic)	453
53440	Sling operation for correction of male urinary incontinence (eg, fascia or synthetic)	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 87 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
53442	Removal or revision of sling for male urinary incontinence (eg, fascia or synthetic)	71,87,327 422 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
57287	Removal or revision of sling for stress incontinence (eg, fascia or synthetic)	208 DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT 285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 327,453 464 UTERINE PROLAPSE; CYSTOCELE
57288	Sling operation for stress incontinence (eg, fascia or synthetic)	453, 464

Evidence

1) **Welk 2011**, review of male slings for post-prostatectomy urinary incontinence (PPI)
    a. Three principal slings are described in the literature.
        i. The bone-anchored sling has success rates of 40 – 88%, with some series having a mean follow-up of 36 – 48 months. It is associated with a mesh infection rate of 2 – 12%, which usually requires sling explantation.
        ii. The retrourethral transobturator sling has a success rate of 76 – 91% among three large case series with follow-ups of 12 – 27 months. There is a low reported explantation rate.
        iii. The adjustable retropubic sling has a success rate of 72 – 79% with follow-ups of 26 – 45 months. Erosion (3 – 13%) and infection (3 – 11%) can lead to explantation.
    b. Conclusion: Most male slings have a similar reported efficacy. Most case series define success as either dry or improved. True cure rates are lower. Mid- and long-term data are now available that indicate the male sling is a viable option for PPI. The use of male slings in severe urinary incontinence, radiated patients, and non-radical prostatectomy patients is still unclear. Further study is needed to try and define criteria for the use of male slings, and to directly compare different procedures.

Other payers:
All private payers surveyed cover sling operations for male urinary incontinence, generally after failure of conservative management (e.g., pelvic floor muscle training, electrical stimulation, and biofeedback).

HERC staff summary:
Male urethral slings are considered standard of care for moderate to severe urinary incontinence after procedures such as TURP and radical prostatectomy. There is little evidence evaluating outcomes. However, similar procedures for female urinary incontinence are covered with an appropriate guideline on the urinary incontinence line.

HERC staff recommendations:

1) Add CPT 53440 (Sling operation for correction of male urinary incontinence (eg, fascia or synthetic)) ad 53442 (Removal or revision of sling for male urinary incontinence (eg, fascia or synthetic)) to line 453 URINARY INCONTINENCE
2) Remove CPT 53440 and 53442 from lines 71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES, 87 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM, and 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
    a. Not associated with GN 47
    b. Similar sling procedures for female surgeries are not included on these lines
3) No changes required to GN 47 URINARY INCONTINENCE

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REVIEW ARTICLE

The male sling for post-prostatectomy urinary incontinence: a review of contemporary sling designs and outcomes

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Accepted for publication 21 April 2011

What's known on the subject? and What does the study add?
Long-term cure and improved rates for the bone anchored sling range from 40–88%. Midterm cure and improved rates for the retrourethral transobturator sling rage from 76–91%. Midterm cure and improved rates for the adjustable retropubic sling rage from 72–79%.

Potential complications common to all urethral slings include postoperative urinary retention, perineal pain, and urethral erosion/device infection. All male urethral slings have primarily been studied in post radical prostatectomy patients, with inconsistent success among patients with prior pelvic radiation.

OBJECTIVE

- To examine the outcomes and adverse events associated with novel male sling designs described in the last decade.

METHODS

- A literature review was carried out using Medline, EmBase, Cochrane Registered Trials Database and the Center for Reviews and Dissemination Database.

RESULTS

- Three principal slings are described in the literature. The bone-anchored sling has success rates of 40–88%, with some series having a mean follow-up of 36–48 months. It is associated with a mesh infection rate of 2–12%, which usually requires sling explantation.
- The retrourethral transobturator sling has a success rate of 76–91% among three large case series with follow-ups of 12–27 months. There is a low reported explantation rate.
- The adjustable retropubic sling has a success rate of 72–79% with follow-ups of 26–45 months. Erosion (3–13%) and infection (3–11%) can lead to explantation.

CONCLUSIONS

- Most male slings have a similar reported efficacy. Most case series define success as either dry or improved. True cure rates are lower. Mid- and long-term data are now available that indicate the male sling is a viable option for PPI.
- The use of male slings in severe UI, radiated patients, and non-radical prostatectomy patients is still unclear. Further study is needed to try and define criteria for the use of male slings, and to directly compare different procedures.

KEYWORDS

male slings, urinary incontinence, post-prostatectomy incontinence

INTRODUCTION

Prostate cancer is the most common solid organ cancer in men. It accounts for 22–28% of all male cancers, and >500 000 men are diagnosed a year in the USA and Europe [1,2]. Mortality rates are estimated at ≈10%, and are slowly declining [1,2]. The improving mortality rates are contrasted by the continued long-term morbidity related to prostate cancer treatment.

A significant part of this morbidity is the stress urinary incontinence (SUI) that can result from radical prostatectomy (RP) [3]. Risk factors for post-prostatectomy UI (PPI) are advanced age, surgical technique, and RP associated with pelvic radiation or a previous TURP [4]. The Prostate Cancer Outcomes Study isolated a population level

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Artificial Urinary Sphincters

Question: Should artificial urinary sphincters (AUS) be paired with urinary incontinence?

Question source: HSD claims reconsideration

Issue: HSD has received several claims for the procedure codes for insertion of artificial urinary sphincters paired with diagnosis codes for urinary incontinence. The majority of CPT codes (CPT 53445-53449) for artificial urinary sphincters are not paired with urinary incontinence; however, the CPT codes for removal and removal/replacement of AUS are paired with urinary incontinence. On review of past minutes, no previous review or discussion of artificial urinary sphincters was found.

An artificial urinary sphincter (AUS) is composed of a pressure regulating balloon placed in the pre-vesical space using an abdominal suprapubic incision; an inflatable cuff is placed around the urethra using a perineal incision; and a control pump is placed in the scrotum via the abdominal incision. The intervention is expensive and requires invasive surgery and experienced surgeons, but is generally considered the gold standard for treatment of severe or persistent incontinence in men. AUS is most commonly placed for postprostatectomy stress urinary incontinence. There is some utilization for female urinary stress incontinence.

Current Prioritized List status

CPT code	**Code description**	**Current Placement**
53445	Insertion of inflatable urethral/bladder neck sphincter, including placement of pump, reservoir, and cuff	71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES 87 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
53446	Removal of inflatable urethral/bladder neck sphincter, including pump, reservoir, and cuff	87,327, 422 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT 453 URINARY INCONTINENCE
53447	Removal and replacement of inflatable urethral/bladder neck sphincter including pump, reservoir, and cuff at the same operative session	71,87,327
53448	Removal and replacement of inflatable urethral/bladder neck sphincter including pump, reservoir, and cuff through an infected field at the same operative session including irrigation and debridement of infected tissue	87,327,422,453

53449	Repair of inflatable urethral/bladder neck sphincter, including pump, reservoir, and cuff	71,87,327
HCPCS code		
C1815	Prosthesis, urinary sphincter (implantable)	71,87,327
ICD-10 Code		
N36.42	Intrinsic sphincter deficiency (ISD)	453 URINARY INCONTINENCE

Utilization:

2 OHP patients received artificial urinary sphincters in 2018, both for urinary stress incontinence (currently non-paired diagnosis)

Evidence

1) **Silva 2014,** Cochrane review of surgery for stress urinary incontinence due to presumed sphincter deficiency after prostate surgery
    1) N=1 study (45 patients) (Imamoglu 2005)
        i. 45 men with urinary incontinence lasting 6 months to 1 year after radical prostatectomy
        ii. RCT of artificial urethral sphincter (AUS) implantation (AMS 800) vs Macroplastique injection
        iii. Follow-up ranged from 6 to 120 months.
    2) In the trial as a whole, the men treated with AUS were more likely to be dry (18/20, 82%) than those who had the injectable treatment (11/23, 46%) (odds ratio (OR) 5.67, 95% confidence interval (CI) 1.28 to 25.10). However, this effect was only statistically significant for the men with more severe ('total') incontinence (OR 8.89, 95% CI 1.40 to 56.57) and the CIs were wide.
    3) There were more severe complications in the group undergoing AUS, and the costs were higher. AUS implantation was complicated in 5/22 (23%) men: the implant had to be removed from one man because of infection and in one man due to the erosion of the cuff, in one man the pump was changed due to mechanical failure, in one man there was migration to the intraperitoneal region, and one man experienced scrotal erosion. In the injectable group, 3/23 (13%) men had a complication: one man treated with Macroplastique injection had to be catheterized because of urinary retention and two men developed urinary tract infections.
    4) Authors' conclusions: The evidence available at present was of very low quality because we identified only one small randomized clinical trial. Although the result was favorable for the implantation of AUS in the group with severe incontinence, this result should be considered with caution due to the small sample size and uncertain methodological quality of the study found.
2) **Van der Aa 2012,** systematic review of artificial urinary sphincter in male non-neurogenic incontinence

1) N=12 studies (623 patients) [included Imamoglu 2005 as in Silva 2014]
    i. Only three studies were prospective.
2) Continence, evaluated only by patient-reported pad use and various questionnaires, was achieved in 61–100% of cases (no pad or one pad per day). Dry rates (no pad) were only available in seven studies and varied from 4% to 86%.
3) A pooled analysis showed that infection or erosion occurred in 8.5% of cases (3.3–27.8%), mechanical failure in 6.2% of cases (2.0–13.8%), and urethral atrophy in 7.9% (1.9–28.6%). Reoperation rate was 26.0% (14.8–44.8%).
4) Patient satisfaction was evaluated in four studies with four different tools and seems to improve after AUS implantation.
5) Conclusions: Quality of evidence supporting the use of AUS in non-neurogenic male patients with SUI is low, based on heterogeneous data, low-quality studies, and mostly out-of-date efficacy outcome criteria. AUS outcomes need to be revisited to be compared with new surgical alternatives, all of which should be prospectively evaluated according to current evidence-based medicine standards.

3) **Lipp 2014**, Cochrane review of artificial devices for urinary incontinence in women
    1) N=8 trials (787 women)
    2) Results
        i. No trials listed using artificial urinary sphincters

<u>Expert guidelines</u>

1) **Lucas 2015**, European Urology Association guideline on urinary incontinence
    i. AUS in women
        1. The major advantage of AUS over other anti-incontinence procedures is the perceived ability to be able to void normally. However, voiding dysfunction is a known side effect, with a lack of data making it difficult to assess its importance. Because of significant differences in design between devices and in selection criteria between case series, results obtained with specific devices cannot be extrapolated generally to the use of adjustable devices.
        2. A previous review of mechanical devices concluded that there was insufficient evidence to support the use of AUS in women
    ii. AUS in men
        1. AUS is the standard treatment for moderate-to-severe male SUI. Most data available on the efficacy and adverse effects of AUS implantation are from older retrospective cohort studies with RCTs not performed due to the lack of a comparator. Men considering insertion of an AUS should understand that if the ability of an individual to operate the pump is uncertain, it may not be appropriate to implant an AUS. There are several recognized complications of AUS implantation, e.g. mechanical dysfunction, urethral constriction by fibrous tissue, erosion and infection.
        2. Evidence
            a. there are two systematic reviews presenting limited evidence, of generally poor quality, except for one RCT comparing with bulking agents. A continence rate of about 80% can be

expected, while this may be lower in men who have undergone pelvic radiotherapy.

Other policies

1) NICE 2019

ii. Do not offer women an artificial urinary sphincter to manage stress urinary incontinence unless previous surgery has failed.

2) Aetna 2019

iii. Aetna considers the implantation of an artificial urinary sphincter (AUS) medically necessary for the treatment of urinary incontinence (UI) due to intrinsic urethral sphincter deficiency (IUSD) for members with any of the following indications:

1. Children with intractable UI due to IUSD who are refractory to behavioral or pharmacological therapies and are unsuitable candidates for other types of surgical procedures for correction of UI; *or*
2. Members who are 6 or more months post-prostatectomy who have had no improvement in the severity of UI despite trials of behavioral and pharmacological therapies; *or*
3. Members with epispadias-exstrophy in whom bladder neck reconstruction has failed; *or*
4. Women with intractable UI who have failed behavioral, pharmacological, and other surgical treatments.

3) MODA 2019

i. Artificial Urinary Sphincters (HCS-0067A) are covered for the treatment of urinary incontinence due to intrinsic urethral sphincter deficiency with 1 or more of the following:

1. Patient is 6 or more months post-prostatectomy and has not had improvement in the severity of urinary incontinence despite trying pharmacological therapy and behavior modification
2. Patient has epispadias-exstrophy and has not had success with bladder neck reconstruction surgery
3. Patient is a woman with intractable urinary incontinence who has failed behavioral modification, pharmacological therapy, and other surgical treatments
4. Patient is a child with intractable urinary incontinence due to intrinsic urethral sphincter deficiency and has been refractory to behavioral modification or pharmacological therapy and is an unsuitable candidate for other surgical procedures for the correction of the urinary incontinence. Request for indications other than those listed above, is considered experimental and investigational because its effectiveness has not been established.

Artificial Urinary Sphincters

HERC staff summary

Artificial urinary sphincters (AUS) are considered standard of care in men with moderate to severe urinary incontinence following radical prostatectomy; however, the evidence to support this technology is limited and considered of very low quality. AUS for men with such moderate to severe urinary incontinence is recommended by expert groups and is covered by private payers. AUS for urinary incontinence in women has little or no evidence to support its use, but is recommended by trusted sources and covered by private payers for women with intractable urinary incontinence who have failed previous surgery, behavioral and pharmacologic therapy.

Currently, initial placement of AUS is not paired with urinary incontinence on the Prioritized List. However, if the patient already has an AUS, removal as well as removal and replacement are covered. AUS currently also appears on several lines with no appropriate diagnoses, as AUS is only used for urinary incontinence caused by intrinsic sphincter deficiency.

HERC staff recommendations:

1) Remove the CPT codes for insertion/removal/reinsertion of artificial urinary sphincters (CPT 53445-53449; HCPCS C1815) from lines 71 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES, 87 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM, and 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
    a. Lack of appropriate diagnoses on these lines; the only appropriate diagnosis to pair is ICD-10 N36.42 Intrinsic sphincter deficiency (ISD)
2) Add CPT codes for insertion of AUS to line 453 URINARY INCONTINENCE
    a. CPT 53445 Insertion of inflatable urethral/bladder neck sphincter, including placement of pump, reservoir, and cuff
    b. CPT 53447 Removal and replacement of inflatable urethral/bladder neck sphincter including pump, reservoir, and cuff at the same operative session
    c. CPT 53449 Repair of inflatable urethral/bladder neck sphincter, including pump, reservoir, and cuff
    d. HCPCS C1815 Prosthesis, urinary sphincter (implantable)
3) Keep removal and removal/replacement CPT codes for AUS (CPT 53446, 53448) on line 453 URINARY INCONTINENCE and on line 422 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
4) Add a new guideline to line 453 as shown below
    a. Requirements based on standard commercial insurance criteria

    GUIDELINE NOTE XXX ARTIFICIAL URINARY SPHINCTERS

    Line 452

    Artificial urinary sphincters are included on this line only for patients with intrinsic sphincter deficiency with any of the following indications:

        1) Children with intractable urinary incontinence due to intrinsic sphincter deficiency who are refractory to behavioral or pharmacological therapies and are unsuitable candidates for other types of surgical procedures for correction of urinary incontinence; *or*

2) Patients who are 6 or more months post-prostatectomy who have had no improvement in the severity of urinary incontinence despite trials of behavioral and pharmacological therapies; *or*
3) Members with epispadias-exstrophy in whom bladder neck reconstruction has failed; *or*
4) Women with intractable urinary incontinence who have failed behavioral, pharmacological, and other surgical treatments.

Surgery for stress urinary incontinence due to presumed sphincter deficiency after prostate surgery (Review)

Silva LA, Andriolo RB, Atallah ÁN, da Silva EMK

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 9

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[Intervention Review]

Surgery for stress urinary incontinence due to presumed sphincter deficiency after prostate surgery

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ABSTRACT

Background

Incontinence after prostatectomy for benign or malignant disease is a well-known and often a feared outcome. Although small degrees of incidental incontinence may go virtually unnoticed, larger degrees of incontinence can have a major impact on a man's quality of life.

Conceptually, post-prostatectomy incontinence may be caused by sphincter malfunction or bladder dysfunction, or both. Most men with post-prostatectomy incontinence (60% to 100%) have stress urinary incontinence, which is involuntary urinary leakage on effort or exertion, or on sneezing or coughing. This may be due to intrinsic sphincter deficiency and may be treated with surgery for optimal management of incontinence. Detrusor dysfunction is more common after surgery for benign prostatic disease.

Objectives

To determine the effects of surgical treatment for urinary incontinence related to presumed sphincter deficiency after prostate surgery for:

- men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) - transurethral resection of prostate (TURP), photo vaporisation of the prostate, laser enucleation of the prostate or open prostatectomy - and

- men with prostate cancer - radical prostatectomy (retropubic, perineal, laparoscopic, or robotic).

Search methods

We searched the Cochrane Incontinence Group Specialised Register, which contains trials identified from Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE in process, ClinicalTrials.gov, and handsearching of journals and conference proceedings (searched 31 March 2014); MEDLINE (January 1966 to April 2014); EMBASE (January 1988 to April 2014); and LILACS (January 1982 to April 2014). We handsearched the reference lists of relevant articles and conference proceedings. We contacted investigators to locate studies.

Selection criteria

Randomised or quasi-randomised trials that include surgical treatments of urinary incontinence after prostate surgery.

Data collection and analysis

Two authors independently screened the trials identified, appraised quality of papers, and extracted data.

Main results

Only one study with 45 participants met the inclusion criteria. Men were divided in two sub-groups (minimal or total incontinence) and each group was randomised to artificial urethral sphincter (AUS) implantation or Macroplastique injection. Follow-up ranged from six to 120 months. In the trial as a whole, the men treated with AUS were more likely to be dry (18/20, 82%) than those who had the injectable treatment (11/23, 46%) (odds ratio (OR) 5.67, 95% confidence interval (CI) 1.28 to 25.10). However, this effect was only statistically significant for the men with more severe ('total') incontinence (OR 8.89, 95% CI 1.40 to 56.57) and the CIs were wide. There were more severe complications in the group undergoing AUS, and the costs were higher. AUS implantation was complicated in 5/22 (23%) men: the implant had to be removed from one man because of infection and in one man due to the erosion of the cuff, in one man the pump was changed due to mechanical failure, in one man there was migration to the intraperitoneal region, and one man experienced scrotal erosion. In the injectable group, 3/23 (13%) men had a complication: one man treated with Macroplastique injection had to be catheterised because of urinary retention and two men developed urinary tract infections.

Authors' conclusions

The evidence available at present was of very low quality because we identified only one small randomised clinical trial. Although the result was favourable for the implantation of AUS in the group with severe incontinence, this result should be considered with caution due to the small sample size and uncertain methodological quality of the study found.

PLAIN LANGUAGE SUMMARY

Surgery for urinary incontinence due to presumed sphincter deficiency after prostate surgery

Background

Urinary leakage (incontinence) after surgery to remove the prostate (prostatectomy) for benign or malignant disease is a well-known and often feared outcome. Although a small amount of incontinence may not cause a problem, larger degrees of incontinence can have a major impact on a man's quality of life. Improvement in urinary leakage may occur six to 12 months after the prostatic surgery, but for men with persistent bothersome leakage despite conservative therapy such as pelvic floor exercises, surgery may be offered.

Study characteristics

We searched scientific databases for trials that had considered the effectiveness of the surgical treatments of urinary incontinence after prostate surgery in men. The trials had to compare surgical treatment versus no treatment, non-surgical treatment, or another surgical treatment. The evidence is current to April 2014.

Key results and quality of the evidence

There are five main types of surgery and, despite some of them being in use since the 1990s, we found only one trial that met the inclusion criteria. There was very low quality evidence that the implantation of an artificial urinary sphincter (a manufactured device to prevent urine leaking out) might be more effective than injectable treatment, but with more adverse effects and higher costs. There was no evidence about the other types of surgery.

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European Association of Urology

Platinum Priority – Review – Incontinence

Editorial by Jaspreet S. Sandhu on pp. 690–691 of this issue

The Artificial Urinary Sphincter After a Quarter of a Century: A Critical Systematic Review of Its Use in Male Non-neurogenic Incontinence

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Abstract

Context: The artificial urinary sphincter (AUS) has historically been considered the gold standard for the surgical management of non-neurogenic stress urinary incontinence (SUI) in men. As new surgical alternatives attempt to offer alternatives to treat male SUI, a contemporary assessment of the evidence supporting the use of AUS appears mandatory for clinical decision making.
Objective: To conduct a critical systematic review of long-term outcomes after AUS implantation in male patients with non-neurogenic SUI.
Evidence acquisition: A literature search was conducted in PubMed/Medline and Embase databases using the keywords *urinary incontinence* and *urinary sphincter, artificial* and *male*, restricted to articles published in Dutch, English, French, and German between 1989 and 2011. Studies were included if they reported outcomes after AUS implantation in patients with non-neurogenic SUI with a minimum follow-up of 2 yr. Studies with heterogeneous populations were included if information about non-neurogenic patients was displayed separately.
Evidence synthesis: Twelve reports were identified, gathering data about 623 patients. Only three studies were prospective. Continence, evaluated only by patient-reported pad use and various questionnaires, was achieved in 61–100% of cases (no pad or one pad per day). Dry rates (no pad) were only available in seven studies and varied from 4% to 86%. A pooled analysis showed that infection or erosion occurred in 8.5% of cases (3.3–27.8%), mechanical failure in 6.2% of cases (2.0–13.8%), and urethral atrophy in 7.9% (1.9–28.6%). Reoperation rate was 26.0% (14.8–44.8%). Patient satisfaction was evaluated in four studies with four different tools and seems to improve after AUS implantation.
Conclusions: Quality of evidence supporting the use of AUS in non-neurogenic male patients with SUI is low, based on heterogeneous data, low-quality studies, and mostly out-of-date efficacy outcome criteria. AUS outcomes need to be revisited to be compared with new surgical alternatives, all of which should be prospectively evaluated according to current evidence-based medicine standards.

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Mechanical devices for urinary incontinence in women (Review)

Lipp A, Shaw C, Glavind K

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[Intervention Review]

Mechanical devices for urinary incontinence in women

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ABSTRACT

Background

Incontinence can have a devastating effect on the lives of sufferers with significant economic implications. Non-surgical treatments such as pelvic floor muscle training and the use of mechanical devices are usually the first line of management, particularly when a woman does not want surgery or when she is considered unfit for surgery. Mechanical devices are inexpensive and do not compromise future surgical treatment.

Objectives

To determine whether mechanical devices are useful in the management of adult female urinary incontinence.

Search methods

For this second update we searched the Cochrane Incontinence Group Specialised Register, which contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE in process, ClinicalTrials.gov, WHO ICTRP and handsearching of journals and conference proceedings (searched 21 August 2014), EMBASE (January 1947 to 2014 Week 34), CINAHL (January 1982 to 25 August 2014), and the reference lists of relevant articles.

Selection criteria

All randomised or quasi-randomised controlled trials of mechanical devices in the management of adult female urinary incontinence determined by symptom, sign or urodynamic diagnosis.

Data collection and analysis

The reviewers assessed the identified studies for eligibility and risk of bias and independently extracted data from the included studies. Data analysis was performed using RevMan software (version 5.3).

Main results

One new trial was identified and included in this update bringing the total to eight trials involving 787 women. Three small trials compared a mechanical device with no treatment and although they suggested that use of a mechanical device might be better than no treatment, the evidence for this was inconclusive. Four trials compared one mechanical device with another. Quantitative synthesis of data from these trials was not possible because different mechanical devices were compared in each trial using different outcome

measures. Data from the individual trials showed no clear difference between devices, but with wide confidence intervals. One trial compared three groups: a mechanical device alone, behavioural therapy (pelvic floor muscle training) alone and behavioural therapy combined with a mechanical device. While at three months there were more withdrawals from the device-only group, at 12 months differences between the groups were not sustained on any measure.

Authors' conclusions

The place of mechanical devices in the management of urinary incontinence remains in question. Currently there is little evidence from controlled trials on which to judge whether their use is better than no treatment and large well-conducted trials are required for clarification. There was also insufficient evidence in favour of one device over another and little evidence to compare mechanical devices with other forms of treatment.

PLAIN LANGUAGE SUMMARY

Mechanical devices for urinary incontinence in women

Urinary incontinence is involuntary loss of urine. The common types are stress and urge incontinence. Mechanical devices are made of plastic or other materials. They are placed within the urethra or vagina in order to stop or control the leakage of urine. This review of trials found that using mechanical devices might be better than no treatment but the evidence is weak. There was not enough evidence to recommend any specific type of device or to show whether mechanical devices are better than other forms of treatment such as pelvic floor muscle training.

BACKGROUND

Description of the condition

Efficient urinary control depends on normal functioning detrusor (bladder) muscles, nerves, proximal urethral support, bladder neck closure and a normal urethra (Bourcier 1995).

Stress urinary incontinence is the most common type of incontinence, occurring in about half of incontinent women when lack of support at the bladder neck inhibits urethral closure. As a result, activities that increase intra-abdominal pressure can cause involuntary leakage during effort, exertion, sneezing or coughing. Urgency urinary incontinence accounts for around 10% of incontinence and occurs when involuntary detrusor muscle contraction causes a rise in intravesical (bladder) pressure, a condition known as detrusor overactivity. In another 30% of cases, both stress and urgency urinary incontinence are present, with either type being predominant, known as mixed urinary incontinence (Hannestad 2000, Hay-Smith 2009,)

It is widely believed that the most effective treatment for severe or persistent stress urinary incontinence is surgery (Downs 1996). Nevertheless, to avoid surgical risk, non-surgical measures are usually the first line of management for stress urinary incontinence. Non-surgical treatments include lifestyle interventions (such as weight reduction), pelvic floor muscle training (PFMT; Dumoulin 2014), vaginal cones (Herbison 2013), electrical stimulation devices (Berghmans 2013), oral medication (for example alpha-adrenergic agonists (Alhasso 2005) or selective noradrenaline reuptake inhibitors (Mariappan 2005)), scheduled voiding regimens (Ostaszkiewicz 2004), local or systemic oestrogen treatment (Cody 2012) and mechanical devices within the urethra or the vagina (the subject of the current review). These modalities, which might be able to provide some extrinsic support for the bladder neck and urethra, are relatively inexpensive and do not compromise future surgical treatment.

Description of the intervention

The use of mechanical devices for urinary incontinence in women has been said to date back to Egyptian times (Edwards 1970). Despite this long tradition, and perhaps because of the lack of evidence, mechanical devices are not often used in the management of incontinence today.

Over the past three decades efforts have been made to develop devices with evidence-based designs to control urinary incontinence. The devices that have been used include:

- standard contraceptive diaphragm (Realini 1990; Suarez 1991);

Guidelines on Urinary Incontinence

M.G. Lucas (Chair), D. Bedretdinova (Guidelines Associate), L.C. Berghmans, J.L.H.R. Bosch, F.C. Burkhard, F. Cruz, A.K. Nambiar, C.G. Nilsson, A. Tubaro, R.S. Pickard

European Association of Urology

TABLE OF CONTENTS PAGE

1. INTRODUCTION 6
1.1 Aim 6
1.1.1 Use in different healthcare settings and by healthcare professionals 6
1.2 Publication history 6
1.3 Panel composition 7

2. METHODS 7
2.1 PICO questions 7
2.2 Search strategies 7
2.3 Terminology 8

3. DIAGNOSTIC EVALUATION 9
3.1 History and physical examination 9
3.2 Patient questionnaires 9
3.2.1 Questions 9
3.2.2 Evidence 9
3.3 Voiding diaries 12
3.3.1 Questions 12
3.3.2 Evidence 12
3.4 Urinalysis and urinary tract infection 12
3.4.1 Questions 12
3.4.2 Evidence 13
3.5 Post-voiding residual volume 13
3.5.1 Question 13
3.5.2 Evidence 13
3.6 Urodynamics 13
3.6.1 Question 14
3.6.2 Evidence 14
3.6.2.1 Variability 14
3.6.2.2 Diagnostic accuracy 14
3.6.2.3 Does urodynamics influence the outcome of conservative therapy 14
3.6.2.4. Does urodynamics influence the outcome of surgery for stress urinary incontinence? 14
3.6.2.5 Does urodynamics help to predict complications of surgery? 14
3.6.2.6 Does urodynamics influence the outcome of surgery for detrusor-overactivity? 15
3.6.2.7 Does urodynamics influence the outcome of treatment for post-prostatectomy urinary incontinence in men? 15
3.7 Pad testing 15
3.7.1 Question 16
3.7.2 Evidence 16
3.8 Imaging 16
3.8.1 Questions 16
3.8.2 Evidence 16

4. DISEASE MANAGEMENT 17
4.1 Conservative management 17
4.1.1 Simple clinical interventions 17
4.1.1.1 Underlying disease/cognitive impairment 17
4.1.1.1.1 Question 17
4.1.1.1.2 Evidence 17
4.1.1.2 Adjustment of medication 18
4.1.1.2.1 Question 18
4.1.1.2.2 Evidence 18
4.1.1.3 Constipation 18
4.1.1.3.1 Question 18
4.1.1.3.2 Evidence 18
4.1.1.4 Containment 19

4.1.1.4.1 Question 19
4.1.1.4.2 Evidence 19
4.1.1.4.3 Question 19
4.1.1.4.4 Evidence 19
4.1.1.4.5 Question 19
4.1.1.4.6 Evidence 19
4.1.1.4.7 Question 20
4.1.1.4.8 Evidence 20
4.1.2 Lifestyle interventions 20
4.1.2.1 Caffeine reduction 20
4.1.2.1.1 Question 20
4.1.2.1.2 Evidence 20
4.1.2.2 Physical exercise 21
4.1.2.2.1 Question 21
4.1.2.2.2 Evidence 21
4.1.2.3 Fluid intake 21
4.1.2.3.1 Question 21
4.1.2.3.2 Evidence 21
4.1.2.4 Obesity and weight loss 22
4.1.2.4.1 Question 22
4.1.2.4.2 Evidence 22
4.1.2.5 Smoking 22
4.1.2.5.1 Question 22
4.1.2.5.2 Evidence 22
4.1.2.6 Recommendations for lifestyle interventions 22
4.1.3 Behavioural and Physical therapies 22
4.1.3.1 Bladder Training 23
4.1.3.1.1 Questions 23
4.1.3.1.2 Evidence 23
4.1.3.2 Pelvic floor muscle training (PFMT) 23
4.1.3.2.1 Question 23
4.1.3.2.2 Evidence 24
4.1.3.2.3 Efficacy of PFMT in SUI, UUI and MUI in women 24
4.1.3.2.4 PFMT in the elderly 24
4.1.3.2.5 PFMT and Radical prostatectomy 24
4.1.3.3 Prompted voiding 25
4.1.3.3.1 Electrical stimulation 25
4.1.3.3.2 Question 25
4.1.3.3.3 Evidence 25
4.1.3.4 Posterior tibial nerve stimulation 26
4.1.3.4.1 Question 26
4.1.3.4.2 Evidence 26
4.1.3.5 Recommendations for behavioural and physical therapies 27
4.1.4 Conservative therapy in mixed urinary incontinence 27
4.1.4.1 Question 27
4.1.4.2 Evidence 27
4.1.4.3 Recommendations conservative therapy in mixed urinary incontinence 27
4.2 Pharmacological management 28
4.2.1 Antimuscarinic drugs 28
4.2.1.1 Question 28
4.2.1.2 Evidence 28
4.2.2 Comparison of antimuscarinic agents 29
4.2.2.1 Question 29
4.2.2.2 Evidence 29
4.2.3 Antimuscarinic drugs versus non-drug treatment 30
4.2.3.1 Question 30
4.2.3.2 Evidence 30
4.2.3.3 Recommendations for antimuscarinic drugs 31
4.2.4 Antimuscarinic agents: adherence and persistence 31

4.2.4.1 Question 31
4.2.4.2 Evidence 31
4.2.5 Antimuscarinic agents, the elderly and cognition 32
4.2.5.1 Question 32
4.2.5.2 Evidence 32
4.2.5.2.1 Oxybutynin 32
4.2.5.2.2 Solifenacin 32
4.2.5.2.3 Tolterodine 32
4.2.5.2.4 Darifenacin 32
4.2.5.2.5 Trospium chloride 32
4.2.5.2.6 Fesoterodine 33
4.2.5.2.7 Duloxetine in the elderly 33
4.2.5.2.8 Mirabegron 33
4.2.5.2.9 Applicability of evidence to general elderly population 33
4.2.5.2.10 Anticholinergic load 33
4.2.5.2.11 Question 33
4.2.5.2.12 Evidence 33
4.2.5.2.13 Additional recommendations for antimuscarinic drugs in the elderly 34
4.2.6 Mirabegron 34
4.2.7 Drugs for stress urinary incontinence 34
4.2.7.1 Questions 35
4.2.7.2 Evidence 35
4.2.8 Oestrogen 36
4.2.8.1 Questions 36
4.2.8.2 Evidence 36
4.2.9 Desmopressin 36
4.2.9.1 Questions 36
4.2.9.2 Evidence 37
4.2.9.2.1 Improvement of incontinence 37
4.2.9.2.2 Monitoring for hyponatraemia 37
4.2.10 Drug treatment in mixed urinary incontinence 37
4.2.10.1 Question 37
4.2.10.2 Evidence 37
4.3 Surgical management 38
4.3.1 Women with uncomplicated stress urinary incontinence 38
4.3.1.1 Mid-urethral slings 38
4.3.1.1.1 Questions 38
4.3.1.1.2 Evidence 38
4.3.1.2 Adjustability 39
4.3.1.2.1 Questions 39
4.3.1.2.2 Evidence 39
4.3.1.3 Single-incision slings 39
4.3.1.3.1 Questions 39
4.3.1.3.2 Evidence 39
4.3.1.4 Open and laparoscopic surgery for stress urinary incontinence 41
4.3.1.4.1 Question 41
4.3.1.4.2 Evidence 41
4.3.1.5 Bulking agents 42
4.3.1.5.1 Question 42
4.3.1.5.2 Evidence 42
4.3.2 Complicated stress urinary incontinence in women 43
4.3.2.1 Colposuspension or sling following failed surgery 43
4.3.2.1.1 Question 43
4.3.2.1.2 Evidence 43
4.3.2.2 External compression devices 44
4.3.2.2.1 Questions 44
4.3.2.2.2 Evidence 44
4.3.3 Women with both stress urinary incontinence and pelvic organ prolapse 45
4.3.3.1 Questions 45

4.3.3.2 Evidence 45
4.3.4 Urethral diverticulum 47
4.3.4.1 Surgical treatment 47
4.3.5 Men with stress urinary incontinence 48
4.3.5.1 Bulking agents in men 48
4.3.5.1.1 Question 48
4.3.5.1.2 Evidence 48
4.3.5.2 Fixed male sling 48
4.3.5.2.1 Question 48
4.3.5.2.2 Evidence 48
4.3.5.3 Adjustable slings in males 49
4.3.5.3.1 Question 49
4.3.5.3.2 Evidence 49
4.3.5.4 Compression devices in males 49
4.3.5.4.1 Question 49
4.3.5.4.2 Evidence 50
4.3.6 Surgical interventions for refractory detrusor-overactivity 51
4.3.6.1 Bladder wall injection of botulinum toxin A 51
4.3.6.1.1 Question 51
4.3.6.1.2 Evidence 51
4.3.6.2 Sacral nerve stimulation (neuromodulation) 52
4.3.6.2.1 Question 52
4.3.6.2.2 Evidence 52
4.3.6.3 Cystoplasty/urinary diversion 52
4.3.6.3.1 Augmentation cystoplasty 52
4.3.6.3.2 Detrusor myectomy (bladder auto-augmentation) 53
4.3.6.3.3 Urinary diversion 53
4.3.7 Surgery in patients with mixed urinary incontinence 54
4.3.7.1 Question 54
4.3.7.2 Evidence 54
4.3.8 Surgery for urinary incontinence in the elderly 54

5. REFERENCES 60

6. CONFLICT OF INTEREST 75

1. INTRODUCTION

Urinary incontinence (UI) is an extremely common complaint in every part of the world. It causes a great deal of distress and embarrassment, as well as significant costs, to both individuals and societies. Estimates of prevalence vary according to the definition of incontinence and the population studied. However, there is universal agreement about the importance of the problem in terms of human suffering and economic cost.

1.1 Aim

These Guidelines from the European Association of Urology (EAU) Working Panel on Urinary Incontinence are written by urologists primarily for urologists, though we recognise that they are likely to be referred to by other professional groups. They aim to provide sensible and practical evidence-based guidance on the clinical problem of UI rather than an exhaustive narrative review. Such a review is already available from the International Consultation on Incontinence [1], and so the EAU Guidelines do not describe the causation, basic science, epidemiology and psychology of UI. The focus of these Guidelines is entirely on assessment and treatment reflecting clinical practice. The Guidelines also do not consider patients with UI caused by neurological disease, or in children, as this is covered by complementary EAU Guidelines [2, 3].

The EAU Panel knew that they would find little evidence for some issues and a lot of evidence for others. This difference, to some extent, reflects the greater funding available for industry-sponsored trials of drugs, the results of which are required for licensing in Europe and the USA. The less stringent regulatory requirements for the introduction of new devices or surgical techniques means that there are far fewer high-quality studies regarding these interventions. Although the lack of high-quality evidence means that judgements about the worth of interventions are prone to bias, the Panel took the view that clinicians still require some guidance concerning clinical practice. In these circumstances, we have summarised the available evidence and made recommendations based on expert opinion, with uncertainty reflected by a lower grade of recommendation.

The elderly

The panel decided to include a separate but complimentary set of recommendations referring to the elderly population within each section. Older people with UI deserve special consideration for a number of reasons. Physiological changes with natural ageing mean that all types of UI become more common with increasing age. Urinary incontinence commonly co-exists with other comorbid conditions, reduced mobility, and impaired cognition and may require specific interventions, such as assisted toileting.

For the elderly person expectations of assessment and treatment may need to be modified to fit in with specific circumstances, needs, and preferences, while taking into account any loss of capacity for consent. When the urologist is dealing with a frail elderly patient with urinary incontinence, collaboration with other healthcare professionals such as elderly care physicians is recommended.

*1.1.1 **Use in different healthcare settings and by healthcare professionals***

The Panel recognises that a patient's first point of contact may not always be a urologist, and that the healthcare professional delivering specific treatments such as physiotherapy, may also not be a urologist. For this reason, some healthcare professionals may find that the Guidelines do not explain a particular topic in enough detail for their needs, e.g. delivery modalities for pelvic floor muscle training (PFMT).

1.2 Publication history

The 2012 edition of these Guidelines was completely rewritten using new methodology and based on new searches up to July 2011 and those carried out for ICUD and NICE (2006) documents.

The 2013 edition was updated with searches to September 2012 and included a new appendix on non obstetric fistula derived from the ICUD 2013, but the contained evidence has not yet been assessed according to the EAU methodology (see Appendix A available online at www.uroweb.org). In the 2014 edition additional searches were done for patient reported outcome measures (PROMS), urethral diverticulum, containment, prolapse reduction stress test, anticholinergic load, and mirabegron. In this 2015 edition searches were done on the 'Assessment and Diagnosis' chapter and on the subject of mirabegron in the 'Drug Treatment' chapter (Table 1).

A quick reference guide, presenting the main findings of the Urinary Incontinence Guidelines, is also available, as well as two scientific publications in the journal of the EAU, European Urology [4, 5]. All texts can be viewed and downloaded for personal use at the society website:
http://www.uroweb.org/guidelines/online-guidelines/.

This document was peer-reviewed prior to publication.

1.3 Panel composition

The EAU Urinary Incontinence Panel consists of a multidisciplinary group of experts, including urologists, a gynaecologist and a physiotherapist.

2. METHODS

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

This 2015 version has been updated and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format.

The current Guidelines provide:

- A clear pathway (algorithm) for common clinical problems. This can provide the basis for thinking through a patient's management and also for planning and designing clinical services.
- A brief but authoritative summary of the current state of evidence on clinical topics, complete with references to the original sources.
- Clear guidance on what to do or not to do, in most clinical circumstances. This should be particularly helpful in those areas of practice for which there is little or no high-quality evidence.

2.1 PICO questions

The 'PICO' framework was used to develop a series of clinical questions that would provide the basis of presentation of the guidelines [6, 7]. There are four elements to each clinical question:

- Population (P)
- Intervention (I)
- Comparison (C)
- Outcome (O)

The wording of each PICO is important because it informs the subsequent literature research. For each search, the EAU Panel listed every possible wording variation.

In these Guidelines, the four traditional domains of urological practice are presented as separate chapters, namely assessment and diagnosis, conservative management, drug therapy and surgical treatments.

In this third edition of these new EAU Guidelines for Urinary Incontinence, the Panel has focused largely on the management of a 'standard' patient. The Panel has referred in places to patients with 'complicated incontinence', by which we mean patients with associated morbidity, a history of previous pelvic surgery, surgery for UI, radiotherapy and women with associated genitourinary prolapse. This third edition does not review the prevention of UI, and the management of fistula (available online at the society website). These issues will be fully addressed using our standard methodology in future editions.

2.2 Search strategies

A number of significant narrative reviews, systematic reviews and guidance documents have been produced within the last few years. The Panel agreed that the literature searches carried out by these reviews would be accepted as valid. Thus, for each PICO question, a search was carried out with a start date that was the same as the cut-off date for the search associated with the most recent systematic review for the PICO topic. This pragmatic selection approach, while being a compromise and open to criticism, made the task of searching the literature for such a large subject area possible within the available resources. For each section, the latest cut-off date for the relevant search is indicated. Thus, for each PICO, a subsequent literature search was carried out (confined to Medline and Embase and to English language articles), which produced an initial list of abstracts. The abstracts were each assessed by two Panel members, who selected the studies relevant to the PICO question, and the full text for these were retrieved (Table 1).

Table 1: Initial list of abstracts	
Chapter	*Latest 'cut-off' date for search*
Assessment and diagnosis	- PROMS & Questionnaires: 30 April 2014 - Urinalysis and urinary tract infection: 1 May 2014 - Post-voiding residual volume: 12 May 2014 - Pad testing: 29 September 2014 - Urodynamics: 7 May 2014 - Imaging: 12 May 2014
Conservative therapy	28 June 2012 - Containment: 10 July 2013
Drug therapy	28 June 2012 - Anticholinergic load: 29 April 2013 - Mirabegron: 25 April 2014
Surgical therapy	9 July 2012 - POP & OAB: 29 April 2013 - Prolapse reduction stress test: 16 May 2013 - Urethral diverticulum: 7 May 2013

Each PICO was then assigned to a Panel member, who read the papers and extracted the evidence for incorporation into standardised evidence tables. From 2012 onwards we have used a purpose designed web based application in which original papers are downloaded and appraised online according to a standardised format which is based on Scottish Intercollegiate Guidelines Network (SIGN) documents. The web application is progressively populated with evidence appraisals which can be displayed in tabular format showing summaries of data quality as well as summaries of outcomes.

The existing evidence from previous systematic reviews and new evidence were then discussed for each PICO in turn at a Panel meeting generating consensus conclusions. To help standardise the approach, modified process forms (data extraction and considered judgment) from SIGN were used.

The quality of evidence for each PICO is commented on in the text, aiming to synthesise the important clinical messages from the available literature and is presented as a series of levels of evidence summaries in the EAU format as described in the Introduction chapter of the complete Guidelines book.

From the evidence summaries, the Panel then produced a series of action-based recommendations, again graded according to EAU standards. These grades aim to make it clear what the clinician should or should not do in clinical practice, not merely to comment on what they might do.

The Panel has tried to avoid extensive narrative text. Instead, algorithms are presented for both initial and specialised management of men and women with non-neurogenic UI. Each decision node of these algorithms is clearly linked back to the relevant evidence and recommendations.

It must be emphasised that clinical guidelines present the best evidence available to the Panel at the time of writing. There remains a need for ongoing re-evaluation of the current guidelines by the Panel. However, adherence to guideline recommendations will not necessarily result in the best outcomes for patients. Guidelines can never replace clinical expertise when making treatment decisions for individual patients; they aim to focus decisions by addressing key clinical questions, and provide a strong basis for management decisions. Clinical decisions must also take into account the patient's personal values, preferences and specific circumstances.

2.3 Terminology

Evidence summaries provide a succinct summary of what the currently available evidence tells us about an individual clinical question. They are presented according to the levels of evidence used by the EAU.

Recommendations have been deliberately written as 'action-based' sentences. The following words or phrases are used consistently throughout the Guidelines, as follows:

- **Consider** an action. This word is used when there is not enough evidence to say whether the action causes benefit or risk to the patient. However, in the opinion of the Panel, the action may be justified in some circumstances. Action is optional.
- **Offer** an action. This word is used when there is good evidence to suggest that the action is effective, or that, in the opinion of the Panel, it is the best action. Action is advisable.

- **Carry out (perform)** an action. **Do** something. This phrase is used when there is strong evidence that this is the only best action in a certain clinical situation. Action is mandatory.
- **Do not** perform (i.e. avoid) an action. This phrase is used when there is high-level evidence that the action is either ineffective or is harmful to the patient. Action is contraindicated.

3. DIAGNOSTIC EVALUATION

3.1 History and physical examination

Taking a careful clinical history is fundamental to the clinical process. Despite the lack of formal evidence, there is universal agreement that taking a history should be the first step in the assessment of anyone with UI. The history should include details of the type, timing and severity of UI, associated voiding and other urinary symptoms. The history should allow UI to be categorised into stress urinary incontinence (SUI), urgency urinary incontinence (UUI) or mixed urinary incontinence (MUI). It should also identify patients who need rapid referral to an appropriate specialist. These include patients with associated pain, haematuria, a history of recurrent urinary tract infection (UTI), pelvic surgery (particularly prostate surgery) or radiotherapy, constant leakage suggesting a fistula, voiding difficulty or suspected neurological disease. In women, an obstetric and gynaecological history may help to understand the underlying cause and identify factors that may impact on treatment decisions. The patient should also be asked about other ill health and for the details of current medications, as these may impact on symptoms of UI.

Similarly, there is little evidence that carrying out a clinical examination improves care, but wide consensus suggests that it remains an essential part of assessment of people with UI. It should include abdominal examination, to detect an enlarged bladder or other abdominal mass, and perineal and digital examination of the rectum (prostate) and/or vagina. Examination of the perineum in women includes an assessment of oestrogen status and a careful assessment of any associated pelvic organ prolapse (POP). A cough test may reveal SUI if the bladder is sufficiently full and pelvic floor contraction together with urethral mobility can be assessed digitally.

3.2 Patient questionnaires

This section includes symptom scores, symptom questionnaires, scales, indexes, PROMs and health-related quality of life (HRQoL) measures. The latter include generic or condition specific.

Questionnaires should have been validated for the language in which they are being used, and, if used for outcome evaluation, must have been shown to be sensitive to change. The methodology for questionnaire development was reviewed in the 5th International Consultation on Incontinence in 2012 [8].

*3.2.1 **Questions***

- In patients with UI, can the use of Questionnaires/PROMS differentiate between stress, urgency and mixed incontinence, and does this differentiation impact on QoL after treatment?
- In adults with UI, does assessment using either urinary symptom or QoL questionnaires improve treatment outcome for UI?
- In adults with UI, does assessment of the patient perspective (concerns or expectations) improve patient outcomes, regarding either urinary symptoms or QoL, compared to no patient-reported assessment?

*3.2.2 **Evidence***

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs, most have taken place in adults without UI. This limits the extent to which results and conclusions from these studies can be applied in adults with UI. Some questionnaires (QUID, 3IQ) have potential to discriminate UI types in women [9, 10]. In men ICIQ-UI-SF score does not differentiate UI types [11].

Some are responsive to change and may be used to measure outcomes, though evidence on their sensitivity is inconsistent [12-14].

No evidence was found to indicate whether use of QoL or condition specific questionnaires have an impact on outcome of treatment.

The table shows a summary of the ICUD review 2012 with recent additions. Criteria on which questionnaires are assessed include validity, reliability and resposiveness to change.

	Category A (all 3 criteria fulfilled)*	Category B (2 criteria fulfilled)*	Category C (only 1 criterion fulfilled)*
Symptom measures and health related QOL measures	ICIQ-UI Short Form, ICIQFLUTS,ICIQ-MLUTS IIQ and IIQ-7, I-QOL (ICIQ-Uqol), ISS, KHQ, LIS (?-interview), N-QoL, OAB-q SF, OAB-q (ICIQ-OABqol), PFDI and PFDI-20, PFIQ and PFIQ-7, PRAFAB, UISS;	Contilife, EPIQ, LUTS tool IOQ,YIPS;	ABSST ISI, ISQ, UIHI, UIQ
Measure of patient satisfaction (patient's measure of treatment satisfaction)	BSW, OAB-S, OABSAT-q, TBS	PPQ	EPI, GPI, PSQ
Goal attainment scales		SAGA	
Screening tools (used to identify patients with UI)	B-SAQ, OAB-SS, OABV8, OAB-V3, QUID	ISQ, USP	3IQ, CLSS, MESA, PUF
patient symptom scale			
Assessment of symptom bother and overall bother	PPBC, UDI or UDI-6, LUSQ, PGI-I and PGI-S;	PFBQ, SSI and SII	PMSES, POSQ, UI-4
Assessment of the impact of urgency	IUSS, U-IIQ, UU Scale, U-UDI	PPIUS, SUIQ, UPScore, UPScale, UQ, USIQ-QOL, USIQ-S, USS	
Questionnaires to assess sexual function and urinary symptoms		FSFI, ICIQ-VS, PISQ, SQoL-F	SFQ
Treatment adherence measures		MASRI	

** Criteria on which questionnaires are assessed include validity, reliability and resposiveness to change.*

3IQ = Three Incontinence Questions Questionnaire ABSST = Actionable Bladder Symptom Screening Tool B-SAQ = Bladder Self-Assessment Questionnaire BSW = Benefit, Satisfaction with treatment and Willingness CLSS = Core Lower Urinary Tract Symptom Score Contlife® = Quality of Life Assessment Questionnaire Concerning Urinary Incontinence EPIQ = Epidemiology of Prolapse and Incontinence Questionnaire FSFI = Female Sexual Function Index ICIQ = International Consultation on Incontinence Modular Questionnaire ICIQ-FLUTS = ICIQ-Female Lower Urinary Tract Symptoms ICIQ-MLUTS = ICIQ-Male Lower Urinary Tract Symptoms ICIQ-VS = International Consultation on Incontinence Questionnaire – Vaginal Symptoms IIQ (IIQ-7) = Incontinence Impact Questionnaire (short form) IOQ = Incontinence Outcome Questionnaire I-QOL (ICIQ-Uqol) = Urinary Incontinence-Specific Quality of Life Instrument ISI = Incontinence Severity Index ISQ = Incontinence Stress Index ISS = Incontinence Symptom Severity Index IUSS = Indevus Urgency Severity KHQ = King's Health Questionnaire LIS = Leicester Impact Scale LUSQ = Leicester Urinary Symptom Questionnaire LUTS Tool = Lower Urinary Tract Symptoms Tool MASRI = Medication Adherence Self-Report Inventory MESA = Medial Epidemiological and Social Aspects of Aging Questionnaire N-QoL = Nocturia Quality of Life Questionnaires OAB-q (ICIQ-OABqol) = Overactive Bladder Questionnaire OAB-S = Overactive Bladder Satisfaction measure OAB-SAT-q = OAB Satisfaction questionnaire OAB-SS = Overactive Bladder Symptom Score OAB-v3 = OAB short form OAB-v8 = OAB Awareness Tool	PFBQ = Pelvic Floor Bother Questionnaire PFDI (PFDI-20) = Pelvic Floor Distress Inventory (short form) PFIQ (PFIQ-7) = Pelvic Floor Impact Questionnaire (short form) PRAFAB = Protection, Amount, Frequency, Adjustment, Body image) PGI-I and PGI-S = Patient Global Impression of Severity and Improvement PISQ = Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire PMSES = Broome Pelvic Muscle Exercise Self-Efficacy Scale POSQ = Primary OAB Symptom Questionnaire PPBC = Patient Perception of Bladder Condition PPIUS = Patient's Perception of Intensity of Urgency Scale PPQ = Patient Preparation Questionnaire PUF = patient symptom scale (Pelvic Pain, Urgency and Frequency) QUID = Questionnaire for Urinary Incontinence Diagnosis SAGA = Self-Assessment Goal Achievement Questionnaire SQoL-F = Sexual Quality of Life - Female SSI and SII = Symptom Severity Index and Symptom Impact Index for Stress Incontinence in women SUIQ = Stress/Urge Incontinence Questionnaire TBS = Treatment Benefit Scale UDI (UDI-6) = Urogenital Distress Inventory (-6) UI-4 = Urinary Incontinence -4 Questionnaire UIHI = Urinary Incontinence Handicap Inventory U-IIQ = Urge Incontinence Impact Questionnaire UIQ = Urinary Incontinence Questionnaire UISS = Urinary Incontinence Severity Score UPScale = Urgency Perception Scale UPScore = Urgency Perception Score UQ = Urgency Questionnaire USIQ-QOL = Urgency Severity & Intensity Questionnaire: Symptom Severity USIQ-S = Urgency Severity & Intensity Questionnaire: Quality of Life USP = Urinary Symptom Profile USS = Urinary Sensation Scale

To date, there is no one questionnaire that fulfills all requirements for assessment of people with UI. The clinician must evaluate the tools that exist to use alone or in combination for assessment, and monitoring of treatment outcome [15].

The questionnaires can be found on the following internet resource sites: www.iciq.net, www.proqolid.org, www.mapi-institute.com, www.pfizerpatientreportedoutcomes.com, www.ncbi.nlm.nih.gov.

Evidence summary	**LE**
Validated condition specific symptom scores assist in the screening for, and categorisation of UI.	3
Validated symptom scores measure the severity of UI.	3
Both condition specific and general health status questionnaires measure current health status, and change following treatment.	3

Recommendation	GR
Use a validated and appropriate questionnaire when standardised assessment is required	B*

** Recommendation based on expert opinion.*

3.3 Voiding diaries

Measurement of the frequency and severity of LUTS is an important step in the evaluation and management of lower urinary tract dysfunction, including UI. Voiding diaries are a semi-objective method of quantifying symptoms, such as frequency of urinary incontinence episodes. They also quantify urodynamic variables, such as voided volume and 24-hour or nocturnal total urine volume. Voiding diaries are also known as micturition time charts, frequency/volume charts and bladder diaries.

Discrepancy between diary recordings and the patient rating of symptoms, e.g. frequency or UI, can be useful in patient counselling. In addition, voided volume measurement can be used to support diagnoses, such as overactive bladder (OAB) or polyuria. Diaries can also be used to monitor treatment response and are widely used in clinical trials. In patients with severe UI, a voiding diary is unlikely to accurately report 24 hour urine output and so voided volume may be lower than total bladder capacity.

3.3.1 Questions

- In adults with UI, what are the reliability, diagnostic accuracy and predictive value of a voiding diary compared to patient history or symptom score?

3.3.2 Evidence

Two recent articles have suggested a consensus has been reached in the terminology used in voiding diaries [16, 17]:

- **Micturition time charts** record only the times of micturitions for a minimum of 24 continuous hours.
- **Frequency volume charts** record voided volumes and times of micturitions for a minimum of 24 hours.
- **Voiding diaries** include information on incontinence episodes, pad usage, fluid intake, degree of urgency and degree of UI.

Several studies have compared patients' preference for, and the accuracy of, electronic and paper voiding diaries in voiding dysfunction [18-22]. Several studies have compared shorter (3 or 5 days) and longer diary durations (7 days) [23-28].

Two studies have demonstrated the reproducibility of voiding diaries in both men and women [23, 28]. Further studies have demonstrated variability of diary data within a 24-hour period and compared voided volumes recorded in diaries with those recorded on uroflowmetry [29, 30]. Other studies have investigated the correlation between data obtained from voiding diaries and standard symptom evaluation [31-34].

Evidence summary	LE
Voiding diaries of 3-7 days duration are a reliable tool for the objective measurement of mean voided volume, daytime and night-time frequency and incontinence episode frequency.	2b
Voiding diaries are sensitive to change and are a reliable measure of outcome.	2b

Recommendations	GR
Ask patients with urinary incontinence to complete a voiding diary to evaluate co-existing storage and voiding dysfunction.	A
Use a diary duration of between 3 and 7 days.	B

3.4 Urinalysis and urinary tract infection

Reagent strip ('dipstick') urinalysis may indicate urinary tract infection (UTI), proteinuria, haematuria or glycosuria requiring further assessment. Refer to the Urological Infections Guideline for diagnosis and treatment of UTI [35].

3.4.1 Questions

- In adults with UI, what is the diagnostic accuracy of urinalysis to detect UTI?
- In adults with UI does treatment of UTI or asymptomatic bacteriuria cure or improve UI compared to no treatment?

3.4.2 ***Evidence***

Urinalysis negative for nitrite and leucocyte esterase has high specificity to exclude UTI in people with UI [36] and despite lower sensitivity should be included, with urine culture when necessary, in the evaluation of all patients with UI. Urinary incontinence may occur during symptomatic UTI [37] and existing UI may worsen during UTI [38]. The rate and severity of UI was unchanged after eradication of asymptomatic bacteriuria in nursing home residents [39].

Evidence summary	**LE**
Urinalysis negative for nitrite and leucocyte esterase reliably excludes UTI.	1
UI may be a symptom during UTI.	3
The presence of a symptomatic UTI worsens symptoms of UI.	3
Elderly nursing home patients with UI do not benefit from treatment of asymptomatic bacteriuria.	2

Recommendations	**GR**
Do urinalysis as a part of the initial assessment of a patient with urinary incontinence.	A*
If a symptomatic urinary tract infection is present with urinary incontinence, reassess the patient after treatment.	A*
Do not routinely treat asymptomatic bacteriuria in elderly patients to improve urinary incontinence.	B

** Recommendation based on expert opinion.*

3.5 Post-voiding residual volume

Post-voiding residual (PVR) volume is the amount of urine that remains in the bladder after voiding. It indicates poor voiding efficiency, which may result from a number of contributing factors. It is important because it may worsen symptoms and, more rarely, may be associated with UTI, upper urinary tract dilatation and renal insufficiency. Both bladder outlet obstruction and detrusor underactivity contribute to the development of PVR. Post-voiding residual can be measured by catheterisation or ultrasound (US). The prevalence of PVR is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume.

3.5.1 ***Question***

In adults with UI, what is the value of measuring PVR?

3.5.2 ***Evidence***

Most studies investigating PVR have not included patients with UI. Although some studies have included women with UI and men and women with LUTS, they have also included children and adults with neurogenic UI. In general, the data on PVR can be applied with caution to adults with non-neurogenic UI. The results of studies investigating the best method of measuring PVR [40-45] have led to the consensus that US measurement of PVR is better than catheterisation.

In peri- and postmenopausal women without significant LUTS or pelvic organ symptoms, 95% of women had a PVR < 100 mL [46]. In women with UUI, a PVR > 100 mL was found in 10% of cases [47]. Other research has found that a high PVR is associated with POP, voiding symptoms and an absence of SUI [46, 48-50].

In women with SUI, the mean PVR was 39 mL measured by catheterisation and 63 mL measured by US, with 16% of women having a PVR > 100 mL [47].

Evidence summary	**LE**
Lower urinary tract symptoms coexisting with UI are associated with a higher rate of post-voiding residual compared to asymptomatic subjects.	2

Recommendations	**GR**
Use ultrasound to measure post-voiding residual.	A
Measure post-voiding residual in patients with urinary incontinence who have voiding symptoms.	B
Measure post-voiding residual when assessing patients with complicated urinary incontinence.	C
Post-voiding residual should be monitored in patients receiving treatments that may cause or worsen voiding dysfunction.	B

3.6 Urodynamics

Urodynamic testing is widely used as an adjunct to clinical diagnosis, in the belief that it may help to provide or confirm diagnosis, predict treatment outcome, or facilitate discussion during a consultation. For all these

reasons, urodynamics is often performed prior to invasive treatment for UI. These Guidelines will focus on invasive tests, including multichannel cystometry, ambulatory monitoring and video-urodynamics, and different tests of urethral function, such as urethral pressure profilometry, Valsalva leak point pressure estimation and retrograde urethral resistance measurement.

3.6.1 ***Question***

In adults with UI, what is the diagnostic accuracy and predictive value of uroflowmetry, i.e. the measurement of maximum urinary flow rate (Q_{max}), and urodynamic testing?

3.6.2 ***Evidence***

3.6.2.1 Variability

In common with most physiological tests there is variability in urodynamics results. Numerous small studies of multichannel cystometry have been done over many years in differing populations. Whilst in healthy women the same session repeatability has been shown to be poor [51], in those with incontinence it may be acceptable [52]. Measurement of urethral closure pressure (MUCP) correlates poorly with incontinence severity [53] and there is conflicting evidence about its reproducibility [54, 55]. One method of recording MUCP cannot be compared meaningfully to another [56].

Abdominal or Valsalva leak point pressures may correlate to incontinence severity [57] but the tests are not standardised and there is no evidence about reproducibility.

No studies on the reliability of ambulatory monitoring were found.

3.6.2.2 Diagnostic accuracy

The diagnostic accuracy of urodynamics is assessed in terms of its correlation with clinical diagnosis and incontinence severity. The problem is that clinical diagnosis and urodynamic findings often do not correlate [58, 59], and normal healthy people may have urodynamic abnormalities.

The diagnostic accuracy of urethral pressure profilmetry [53] and 'Urethral Retro resistance' is generally poor [60]. Urethral reflectometry may have greater diagnostic accuracy but its clinical role remains unclear [61].

Ambulatory urodynamics may detect unexpected physiological variance from normal more often than conventional cystometry, but the clinical relevance of this is uncertain [62, 63].

3.6.2.3 Does urodynamics influence the outcome of conservative therapy

A recent Cochrane review of seven RCTs showed that use of urodynamic tests increased the likelihood of prescribing drugs or avoiding surgery However, there was no evidence that this influence on decision making altered the clinical outcome of treatment [64]. Subanalysis of an RCT comparing fesoterodine to placebo [65] and another dose finding study of botulinum toxin [66] showed no predictive value for treatment response, by the urodynamic diagnosis of DO.

3.6.2.4. Does urodynamics influence the outcome of surgery for stress urinary incontinence?

Post-hoc analysis of surgical RCTs has shown the risk of failure of SUI surgery is higher in women who have worse leakage or urodynamically demonstrable SUI [67].

A high quality RCT (n= 630) compared office evaluation alone to office evaluation and urodynamics in women with clinical demonstrable SUI about to undergo surgery for SUI. Whilst urodynamics changed the clinical diagnosis in 56% of women [68]) there was no difference in levels of UI or any secondary outcome at 12 months' follow-up after surgery [69]. Another similar study was closed with only 59 women [70] after finding no difference in outcome. It was then redesigned to randomise only women (N=109) in whom urodynamic findings were contradictory, to immediate surgery or treatment tailored to urodynamic findings. In this trial, performing immediate surgery irrespective of the result of urodynamics did not result in inferior outcomes [71].

In observational studies there is no consistent correlation between the result of urethral function tests and subsequent success or failure of SUI surgery.

3.6.2.5 Does urodynamics help to predict complications of surgery?

There have been no RCTs designed to answer this question.

The presence of pre-operative DO has consistently been associated with development of postoperative UUI.

Whilst post-hoc analysis of an RCT comparing the autologous fascial sling to Burch colposuspension showed inferior outcomes for women who suffered pre-operative urgency [72]. Pre-operative urodynamics failed to predict this outcome [73].

Whilst low pre-operative flow rate has been shown to correlate with post operative voiding dysfucntion [74, 75], post hoc analysis of two high quality surgical trials showed that no pre-operative urodynamic parameter had the ability to predict post operative voiding dysfunction [76, 77].

3.6.2.6 Does urodynamics influence the outcome of surgery for detrusor-overactivity?

No studies were found on the relationship between urodynamic testing and subsequent surgical outcome for DO. However, most studies reporting surgical outcomes for DO have included only patients with urodynamically proven DO or DO incontinence.

3.6.2.7 Does urodynamics influence the outcome of treatment for post-prostatectomy urinary incontinence in men?

There are no RCTs examining the clinical usefulness of urodynamics in post-prostatectomy UI. Whilst urodynamics will distinguish causes of incontinence, its ability to predict outcome of surgery for incontinence for these men is uncertain [78, 79].

Evidence summary	**LE**
Most urodynamic parameters show variability within the same session and over time, and this limits their clinical usefulness.	3
Different techniques of measuring urethral function may have good test-retest reliability, but do not consistently correlate to other urodynamic tests or to the severity of UI.	3
There is limited evidence that ambulatory urodynamics is more sensitive than conventional urodynamics for diagnosing SUI or DO.	2
There may be inconsistency between history and urodynamic results.	3
Preliminary urodynamics can influence the choice of treatment for UI, but does not affect the outcome of conservative therapy or drug therapy for SUI.	1a
Preliminary urodynamics in women with uncomplicated, clinically demonstrable SUI does not improve the outcome of surgery for SUI.	1b
There is no evidence that urodynamic tests of urethral function predict outcome of surgery for SUI in women.	3
There is consistent low-level evidence that pre-operative DO is associated with poorer outcomes of mid-urethral sling surgery in women.	3
There is no evidence that urodynamics predicts the outcomes of treatment for post prostatectomy incontinence in men.	4

Recommendations	**GR**
(NB: Concerning only neurologically intact adults with urinary incontinence)	
Clinicians carrying out urodynamics in patients with urinary incontinence should: • Ensure that the test replicates the patient's symptoms. • Interpret results in the context of the clinical problem. • Check recordings for quality control. • Remember there may be physiological variability within the same individual.	C
Advise patients that the results of urodynamics may be useful in discussing treatment options, although there is limited evidence that performing urodynamics will predict the outcome of treatment for urinary incontinence.	C
Do not routinely carry out urodynamics when offering conservative treatment for urinary incontinence.	B
Perform urodynamics if the findings may change the choice of invasive treatment.	B
Do not use urethral pressure profilometry or leak point pressure to grade severity of incontinence or predict the outcome of treatment.	C
Urodynamic practitioners should adhere to the standards laid out in the ICS document "Good Urodynamic Practice" [80].	C

3.7 Pad testing

Measurement of urine loss using an absorbent pad worn over a set period of time or during a protocol of physical exercise can be used to quantify the presence and severity of UI, and of response to treatment.

3.7.1 ***Question***

- In adults with UI, what is the reliability, diagnostic accuracy and predictive value of pad testing?
- In adults with UI is one type of pad test better than another?

3.7.2 ***Evidence***

The clinical usefulness of pad tests for people with UI has been assessed in two systematic reviews [81, 82]. A 1-hour pad test using a standardised exercise protocol and a diagnostic threshold of 1.4 g shows good specificity but lower sensitivity for symptoms of SUI and MUI. A 24-hour pad test using a threshold of 4.4 g is more reproducible but is difficult to standardise with variation according to activity level [83]. Pad test with a specific short graded exercise protocol also has diagnostic value but a negative test should be repeated or the degree of provocation increased [84]. The usefulness of pad tests in quantifying severity and predicting outcome of treatment is uncertain [81, 85] although early post-operative testing may predict future continence in men after prostatectomy [86]. Pad test is responsive to change following successful treatment [87]. There is no evidence that one type of pad test is superior to another.

Evidence summary	**LE**
A pad test can diagnose UI accurately.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
24 hours is sufficient duration for home-based testing balancing diagnostic accuracy and adherence.	2
Change in leaked urine volume on pad tests can be used to measure treatment outcome.	2

Recommendations	**GR**
Have a standardised duration and activity protocol for pad test.	B
Use a pad test when quantification of urinary incontinence is required.	C
Use repeat pad test after treatment if an objective outcome measure is required.	C

3.8 Imaging

Imaging improves our understanding of the anatomical and functional abnormalities that may cause UI. In clinical research, imaging is used to understand the relationship between conditions of the central nervous system (CNS) or of the lower urinary tract (LUT) and UI, and to investigate the relationship between lower urinary tract and pelvic floor imaging and treatment outcome.

Ultrasound (US) and magnetic resonance imaging (MRI) have replaced X-ray imaging. Ultrasound is preferred to MRI because of its ability to produce three-dimensional and four-dimensional (dynamic) images at lower cost and wider availability. Studies on LUT imaging in patients with UI often include an evaluation of surgical outcomes, making design and conduct of these trials challenging.

3.8.1 ***Questions***

In adults with UI:

- What is the reliability and accuracy of imaging in the diagnosis of UI?
- Do the results of imaging influence the choice of treatment for UI?
- Do the results of imaging, help predict outcome of treatment for UI?
- Do the results of imaging help evaluate outcome of treatments for UI?

3.8.2 ***Evidence***

Many studies have evaluated the imaging of bladder neck mobility by US and MRI, and concluded that UI cannot be identified by a particular pattern of urethrovesical movements [88]. In addition, the generalised increase in urethral mobility after childbirth does not appear to be associated with de novo SUI [89].

There is a general consensus that MRI provides good global pelvic floor assessment, including POP, defecatory function and integrity of the pelvic floor support [90]. However, there is a large variation in MRI interpretation between observers [91] and little evidence to support its clinical usefulness in the management of UI.

Studies have assessed the use of imaging to assess the mechanism of mid-urethral sling insertion for SUI. One study suggested that mid-urethral sling placement decreased mobility of the mid-urethra but not mobility of the bladder neck [92]. In addition, the position of mid-urethral slings with respect to the pubis has been associated with the cure of UI [93].

Several imaging studies have investigated the relationship between sphincter volume and function in women [94] and between sphincter volume and surgery outcome in men and women [95, 96]. In patients undergoing

radical prostatectomy, longer membranous urethra before and after surgery was associated with higher rate of continence [97]. However, no imaging test has been shown to predict the outcome of treatment for UI. Imaging of the pelvic floor can identify levator ani detachment and hiatus size, although there is little evidence of a relationship to clinical benefit after treatment of treating UI.

Detrusor wall thickness
As overactive bladder syndrome (OAB) has been linked to detrusor overactivity, it has been hypothesised that frequent detrusor contractions may increase detrusor/bladder wall thickness (DWT/BWT). However, there is no evidence if BWT/DWT imaging improves management OAB in real life practice. No consensus exists as to the relation between OAB and increased BWT/DWT [98-102].

Evidence summary	LE
Imaging can reliably be used to measure bladder neck and urethral mobility, although there is no evidence of clinical benefit for patients with UI.	2b
There is no consistent evidence that bladder (detrusor) wall thickness measurement is useful in the management of UI.	3

Recommendation	GR
Do not routinely carry out imaging of the upper or lower urinary tract as part of the assessment of urinary incontinence.	A

4. DISEASE MANAGEMENT

4.1 Conservative management

In clinical practice, it is a convention that non-surgical therapies are tried first because they usually carry the least risk of harm. They are often used in combination which makes it difficult to determine which components are effective. Containment devices play an important role, especially for individuals who prefer to avoid the risks of interventional treatments, or in whom active treatment is impossible for any reason.

*4.1.1 **Simple clinical interventions***

4.1.1.1 Underlying disease/cognitive impairment

Urinary incontinence, especially in the elderly, can be worsened or caused by underlying diseases, especially conditions that cause polyuria, nocturia, increased abdominal pressure or CNS disturbances. These conditions include:

- cardiac failure [103]
- chronic renal failure
- diabetes [103, 104]
- chronic obstructive pulmonary disease [105]
- neurological disease including stroke and multiple sclerosis
- general cognitive impairment
- sleep disturbances, e.g. sleep apnoea
- obesity.

It is possible that correction of the underlying disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients often suffer from more than one condition. In addition, interventions may be combined and individualised, making it impossible to decide which alteration in an underlying disease has affected a patient's UI.

4.1.1.1.1 Question

In adults with UI, does correcting an underlying disease or cognitive impairment improve UI compared to no correction of underlying disease?

4.1.1.1.2 Evidence

One study showed no correlation between earlier intensive treatment of type 1 diabetes mellitus and the prevalence of UI in later life versus conventional treatment [106].

Evidence summary	LE
Improved diabetic control does not improve UI.	3

4.1.1.2 Adjustment of medication

Although UI is listed as an adverse effect of many drugs in drug compendia, this mainly results from uncontrolled individual patient reports and post-marketing surveillance. Few controlled studies have used the occurrence of UI as a primary outcome or were powered to assess the occurrence of statistically significant UI or worsening rates against placebo. In most cases, it is therefore not possible to be sure that a drug causes UI.

In patients with existing UI, particularly the elderly, it may be difficult or impossible to distinguish between the effects of medication, comorbidity or ageing on UI.

Although changing drug regimens for underlying disease may be considered as a possible early intervention for UI, there is very little evidence of benefit [58]. There is also a risk that stopping or altering medication may result in more harm than benefit.

4.1.1.2.1 Question

In adults with UI, does adjustment of medication improve UI compared to no change in treatment?

4.1.1.2.2 Evidence

Oestrogenic drugs including conjugated equine oestrogens, oestradiol, tibolone and raloxifene, are used as hormone replacement therapy (HRT) for women with natural or therapeutic menopause. Studies of HRT with nonurogenital primary outcomes have looked for change in urinary continence in secondary analyses. Large trials using conjugated equine oestrogens showed a higher rate of development or worsening of UI compared to placebo [107-110]. In a single RCT use of raloxifene was not associated with development or worsening of UI [111]. Three small RCTs using oral oestriol or oestradiol as HRT for vulvovaginal atrophy suggested that UI symptoms were improved although the evidence was unclear [58, 112, 113].

Evidence summary	LE
There is very little evidence that alteration of medication can cure or improve sumptoms of urinary incontinence.	3
Systemic hormone replacement therapy using conjugate equine estrogens in previously continent women increases the risk of developing UI and worsens pre-existing UI.	1a

Recommendations	GR
Take a drug history from all patients with urinary incontinence.	A
For women taking oral conjugated equine oestrogen as hormone replacement therapy who develop or worsen UI, suggest discussion of alternative hormone replacement therapies with the relevant clinician.	A
Advise women who are taking systemic oestradiol who suffer from UI, that stopping the oestradiol is unlikely to improve their incontinence.	A
Review any new medication associated with the development or worsening of urinary incontinence.	C

4.1.1.3 Constipation

Several studies have shown strong associations between constipation, UI and OAB. Constipation can be improved by behavioural, physical and medical treatments.

4.1.1.3.1 Question

Does treatment for constipation improve UI?

4.1.1.3.2 Evidence

One RCT found that a multimodal intervention in elderly patients, involving assisted toileting, fluid intake, etc, reduced the occurrence of UI and constipation, while behavioural therapy appeared to improve both [114].
An observational study comparing women with UI and women with pelvic organ prolapse (POP) to controls found that a history of constipation was associated with both prolapse and UI [115]. Two, large, cross-sectional population-based studies [116, 117] and two longitudinal studies [118, 119] showed that constipation was a risk factor for LUTS.

In conclusion, constipation appears to be associated with UI. However, there is no evidence to show whether or not treating constipation improves UI, although both constipation and UI appear to be improved by certain behavioural interventions.

Evidence summary	LE
There is a consistent association between a history of constipation and the development of UI and pelvic organ prolapse.	3
There is no evidence that treatment of constipation improves UI.	4
Multimodal behavioural therapy improves both constipation and UI in the elderly.	1b

Recommendation	GR
Adults with urinary incontinence who also suffer from constipation should be given advice about bowel management in line with good medical practice.	C

4.1.1.4 Containment

Containment is important for people with UI when active treatment does not cure the problem, or when it is not available or not possible. Some individuals may prefer to choose containment rather than undergo active treatment with its associated risks. This includes the use of absorbent pads, urinary catheters, external collection devices and penile clamps for men; and intravaginal devices for women. Studies of catheter use are not specific to patients with non-neurogenic UI. Detailed literature summaries can be found in the current ICUD monograph [1] and in European Association of Urological Nurses guidance documents [120-122]. A useful resource for health care professionals and patients can be found at:
http://www.continenceproductadvisor.org/.org

4.1.1.4.1 Question

For adults with UI, is one type of containment device better than another?

4.1.1.4.2 Evidence

One RCT involving elderly women in care comparing management with pads to indwelling urethral catheter found no difference in dependency level or skin integrity score at six months [123]. Use of an external sheath was compared with indwelling catheterisation over 30 days in an RCT involving elderly men resident in hospital [124]. There were no differences in bacteriuria or symptomatic UTI but the sheath was more comfortable. A short-term crossover RCT in men with UI found that disease specific QoL was better when using an external sheath and more men preferred it, compared to pads [125].

4.1.1.4.3 Question

For men or women with UI is one type of pad better than another?

4.1.1.4.4 Evidence

A systematic review of six RCTs comparing different types of pads found that pads filled with superabsorbent material were better than standard pads, whilst evidence that disposable pads were better than washable pads was inconsistent [126]. For men with light UI a randomised crossover trial found that a leaf-shaped type of pad was preferred to rectangular pads [127]. A series of three crossover RCTs examined performance of different pad designs for differing populations [128]. For women with light UI, disposable insert pads were most effective. In adults with moderate/severe incontinence, disposable pull-up pants were more effective for women, whilst for men disposable diapers were more effective during the day and washable diapers at night.

4.1.1.4.5 Question

For men or women with UI is one type of catheter or external collection device better than another?

4.1.1.4.6 Evidence

A Cochrane review summarised three RCTs comparing different types of long-term indwelling catheters and found no evidence that one catheter material or type of catheter was superior to another [129]. A systematic review of non-randomised studies found no differences in any UTI outcome or for upper urinary tract changes between use of suprapubic or urethral catheter drainage, but patients with suprapubic catheters were less likely to have urethral complications [130]. For people using intermittent catheterisation, a Cochrane review found no evidence that one type of catheter or regimen of catheterisation was better than another [131]. A Cochrane review summarising five trials comparing washout policies in adults with indwelling urinary catheters found inconsistent evidence of benefit [132].

A further Cochrane review summarising eight trials testing whether antibiotic prophylaxis was beneficial for adults using intermittent or indwelling catheterisation found it reduced incidence of symptomatic UTI but possible harms were not assessed [133].

A randomised crossover study comparing six different brands of sheath devices found that men preferred sheaths [134].

4.1.1.4.7 Question
For men and women with UI are external pressure devices more effective than standard treatment and is one device better than another?

4.1.1.4.8 Evidence
A crossover RCT in men with post-prostatectomy incontinence found a hinge-type penile clamp to be more effective than circular clamps for control of UI and was preferred by participants although it reduced penile blood flow [135].

A Cochrane review summarised seven trials comparing mechanical devices in women with UI finding limited evidence that SUI was reduced by intravaginal devices, no evidence on the effectiveness of intraurethral devices and that there was no difference in control of UI between intravaginal and intraurethral devices [136]. There was no difference in outcome at 12 months in women with SUI between vaginal pessary alone; PFMT alone; and vaginal pessary + PFMT though vaginal pessary was inferior to PFMT at three months for bother from UI.

Evidence summary	**LE**
Pads with greater absorbency are more effective.	1b
Hinge-type penile clamps control SUI in men.	2a
Vaginal devices control SUI in women.	2a
Vaginal devices are no better than PFMT for women with SUI.	2a
A sheath-type external collection device for men is better than pads for improvement in incontinence related QoL.	2a

Recommendations	**GR**
Ensure that adults with UI and/or their carers are informed regarding available treatment options before deciding on containment alone.	A*
Suggest use of disposable insert pads for women and men with light urinary incontinence.	A*
In collaboration with other healthcare professionals with expertise in UI help adults with moderate/severe urinary incontinence to select the individually best containment regimen considering pads, external devices and catheters, and balancing benefits and harms.	A*
Choice of pad from the wide variety of different absorbent materials and designs available should be made with consideration of the individual patient's circumstance, degree of incontinence and preference.	B

** Based on expert opinion.*

*4.1.2 **Lifestyle interventions***
Examples of lifestyle factors that may be associated with incontinence include obesity, smoking, level of physical activity and diet. Modification of these factors may improve UI.

4.1.2.1 Caffeine reduction
Many drinks contain caffeine, particularly tea, coffee and cola. Anecdotal evidence of urinary symptoms being aggravated by excessive caffeine intake has focused attention on whether caffeine reduction may improve UI. However, a cross-sectional population survey found no statistical association between caffeine intake and UI [137]. Lack of knowledge about caffeine content of different drinks has made the role of caffeine reduction in alleviating UI difficult to assess.

4.1.2.1.1 Question
In adults with UI, does caffeine reduction improve UI or QoL compared to no caffeine reduction?

4.1.2.1.2 Evidence
Four studies were found on the effect of caffeine reduction on UI [138-141]. They were of moderate quality and the results were inconsistent. The studies were mainly in women, so results can only be cautiously generalised

to men [139, 140]. One RCT showed that reducing caffeine intake as an adjunct to behavioural therapy resulted in reduced urgency but not reduced UI compared to behavioural therapy alone [139]. Another RCT found that reducing caffeine had no benefit for UI [140]. A further interventional study in the elderly showed borderline significance for the benefit of reducing caffeine intake on UI [141]. In a large prospective cohort study there was no evidence that caffeine reduction reduced the risk of progression of UI over 2 years [142].

Evidence summary	LE
Reduction of caffeine intake does not improve UI.	2
Reduction in caffeine intake may improve symptoms of urgency and frequency.	2

4.1.2.2 Physical exercise

Regular physical activity may strengthen the pelvic floor musculature and possibly decrease the risk of developing UI, especially SUI. However, it is also possible that heavy physical exercise may aggravate UI.

4.1.2.2.1 Question

Does physical exercise cause, improve or exacerbate UI in adults?

4.1.2.2.2 Evidence

The association between exercise and UI is unclear. Four studies [137, 143-145] in differing populations concluded that strenuous physical exercise increases the risk of SUI during periods of physical activity. There is also consistent evidence that physically active females and elite athletes experience higher levels of SUI than control populations [146-151]. On the other hand, the presence of UI may prevent women from taking exercise [152]. There is no evidence that strenuous exercise predisposes athletes to the development of SUI later in life [153]. Lower levels of UI have been observed in cohorts of women who undertake moderate exercise, but it remains unclear whether taking exercise can prevent development of UI [154, 155].

The elderly

Three RCTs in the elderly confirmed that exercise, as a component of a multidimensional regime including PFMT and weight loss, was effective in improving UI in women. It is not clear which component of such a scheme is most important [114, 156, 157].

Evidence summary	LE
Female athletes may experience UI during intense physical activity but not during common activities.	3
Strenuous physical activity does not predispose to UI for women later in life.	3
Moderate exercise is associated with lower rates of UI in middle-aged or older women.	2b

4.1.2.3 Fluid intake

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with UI to relieve symptoms. Advice on fluid intake given by healthcare professionals should be based on 24-hour fluid intake and urine output measurements. Form a general health point of view it should be advised that fluid intake should be sufficient to avoid thirst and that low or high 24-hour urine output should be investigated.

4.1.2.3.1 Question

In adults with UI, what is the effect of modifying fluid intake compared to not modifying fluid intake on symptoms and QoL?

4.1.2.3.2 Evidence

The few RCTs [140, 158, 159] provide inconsistent evidence. In most studies, the instructions for fluid intake were individualised and it is difficult to assess participant adherence to protocol. All available studies were in women.

A recent RCT [159] showed that a reduction in fluid intake by 25% improved symptoms in patients with OAB but not UI. Personalised fluid advice compared to generic advice made no difference to continence outcomes in people receiving antimuscarinics for OAB, according to an RCT comparing drug therapy alone to drug therapy with behavioural advice [160].

Evidence summary	LE
There is conflicting evidence on whether fluid modification changes symptoms of UI and QoL.	2

4.1.2.4 Obesity and weight loss

Obesity has been identified as a risk factor for UI in many epidemiological studies [137, 161]. There is evidence that the prevalence of both UUI and SUI increases proportionately with rising body mass index. The proportion of patients who undergo surgery for incontinence who are overweight or obese is higher than that of the general population.

4.1.2.4.1 Question

In adults with UI, does weight loss lead to an improvement in symptoms of UI or QoL?

4.1.2.4.2 Evidence

All the available evidence relates to women. The prevalence of UI in overweight individuals is well established [137, 161]. Obesity appears to confer a four-fold increased risk of UI [162].

Two systematic reviews plus 1 large RCT concluded that weight loss was beneficial in improving symptoms of UI [163-165]. Five further RCTs reported a similar beneficial effect on incontinence following surgical weight reduction programmes [166-170].

Two large studies in women with diabetes, for whom weight loss was the main lifestyle intervention showed UI did not improve but there was a lower subsequent incidence of UI among those who lost weight [166, 171]. There have been other cohort studies and case-control studies suggesting similar effects, including surgery for the morbidly obese [106, 165, 172-177]. For example, in a longitudinal cohort study, a weight loss of 5-10% was associated with a significant reduction in UI measured by pad test [178].

Evidence summary	**LE**
Obesity is a risk factor for UI in women.	1b
Weight loss (> 5%) in obese women improves UI.	1b
Weight loss in obese adults with diabetes mellitus reduces the risk of developing UI.	1b

4.1.2.5 Smoking

Smoking cessation is now a generalised public health measure. Smoking, especially if > 20 cigarettes per day, is considered to intensify UI.

4.1.2.5.1 Question

In adults with UI, does smoking cessation improve patient outcomes regarding either urinary symptoms or QoL compared to continued smoking?

4.1.2.5.2 Evidence

The effect of smoking cessation on UI was described as uncertain in a Cochrane review [164].

Evidence summary	**LE**
There is no evidence that smoking cessation will improve the symptoms of UI.	4

4.1.2.6 Recommendations for lifestyle interventions

Recommendations	**GR**
Encourage obese women suffering from any urinary incontinence to lose weight (> 5%).	A
Advise adults with urinary incontinence that reducing caffeine intake may improve symptoms of urgency and frequency but not incontinence.	B
Patients with abnormally high or abnormally low fluid intake should be advised to modify their fluid intake appropriately.	C
Counsel female athletes experiencing urinary incontinence with intense physical activity that it will not predispose to urinary incontinence in later life.	C
Patients with urinary incontinence who smoke should be given smoking cessation advice in line with good medical practice.	A

4.1.3 ***Behavioural and Physical therapies***

Terminology relating to behavioural and physical therapies remains confusing because of the wide variety of ways in which treatment regimes and combinations of treatments have been delivered in different studies [179]. The terms are used here to encompass all those treatments which require a form of self-motivated personal

retraining by the patient and also includes those techniques which are used to augment this effect.

Approaches include bladder training (BT) and pelvic floor muscle training (PFMT), but terms such as bladder drill, bladder discipline and bladder re-education and behaviour modification are also used. Almost always in clinical practice, these will be introduced as part of a package of care including lifestyle changes, patient education and possibly some cognitive therapy as well. The extent to which individual therapists motivate, supervise and monitor these interventions is likely to vary but it is recognised that these influences are important components of the whole treatment package.

4.1.3.1 Bladder Training

Patients may be asked to void according to a fixed voiding schedule. Alternatively, patients may be encouraged to follow a schedule established by their own bladder diary/voiding chart (habit training). 'Timed voiding' is voiding initiated by the patient, while 'prompted voiding' is voiding initiated by the caregiver. Timed and habit voiding are recommended to patients who can void independently. Bladder training can be offered to any patient with any form of UI, as a first-line therapy for at least a short period of time. The ideal form or intensity of a BT programme for UI is unclear. It is also unclear whether or not BT can prevent the development of UI.

4.1.3.1.1 Questions

In adults with UI:

- Is BT better than no treatment for cure or improvement of UI?
- Is BT better than other conservative treatments for cure or improvement of UI?
- Does BT as an adjunct to other conservative treatments cure or improve UI?
- Are the benefits of BT durable in the longer term?
- Are there any patient groups for whom BT is more effective?

4.1.3.1.2 Evidence

There have been three systematic reviews on the effect of BT compared to standard care [58, 164, 180] confirming that BT is more effective than no treatment in improving UI. The addition of BT to anticholinergic therapy seems to confer no addional effect apart from the reduction of frequency and nocturia.

BT alone is inferior to a high-intensity programme of PFMT to improve SUI in elderly women [181]. Bladder training is better than intravaginal pessaries to control SUI, although the improvement may only be short-term.

Whatever the method of training used, any benefit of BT on UI is likely to be of short duration unless the BT programme is practised repeatedly. No adverse events have been reported with BT. Biofeedback combined with BT increased continence rates and improved MUI in two RCTs [180].

Evidence summary	**LE**
Behavioural interventions are effective for improvement of UI in women.	1b
The effectiveness of bladder training diminishes after the treatment has ceased.	2
The comparative benefit of bladder training and drugs for the improvement of UUI remains uncertain.	2
The combination of bladder training with antimuscarinic drugs does not result in greater improvement of UI but may have other benefits.	1b
Bladder training is better than pessary alone.	1b

For recommendations see section 4.1.3.5.

4.1.3.2 Pelvic floor muscle training (PFMT)

Pelvic floor muscle training is used to improve function of the pelvic floor, improving urethral stability. There is some evidence that improving pelvic floor function may inhibit bladder contraction in patients with OAB [182].

PFMT may be used to prevent UI, e.g. in childbearing women before birth, in men about to undergo radical prostatectomy, or as part of a planned recovery programme after childbirth or surgery. Most often, PFMT is used to treat existing UI, and may be augmented with biofeedback (using visual, tactile or auditory stimuli), surface electrical stimulation or vaginal cones.

4.1.3.2.1 Question

In adult men and women suffering from UI, does treatment with PFMT (given either alone or augmented with biofeedback, electrical stimulation or vaginal cones) improve or cure UI or improve QoL, compared to no treatment, sham treatment or other conservative treatments, e.g. bladder training, electrical stimulation or vaginal cones?

4.1.3.2.2 Evidence

In a recent UK Health Technology Appraisal (HTA), the role of PFMT in the care of women with SUI was analysed in direct comparisons of treatments and a mixed treatment comparison model, which compared different 'packages' of care [164]. This extensive meta-analysis reviewed data from 37 interventions and 68 direct comparisons, while the mixed treatment comparisons examined combinations of 14 different types of intervention from 55 separate trials. The mixed treatment comparison used both indirect and direct comparisons and may provide more accurate estimates of effect. Where relevant, the Technology Appraisal has influenced the evidence and recommendations in these Guidelines. The Agency for Healthcare Research and Quality (AHRQ) review of nonsurgical treatment of UI in adult women also included indirect comparison methods as well as conventional meta-analysis [180].

4.1.3.2.3 Efficacy of PFMT in SUI, UUI and MUI in women

This question has been addressed by several systematic reviews [164, 180, 183], all report inconsistency between studies because of poor reporting of technique and different outcome measures. Meta-analysis showed that PFMT was effective for cure or improvement of incontinence, and improvement in QoL. The effect applies in women with SUI, UUI and MUI though the effect in MUI is lower than in women with pure SUI. A Cochrane review comparing different approaches to delivery of PFMT(21 RCTs) concluded that increased intensity of delivery of the therapy improves response and that there is no consistent difference between group therapy and individualised treatment sessions [184]. No other consistent differences between techniques were found.

With regard to the durability of PFMT, another RCT reported 15-year follow-up outcomes of an earlier RCT, showing that long-term adherence to treatment was poor and half of patients had progressed to surgery [185].

Numerous systematic reviews have addressed the question of whether the effects of PFMT and BT are additive [164, 180, 186]. These reviews are confounded by differences in patient selection and have arrived at conflicting conclusions leaving uncertainty about the extent to which one treatment may augment the other. Similarly, there remains uncertainty about the additional value of biofeedback with systematic reviews reaching differing conclusions [180, 186].

Comparison of PFMT to other treatments was extensively reviewed by both AHRQ and the 2010 UK HTA [164, 180], which considered additional non-randomised data as part of a mixed treatment comparison. The UK HTA resulted in a number of different findings from those based solely on direct comparisons. In conclusion, the HTA, using a revised methodology, supported the general principle that greater efficacy was achieved by adding together different types of treatment and by increasing intensity.

4.1.3.2.4 PFMT in the elderly

The effect of PFMT in women with SUI does not seem to decrease with increased age: in trials with older women with SUI it appeared both primary and secondary outcome measures were comparable to those in trials focused on younger women [156, 181, 187].

4.1.3.2.5 PFMT and Radical prostatectomy

A Cochrane review concluded that there was no benefit at 12 months post-surgery for men who received postoperative PFMT for the treatment of post-prostatectomy urinary incontinence (PPI) and that the benefits of conservative treatment of PPI remain uncertain [188]. There have been further RCTs which leave uncertainty about whether or not PFMT leads to earlier recovery of continence [189-193]. Two additional RCTs have shown that written instructions alone offer similar levels of improvement to supervised PFMT [194, 195]. One RCT found that PFMT was helpful in men who had been incontinent for at least one year after prostatectomy, and who had had no previous therapy [196].

Evidence summary	LE
PFMT for Women with UI	
PFMT is better than no treatment for improving UI and QoL in women with SUI and MUI.	1
Higher-intensity, supervised treatment regimes, and the addition of biofeedback, confer greater benefit in women receiving PFMT.	1
Short-term benefits of intensive PFMT are not maintained at 15-year follow-up.	2
PFMT for post-prostatectomy UI	**LE**
PFMT does not cure UI in men post-prostatectomy.	1b
There is conflicting evidence as to whether PFMT speeds the recovery of continence following radical prostatectomy.	1b
There is conflicting evidence on whether the addition of bladder training, electrical stimulation or biofeedback increases the effectiveness of PFMT alone.	2
There is no evidence that pre-operative PFMT prevents UI following radical prostatectomy though it may lead to earlier recovery of continence.	2

For recommendations see section 4.1.3.5.

4.1.3.3 Prompted voiding

The term prompted voiding implies that carers, rather than the patient, initiate the decision to void and this applies largely to an assisted care setting.

Prompted voiding is the giving of positive reinforcement for requesting toileting assistance, either spontaneously or following verbal prompts from a caregiver. Two systematic reviews (9 RCTs) [197, 198]. Confirmed a positive effect on continence outcomes of prompted voiding in comparison to standard care [198].

Timed voiding is defined as fixed, pre-determined, time intervals between toileting, applicable for those withor without cognitive impairment. A Cochrane review of timed voiding reviewed two RCTs finding inconsistent improvement in continence compared with standard care in cognitively impaired adults [199].

Evidence summary	LE
Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.	1b

For recommendations see section 4.1.3.5.

4.1.3.3.1 Electrical stimulation

The details and methods of delivery of electrical stimulation vary considerably.

Electrical stimulation (ES) can also be combined with other forms of conservative therapy, e.g. PFMT and biofeedback. Electrical stimulation is often used to assist women who cannot initiate contractions to identify their pelvic floor muscles. Electrical stimulation is also used in patients with OAB and UUI, for detrusor inhibition. It has been suggested that ES probably targets the pelvic floor directly in SUI and the detrusor muscle or pelvic floor muscle or afferent innervation in UUI.

4.1.3.3.2 Question

In adults with UI, does treatment with ES improve or cure symptoms of UI or QoL compared to no treatment or sham treatment?

4.1.3.3.3 Evidence

Most evidence on ES refers to women with SUI. The topic has been included in two health technology appraisals [164, 180] and three systematic reviews [58, 200, 201].

The reviews include analysis of 15 trials and use different comparison methods, but conflict in their assessment of whether ES is more effective than sham stimulation and whether ES adds to the benefit of PFMT alone. Studies were considered to be of generally low quality, with a variety of stimulation parameters, treatment regimens and outcome parameters.

A systematic review reported two RCTs in which ES had been compared to oxybutynin in patients with UUI, showing similar efficacy [202].

A Cochrane review of ES in men with UI (6 RCTs) concluded that, in the short-term, there was limited evidence

of ES augmenting effectiveness of PFMT and there was better improvement of incontinence than with sham stimulation [203].

Electromagnetic stimulation has been promoted as an alternative to electrical stimulation but no evidence of effectiveness was found [204].

Evidence summary	LE
In adults with UI, there is inconsistent evidence whether ES is effective in improving UI compared to sham treatment or adds any benefit to PFMT.	1
The comparative benefit of electrical stimulation and antimuscarinic drugs, for improvement of patients with UUI, remains uncertain.	1

For recommendations see section 4.1.3.5.

4.1.3.4 Posterior tibial nerve stimulation

Electrical stimulation of the posterior tibial nerve (PTNS) delivers electrical stimuli to the sacral micturition centre via the S2-S4 sacral nerve plexus. Stimulation is done percutaneously with a fine, 34-G, needle, inserted just above the medial aspect of the ankle (P-PTNS). Transcutaneous stimulation is also available (T-PTNS). Treatment cycles typically consist of 12 weekly treatments of 30 minutes.

4.1.3.4.1 Question

In adults suffering from UUI, what is the clinical effectiveness of PTNS compared to sham treatment or alternative treatment such as antimuscarinic drugs?

4.1.3.4.2 Evidence

P-PTNS

The reviewed studies included two RCTs of PTNS against sham treatment [205, 206] and one comparing PTNS to tolterodine in patients with UUI [207] The results of studies of PTNS in women with refractory UUI are consistent. Considered together, these results suggest that PTNS improves UUI in women who have had no benefit from antimuscarinic therapy or who are not able to tolerate these drugs. However, there is no evidence that PTNS cures UUI in women. In addition, PTNS is no more effective than tolterodine for improvement of UUI in women. In men there is insufficient evidence to make a conclusion about efficacy.

In patients who initially respond to PTNS, the improvement is maintained in some patients at 2 years with continued treatment (approximately monthly) [208].

T-PTNS

A small RCT compared transcutaneous PTNS plus standard treatment (PFMT and BT) with PFMT and BT alone in older women [209]. Women in the T-TPNS group were more likely to achieve Improvement at the end of therapy.

Evidence summary	LE
P-PTNS appears effective for improvement of UUI, in women who have had no benefit from antimuscarinic medication.	2b
P-PTNS is no more effective than tolterodine for improvement of UUI in women.	1b
No serious adverse events have been reported for P-PTNS in UUI.	3
There is limited evidence for effectiveness of T-PTNS.	2a

4.1.3.5 *Recommendations for behavioural and physical therapies*

Recommendations	GR
Offer supervised intensive PFMT, lasting at least 3 months, as a first-line therapy to women with stress urinary incontinence or mixed urinary incontinence.	A
PFMT programmes should be as intensive as possible.	A
Offer PFMT to elderly women with urinary incontinence.	B
Consider using biofeedback as an adjunct in women with stress urinary incontinence.	A
Offer instruction on PFMT to men undergoing radical prostatectomy to speed recovery of incontinence.	B
Offer bladder training as a first-line therapy to adults with urgency urinary incontinence or mixed urinary incontinence.	A
Us a trial of prompted voiding for adults with incontinence, who are cognitively impaired.	A
Do not offer electrical stimulation with surface electrodes (skin, vaginal, anal) alone for the treatment of stress urinary incontinence.	A
Consider offering electrical stimulation as an adjunct to behavioural therapy in patients with urgency Urinary incontinence.	B
Do not offer magnetic stimulation for the treatment of incontinence or overactive bladder in adult women.	B
Do not offer PTNS to women or men who are seeking a cure for urgency urinary incontinence.	A
Offer, if available, P-PTNS as an option for improvement of urgency urinary incontinence in women who have not benefitted from antimuscarinic medication.	B
Support other healthcare professionals in use of rehabilitation programmes including prompted voiding for care of elderly care-dependent people with urinary incontinence.	A

PFMT = pelvic floor muscle training; P-PTNS = percutaneous posterior tibial nerve stimulation; T-PTNS = transcutaneous posterior tibial nerve stimulation.

4.1.4 ***Conservative therapy in mixed urinary incontinence***

About one-third of women with UI have mixed urinary incontinence (MUI) with symptoms of both stress UI (SUI) and urgency UI (UUI), and this becomes more common with increasing age. In terms of evidence base, many studies include patients with MUI, but it is rare for these studies to provide a separate analysis of patients with MUI.

4.1.4.1 *Question*

In adults with MUI, is the outcome of conservative therapy different to that obtained with the same treatment in patients with either pure SUI or pure UUI?

4.1.4.2 *Evidence*

No specific systematic reviews were found that addressed the above question. However, a Cochrane report on pelvic floor muscle training (PFMT) [183] concluded that training was less likely to result in a cure in patients with MUI than in patients with pure SUI, though it is not clear from the report how this conclusion was reached.

A small RCT (n = 71) compared delivery of PFMT, with or without an instructive audiotape. It showed equal efficacy for different types of UI [210].

Following a RCT of PFMT, a review of 88 women available for follow-up at 5 years found that outcomes were less satisfactory in women with MUI than in women with pure SUI [211].

Evidence summary	LE
Pelvic floor muscle training appears less effective for MUI than for SUI alone.	2
Electrical stimulation is equally effective for MUI and SUI.	1b

4.1.4.3 *Recommendations conservative therapy in mixed urinary incontinence*

Recommendations	GR
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
Warn patients with mixed urinary incontinence that the chance of success of pelvic floor muscle training is lower than for stress urinary incontinence alone.	B

4.2 Pharmacological management

4.2.1 ***Antimuscarinic drugs***

Antimuscarinic (anticholinergic) drugs are currently the mainstay of treatment for UUI. They differ in their pharmacological profiles, e.g. muscarinic receptor affinity and other modes of action, in their pharmacokinetic properties, e.g. lipid solubility and half-life, and in their formulation.

The evaluation of cure or improvement of UI is made harder by the lack of a standard definition of improvement and the failure to use cure as a primary outcome. In general, systematic reviews note that the overall treatment effect of drugs is usually small but larger than placebo. Dry mouth is the commonest side effect, though constipation, blurred vision, fatigue and cognitive dysfunction may occur.

The immediate release (IR) formulation of oxybutynin is the prototype drug in the treatment of UUI. Oxybutynin IR provides maximum dosage flexibility, including an off-label 'on-demand' use. Immediate-release drugs have a greater risk of side effects than extended release (ER) formulations because of differing pharmacokinetics. A transdermal delivery system (TDS) and gel developed for oxybutynin gives a further alternative formulation.

4.2.1.1 Question

In adults with UUI, are antimuscarinic drugs better than placebo for improvement or cure of UUI and for the risk of adverse effects?

4.2.1.2 Evidence

Five systematic reviews of individual antimuscarinic drugs versus placebo were reviewed for this section [180, 212-215] as well as studies published since these reviews up until September 2013. Most studies included patients with a mean age of 55-60 years. Both female and male subjects were included in different studies but results cannot be generalised across sexes. Only short-term rates for improvement or cure of UUI are reported. The evidence reviewed was consistent, indicating that ER and IR formulations of antimuscarinics offer clinically significant short-term cure and improvement rates for UUI compared to placebo.

Cure of UI was deemed to be the most important outcome measure. Risk of adverse events was best represented by withdrawal from a trial because of adverse events although this does not reflects real life practice. Table 4 shows a summary of the findings from the most recent systematic review [180]. In summary, every drug where cure of UI was available shows superiority compared to placebo in achieving UI, but the absolute size of effect is small.

Table 4. Summary of cure rates and discontinuation rates of antimuscarinic drugs from RCTs which reported these outcomes [180]

Drug	No. of Studies	Patients	Relative risk (95% CI) (of curing UI)	Number needed to treat (95% CI) (to achieve one cure of UI)
Cure of incontinence				
Fesoterodine	2	2465	1.3 (1.1-1.5)	8 (5-17)
Oxybutynin (includes IR)	4	992	1.7 (1.3-2.1)	9 (6-16)
Propiverine (includes IR)	2	691	1.4 (1.2-1.7)	6 (4-12)
Solifenacin	5	6304	1.5 (1.4-1.6)	9 (6-17)
Tolterodine (includes IR)	4	3404	1.2 (1.1-1.4)	12 (8-25)
Trospium (includes IR)	4	2677	1.7 (1.5-2.0)	9 (7-12)
Discontinuation due to adverse events				
			Relative Risk (95% CI) (of discontinuation)	**NNT (95% CI) (of one discontinuation)**
Darifenacin	7	3138	1.2 (0.8-1.8)	
Fesoterodine	4	4433	2.0 (1.3-3.1)	33 (18-102)
Oxybutynin (includes IR)	5	1483	1.7 (1.1-2.5)	16 (8-86)
Propiverine (includes IR)	2	1401	2.6 (1.4-5)	29 (16-27)
Solifenacin	7	9080	1.3 (1.1-1.7)	78 (39-823)
Tolterodine (includes IR)	10	4466	1.0 (0.6-1.7)	
Trospium (includes IR)	6	3936	1.5 (1.1-1.9)	56 (30-228)

Darifenacin
The cure rates for darifenacin were not included in the AHRQ review. Continence rates were 29-33% for darifenacin compared to 17-18% for placebo [180].

Transcutaneous oxybutynin
Transdermal oxybutynin has shown a significant improvement in the number of incontinence episodes and micturitions per day versus placebo and other oral formulations but incontinence was not reported as an outcome [180].

Oxybutynin topical gel was superior to placebo for improvement of UUI with a higher proportion of participants being cured [180].

Evidence summary	LE
All formulations of Fesoterodine, Oxybutynin, Propiverine, Solifenacin, Tolterodine, Darifenacin and Trospium, provide a significantly better rate of cure or improvement of UUI compared to placebo.	1a
All formulations of Fesoterodine, Oxybutynin, Propiverine, Solifenacin, Tolterodine, Darifenacin and Trospium, result in higher rates of dry mouth compared to placebo.	1b

*4.2.2 **Comparison of antimuscarinic agents***
Head-to-head comparison trials of the efficacy and side effects of different antimuscarinic agents are of interest for decision making in real life practice.

4.2.2.1 Question
In adults with UUI, does one type of antimuscarinic drug result in a greater likelihood of cure or improvement in UUI, and/or a greater improvement in QoL, and/or a lesser likelihood of adverse effects compared to an alternative antimuscarinic drug?

4.2.2.2 Evidence
There are over 40 RCTs and five systematic reviews [180, 202, 212, 214, 216]. Nearly all the primary studies were industry sponsored. Upward dose titration is often included in the protocol for the experimental arm, but not for the comparator arm.

In general, these studies have been designed for regulatory approval. They have short treatment durations (12 weeks) and a primary outcome of a change in OAB symptoms rather than a cure of, or an improvement in, UUI, which were generally analysed as secondary outcomes. The clinical utility of these trials in real life practice in questionable. Most trials were of low or moderate quality [214].

The 2012 AHRQ review included a specific section addressing comparisons of antimuscarinic drugs (Table 5).

Table 5: Comparison of antimuscarinic drugs as reviewed in the 2012 AHRQ review [180]

Experimental drug versus standard drug	No. of studies	Patients	Relative risk (95% CI) of curing UI
Efficacy			
Fesoterodine vs. tolterodine ER (continence)	2	3312	1.1 (1.04-1.16)
Oxybutynin ER vs. tolterodine ER (improvement)	3	947	1.11 (0.94-1.31)
Solifenacin vs. tolterodine ER	1	1177	1.2 (1.08-1.34)
Trospium vs. oxybutynin	1	357	1.1 (1.04-1.16)
Discontinuation due to adverse events			
			RR – 95% CI of discontinuation
Solifenacin vs. tolterodine ER	3	2755	1.28 (0.86-1.91)
Trospium vs. oxybutynin	2	2015	0.75 (0.52 -1.1)
Fesoterodine vs. tolterodine	4	4440	1.54 (1.21-1.97)

No antimuscarinic agent improved QoL more than another agent [214]. Dry mouth is the most prevalent adverse effect. Good evidence indicates that, in general, higher doses of any drug are likely to be associated

with higher rates of adverse events. Also, ER formulations of short-acting drugs, and longer-acting drugs are generally associated with lower rates of dry mouth than IR preparations [214, 216]. Oxybutynin IR showed higher rates of dry mouth than tolterodine IR and trospium IR, but lower rates of dry mouth than darifenacin, 15 mg daily [214, 216]. Overall, oxybutynin ER has higher rates of dry mouth than tolterodine ER, although the incidence of moderate or severe dry mouth were similar. Transdermal oxybutynin had a lower rate of dry mouth than oxybutynin IR and tolterodine ER, but had an overall higher rate of withdrawal due to an adverse skin reaction [214]. Solifenacin, 10 mg daily, had higher rates of dry mouth than tolterodine ER [214]. Fesoterodine, 8 mg daily, had a higher rate of dry mouth than tolterodine, 4 mg daily [217, 218]. In general, similar discontinuation rates were observed, irrespective of differences in the occurrence of dry mouth.*

**Doses have been given where the evidence relates to a specific dose level typically from trials with a dose escalation element.*

Evidence summary	**LE**
There is no consistent evidence that one antimuscarinic drug is superior to an alternative antimuscarinic drug for cure or improvement of UUI.	1a
The ER formulation of oxybutynin is superior to the ER and IR formulations of tolterodine for improvement of UUI.	1b
Solifenacin is more effective than tolterodine IR for improvement of UUI.	1b
Fesoterodine, 8 mg daily, is more effective than tolterodine ER, 4 mg daily, for cure and improvement of UUI, but with a higher risk of side effects.	1b
ER formulations and once-daily antimuscarinic drugs are generally associated with lower rates of dry mouth than IR preparations, although trial discontinuation rates are similar.	1b
Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral antimuscarinic drugs, but has a high rate of withdrawal due to skin reaction.	1b
Oxybutynin IR or ER shows higher rates of dry mouth than the equivalent formulation of tolterodine.	1a
There is no evidence that any particular antimuscarinic agent is superior to another for improvement in QoL.	1a

*4.2.3 **Antimuscarinic drugs versus non-drug treatment***

The choice of drug versus non-drug treatment of UUI is an important question.

4.2.3.1 Question

In adults with UUI, does one type of antimuscarinic drug result in a greater likelihood of cure or improvement in UUI and/or greater improvement in QoL, and/or lesser likelihood of adverse effects compared to an alternative non-drug treatment?

4.2.3.2 Evidence

More than 100 RCTs and high-quality reviews are available [202, 214, 215, 219-221]. Most of these studies were independent.

The US HTA [202] found that trials were of low- or moderate-quality. The main focus of the review was to compare the different drugs used to treat UUI. In one study, multicomponent behavioural modification produced significantly greater reductions in incontinence episodes compared to oxybutynin and higher patient satisfaction for behavioural versus drug treatment. One RCT showed a substantial benefit for sacral neuromodulation compared with medical therapy [222]. In men with storage LUTS, no difference in efficacy was found between oxybutynin and behavioural therapy [223]. The combination of BT and solifenacin in women with OAB conferred no additional benefit in terms of continence [224].

Two small RCTs [225, 226], reported a similar improvement in subjective parameters with either transcutaneous electrical nerve stimulation or T-PTNS. However, only oxybutynin treated patients showed significant improvements in objective urodynamic parameters (bladder capacity). The oxybutynin-treated group had more side effects. One study compared tolterodine ER to transvaginal/anal electrical stimulation without differences in UI outcomes [227]. One small RCT found that the addition of P-PTNS to tolterodine ER improved UI and QoL [228].

Evidence summary	LE
There is no consistent evidence to show superiority of drug therapy over behavioural therapy for treatment of UUI.	1b
Behavioural treatment has higher patient satisfaction than drug treatment.	1b
There is no consistent evidence to show superiority of drug therapy over PFMT for treatment of UUI.	1b

4.2.3.3 Recommendations for antimuscarinic drugs

Recommendations	GR
Offer IR or ER formulations of antimuscarinic drugs for adults with urgency urinary incontinence.	A
If IR formulations of antimuscarinic drugs are unsuccessful for adults with urgency urinary incontinence, offer ER formulations or longer-acting antimuscarinic agents.	A
Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth.	B
Offer and encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for urgency urinary incontinence (< 30 days).	A

IR = immediate release; ER = extended release.

*4.2.4 **Antimuscarinic agents: adherence and persistence***

Most studies on antimuscarinic medication are short term (12 weeks). Adherence in clinical trials is considered to be much higher than in real life practice.

4.2.4.1 Question

Do patients with UUI adhere to antimuscarinic drug treatment and persist with prescribed treatment in clinical practice?

4.2.4.2 Evidence

This topic has been reviewed for the development of these Guidelines [229]. Two recent open-label extensions of RCTs of fesoterodine 8 mg showed adherence rates at 2 years from 49-84% [230, 231]. The main drugs studied were oxybutynin and tolterodine IR and ER. Non-persistence rates were high for tolterodine at 12 months, and particularly high (68-95%) for oxybutynin.

'Median days to discontinuation' between < 30 days and 50 days were reported, with a maximum of 273 days, in a military health system where free medication was provided [232].

Data on adherence/persistence from open-label extension populations are questionable as these patients are self-selected to be compliant. Data from pharmacy databses is included in this section.

Several of the RCT trials tried to identify the factors associated with low/lower, adherence or persistence of antimuscarinic. These were identified as:

- low level of efficacy (41.3%)
- adverse events (22.4%)
- cost (18.7%), as higher adherence rates were observed when drugs were provided at no cost to the patient [232].

Other reasons for poor adherence included:

- IR versus ER formulations
- age (lower persistence among younger adults)
- unrealistic expectations of treatment
- gender distribution (better adherence/persistence in female patients)
- ethnic group (African-Americans and other minorities more likely to discontinue or switch treatment)

In addition, the source of data influenced the adherence figures.

Evidence summary	LE
More than half of patients will stop antimuscarinic agents within the first 3 months because of ineffectiveness, adverse events and cost.	2

*4.2.5 **Antimuscarinic agents, the elderly and cognition***

Limited trials have been conducted in elderly people with UI. Issues include the multifactorial etiology of UI in the elderly, comorbidities such as cognitive impairment, the effect of co-medications and the risk of adverse events.

The effects of antimuscarinic agents on cognition have been studied in more detail.

4.2.5.1 Question

What is the comparative efficacy, and risk of adverse effects, particularly the cognitive impact, of treatment with antimuscarinic medication in elderly men and women with UUI?

4.2.5.2 Evidence

Two systematic reviews are available [233, 234]. A community-based cohort study found a high incidence of cognitive dysfunction [235]. Other systematic reviews have included sections on the efficacy and safety of antimuscarinics in elderly patients [180, 214]. A systematic review in 2012 found inconclusive evidence as to the impact of antimuscarinics on cognition [236].

Very few trials specifically investigated the cognitive changes associated with antimuscarinic agents. In general, these trials have measured CNS side effects in a non-specific way and do not allow us to understand the impact on [237, 238].specific populations. There are studies on antimuscarinic effects in elderly persons [239], and in people with dementia with UUI [240]. No specific studies exist in vulnerable patient populations at risk of cognitive dysfunction and deterioration of it while on antimuscarinics.

4.2.5.2.1 Oxybutynin

There is evidence that oxybutynin IR may cause/worsen cognitive dysfunction in adults although there is no consensus about it [237, 239, 241-245].

More rapid functional deterioration might result from the combined use of cholinesterase inhibitors with antimuscarinic agents in elderly patients with cognitive dysfunction [246].

4.2.5.2.2 Solifenacin

One pooled analysis [247] has shown that solifenacin does not increase cognitive impairment in the elderly. No age-related differences in the pharmacokinetics of solifenacin in dfferent age grups was found although more frequent adverse events in subjects over 80 years old were observed. No cognitive effect on healthy elderly volunteers was showen [245]. In a subanalysis of a large trial, solifenacin 5-10 mg improved symptoms and QoL in people ≥ 75 years who had not responded to tolterodine [248]. In patients with mild cognitive impairment, over 65 years, solifenacin showed no difference in efficacy between age groups and a lower incidence of most side effects compared to oxybutynin IR [244, 249].

4.2.5.2.3 Tolterodine

No change in efficacy or side effects related to age have been reported, although a higher discontinuation rate was found for both tolterodine and placebo in elderly patients [237]. Two RCTs in the elderly found a similar efficacy and side effect profile to younger patients [250-253]. Post-hoc analysis has shown little effect on cognition. One non-randomised comparison showed lower rates of depression in elderly participants treated with tolterodine ER compared to oxybutynin IR [254].

4.2.5.2.4 Darifenacin

Two RCTs in the elderly population (one in patients with UUI and the other in volunteers) concluded that darifenacin was effective with no risk of cognitive change, measured as memory scanning tests, compared to placebo [255, 256]. Another study on darifenacin and oxybutynin ER in elderly subjects concluded that the two agents had a similar efficacy, but that cognitive function was more often affected in the oxybutynin ER arm [239].

4.2.5.2.5 Trospium chloride

Trospium is not supposed to cross the blood-brain barrier in healthy individuals. Two (EEG) studies in healthy volunteers showed no effect from trospium whilst tolterodine caused occasional changes and oxybutynin caused consistent changes [257, 258]. No evidence as to the comparative efficacy and side effect profiles of trospium in different age groups in available. However, there is some evidence that trospium does not impair cognitive function [240, 259] and that it is effective compared to placebo in the elderly [260].

4.2.5.2.6 Fesoterodine

There is no evidence comparing the efficacy and side effects of fesoterodine in elderly and younger patients. Pooled analyses of the RCTs of fesoterodine confirmed the efficacy of the 8 mg but not the 4 mg dose in over-75-year olds [261]. Adherence was lower in the over-75 year-old group but the effect on mental status was not reported [230, 262, 263]. No difference between fesoterodine and placebo on cognitive function was reported in healthy older patients [264].

4.2.5.2.7 Duloxetine in the elderly

RCTs comparing duloxetine and placebo included women up to 85 years, but no age stratification of the results is available.

4.2.5.2.8 Mirabegron

No trials of mirabegron have yet been reported in the elderly population with UI.

4.2.5.2.9 Applicability of evidence to general elderly population

It is not clear how much the data from pooled analyses and subgroup analyses from large RCTs can be extrapolated to a general ageing population. Community-based studies of the prevalence of antimuscarinic side effects may be the most helpful [235].

When starting anticholinergics in elderly patients, mental function should be assessed objectively and monitored [265]. No consensus exists as to the best mental function test to detect changes in cognition [246, 261].

4.2.5.2.10 Anticholinergic load

A number of medications have anticholinergic effects and their cumulative effects on cognignition should be considered [266].

4.2.5.2.11 Question

In older people suffering from UI what is the effect of anticholinergic burden (defined by anticholinergic cognitive burden scale, ACB) on cognitive function?

4.2.5.2.12 Evidence

There were no studies specifically in older people with UI, but evidence was available from observational cohort studies relating to the risk in a general population of older people.

Lists of drugs with anticholinergic properties are available from two sources [266, 267].

Two systematic reviews of largely retrospective cohort studies, showed a consistent association between longterm anticholinergic use and cognitive dysfunction [268, 269].

Longitudinal studies in older people over two to four years have found increased rate of decline in cognitive function for patients on definite and possible anticholinergics [270, 271].

Evidence summary	**LE**
All antimuscarinic drugs are effective in elderly patients.	1b
In older people, the cognitive impact of drugs which have anticholinergic effects, is cumulative, and increases with length of exposure.	3
There is inconsistent evidence as to whether oxybutynin IR may worsen cognitive function.	2
Solifenacin, darifenacin and fesoterodine have been shown not to cause increased cognitive dysfunction in elderly people.	1b
There is no evidence as to whether tolterodine and trospium chloride affect cognitive function.	3

4.2.5.2.13 Additional recommendations for antimuscarinic drugs in the elderly

Recommendations	GR
In older people being treated for urinary incontinence, every effort should be made to employ non-pharmacological treatments first.	C
Use antimuscarinic drugs with caution in elderly patients who are at risk of, or have, cognitive dysfunction.	B
In older people who are being prescribed antimuscarinic drugs for control of urinary incontinence, consider modifications to other medications to help reduce anticholinergic load.	C
Check mental function in patients on antimuscarinic medication if they are at risk of cognitive dysfunction.	C

*4.2.6 **Mirabegron***

Mirabegron is the first clinically available beta 3 agonist, available from 2013. Beta 3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation.

Mirabegron has undergone evaluation in industry-sponsored phase 2 and phase 3 trials. Two systematic reviews of all currently reported studies assessing the clinical effectiveness of mirabegron [272, 273] reported that mirabegron at doses of 25, 50 and 100 mg, results in significantly greater reduction in incontinence episodes, urgency episodes and micturition frequency/24 hrs than placebo, with no difference in the rate of common adverse events [272]. The placebo dry rates in most of these trials are between 35-40%, and 43 and 50% for mirabegron. In all trials the statistically significant difference is consistent only for improvement but not for cure of UI. Similar improvement in frequency of incontinence episodes and micturitions/24 hrs was found in people who had previously tried and those who had not previously tried antinmuscarinin agents.

The most common treatment adverse events in the mirabegron groups were hypertension (7.3%), nasopharyngitis (3.4%) and UTI (3%) [272].

In a 12-month, active-controlled RCT of mirabegron 50/100 mg versus tolterdine ER 4 mg, the improvement in efficacy seen at 12 weeks was sustained at 12-month evaluation in all groups. The reported dry rates at 12 months were 43%,45% and 45% for mirabegron 50 mg, 100 mg and tolterodine 4 mg respectively [274].

No risk of QTc prolongation on electrocardiogram [275] and raised intraocular pressure [276] were observed up to 100 mg dose. There is no significant difference in rate of side effects at different doses of mirabegron [274].

Evaluation of urodynamic parameters in men with combined BOO and OAB concluded that mirabegron (50 or 100 mg) did not adversely affect voiding urodynamic parameters compared to placebo [277].

Equivalent adherence was observed for tolterodine and mirabegron at 12 months (5.5% and 3.6%), although the incidence of dry mouth was significantly higher in the tolterodine group [274]. In mirabegron treated patients, improvement in objective outcome measures correlates directly with clinically relevant PROMs (OAB-q and PPBC) [278, 279].

Evidence summary	LE
Mirabegron is better than placebo for improvement of UUI symptoms	1a
There is no evidence that mirabegron is better than placebo for curing incontinence.	1b
Mirabegron is no more effective than tolterodine.	1b
Adrenergic-mediated side effects of mirabegron appear mild and not clinically significant in a trial setting.	1a
Discontinuation rates from mirabegron are similar to tolterodine in a trial setting.	1b

Recommendation	GR
Offer mirabegron to people with urgency urinary incontinence, but warn patients receiving mirabegron that the possible long-term side effects remain uncertain.	B

*4.2.7 **Drugs for stress urinary incontinence***

Trials have focused on the effect of alpha-adrenoceptors in increasing the closure urethral pressure in women as a means of improving SUI.

A Cochrane review [280] found 22 trials of adrenergic drugs in women with predominant SUI in comparison to placebo or PFMT. Eleven of these trials involved phenylpropanolamine (withdrawn in some countries because of an increased risk of haemorrhagic stroke). The review found weak evidence that these drugs are better than placebo at improving UI in women. Comparative trials with PFMT gave inconsistent results. No new trials were published between 2007 and 2010. At present, these drugs are not licensed for use in UI.

Duloxetine inhibits the presynaptic re-uptake of the neurotransmitters, serotonin (5-HT) and norepinephrine (NE). In the sacral spinal cord, an increased concentration of 5-HT and NE in the synaptic cleft increases stimulation of 5-HT and NE receptors on the pudendal motor neurones, which in turn increases the resting tone and contraction strength of the urethral striated sphincter.

4.2.7.1 Questions

- In adults with SUI, does duloxetine cure or improve UI and/or improve QoL compared to no treatment?
- In adults with SUI, does duloxetine result in a greater cure or improvement of UI, or a greater improvement in QoL, or a lesser likelihood of adverse effects, compared to any other intervention?

4.2.7.2 Evidence

Duloxetine was evaluated as a treatment for female SUI or MUI in two systematic reviews [215, 280] of 10 RCTs, and one subsequent RCT. The typical dose of duloxetine was 80 mg daily, with dose escalation up to 120 mg daily allowed in one study, over a period of 8-12 weeks. One RCT extended the observation period up to 36 weeks and used the Incontinence Quality of Life (I-QoL) score as a primary outcome.

Improvement in UI compared to placebo was observed with no clear differences between SUI and MUI. One study reported cure for UI in about 10% of patients. An improvement in I-QoL was not found in the study using IQoL as a primary endpoint. In a further study comparing duloxetine, 80 mg daily, with PFMT alone, PFMT + duloxetine, and placebo [281], duloxetine reduced leakage compared to PFMT or no treatment. Global improvement and QoL were better for combined therapy than no treatment. There was no significant difference between PFMT and no treatment.

Two open-label studies with a follow-up of 1 year or more evaluated the long-term effect of duloxetine in controlling SUI however both had high discontinuation rates [282, 283].

Duloxetine, 80 mg daily, which could be increased up to 120 mg daily, was investigated in a 12-week study in patients, who had OAB but not SUI [284]. Episodes of UUI were also significantly reduced by duloxetine.

One study [285] compared PFMT + duloxetine versus PFMT + placebo, for 16 weeks, followed by 8 weeks of PFMT alone in males with post-prostatectomy incontinence. Duloxetine + PFMT significantly improved UI, but the effect did not last to the end of the study, indicating that duloxetine only accelerates cure and does not increase the percentage of patients cured.

All studies had a high patient withdrawal rate of about 20-40% in short-term studies and up to 90% in long-term studies. Cause of the high withdrawal rate included lack of efficacy and high incidence of adverse events, including nausea and vomiting (40% or more of patients), dry mouth, constipation, dizziness, insomnia, somnolence and fatigue.

Evidence summary	**LE**
Duloxetine does not cure UI.	1a
Duloxetine, 80 mg daily improves SUI and MUI in women.	1a
Duloxetine causes significant gastrointestinal and CNS side effects leading to a high rate of treatment discontinuation.	1a
Duloxetine, 80 mg daily, can improve SUI in men.	1b
Duloxetine 80 mg - 120 mg daily can improve UUI in women.	1b

Recommendations	**GR**
Duloxetine should not be offered to women or men who are seeking a cure for their incontinence.	A
Duloxetine can be offered to women or men who are seeking temporary improvement in incontinence symptoms.	B*
Duloxetine should be initiated using dose titration because of high adverse effect rates.	A

** Downgraded based on expert opinion.*

4.2.8 ***Oestrogen***

Oestrogen treatment for UI has been tested using oral, transdermal and vaginal routes of administration. Available evidence suggests that vaginal oestrogen treatment with oestradiol and oestriol is not associated with the increased risk of thromboembolism, endometrial hypertrophy, and breast cancer seen with systemic administration [286-288]. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women.

4.2.8.1 Questions

- In women with UI, does oral (systemic) oestrogen cure or improve UI compared to no treatment?
- In women with UI, does vaginal (local) oestrogen cure or improve UI compared to no treatment or other active treatment?

4.2.8.2 Evidence

In women with SUI the use of oral conjugated equine estrogens, estradiol, or estrone showed no improvement [289-291]. Two placebo-controlled trials using sub-cutaneous estradiol or oral estriol showed no benefit for improvement of UI [292].

A recent Cochrane systematic review looked at the use of oestrogen therapy in postmenopausal women [286] given local oestrogen therapy. There is also a more recent narrative review of oestrogen therapy in urogenital diseases [293]. No new RCTs have been published up to September 2012. The Cochrane review (search date June 2012) found that vaginal oestrogen treatment improved symptoms of UI in the short-term [286]. The review found single, small, low quality trials comparing vaginal oestrogen treatment with phenylpropanolamine, PFMT, electrical stimulation and its use as an adjunct to surgery for SUI. Local oestrogen was less likely to improve UI than PFMT but no differences in UI outcomes were observed for the other comparisons. A single trial of local oestrogen therapy comparing a ring device to pessaries found no difference in UI outcomes although more women preferred the ring device. No adverse effects of vaginal administration of estradiol for vulvovaginal atrophy over 2 years was seen in one trial [294].

Vaginal oestrogen therapy can be given as conjugated equine oestrogen, oestriol or oestradiol in vaginal pessaries, vaginal rings or creams. Current data do not allow differentiation among the various types of oestrogens or delivery methods. The ideal treatment duration and the long-term effects are uncertain. One RCT compared oestradiol ring pessary with treatment with oxybutynin ER showing no difference in outcomes [295].

Evidence summary	**LE**
Vaginal oestrogen therapy improves UI for post-menopausal women.	1b
Oral oestrogen therapy does not improve UI.	1a
Vaginal oestrogen therapy in post-menopausal women may improve or cure UUI.	1a
There is no consistent evidence that vaginal oestrogen therapy cures SUI.	2
There is no evidence that one method of vaginal delivery is better than another	4
There is no evidence available on the neoadjuvant or adjuvant use of local oestrogens at the time of surgery for UI.	1a
There is no evidence that oestrogen therapy by non-vaginal route confers any improvement in UI.	1a

Recommendations	**GR**
Offer post-menopausal women with urinary incontinence vaginal oestrogen therapy particularly if other symptoms of vulvovaginal atrophy are present.	A
Do not offer oral (systemic) oestrogen replacement therapy as treatment for urinary incontinence.	A
Vaginal oestrogen therapy should be long-term and in an appropriate dose.	C

4.2.9 ***Desmopressin***

Desmopressin is a synthetic analogue of vasopressin (also known as antidiuretic hormone). It can be taken orally, nasally or by injection. Desmopressin is most commonly used to treat diabetes insipidus and, when used at night, to treat nocturnal enuresis.

4.2.9.1 Questions

- In adults with UI, does desmopressin cure or improve UI and/or improve QoL compared to no treatment?
- In adults with UI, does desmopressin result in a lesser likelihood of adverse effects, compared to any other intervention?

4.2.9.2 Evidence

4.2.9.2.1 Improvement of incontinence

Few studies have examined the use of desmopressin exclusively for the treatment of UI. No evidence was found that demonstrated any effect on nocturnal incontinence. Two RCTs have compared desmopressin to placebo with daytime UI as an outcome measure. Improved continence was shown during the first 4 hours after taking desmopressin in women [296]. The continuous use of desmopressin improved frequency and urgency, but did not improve UI in men and women with OAB [297]. There is no evidence reporting desmopressin cure rates for UI and no evidence that compares desmopressin with other non-drug treatments for UI.

4.2.9.2.2 Monitoring for hyponatraemia

The use of desmopressin carries a risk of developing hyponatraemia (please refer to the EAU Guidelines on Male LUTS).

Evidence summary	**LE**
The risk of UI is reduced within 4 hours of taking oral desmopressin, but not after 4 hours.	1b
Continuous use of desmopressin does not improve or cure UI.	1b
Regular use of desmopressin may lead to hyponatraemia.	3

Recommendations	**GR**
Offer desmopressin to patients requiring occasional short-term relief from daytime urinary incontinence and inform them that this drug is not licensed for this indication.	B
Do not use desmopressin for long-term control of urinary incontinence.	A

4.2.10 ***Drug treatment in mixed urinary incontinence***

4.2.10.1 Question

In adults with MUI, is the outcome of a drug treatment different to that with the same treatment in patients with either pure SUI or pure UUI?

4.2.10.2 Evidence

Many RCTs include patients with MUI with predominant symptoms of either SUI or UUI but few report outcomes separately for those with MUI compared to pure SUI or UUI groups.

Tolterodine

In an RCT of 854 women with MUI, tolterodine ER was effective for improvement of UUI, but not SUI suggesting that the efficacy of tolterodine for UUI was not altered by the presence of SUI [298]. In another study (n = 1380) tolterodine was equally effective in reducing urgency and UUI symptoms, regardless of whether there was associated SUI [299]. Similar results were found for solifenacin [300, 301].

Duloxetine

In one RCT of duloxetine vs. placebo in 588 women, subjects were stratified into either stress-predominant, urgency-predominant or balanced MUI groups. Duloxetine was effective for improvement of incontinence and QoL in all subgroups [302].

Duloxetine was found to have equal efficacy for SUI and MUI in an RCT (n = 553) following secondary analysis of respective subpopulations [303].

Evidence summary	**LE**
Limited evidence suggests that antimuscarinic drugs are effective for improvement of UUI component in patients with MUI.	2
Duloxetine is effective for improvement of both SUI and UUI in patients with MUI.	1b

Recommendations	**GR**
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
Offer antimuscarinic drugs to patients with urgency-predominant mixed urinary incontinence.	A*
Consider duloxetine for patients with MUI unresponsive to other conservative treatments and who are not seeking cure.	B

4.3 Surgical management

In line with the recommendations from the UK National Institute for Healthcare and Clinical Excellence (NICE) [58] the Panel agreed that surgeons and centres performing surgery should:

- be properly trained in each procedure;
- not be trained by someone who is not surgically qualified;
- perform sufficient numbers of a procedure to maintain expertise of him/herself and the surgical team;
- be able to offer alternative surgical treatments;
- be able to deal with the complications of surgery;
- provide suitable arrangements for follow-up long-term if necessary.

The section considers surgical options for the following situations:

- Women with uncomplicated SUI. This means no history of previous surgery, no neurological lower urinary tract dysfunction (LUTD), no bothersome genitourinary prolapse, and not considering further pregnancy.
- Women with complicated SUI. Neurogenic LUTD is reviewed in the EAU Guidelines on Neurogenic Lower Urinary Tract Dysfunction [2].
- Associated genitourinary prolapse has been included in these Guidelines in terms of treating the incontinence, but no attempt has been made to comment on treatment of prolapse itself.
- Men with SUI, mainly in men with post-prostatectomy incontinence without neurological disease affecting the lower urinary tract.
- Patients with refractory DO incontinence.

The Panel has tried to acknowledge emerging techniques as they think appropriate and have made a strong recommendation (section 4.3.1.5.2) that new devices are only used as part of a structured research programme.

*4.3.1 **Women with uncomplicated stress urinary incontinence***

4.3.1.1 Mid-urethral slings

Early clinical studies identified that slings should be made from monofilament, non-absorbable material, typically polypropylene, and constructed as a 1-2 cm wide mesh with a relatively large pore size (macroporous). Mid-urethral slings are now the most frequently used surgical intervention in Europe for women with SUI.

4.3.1.1.1 Questions

In women with SUI, what is the effectiveness in curing SUI and adverse effects at 1 year of:

- mid-urethral synthetic sling insertion compared to Burch colposuspension?
- one method of insertion of a mid-urethral synthetic sling compared to another method?
- one direction of insertion of a mid-urethral synthetic sling compared to another direction of insertion?

4.3.1.1.2 Evidence

For the purpose of these Guidelines, a new meta-analysis was performed.

Mid-urethral sling insertion compared to colposuspension

Thirteen RCTs (n = 1037) compared mid-urethral sling (retropubic) and colposuspension (open and laparoscopic). The meta-analysis found no difference in patient-reported cure rates at 12 months [304-314]. The overall patient-reported cure rate was 75%. There was weak evidence of higher clinician-reported cure rates at 12 months after mid-urethral sling (83%) compared to colposuspension (78%) [307-314]. However, longer term follow-up for up to 5 years reported no difference in effectiveness, though the numbers of participants lost to follow-up was high [87, 306]. Voiding dysfunction was more likely for colposuspension (relative risk 0.34, 95% CI 0.16-0.7) whilst bladder perforation was higher for the mid-urethral sling (15% vs. 9%, and 7% vs. 2%, respectively) [305, 307, 315-317].

Transobturator route versus retropubic route

The EAU Panel meta-analysis identified 34 RCTs (5786 women) comparing insertion of the mid-urethral sling by the retropubic and transobturator routes. There was no difference in cure rates at 12 months in either patient-reported or clinically reported cure rates (77% and 85%, respectively) [4]. Voiding dysfunction was less common (4%) following transobturator insertion compared to retropubic insertion (7%), as was the risk of bladder perforation (0.3%) or urethral perforation (5%). The risks of *de novo* urgency and vaginal perforation were 6% and 1.7%, respectively. Chronic perineal pain at 12 months after surgery was reported by 21 trials and meta-analysis showed a higher rate in women undergoing transobturator insertion (7%) compared to retropubic insertion (3%).

Insertion using a skin-to-vagina direction versus a vagina-to-skin direction
A Cochrane systematic review and meta-analysis found that the skin-to-vagina direction (top - down) for retropubic insertion of mid-urethral slings was less effective than the vagina-to-skin (bottom - up) direction and was associated with higher rates of voiding dysfunction, bladder perforation and vaginal erosion [318]. A further systematic review and meta-analysis found that the skin-to-vagina (outside in) direction of transobturator insertion of mid-urethral slings was equally effective compared to the vagina-to-skin route (inside out) using direct comparison. However, indirect comparative analysis gave weak evidence for a higher rate of voiding dysfunction and bladder injury [319].

4.3.1.2 Adjustability

4.3.1.2.1 Questions

- In women with SUI, does an adjustable sling cure SUI and improve QoL or does it cause adverse outcome(s)?
- How does an adjustable sling compare to other surgical treatments for SUI?

4.3.1.2.2 Evidence

There are no RCTs investigating outcome of adjustable sling insertion for women with SUI. There are limited data from cohort studies on adjustable tension slings with variable selection criteria and outcome definition. Few studies include sufficient numbers of patients or have a long enough follow-up to provide useful evidence. The available devices have differing designs, making it difficult to use existing data to make general conclusions about adjustable slings as a class of procedure.

4.3.1.3 Single-incision slings

4.3.1.3.1 Questions

- In women with SUI, do single-incision slings cure UI or improve QoL, or cause adverse outcomes?
- How does a single-incision sling compare to other surgical treatments for SUI?

4.3.1.3.2 Evidence

Although there have been many studies published on single-incision devices, it should be noted that there are significant differences in technical design between devices and it may be misleading to make general statements about them as a class of operations. It should also be noted that some devices have been withdrawn from the market (eg TVT Secur, Minitape), and yet evidence relating to these may be included in current meta analyses.
There was evidence to suggest single-incision slings are quicker to perform and cause less postoperative thigh pain, but there was no difference in the rate of chronic pain. There was not enough evidence to conclude any difference between single-incision slings in direct comparisons.

The most recent meta-analysis [320] and a reanalysis of the Cochrane review data by our panel (excluding TVT Secur data) have demonstrated that there was no difference in efficacy between available single incision devices and conventional mid-urethral slings. However, not all single incision devices have been subjected to RCT evaluation and it may be unsafe to assume that they are collectively technically similar devices.

Generalisability of evidence to adult women with SUI
Analysis of the population studied in trials included in this meta-analysis suggests that the evidence is generalisable to women, who have predominantly SUI, and no other clinically severe lower genitourinary tract dysfunction. The evidence is not adequate to guide choice of surgical treatment for those women with MUI, severe POP, or a history of previous surgery for SUI.
The results of the EAU Panel meta-analysis [4] were consistent with those of the Cochrane systematic review [318], except that in the EAU Panel meta-analysis the objective cure rates appeared slightly higher for retropubic (88%) compared to transobturator insertion (84%). The EAU Panel finding is consistent with an additional systematic review and meta-analysis [321] and the difference may result from the Panel's decision to only consider trial data with at least 12 months of follow-up.

Sexual function after mid-urethral tape surgery
A systematic review concluded there was a lack of RCTs addressing the effects of incontinence surgery on sexual function but noting a reduction in coital incontinence [322]. One recent RCT [323] and another cohort study [324] have shown that overall sexual activity improves after sling surgery.

SUI surgery in the elderly
There are no RCTs comparing surgical treatment in older versus younger women, although subgroup analyses

of some RCTs have included a comparison of older with younger cohorts. Definitions of "elderly" vary from one study to another so no attempt was made to define the term here. Instead, the Panel attempted to identify those studies which have addressed age difference as an important variable.

An RCT of 537 women comparing retropubic to transobturator tape, showed that increasing age was an independent risk factor for failure of surgery over the age of 50 [325]. An RCT assessing risk factors for the failure of TVT versus transobturator tension-free vaginal tape (TVT-O) in 162 women found that age is a specific risk factor (adjusted OR 1.7 per decade) for recurrence at 1 year [326]. In a subanalysis of a trial cohort of 655 women at 2 years' follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up (OR 3.7, 95% CI 1.7-7.97), are less likely to report objective or subjective improvement in stress and urgency UI, and are more likely to undergo retreatment for SUI (OR 3.9, 95% CI 1.3-11.48). There was no difference in time to postoperative normal voiding [72].

Another RCT comparing immediate TVT versus no surgery (delayed TVT) in older women, confirmed efficacy of surgery in terms of QOL and satisfaction, but with higher complication rates [327].

A cohort study of 256 women undergoing inside-out transobturator tape reported similar efficacy in older versus younger women, but found a higher risk of de novo urgency in older patients [328].

Evidence summary	**LE**
Compared to colposuspension, the retropubic insertion of a mid-urethral synthetic sling gives equivalent patient-reported cure of SUI at 5 years.	1a
Mid-urethral synthetic sling inserted by either the transobturator or retropubic route gives equivalent patient-reported outcome at 12 months.	1a
The skin-to-vagina (top down) direction of retropubic insertion of mid-urethral sling is less effective than a vagina-to-skin (bottom up) direction.	1a
Mid-urethral sling insertion is associated with a lower rate of a new symptom of urgency, and voiding dysfunction, compared to colposuspension.	1a
The retropubic route of insertion is associated with a higher intra-operative risk of bladder perforation and a higher rate of voiding dysfunction than the transobturator route.	1a
The transobturator route of insertion is associated with a higher risk of chronic pain and vaginal erosion and extrusion at 12 months than the retropubic route.	1a
The skin-to-vagina direction of both retropubic and transobturator insertion is associated with a higher risk of postoperative voiding dysfunction.	1b
Adjustable mid-urethral synthetic sling devices may be effective for cure or improvement of SUI in women.	3
There is no evidence that adjustable slings are superior to standard mid-urethral slings.	4
The comparative efficacy of single-incision slings against conventional mid-urethral slings is uncertain.	1c
Operation times for insertion of single-incision mid-urethral slings are shorter than for standard retropubic slings.	1b
Blood loss and immediate postoperative pain are lower for insertion of single-incision slings compared with conventional mid-urethral slings.	1b
There is no evidence that other adverse outcomes from surgery are more or less likely with single-incision slings than with conventional mid-urethral slings.	1b
Older women benefit from surgical treatment for UI.	1
The risk of failure from surgical repair of SUI, or suffering adverse events, appears to increase with age.	2
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4
In women undergoing surgery for SUI, coital incontinence is likely to improve.	3
Overall, sexual function is unlikely to deteriorate following SUI surgery.	3
There is no consistent evidence that the risk of postoperative sexual dysfunction differs between midurethral sling procedures.	3

**NB: Most evidence on single-incision slings is from studies using the tension-free vaginal tape secure (TVTS) device and although this device is no longer available, many women still have the device in place.*

4.3.1.4 Open and laparoscopic surgery for stress urinary incontinence

Open colposuspension was previously considered the gold standard surgical intervention for SUI, and was used as the comparator in RCTs of newer, less invasive, surgical techniques. These include laparoscopic techniques, which have enabled colposuspension to be performed with a minimally invasive approach.

Although the outcome of open and laparoscopic procedures should be considered in absolute terms, it is also important to consider any associated complications, adverse events and costs. The outcome parameters used to evaluate surgery for SUI have included:

- continence rate and number of incontinence episodes;
- general and procedure-specific complications;
- generic, specific (UI) and correlated (sexual and bowel) QoL.

4.3.1.4.1 Question

In women with SUI, what is the effectiveness of open and laparoscopic surgery, compared to other surgical procedures, measured in terms of cure or improvement of incontinence or QoL, or the risk of adverse events?

4.3.1.4.2 Evidence

Four systematic reviews were found, which covered the subject of open surgery for SUI, including 46 RCTs [2, 329-331], but no RCTs comparing any operation to a sham procedure.

Open colposuspension

The Cochrane review [332] included 46 trials (4738 women) having open colposuspension. In most of these trials, open colposuspension was used as the comparator to an experimental procedure. Consequently, for this review we have only considered the absolute effect of colposuspension, but have not reviewed all of these comparisons. No additional trials have been reported since this review.

Within the first year, complete continence rates of approximately 85-90% were achieved for open colposuspension, while failure rates for UI were 17% up to 5 years and 21% over 5 years. The re-operation rate for UI was 2%. Colposuspension was associated with a higher rate of development at 5 years of enterocoele/vault/cervical prolapse (42%) and rectocele (49%) compared to tension-free vaginal tape (TVT) (23% and 32%, respectively). The rate of cystocoele was similar in colposuspension (37%) and with TVT (41%).

Four trials compared Burch colposuspension to the Marshall Marchetti Krantz procedure and one trial evaluated Burch colposuspension with paravaginal repair. All showed fewer surgical failures up to 5 years with colposuspension but otherwise similar outcomes.

Anterior colporrhaphy

Anterior colporrhaphy is now considered an obsolete operation for UI. In a Cochrane review [330], 10 trials compared anterior colporrhaphy (385 women) with colposuspension (627 women). The failure rate for UI at follow-up of up to 5 years was worse for anterior colporrhaphy with a higher requirement for re-operation for incontinence.

Autologous fascial sling

The Cochrane review [330, 333] described 26 RCTs, including 2284 women undergoing autologous sling procedure in comparison to other operations.

There were seven trials of autologous fascial sling versus colposuspension. Except for one very high-quality study [334], most of the studies were of variable quality, with a few very small studies, and a short follow-up. The metaanalysis showed that fascial sling and colposuspension had a similar cure rate at 1 year. Colposuspension had a lower risk of voiding difficulty and UTIs, but a higher risk of bladder perforation.

In 12 trials of autologous fascial sling versus mid-urethral synthetic slings, the procedures showed similar efficacy. However, use of the synthetic sling resulted in shorter operating times and lower rates of complications, including voiding difficulty. Six trials compared autologous fascial slings with other materials of different origins, with results favouring traditional autologous fascial slings.

Laparoscopic colposuspension

The Cochrane review [329] identified 22 RCTs, of which 10 trials compared laparoscopic colposuspension to open colposuspension. No other trials have been identified. Although these procedures had a similar subjective cure rate, there was limited evidence suggesting the objective outcomes were less good for laparoscopic

colposuspension. However, laparoscopic colposuspension had a lower risk of complications and shorter duration of hospital stay.

In eight RCTs comparing laparoscopic colposuspension to mid-uretheral slings, the subjective cure rates were similar, while the objective cure rate favoured the mid-urethral sling at 18 months. Complication rates were similar for the two procedures and operating times were shorter for the mid-urethral sling. Comparisons of colposuspension to mid-uretheral sling are covered in section 4.3.1.1.

Evidence summary	**LE**
Open colposuspension and autologous fascial sling are similarly effective for cure of SUI in women.	1b
Laparoscopic colposuspension has similar efficacy to open colposuspension for cure of SUI and a similar risk of voiding difficulty or de novo urgency.	1a
Laparoscopic colposuspension has a lower risk of other complications and shorter hospital stay than open colposuspension.	1a
Autologous fascial sling has a higher risk of operative complications than open colposuspension, particularly voiding dysfunction and postoperative UTI.	1b

4.3.1.5 Bulking agents

4.3.1.5.1 Question

In women with SUI, does injection of a urethral bulking agent cure SUI or improve QoL, or cause adverse outcomes?

4.3.1.5.2 Evidence

There have been two Cochrane systematic reviews [335, 336] and one independent SR [337], which reported on 12 RCTs or quasi-RCTs of injectable agents. In general, the trials were only of moderate quality and small and many of them had been reported in abstract form. Wide confidence intervals meant a meta-analysis was not possible. Since the Cochrane review, two further RCTs have been reported [338, 339].

Each injectable product has been the subject of many case series. Short-term efficacy in reducing the symptoms of SUI has been demonstrated for all materials used. In 2006, NICE published an extensive review of these case series [340]. These case series have added very little to the evidence provided by RCTs. There has been only one placebo-controlled RCT, in which an autologous fat injection was compared with the placebo of a saline injection.

Comparison with open surgery

Two RCTs compared collagen injection to conventional surgery for SUI (autologous sling vs. silicon particles and collagen vs. assorted procedures). The studies reported greater efficacy but higher complication rates for open surgery. In comparison, collagen injections showed inferior efficacy but equivalent levels of satisfaction and fewer serious complications [58, 341].

Another trial found that a periurethral route of injection can carry a higher risk of urinary retention compared to a transurethral injection [342]. A recent small RCT found no difference in efficacy between mid-urethral and bladder neck injection of collagen [338].

Evidence summary	**LE**
Periurethral injection of bulking agent may provide short-term improvement in symptoms (3 months), but not cure, in women with SUI.	2a
Repeat injections to achieve therapeutic effect are often required.	2a
Bulking agents are less effective than colposuspension or autologous sling for cure of SUI.	2a
Adverse effect rates are lower compared to open surgery.	2a
There is no evidence that one type of bulking agent is better than another type.	1b
Transperineal route of injection may be associated with a higher risk of urinary retention compared to the transurethral route.	2b

Recommendations for surgery for uncomplicated stress urinary incontinence in women	**GR**
Offer the mid-urethral sling to women with uncomplicated stress urinary incontinence as the preferred surgical intervention whenever available.	A
Warn women who are being offered a retropubic insertion of midurethral sling about the relatively higher risk of peri-operative complications compared to transobturator insertion.	A
Warn women who are being offered transobturator insertion of mid-urethral sling about the higher risk of pain and dyspareunia in the longer term.	A

Warn women who are being offered a single-incision sling that long-term efficacy remains uncertain.	A
Do a cystoscopy as part of retropubic insertion of a mid-urethral sling, or if difficulty is encountered during transobturator sling insertion, or if there is a significant cystocoele.	C
Offer colposuspension (open or laparoscopic) or autologous fascial sling to women with stress urinary incontinence if mid-urethral sling cannot be considered.	A
Warn women undergoing autologous fascial sling that there is a high risk of voiding difficulty and the need to perform clean intermittent self-catheterisation; ensure they are willing and able to do so.	C
Inform older women with stress urinary incontinence about the increased risks associated with surgery, including the lower probability of success.	B
Inform women that any vaginal surgery may have an impact on sexual function.	B
Only offer new devices, for which there is no level 1 evidence base, as part of a structured research programme.	A*
Only offer adjustable mid-urethral sling as a primary surgical treatment for stress urinary incontinence as part of a structured research programme.	A*
Do not offer bulking agents to women who are seeking a permanent cure for stress urinary incontinence.	A*

** Recommendation based on expert opinion.*

*4.3.2 **Complicated stress urinary incontinence in women***

This section will address surgical treatment for women who have had previous surgery for SUI, which has failed, or those women who have undergone previous radiotherapy affecting the vaginal or urethral tissues. Neurological lower urinary tract dysfunction is is reviewed by the EAU Guidelines on Neurogenic Lower Urinary Tract Dysfunction [2]. Women with associated genitourinary prolapse are included in this edition (see section 4.3.3).

4.3.2.1 Colposuspension or sling following failed surgery

There may be persistent or recurrent SUI, or the development of de novo UUI. This means that careful evaluation including urodynamics becomes an essential part of the work-up of these patients.

4.3.2.1.1 Question

In women who have had failed surgery for SUI, what is the effectiveness of any second-line operation, compared to any other second-line operation, in terms of cure or improvement of UI, QoL or adverse events?

4.3.2.1.2 Evidence

Most of the data on surgery for SUI refer to primary operations. Even when secondary procedures have been included, it is unusual for the outcomes in this subgroup to be separately reported. When they are, the numbers of patients is usually too small to allow meaningful comparisons.

The 4th International Consultation on Incontinence includes a review of this topic [343] up till 2008 and the subject has also been reviewed by Ashok [344] and Lovatsis et al. [345]. A further literature review has been carried out since that time by the Panel.

Cochrane reviews of individual operative techniques have not included separate evaluation of outcomes in women undergoing second-line surgery. However, there is a current protocol to address this issue [346]. Only one RCT was found (abstract only) comparing TVT to laparoscopic colposuspension in women with recurrent SUI. This small study found similar cure rates and adverse events in the short-term for both procedures [317].

Post-hoc subgroup analysis of high-quality RCTs comparing one procedure to another have shown conflicting evidence of relative effectiveness [72, 85, 347, 348]. One large non-randomised comparative series suggested that cure rates after more than two previous operations were 0% for open colposuspension and 38% for fascial sling [349].

Several cohort studies have reported outcomes for TVT specifically for primary and secondary cases. Evidence on the effectiveness of second-line retropubic tapes conflicts with some series showing equivalent outcomes for primary and secondary cases [350, 351], whilst other research has shown inferior outcomes for secondary surgery [352, 353]. Other confounding variables make meaningful conclusions difficult.

Systematic review of older trials of open surgery for SUI suggest that the longer term outcomes of redo open colposuspension may be poor compared to autologous fascial slings [354]. Successful results have been reported from mid-urethral slings after various types of primary surgery, while good outcomes are reported for

both repeat TVT and for 'tightening' of TVT, but data are limited to small case series only.

Evidence summary	LE
There is conflicting evidence whether prior surgery for stress incontinence or prolapse results in inferior outcomes from repeat operations for SUI.	2
Most procedures will be less effective when used as a second-line procedure than when used for primary surgery.	2
In women who have had more than two procedures for SUI, the results of open colposuspension are inferior to autologous fascial sling.	2

4.3.2.2 External compression devices

External compression devices are still widely used in the treatment of recurrent SUI after the failure of previous surgery and if there is thought to be profound intrinsic failure of the sphincter mechanism, characterised by very low leak point pressures or low urethral closure pressures. This should be confirmed by urodynamic evaluation.

The two intracorporeal external urethral compression devices available are the adjustable compression therapy (ACT) device and the artificial urinary sphincter (AUS). Using ultrasound or fluoroscopic guidance, the ACT device is inserted by placement of two inflatable spherical balloons on either side of the bladder neck. Each volume of each balloon can be adjusted through a subcutaneous port placed within the labia majora. More recently, an adjustable artificial urinary sphincter (Flowsecure) has been introduced. It has the added benefit of 'conditional occlusion', enabling it to respond to rapid changes in intra-abdominal pressure.

4.3.2.2.1 Questions

- In women with SUI, does insertion of an external compressive device cure SUI, improve QoL or cause adverse outcomes?
- How do external compression devices compare to other surgical treatments for SUI?

4.3.2.2.2 Evidence

The major advantage of AUS over other anti-incontinence procedures is the perceived ability to be able to void normally [136]. However, voiding dysfunction is a known side effect, with a lack of data making it difficult to assess its importance. Because of significant differences in design between devices and in selection criteria between case series, results obtained with specific devices cannot be extrapolated generally to the use of adjustable devices. A recent consensus report has standardised the terminology used for reporting complications arising from implantation of materials into the pelvic floor region [17].

Artificial urinary sphincter (AUS)

A previous review of mechanical devices concluded that there was insufficient evidence to support the use of AUS in women [355].

There are a few case series in women, including four series (n = 611), with study populations ranging from 45 to 215 patients and follow-up ranging from 1 month to 25 years [356-359]. Case series have been confounded by varying selection criteria, especially the proportion of women who have neurological dysfunction or who have had previous surgery. Most patients achieved an improvement in SUI, with reported subjective cures in 59-88% Common side effects included mechanical failure requiring revision (up to 42% at 10 years) and explantation (5.9-15%). In a retrospective series of 215 women followed-up for a mean of 6 years, the risk factors for failure were older age, previous Burch colposuspension and pelvic radiotherapy [359]. Peri-operative injury to the urethra, bladder or rectum was also a high-risk factor for explantation [357].

A newly introduced artificial sphincter using an adjustable balloon capacity through a self-sealing port, and stress responsive design, has been introduced to clinical use. A series of 100 patients reported 28% explantation at 4 years but the device has undergone redesign and more up-to-date evidence is awaited [360].

Early reports of laparoscopically implanted AUS do not have sufficient patient populations and/or sufficient follow-up to be able to draw any conclusions [361, 362].

Adjustable compression device (ACT)

There are four case series (n = 349), with follow-up ranging from 5 to 84 months [363-366]. Reported outcome ranged from 47% objective cure to 100% subjective improvement. However, most patients required adjustment to achieve continence and 21% required explantation.

Evidence summary	LE
Implantation of an artificial sphincter can improve or cure incontinence in women with SUI caused by sphincter insufficiency.	3
Implantation of the ACT device may improve complicated UI.	3
Complications, mechanical failure and device explantation often occur with both the artificial sphincter and the adjustable compression device.	3
Explantation is more frequent in older women and among those who have had previous Burch colposuspension or pelvic radiotherapy.	3

Recommendations for surgery for complicated stress urinary incontinence in women	GR
The choice of surgery for recurrent stress urinary incontinence should be based on careful evaluation of the individual patient including video-urodynamics.	C
Warn women with recurrent stress urinary incontinence, that the outcome of a surgical procedure, when used as a second-line treatment, is generally inferior to its use as a first-line treatment, both in terms of reduced efficacy and increased risk of complications.	C
Consider secondary synthetic sling, colposuspension or autologous sling as first options for women with complicated stress urinary incontinence.	C
Implantation of AUS or ACT for women with complicated stress urinary incontinence should only be offered in expert* centres.	C
Warn women receiving AUS or ACT that, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	C

AUS = artificial urinary sphincter; ACT = adjustable compression therapy.
** expert centres refers to the comments on surgeon volume in the introduction to the surgical chapter.*

*4.3.3 **Women with both stress urinary incontinence and pelvic organ prolapse***

There is a clear association between the presence of POP and SUI. Although the subject of prolapse is not part of the remit of these Guidelines, the extent to which it impacts on the management of SUI will be addressed. The aim is to assess the options available to women who require surgery for POP and who have associated UI (either symptomatic or after reduction of prolapse), and to assess the value of prophylactic antiincontinence surgery in women with no evidence of UI.

4.3.3.1 Questions

1. In women with POP and UI, does combined surgery for POP and SUI reduce the incidence of postoperative UI compared to POP surgery alone?
2. In continent women with POP, does combined surgery for POP and SUI reduce the incidence of postoperative de novo UI compared to POP surgery alone?
3. In women with POP and occult SUI, (i.e. seen only on prolapse reduction stress testing/urodynamics), does combined surgery for POP and SUI reduce the incidence of postoperative UI compared to POP surgery alone?
4. In women with POP and OAB, does surgery for POP improve OAB symptoms?
5. In adults with POP, what are the reliability, the diagnostic accuracy and predictive value of a prolapse reduction test to identify patients at risk for denovo SUI following prolapse repair?

4.3.3.2 Evidence

A Cochrane review in 2013 included sixteen trials concerning bladder function after surgery for pelvic organ prolapse [367]. After prolapse surgery 434 of 2125 women (20.4%) reported new subjective SUI in 16 trials. New voiding dysfunction was reported in 109 of 1209 (9%) women in 12 trials.

1. In women with POP does combined surgery for POP and SUI reduce the incidence of postoperative UI compared to POP surgery alone?

There are two well-designed RCTs relating to the prevalence of postoperative SUI in women who underwent prolapse surgery with and without an anti-incontinence procedure. Both of these trials involved women with POP who did not complain of symptoms of stress incontinence regardless of objective findings.

One trial compared abdominal sacrocolpopexy with and without Burch colposuspension [368], the other compared vaginal repair with and without a mid-urethral sling (3). In both trials addition of an anti-incontinence surgery reduced the risk of SUI at 12 months. In one trial there was a higher rate of adverse events reported in the combined surgery group [369]. This was also the finding of the Cochrane review and meta-analysis.

Two trials addressed postoperative SUI in patients who had had SUI preoperatively. Borstad et al., in a multicenter trial randomised women with POP and SUI to have a tension-free vaginal tape (TVT) at the time of prolapse repair or 3 months later, if they still had SUI. (n=53). One year after surgery there was no difference between the groups regarding continence, however, 44% of the women without initial TVT never required surgery and 29% were dry [370].

In contrast, Costantini et al. followed up women with POP and SUI randomised to abdominal POP repair with or without Burch colposuspension, (after a median of 97 months) finding that additional SUI surgery did not improve outcome [371]. On the contrary, a higher number of patients had de novo storage symptoms when a Burch colposuspension was performed.

In summary, it is difficult to generalise the results of trials using very different procedures to treat both POP and UI. It seems that with a combined procedure the rate of SUI postoperatively is lower. Studies using mid-urethral slings generally have shown more significant differences in UI outcomes with combined procedures than when other types of anti-incontinence procedure have been used. Individual patient characteristics may play the most important role in shaping treatment decisions. It must be taken into account that, although more women may be dry after combined surgery the risks of repeat surgery, should it become necessary, may outweigh the potential benefits.

2. Continent women with POP

The 2013 Cochrane review included 6 trials showing that postoperative incontinence rates at < 12 months were 19% in the combined surgery group vs. 32% in POP surgery alone. In this group of 438 women, undergoing continence surgery at the time of prolapse prevented 62 (14%) women from developing de novo SUI postprolapse surgery. A long-term update of a previously published RCT comparing POP surgery with or without Burch colposuspension in continent women suggested higher UI rates in women undergoing colposuspension [369].

3. Women with POP and occult SUI

The 2013 Cochrane review included five trials addressing this point. Overall, there was a significantly higher rate of postoperative patient-reported SUI with prolapse surgery alone compared with combined surgery.

4. Women with POP and OAB

There is evidence from 3 case series evaluating patients with concomitant OAB and pelvic organ prolapse assessing incontinence/OAB symptom scores postsurgical repair. Costantini et al. assessed the effect of posterior repair on OAB/DO and reported a 70-75% improvement rate in both parameters along with a 93% anatomic success rate [372].

Kummeling et al. assessed the effect of a modified laparosocopic sacrocolpopexy on urodynamic parameters and reported an improvement with no evidence to support a concomitant prophylactic colposuspension [373]. Lee et al. assessed the value of pre-op UDS and BOOI in predicting the degree of OAB symptoms post anterior prolapse repair. They reported a significant correlation between low pre-op BOOI and improvement in OAB symptom scores post-op [374].

5. Prolapse reduction stress test (PRST)

Data concerning PRST were made available from the CARE trial where significant differences were noted in the detection of urodynamic stress incontinence with prolapse reduction among the various methods studied ranging from 6% (pessary) to 30% (speculum). Manual, swab and forceps showed detection rates of 16%, 20% and 21%, respectively [375]. In the study by Duecy about one third of women were diagnosed with occult SUI using a pessary while two thirds were diagnosed with manual reduction of the prolapse [376]. In a further study occult SUI was only detected by a pessary test in 19% of patients, not by urodynamics, history or clinical examination [377].

Evidence summary	**LE**
Women with prolapse + UI	
Surgery for POP + SUI shows a higher rate of cure in the short-term than POP surgery alone.	1a
There is conflicting evidence on the relative benefit of combined surgery long-term.	1b
Combined surgery for POP+SUI carries a higher risk of adverse events.	1b
Continent women with POP	
Are at risk of developing UI postoperatively.	1a

The addition of a prophylactic anti-incontinence procedure reduces the risk of postoperative UI.	1b
The addition of a prophylactic anti-incontinence procedure increases the risk of adverse events.	1b
Women with POP and OAB	
There is some low-level inconsistent evidence to suggest that surgical repair of POP can improve symptoms of OAB.	3
Women with prolapse and occult SUI	
Surgery for POP + occult SUI shows a higher rate of cure in the short-term than POP surgery alone.	1a
Combined surgery for POP + SUI carries a higher risk of adverse events than POP surgery alone.	1b

Recommendations for women requiring surgery for bothersome POP who have symptomatic or unmasked stress urinary incontinence	**GR**
Offer simultaneous surgery for POP and stress urinary incontinence.	A
Warn women of the increased risk of adverse events with combined surgery compared to prolapse surgery alone.	A
Recommendations for women requiring surgery for bothersome POP without symptomatic or unmasked stress urinary incontinence	**GR**
Warn women that there is a risk of developing de novo stress urinary incontinence after prolapse surgery.	A
Inform women that the benefit of prophylactic stress urinary incontinence surgery is uncertain.	C
Warn women that the benefit of surgery for stress urinary incontinence may be outweighed by the increased risk of adverse events with combined surgery compared to prolapse surgery alone.	A

POP = pelvic organ prolapse.
** based on expert opinion.*

*4.3.4 **Urethral diverticulum***

A female urethral diverticulum is a sac-like protrusion made up by the entire urethral wall or only by the urethralmucosa laying between the periurethral tissues and the anterior vaginal wall. Urethral diverticulum give rise to a variety of symptoms that include pain, urgency, frequency, recurrent UTIs, vaginal discharge, dispareunia, voiding difficulties or urinary incontinence.

1. In a woman with the clinical suspicion of having an urethral diverticulum, what is the best test to confirm the diagnosis?

No robust diagnosctic accuracy studies address this question However, a case series of 27 patients concluded that endoluminal (vaginal or rectal) MRI has better diagnostic accuracy than video cystourethrography VCUG [378]. In a case series of 60 subjects Pathi et al reported that the sensitivity, specificity, positive predictive value and negative predictive value of MRI is 100%, 83%, 92% and 100%, respectively [379]. Dwarkasing et al. also reports 100% specificity and sensitivity of MRI in a case series of 60 patients [380]. However, in a case series of 41 patients, a study reported 25% discrepancy between MRI and surgical findings [381].

2. In a woman who has a bothersome urethral diverticulum, what is the relative effectiveness of available surgical treatments?

4.3.4.1 Surgical treatment

No RCTs were found. Surgical removal is the most commonly reported treatment in contemporary cases series. However, recurrence may occur; Han et al. found a recurrence rate of 33% in U-shaped and of 60% in circumferential diverticulum within 1 year [382], Ingber et al. found a 10.7% recurrence rate in 122 women undergoing diverticulectomy, with a higher risk of recurrence in those with proximal or multiple diverticula or after previous pelvic surgery [383]. SUI may occur in up to 20% of women after diverticulectomy, requiring additional correction [384-387]. De novo SUI seems to be more common in proximal and in large size (>30 mm) diverticula.

Diverticula may undergo neoplastic alterations (6%) including invasive adenocarcinomas [388].

Evidence Statement	
MRI has good sensitivity and specificity for the diagnosis of urethral diverticula, however there is a risk of mis-diagnosis and missing potential intraluminal neoplastic change.	3
Surgical removal of symptomatic urethral diverticula provides good long-term results, however, women should be counselled of the risk of recurrence and de novo SUI.	3

Recommendation	GR
Symptomatic urethral diverticula should be completely surgically removed.	A*

*4.3.5 **Men with stress urinary incontinence***

4.3.5.1 Bulking agents in men

Injection of bulking agents has been used to try and improve the coaptation of a damaged sphincter zone. Initial reports showed limited efficacy in treating incontinence following radical prostatectomy incontinence [389, 390].

4.3.5.1.1 Question

In men with post-prostatectomy incontinence or SUI, does injection of a urethral bulking agent cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.1.2 Evidence

Most studies are case series with small sample sizes. Small cohort studies showed a lack of benefit using a number of different materials [391, 392]. However, polyacrylamide hydrogel resulted in limited improvement in QoL without curing the UI [391]. A Cochrane review on the surgical treatment of post-prostatectomy incontinence found only one study that fulfilled the inclusion criteria [393]. A prospective, randomised study compared the AUS to silicon particles (Macroplastique™) in 45 patients. Eighty-two per cent of patients receiving an AUS were continent compared to 46% receiving silicone particles. In patients with severe incontinence, outcome was significantly worse after silicon bulking injection.

Evidence summary	LE
There is no evidence that bulking agents cure post-prostatectomy incontinence.	2a
There is weak evidence that bulking agents can offer temporary, short-term, improvement in QoL in men with post-prostatectomy incontinence.	3
There is no evidence that one bulking agent is superior to another.	3

4.3.5.2 Fixed male sling

As well as external compression devices and bulking agents, slings have been introduced to treat postprostatectomy incontinence. Fixed slings are positioned under the urethra and fixed by a retropubic or transobturator approach. The tension is adjusted during the surgery and cannot be re-adjusted postoperatively.

For the restoration of continence by these male slings, two concepts are now being proposed:

- continence restoration by urethral compression (InVance®, Istop TOMS, Argus®)
- continence restoration by repositioning the bulb of urethra (AdVance) [394].

In principle, the AUS can be used for all degrees of post-prostatectomy incontinence, while male slings are advocated for mild-to-moderate UI. However, the definitions of mild and moderate UI are not clear. The definition of cure, used in most studies, was no pad use or one security pad per 24 hours. Some authors used a stricter criterion of less than 2 g urine loss in a 24-hour pad test [395].

4.3.5.2.1 Question

In men with post-prostatectomy SUI, does insertion of a fixed suburethral sling cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.2.2 Evidence

Concerning the surgical treatment of post-prostatectomy incontinence, three recent literature reviews are available [396-398]. There are a large number of uncontrolled case series concerning men implanted with several types of slings [399, 400].

For the repositioning sling (AdVance), the benefit after a mean follow-up of 3 years has been published on 136 patients [401]. Earlier data were available from other cohort studies, totalling at least 614 patients with a mean follow-up of between 3 months and 3 years. Subjective cure rates for the device vary between 8.6% and 73.7%, with a mean of 49.5%. Radiotherapy was a negative prognostic factor [399]. Postoperative voiding dysfunction occurred in 5.7-1.3%, while erosions and chronic pain were uncommon (0-0.4%) [395, 401-403]. The overall failure rate was about 20%.

The previously available “InVance®” device has now been removed from the market in some countries.

Evidence summary	LE
There is limited short-term evidence that fixed male slings cure or improve post-prostatectomy incontinence in patients with mild-to-moderate incontinence.	3
Men with severe incontinence, previous radiotherapy or urethral stricture surgery may have less benefit from fixed male slings.	3
There is no evidence that one type of male sling is better than another.	3

4.3.5.3 Adjustable slings in males

Adjustability in male sling surgery attempts to adjust the tension of the sling postoperatively. Three main systems have been used in men: the Remeex® system, the Argus® system and the ATOMS system.

4.3.5.3.1 Question

In men with post-prostatectomy incontinence or SUI, does insertion of an adjustable suburethral sling cure or improve SUI, improve QoL, or cause adverse outcomes?

4.3.5.3.2 Evidence

There are no prospective RCTs. Most studies consist of prospective or retrospective case series, with variable follow-up and different definitions of success. Some have been published only as conference abstracts.

Remeex® system

For the Remeex® system, only two abstracts, with conflicting findings, have been published. One study followed 19 patients for nearly 7 years and reported 70% success, with no explants, infections or erosions. The second study followed 14 patients for 25 months. Only 36% of patients were satisfied and multiple re-adjustments were needed. Mechanical failure was reported in 21% [404].

Argus® system

Data on the Argus® system have been reported for 404 men, but only four series have reported on more than 50 patients [405, 406], with the longest follow-up being 2.4 years. Success rates varied between 17% and 91.6%, with a mean of 57.6% predominantly reporting a subjective cure. The number of implants requiring re-adjustment was reported as between 22.9% and 41.5% [406]. Infection of the device occurred in 5.4- 8% [405]. Erosions were reported in 5-10% [407]. Urethral perforations occurred in 2.7-16% [405]. Pain at the implant site was usually only temporary, but chronic pain has been reported [405, 407]. These complications resulted in explantation rates of 10-15% [406].

The ATOMS system consists of a mesh implant with an integrated adjustable cushion, which uses a titanium port left in the subcutaneous tissue of the lower abdomen for adjustment of cushion volume. Initial reports show objective cure rates of 60.5% and improvement rates of 23.7% but with the need for up to nine postoperative adjustments [408, 409].

Evidence summary	LE
There is limited evidence that adjustable male slings can cure or improve SUI in men.	3
There is limited evidence that early explantation rates are high.	3
There is no evidence that adjustability of the male sling offers additional benefit over other types of sling.	3

4.3.5.4 Compression devices in males

External compression devices can be divided into two types: circumferential and non-circumferential compression of the urethral lumen [396]. The artificial urinary sphincter (AUS) is the standard treatment for moderate-to-severe male SUI. Most data available on the efficacy and adverse effects of AUS implantation are from older retrospective cohort studies with RCTs not performed due to the lack of a comparator. Men considering insertion of an AUS should understand that if the ability of an individual to operate the pump is uncertain, it may not be appropriate to implant an AUS. There are several recognised complications of AUS implantation, e.g. mechanical dysfunction, urethral constriction by fibrous tissue, erosion and infection. The non-circumferential compression devices consist of two balloons placed close to the vesico-urethral anastomotic site. The balloons can be filled and their volume can be adjusted postoperatively through an intrascrotal port.

4.3.5.4.1 Question

In men with post-prostatectomy SUI, does insertion of an external compression device cure SUI, improve QoL,or cause adverse outcomes?

4.3.5.4.2 Evidence

Artificial urinary sphincter

Although the AUS is considered to be the standard treatment for men with SUI, there are two systematic reviews [393, 398] presenting limited evidence, of generally poor quality, except for one RCT comparing with bulking agents [389]. A continence rate of about 80% can be expected, while this may be lower in men who have undergone pelvic radiotherapy [396].

Trigo Rocha et al. published a prospective cohort study on 40 patients with a mean follow-up of 53 months, showing that from all urodynamic parameters, only low bladder compliance had a negative impact on the outcome [410]. Another retrospective study showed that no urodynamic factors adversely altered the outcome of AUS implantation [411].

The transcorporeal technique of placement can be used for repeat surgery but evidence of effectiveness is lacking [412]. The dual-cuff placement was introduced to treat patients who remained incontinent with a single 4 cm cuff in place. However, it has not improved control of UI, while the availability of a 3.5 cm cuff may have eliminated the need for a dual cuff [413, 414]. Patients who experienced complete continence after AUS implantation had a higher erosion risk [415]. One small series reported results of AUS implantation after failure of previous Advance sling, showing no difference in efficacy between secondary and primary implantation [416].

Non-circumferential compression device (ProAct®)

There have been trials to treat post-prostatectomy SUI by insertion of a device consisting of balloons with adjustable volume external to the proximal bulbar urethra. A prospective cohort study (n = 128) described the functional outcome as 'good' in 68%, while 18% of the devices had to be explanted [417]. A subgroup of radiotherapy patients only had 46% success and a higher percentage of urethral erosions.

A quasi-randomised trial comparing a non-circumferential compression device (ProAct®) with bone-anchored male slings found that both types of device resulted in similar improvement of SUI (68% vs. 65%, respectively) [418]. Other prospective series have shown that adverse events were frequent, leading to an explantation rate of 11-58% [398, 419-422]. A questionnaire study showed that 50% of patients were still bothered significantly by persistent incontinence [423].

Other designs of artifical sphincter remain the subject of ongoing evaluation though may have been introduced onto the market.

Evidence summary	**LE**
There is limited evidence that primary AUS implantation is effective for cure of SUI in men.	2b
Long-term failure rate for AUS is high although device replacement can be performed.	3
There are conflicting data on whether previous pelvic radiotherapy affects the outcome of AUS implantation.	3
Men who develop cognitive impairment or lose manual dexterity will have difficulty operating an AUS.	3
The usefulness of tandem-cuff placement is uncertain.	3
There is insufficient evidence to state whether one surgical approach for cuff placement is superior to another.	3
Very limited short-term evidence suggests that the non-circumferential compression device (ProACT®) is effective for treatment of post-prostatectomy SUI.	3
The non-circumferential compression device (ProACT®) is associated with a high failure and complication rate leading to frequent explantation.	3
The rate of explantation of the AUS because of infection or erosion remains high (up to 24% in some series).	3
Mechanical failure is common with the AUS.	3
Revision and reimplantation of AUS is possible after previous explantation or for mechanical failure.	3

Recommendations for surgery in men with stress urinary incontinence	**GR**
Only offer bulking agents to men with mild post-prostatectomy incontinence who desire temporary relief of incontinence symptoms.	C
Do not offer bulking agents to men with severe post-prostatectomy incontinence.	C
Offer fixed slings to men with mild-to-moderate * post-prostatectomy incontinence.	B
Warn men that severe incontinence, prior pelvic radiotherapy or urethral stricture surgery, may worsen the outcome of fixed male sling surgery.	C

Offer AUS to men with moderate-to-severe post-prostatectomy incontinence.	B
Implantation of AUS or ACT for men should only be offered in expert centres.	C
Warn men receiving AUS or ACT that, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	C
Do not offer non-circumferential compression device (ProACT®) to men who have had pelvic radiotherapy.	C

AUS = artificial urinary sphincter; ACT = artificial compression device.
** the terms mild and moderate post prostatectomy incontinence remain undefined.*

*4.3.6 **Surgical interventions for refractory detrusor-overactivity***

4.3.6.1 Bladder wall injection of botulinum toxin A

Onabotulinum toxin A (onabotA; BOTOX®) 100 U dissolved in 10 ml of saline and injected in 20 points of the bladder wall above the trigone (0.5 ml per injection site) is licenced in Europe to treat OAB with persistent or refractory UUI in adults of both gender, despite the small number of males included in the registration trials [424, 425]. Surgeons must realise that other doses of onabotA and other formulations of botulinum toxin A, abobotulinum toxinA and incobotulinum toxin A, are not licensed for use in UUI. Doses for OnabotA are not transposable to the other brands of botulinum toxin A. The continued efficacy of repeat injections is the rule but discontinuation rate may be high. The most important adverse events related to onabotA 100 U injection detected in the regulatory trials were UTI and an increase in PVR that may require clean intermittent catheterisation (CIC) [426].

4.3.6.1.1 Question

In adults with UUI, is bladder wall injection of onabotA better than no treatment for cure or improvement?

4.3.6.1.2 Evidence

Following a dose ranging study in which the 100U of onabotA was established as the ideal dose, two phase III trials randomised (1:1) 1105 OAB incontinent patients whose symptoms were not adequately managed with anticholinergics to receive bladder wall injections of onabotA (100 U) or saline. At baseline the population had in average more than 5 episodes of UUI, around 12 micturitions per day and small PVR. At week 12, in patients treated with onabotA UUI episodes/day were halved and number of micturitions/day reduced by more than 2. A total of 22.9% of the patients in the onabotA arm were fully dry, against 6.5% in the saline arm [427].

QoL was substantially improved in the onabotA arm, as shown by the more than 60% of positive responses in the TBS questionnaire at week 12, which doubled the positive responses in the saline arm. Cohort studies have shown the effectiveness of bladder wall injections of onabotA in the elderly and frail elderly [428], though the success rate might be lower and the PVR (> 150 mL) higher in this group.

A recent RCT compared onabotA injection 100 U to solifenacin (with dose escalation or switch to trospium possible in the solifenacin group) and showed a similar rates of improvement in UUI over the course of 6 months [429]. Patients receiving onabotA were more likely to have cure of UUI (27% vs. 13%, p = 0.003), but also had higher rates of urinary retention during the initial 2 months (5% vs. 0%) and of UTIs (33% vs. 13%). Patients taking antimuscarinics were more likely to have dry mouth.

Evidence summary	**LE**
A single treatment session ofl onabotulinum toxin A (100U) injected in the bladder wall is more effective than placebo at curing and improving UUI and QoL for up to 12 months.	1a
There is no evidence that repeated injections of onabotulinum toxin A have reduced efficacy.	3
There is a high risk of increased PVR when injecting elderly frail patients.	3
The risk of bacteruria after onabotulinum toxin A (100U) injection is high but the clinical significance of this remains uncertain.	1b
Onabotulinum toxin A 100 U is superior to solifenacin for cure of UUI.	1a
Long-term treatment with of onabotulinum toxin A may be associated with a high discontinuation rate.	2

Recommendations	**GR**
Offer bladder wall injections of onabotulinum toxin A (100 units) to patients with urgency urinary incontinence refractory to antimuscarinic therapy.	A
Warn patients of the limited duration of response, risk of UTI and the possible prolonged need to selfcatheterise (ensure that they are willing and able to do so) and risk of UTI.	A

UTI = urinary tract infection.

4.3.6.2 Sacral nerve stimulation (neuromodulation)

In the first stage of a two-stage implantation, an electrode is placed percutaneously under fluoroscopic control in the sacral foramen alongside a sacral nerve, usually S3. In earlier techniques, a temporary wire electrode was used. More recently, a permanent tined electrode has been used for a longer test phase. Patients, in whom selected symptoms of UUI are reduced by more than 50% during the test phase, are candidates for the full implant, including the pulse generator.

4.3.6.2.1 Question

In adults suffering from refractory UUI, what is the clinical effectiveness of sacral nerve neuromodulation compared to alternative treatments?

4.3.6.2.2 Evidence

All randomised studies suffer from the limitation that assessors and patients were not blind to the treatment allocation since all recruited subjects had to respond to a test phase before randomisation. A Cochrane review of the literature until March 2008 [430] identified three RCTs that investigated sacral nerve stimulation in patients with refractory UUI.

One study compared implantation to controls who stayed on medical treatment and received delayed implantation at 6 months. Fifty percent of the immediately implanted group had > 90% improvement in UUI at 6 months compared to 1.6% of the control group [222]. The other RCT [431] achieved similar results, although these patients had already been included in the first report [222]. However, Weil et al. [431] showed that the effect on generic QoL measured by the SF-36, was unclear as it differed between the groups in only one of the eight dimensions.

The results of 17 case series of patients with UUI, who were treated early in the experience with sacral nerve stimulation were reviewed [432]. After a follow-up duration of between 1 and 3 years, approximately 50% of patients with UUI demonstrated > 90% reduction in UI, 25% demonstrated 50-90% improvement, and another 25% demonstrated < 50% improvement. Two case series describing the outcome of sacral nerve neuromodulation, with a mean or median follow-up of at least 4 years [433, 434] reported continued success (> 50% improvement on original symptoms) by about 50 of patients available for follow-up. Cure rates for UUI were 15% [434].

Adverse events occurred in 50% of implanted cases, with surgical revision necessary in 33-41% [433, 434].

In a subanalysis of the RCT, the outcomes of UUI patients, with or without pre-implant DO, were compared. Similar success rates were found in patients with and without urodynamic DO [435].

Evidence summary	**LE**
Sacral nerve neuromodulation is more effective than continuation of failed conservative treatment for cure of UUI, but no sham controls have been used.	1b
In those patients who have been implanted, at longterm 50% improvement of UUI is maintained in at least 50% of patients and 15% may remain cured.	3
One-stage implantation. The use of tined, permanent electrodes results in more patients receiving the final implant than occurs with temporary test stimulation.	4

Recommendation	**GR**
If available, offer sacral nerve modulation to patients who have urgency urinary incontinence refractory to conservative therapy.	A

4.3.6.3 Cystoplasty/urinary diversion

4.3.6.3.1 Augmentation cystoplasty

In augmentation cystoplasty (also known as clam cystoplasty), a detubularised segment of bowel is inserted into the bivalved bladder wall. The distal ileum is the bowel segment most often used but any bowel segment can be used if it has the appropriate mesenteric length. One study did not find any difference between bivalving the bladder in the sagittal or in the coronal plane [436, 437].

There are no RCTs comparing bladder augmentation to other treatments for patients with UUI. Most often, bladder augmentation is used to correct neurogenic DO or small-capacity, low-compliant, bladders caused by fibrosis, tuberculosis, radiation or chronic infection.

The largest case series of bladder augmentation in a mixed population of ideopathic and neurogenic UUI included 51 women [438]. At an average follow-up of 74.5 months, only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UUI. It seems that the results for patients with idiopathic DO (58%) seemed to be less satisfactory than for patients with neurogenic UUI (90%).
Adverse effects were common and have been summarised in a review over 5-17 years of more than 267 cases, 61 of whom had non-neurogenic UUI [439]. In addition, many patients may require clean intermittent selfcatheterisation to obtain adequate bladder emptying (Table 7).

Table 7: Complications of bladder augmentation

Short-term complications	**Affected patients (%)**
Bowel obstruction	2
Infection	1.5
Thromboembolism	1
Bleeding	0.75
Fistula	0.4
Long-term complications	**Affected patients (%)**
Clean intermittent self-catheterisation	38
Urinary tract infection	70% asymptomatic; 20% symptomatic
Urinary tract stones	13
Metabolic disturbance	16
Deterioration in renal function	2
Bladder perforation	0.75
Change in bowel symptoms	25

4.3.6.3.2 Detrusor myectomy (bladder auto-augmentation)
Detrusor myectomy aims to increase bladder capacity and reduce storage pressures by incising or excising a portion of the detrusor muscle, to create a bladder mucosal 'bulge' or pseudodiverticulum. It was initially described as an alternative to bladder augmentation in children [440]. Two case series [441, 442], in adult patients with idiopathic and neurogenic bladder dysfunction, demonstrated poor long-term results caused by fibrosis of the peudodiverticulum This technique is rarely if ever used nowadays.

4.3.6.3.3 Urinary diversion
Urinary diversion remains a reconstructive option for patients, who decline repeated surgery for UI. However, there are no studies that have specifically examined this technique in the treatment of non-neurogenic UI [436].

Evidence summary summary	**LE**
There is limited evidence on the effectiveness of augmentation cystoplasty and urinary diversion in treatment of idiopathic DO.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short-term and long-term severe complications.	3
The need to perform clean intermittent self-catheterisation following augmentation cystoplasty is very common.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty with urinary diversion.	3
Detrusor myectomy is ineffective in adults with UI.	3

Recommendations	**GR**
Only offer augmentation cystoplasty to patients with detrusor overactivity incontinence who have failed conservative therapy, in whom the possibility of botulinum toxin and sacral nerve stimulation has been discussed.	C
Warn patients undergoing augmentation cystoplasty of the high risk of having to perform clean intermittent self-catheterisation; ensure they are willing and able to do so.	C
Do not offer detrusor myectomy as a treatment for urinary incontinence.	C
Only offer urinary diversion to patients who have failed less invasive therapies for the treatment of urinary incontinence and who will accept a stoma.	C

Warn patients undergoing augmentation cystoplasty or urinary diversion of the high risk of short-term and long-term complications, and the possible small risk of malignancy.	C
Life-long follow-up is recommended for patients who have undergone augmentation cystoplasty or urinary diversion.	C

*4.3.7 **Surgery in patients with mixed urinary incontinence***

4.3.7.1 Question

In adults with MUI, is the outcome of surgery different to that obtained with the same treatment in patients with either pure SUI or pure UUI?

4.3.7.2 Evidence

Many RCTs include both patients with pure SUI or pure UUI and patients with MUI. However, very few RCTs report separate outcomes for MUI and pure UI groups.

Transvaginal obturator tape

In an RCT including 96 women with MUI, objective improvement was better for patients treated with transvaginal obturator tape + the Ingelman Sundberg operation versus patients treated with obturator tape alone [443].

Post-hoc analysis of the SISTER trial showed that in women undergoing either autologous fascial sling or Burch colposuspension, the outcomes were poorer for women with a concomitant complaint of pre-operative urgency [72]. A similar post-hoc review of another RCT comparing transobturator and retropubic mid-urethral slings showed that the greater the severity of pre-operative urgency the more likely that treatment would fail [85]. However, an earlier study had found that surgery provided similar outcomes, whether or not urgency was present prior to surgery (this study included only a few patients with urodynamic DO).

Case series tend to show poorer results in patients with MUI compared with those with pure SUI. In a case series of 192 women undergoing mid-urethral sling insertion, overall satisfaction rates were lower for women with mixed symptoms and detrusor overactivity on pre-operative urodynamics compared to those with pure SUI and normal urodynamics (75% vs. 98%, respectively) [444]. Comparison of two parallel cohorts of patients undergoing surgery for SUI, with and without DO, found inferior outcomes in women with MUI [445].

One cohort of 450 women, found that In urgency-predominant MUI, the success rate fell to 52% compared to 80% in stress-predominant MUI [446]. In a study with 1113 women treated with transvaginal obturator tape, SUI was cured equally in stress-predominant MUI or urgency-predominant MUI. However, women with stress-predominant MUI were found to have significantly better overall outcomes than women with urgency-predominant MUI [447].

Overall, the outcome for women with pre-existing urgency incontinence remains uncertain.

Evidence summary	**LE**
Women with MUI are less likely to be cured of their incontinence by SUI surgery than women with SUI alone.	1c
The response of pre-existing urgency symptoms to SUI surgery is unpredictable and symptoms may improve or worsen.	3

Recommendations	**GR**
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
Warn patients with mixed urinary incontinence that surgery is less likely to be successful than surgery in patients with stress urinary incontinence alone.	A
Warn patients with mixed urinary incontinence that one single treatment may not cure UI; it may be necessary to treat other components of the incontinence problem as well as the most bothersome symptom.	A*

** upgraded following panel consensus.*

*4.3.8 **Surgery for urinary incontinence in the elderly***

There are no RCTs comparing surgical treatment in older versus younger women although subgroup analyses of some RCTs have included a comparison of older with younger cohorts.

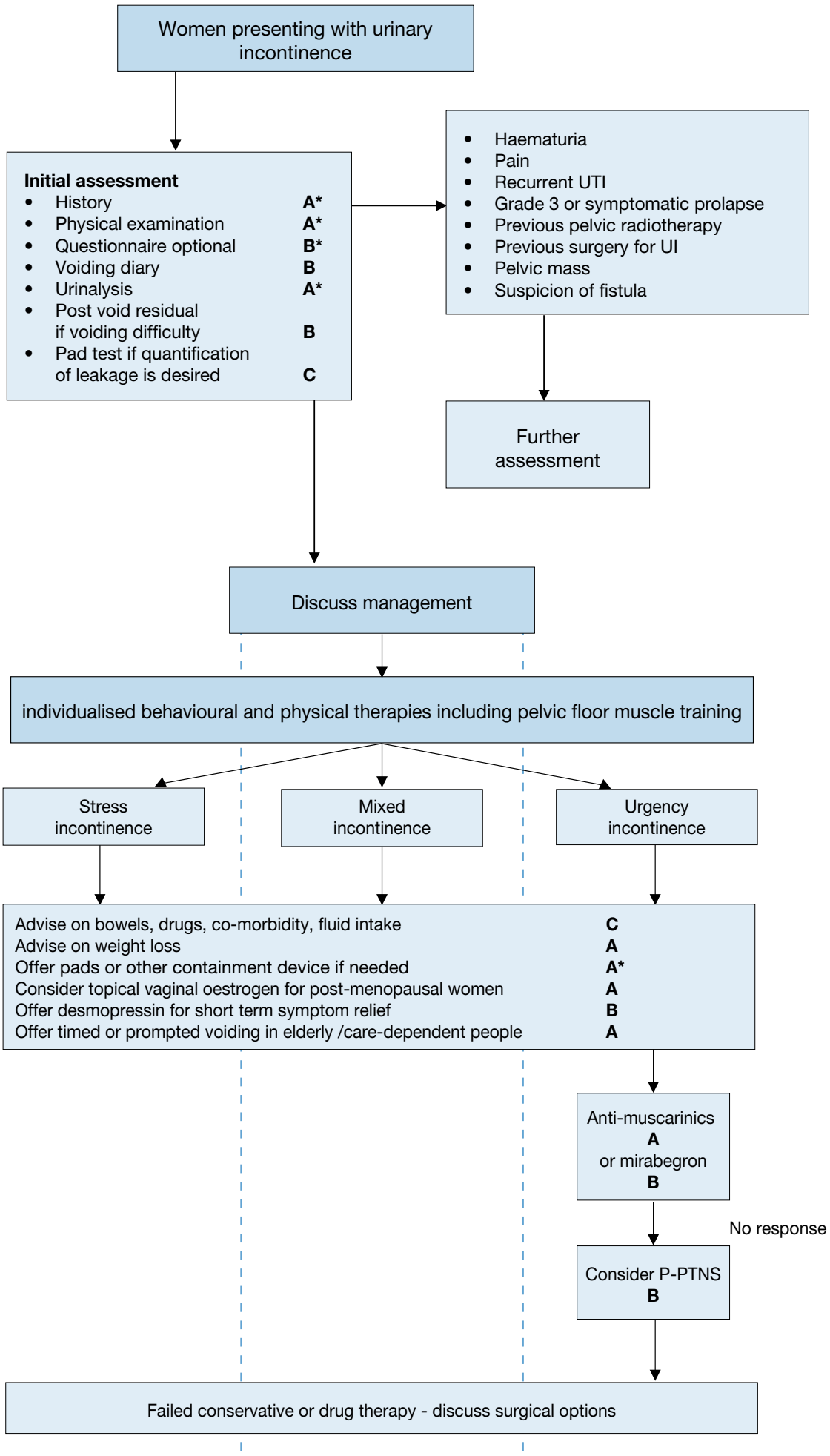
An RCT of 537 women comparing retropubic to transobturator tape, showed that cure rates decreased and failure increased with each decade over the age of 50 [448]. An RCT assessing risk factors for failure of tension free vaginal tape (TVT) versus transobturator tension-free vaginal tape (TVT-O) in 162 women found that age is a specific risk factor (adjusted OR 1.7 per decade) for recurrence at 1 year [326]. In a subanalysis of the SISTER trial cohort of 655 women at 2 years of follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up (OR 3.7, 95% CI 1.7-7.97), are less likely to report objective or subjective improvement in stress and urgency UI, and are more likely to undergo retreatment for SUI (OR 3.9, 95% CI 1.3-11.48). There was no difference in time to normal postoperative voiding [72].

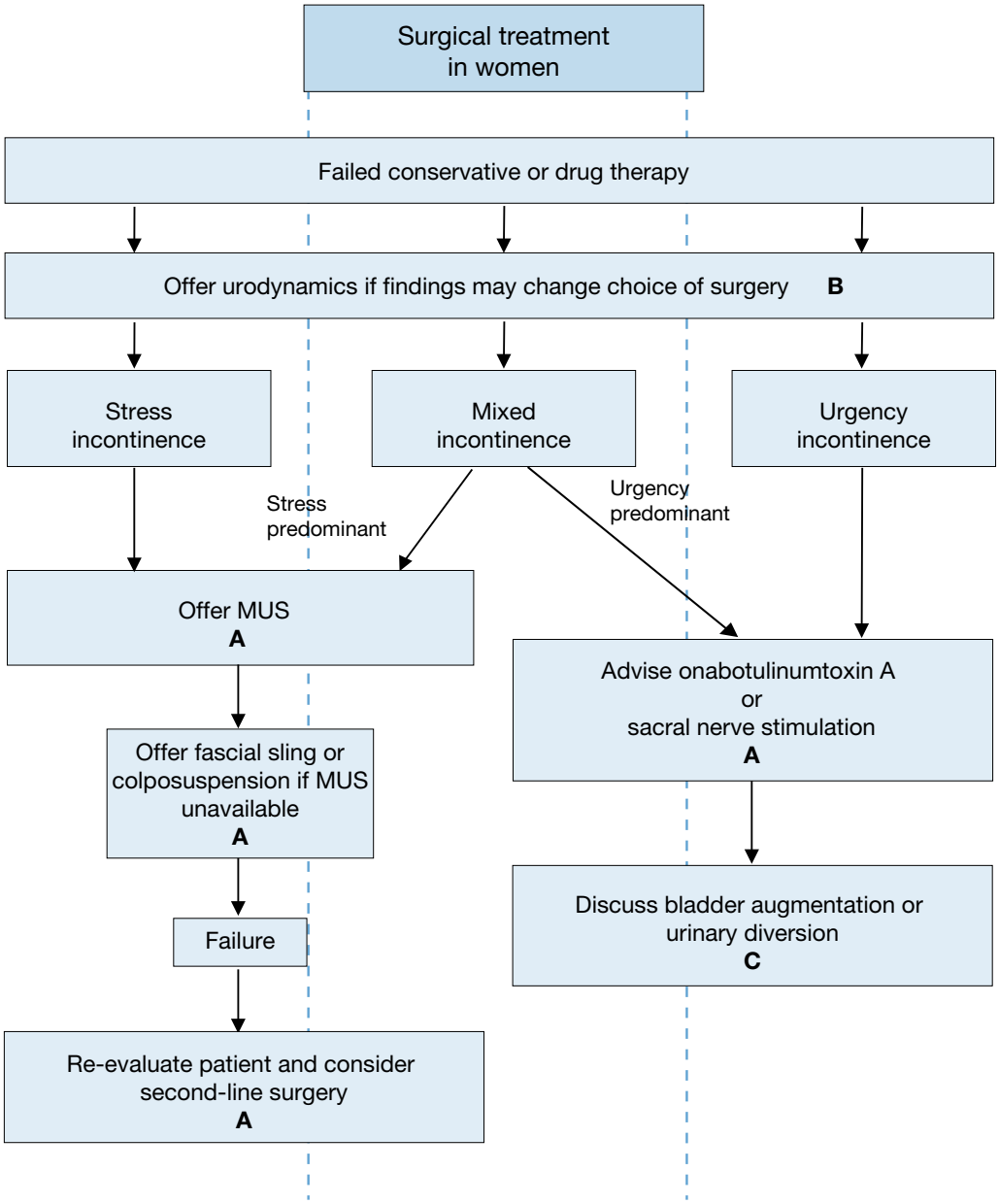
Another RCT compared immediate TVT versus delayed TVT in older women, confirming significant efficacy for the operated women, but the cohort as a whole suffered higher complication rates, particularly bladder perforation (22%) and urinary retention (13%) [327].

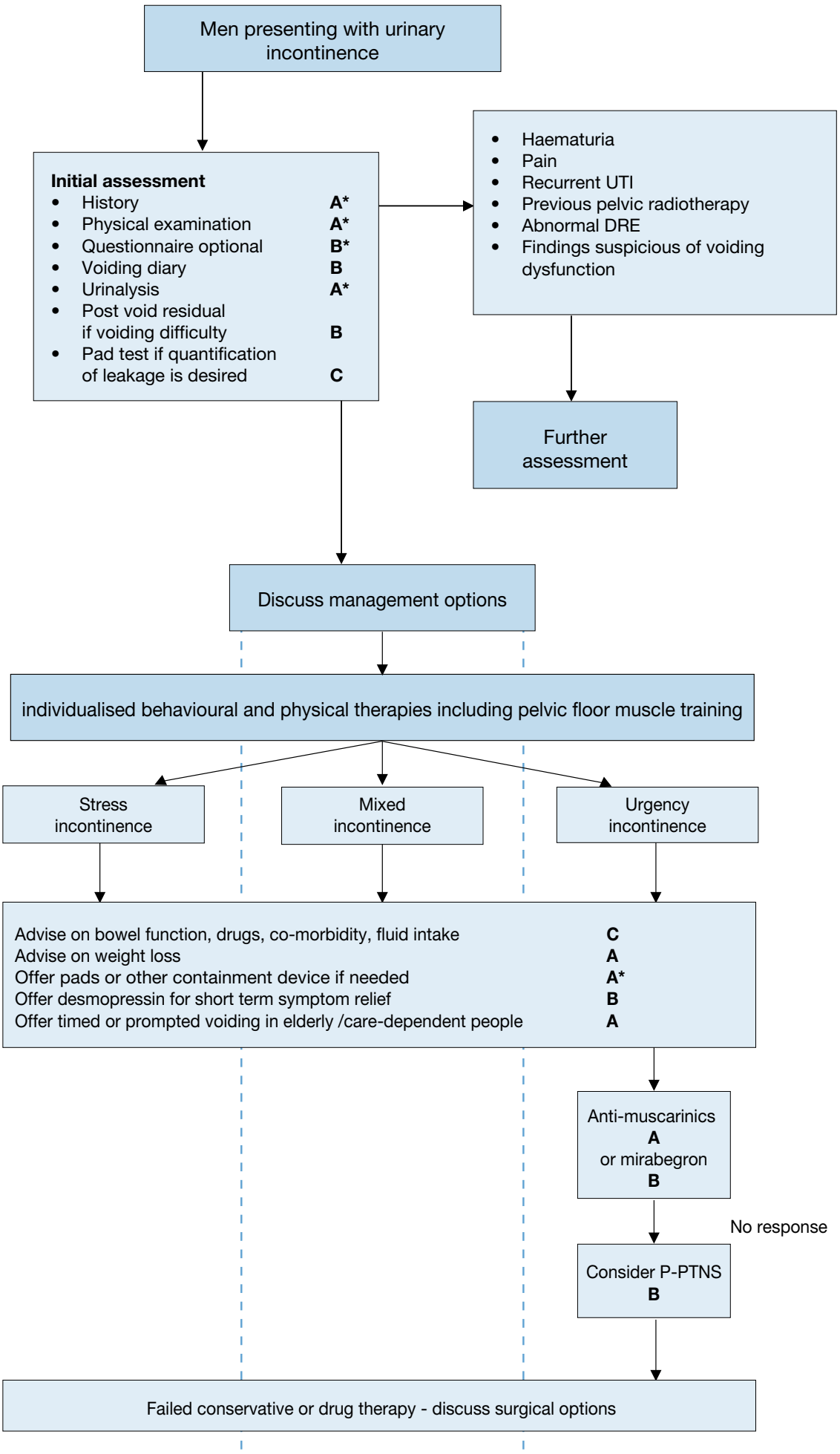
A cohort study of 256 women undergoing inside-out TVT-O reported similar efficacy in older versus younger women but there was a higher risk of de novo urgency in older patients [328].
Cohort studies have shown the effectiveness of onabotulinum toxin A injections in the elderly and frail elderly [428, 449], although a comparison of cohort groups suggests that there is a lower success rate in the frail elderly and also a higher rate of increased PVR (> 150 mL) in this group.

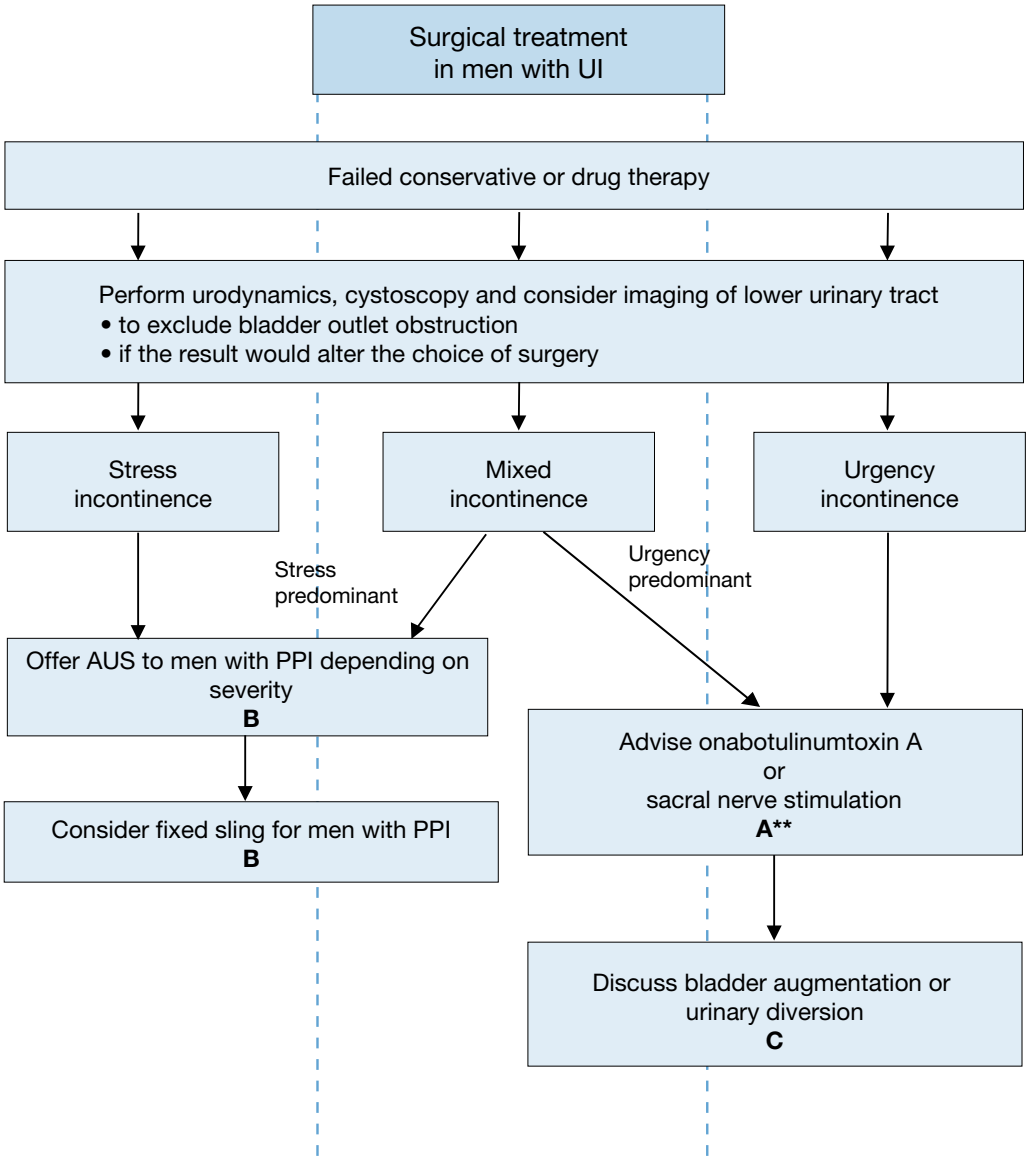
Evidence summary	**LE**
Older women benefit from surgical treatment for incontinence.	1
The risk of failure from surgical repair of SUI, or of suffering adverse events, appears to increase with age.	2
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4

Recommendation	**GR**
Inform older women with urinary incontinence about the increased risks associated with surgery, (including onabotA injection), together with the lower probability of benefit.	B


Women presenting with urinary incontinence
Initial assessment
History A*
Physical examination A*
Questionnaire optional B*
Voiding diary B
Urinalysis A*
Post void residual if voiding difficulty B
Pad test if quantification of leakage is desired C
Haematuria
Pain
Recurrent UTI
Grade 3 or symptomatic prolapse
Previous pelvic radiotherapy
Previous surgery for UI
Pelvic mass
Suspicion of fistula
Further assessment
Discuss management
individualised behavioural and physical therapies including pelvic floor muscle training
Stress incontinence
Mixed incontinence
Urgency incontinence
Advise on bowels, drugs, co-morbidity, fluid intake C
Advise on weight loss A
Offer pads or other containment device if needed A*
Consider topical vaginal oestrogen for post-menopausal women A
Offer desmopressin for short term symptom relief B
Offer timed or prompted voiding in elderly /care-dependent people A
Anti-muscarinics A or mirabegron B
No response
Consider P-PTNS B
Failed conservative or drug therapy - discuss surgical options


Surgical treatment in women
Failed conservative or drug therapy
Offer urodynamics if findings may change choice of surgery B
Stress incontinence
Mixed incontinence
Urgency incontinence
Stress predominant
Urgency predominant
Offer MUS A
Offer fascial sling or colposuspension if MUS unavailable A
Failure
Re-evaluate patient and consider second-line surgery A
Advise onabotulinumtoxin A or sacral nerve stimulation A
Discuss bladder augmentation or urinary diversion C


Men presenting with urinary incontinence
Initial assessment
History A*
Physical examination A*
Questionnaire optional B*
Voiding diary B
Urinalysis A*
Post void residual if voiding difficulty B
Pad test if quantification of leakage is desired C
Haematuria
Pain
Recurrent UTI
Previous pelvic radiotherapy
Abnormal DRE
Findings suspicious of voiding dysfunction
Further assessment
Discuss management options
individualised behavioural and physical therapies including pelvic floor muscle training
Stress incontinence
Mixed incontinence
Urgency incontinence
Advise on bowel function, drugs, co-morbidity, fluid intake C
Advise on weight loss A
Offer pads or other containment device if needed A*
Offer desmopressin for short term symptom relief B
Offer timed or prompted voiding in elderly /care-dependent people A
Anti-muscarinics A or mirabegron B
No response
Consider P-PTNS B
Failed conservative or drug therapy - discuss surgical options



** *Available evidence on onabutulinumtoxinA and sacral nerve stimulation refers mainly to women.*

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6. CONFLICT OF INTEREST

All members of the Urinary Incontinence Guidelines Panel have provided disclosure statements on all relationships that they have and that might be perceived to be a potential source of conflict of interest. This information is publically accessible through the European Association of Urology website. This Guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

NICE National Institute for Health and Care Excellence

NICE guideline

Urinary incontinence and pelvic organ prolapse in women: management

NICE guideline

Published: 2 April 2019
nice.org.uk/guidance/ng123

Artificial urinary sphincters

1.5.12 Do not offer women an artificial urinary sphincter to manage stress urinary incontinence unless previous surgery has failed. **[2006, amended 2019]**

1.5.13 For women who have had an artificial urinary sphincter inserted:

- offer postoperative follow-up **and**
- ensure access to review if needed. **[2006, amended 2019]**

Procedures that should not be offered

1.5.14 Do not offer women the following procedures to treat stress urinary incontinence:

- anterior colporrhaphy
- needle suspension
- paravaginal defect repair
- porcine dermis sling
- the Marshall–Marchetti–Krantz procedure. **[2019]**

Follow-up after surgery

1.5.15 Offer a follow-up appointment within 6 months to all women who have had a surgical procedure to treat stress urinary incontinence. **[2019]**

1.5.16 For women who have had retropubic mid-urethral mesh sling surgery, the follow-up appointment should include a vaginal examination to check for exposure or extrusion of the mesh sling. **[2019]**

1.5.17 Providers should ensure that women who have had surgery for stress urinary incontinence have access to further referral if they have recurrent symptoms or suspected complications. See also assessing complications associated with mesh surgery in this guideline. **[2019]**

1.5.18 For women whose primary surgical procedure for stress urinary incontinence

Urinary Incontinence Treatment

Date of Origin: 07/2002 **Last Review Date: 03/27/2019** **Effective Date: 04/01/2019**

Dates Reviewed: 01/2004, 02/2005, 01/2006, 02/2007, 03/2008, 03/2009, 02/2011, 02/2012, 02/2013, 02/2014, 10/2015, 03/2016, 06/2017, 08/2018, 03/2019

Developed By: Medical Necessity Criteria Committee

I. Description

A number of procedures have been investigated for the treatment of urinary incontinence, including pelvic floor muscle exercises, behavioral therapy, sacral nerve stimulation, pelvic floor stimulation, surgery, and radiofrequency energy.

InterStim Continence Control Therapy is **sacral nerve stimulation** that involves the implantation, into the lower back, of electrical leads that are in contact with the sacral nerve root. The wire leads extend through an incision in the abdomen and are connected to an inserted pulse generator to deliver controlled electrical impulses. The physician programs the pulse generator and the individual is able to switch the pulse generator on and off.

Percutaneous tibial nerve stimulation with Urgent® PC by Uroplasty involves the placement of a fine needle electrode into the lower, inner aspect of the leg, near the tibial nerve. The needle electrode is connected to pulse generator that delivers an electrical pulse to the tibial nerve that travels to the sacral plexus. The sacral plexus is responsible for regulating bladder and pelvic floor function. The treatment protocol is for 12 treatments, once a week.

An **artificial urinary sphincter** is a device that involves an inflatable cuff that fits around the urethra. A balloon regulates the pressure of the cuff and a bulb controls inflation and deflation of the cuff. The balloon is surgically placed and the control pump is typically placed in the scrotum for men and the labia for women. The cuff is inflated to prevent incontinence and deflated to allow the patient to urinate.

Injectable bulking agents may be effective in decreasing urinary incontinence in men and women with intrinsic sphincter disorder. The bulking agent increases bladder-outlet resistance and/or increases urethral length. The agent is injected into the submucosal tissues of the urethra or bladder neck and/or into the tissues adjacent to the urethra. The injections increase tissue bulk, thereby increasing outlet resistance.

Posterior tibial nerve stimulation (PTNS) is a minimally invasive neuromodulation system designed to deliver retrograde electrical stimulation to the sacral nerve plexus through percutaneous of the posterior tibial nerve. PTNS is indicated for treatment of urinary urgency, urinary frequency, and urge incontinence. The specific mechanism of action of neuromodulation is unclear, although theories include improved blood flow and change in neurochemical balance along the neurons.

Pelvic floor stimulation involves the electrical stimulation of pelvic floor muscles using either a probe wired to a device for controlling the electrical stimulation, or extracorporeal pulse magnetic innervation.

Innova is a commonly used electrical stimulator that consists of a battery-operated stimulator with a vaginal or rectal electrode. Treatment is performed in the privacy of the patient's home. Extracorporeal Magnetic Innervation Therapy (ExMI) is a noninvasive conservative treatment for urinary incontinence in adult women. This therapy utilizes a changing magnetic field to induce electrical depolarization of nerves and muscles of the pelvic floor. The use of this device consists of a patient sitting fully clothed in a specialized chair in which the perineum rests on the central axis of a pulsing magnetic field.

Radiofrequency energy has been investigated as a technique to shrink and stabilize the endopelvic fascia or the urethra. The SURx Transvaginal System is a radiofrequency device that has been specifically designed as a transvaginal treatment of urinary stress incontinence. The Renessa System is a non-surgical radiofrequency device that uses a balloon catheter system to deliver low temperature radiofrequency energy to the submucosa of the bladder neck and urethra. The controlled heat applied by a radiofrequency device, causes the tissue in the lower urinary tract to become firmer after healing and therefore, increases resistance to involuntary leakage.

II. Criteria: CWQI HCS-0067A and B

A. Moda Health covers 1 or more of the following:
    a. Implantation of the InterStim (Medtronic), a device for unilateral stimulation of the **sacral nerve** will be covered to plan benefits for the treatment of urge urinary incontinence or symptoms of urge-frequency when **1 or more** of the following criteria are met:
        i. A **trial** of InterStim device for sacral nerve stimulation is medically indicated when **ALL** of the following are met:
            1. Documentation of 12 months of urge urinary incontinence or symptoms of urge-frequency and the condition has resulted in significant disability (the frequency and/or severity of symptoms are limiting the member's ability to participate in daily activities)
            2. The patient must be refractory to three month trial conventional therapy with **ALL** of the following:
                a. At least 2 different anti- cholinergic drugs or 1 anti-cholinergic and 1 beta-3 adrenergic receptor agonist

b. behavioral treatments such as pelvic floor exercise, biofeedback, timed voids, or fluid management

ii. **Permanent** placement of the InterStim device is medically indicated when **ALL** of the following criteria are met:

1. Documentation of 12 months of urge urinary incontinence or symptoms of urge-frequency and the condition has resulted in significant disability (the frequency and/or severity of symptoms are limiting the member's ability to participate in daily activities)
2. The Patient must be must be refractory to three month trial conventional therapy with ALL of the following:
    a. At least 2 different anti- cholinergic drugs or 1 anti-cholinergic and 1 beta-3 adrenergic receptor agonist
    b. behavioral treatments such as pelvic floor exercise, biofeedback, timed voids, or fluid management
3. A trial of the device has provided at least 50% decrease in incontinence symptoms

b. Implantation of the InterStim (Medtronic), a device for unilateral stimulation of the **sacral nerve** will be covered to plan benefits for the treatment of non-obstructive urinary retention when **1 or more** of the following criteria are met:

i. A **trial** of sacral nerve stimulation is medically indicated when **ALL** of the following are met:

1. Documentation of 12 months of urinary retention and the condition has resulted in significant disability (the frequency and/or severity of symptoms are limiting the member's ability to participate in daily activities)
2. Pharmacotherapies (e.g. alpha blockers and cholinergics, and antibiotics for urinary tract infections) as well as intermittent catheterization have failed or are not well-tolerated

ii. **Permanent** placement of Sacral Nerve stimulation is medically indicated when **ALL** of the following criteria are met:

1. Documentation of 12 months of urinary retention and the condition has resulted in significant disability (the frequency and/or severity of symptoms are limiting the member's ability to participate in daily activities)
2. Pharmacotherapies (e.g. alpha blockers and cholinergics, and antibiotics for urinary tract infections) as well as intermittent catheterization have failed or are not well-tolerated
3. A trial of the device has provided at least 50% decrease in residual urine volume

c. Moda Health considers removal of an InterStim device medically necessary even when the initial implantation of the InterStim was not indicated

d. The **InterStim** is considered experimental and investigational and is not covered for all other indications because its effectiveness for indications other than the ones listed above has not been established. (Note: bilateral sacral nerve stimulation is considered experimental and investigational for the treatment of urinary incontinence because the effectiveness of this approach has not yet been established).

e. **Posterior tibial nerve stimulation (PTNS)** is medically necessary when **ALL** of the following criteria are met:

i. The patient has documentation of urinary urge incontinence, urge frequency, or urge frequency for at least 12 months severe enough that the condition has resulted in a significant disability (the frequency and/or severity of symptoms are limiting the member's ability to participate in daily activities)
ii. The patient has failed a three month trial of conservative treatment including pharmacotherapies, Kegel exercises, and behavior modification. (e.g., pelvic floor exercise, biofeedback, timed voids, and fluid management)
iii. Percutaneous tibial nerve stimulations considered experimental and investigational when criteria are not met
iv. The requested treatment plan is for 12 treatments, once a week.

f. **Artificial Urinary Sphincters (HCS-0067A)** is covered for the treatment of urinary incontinence due to intrinsic urethral sphincter deficiency with **1 or more of the following:**
   i. Patient is 6 or more months post-prostatectomy and has not had improvement in the severity of urinary incontinence despite trying pharmacological therapy and behavior modification
   ii. Patient has epispadias-exstrophy and has not had success with bladder neck reconstruction surgery
   iii. Patient is a woman with intractable urinary incontinence who has failed behavioral modification, pharmacological therapy, and other surgical treatments
   iv. Patient is a child with intractable urinary incontinence due to intrinsic urethral sphincter deficiency and has been refractory to behavioral modification or pharmacological therapy and is an unsuitable candidate for other surgical procedures for the correction of the urinary incontinence. Request for indications other than those listed above, is considered experimental and investigational because its effectiveness has not been established.
g. **Periurethral Injections of Bulking Agents** will be covered to plan limitations when **All** of the following criteria is met:
   i. The bulking agent is cleared by the FDA for urinary incontinence (e.g., Coaptite [calcium hydroxylapatite], Contigen [glutaraldehyde crossed-linked collagen], Durasphere [carbon-coated spheres/beads], Macroplastique [polydimethylsiloxane], Uryx [ethylene vinyl alcohol copolymer])
   ii. Patient has urinary incontinence resulting from intrinsic sphincter deficiency that is refractory to 12 months conservative management (e.g. Kegel exercises, biofeedback, electrical stimulation, and/or pharmacotherapies); or
   iii. The member has stress incontinence for six months and **ALL** of the following**:**
      1. No other causes of stress incontinence (urinary tract infection, etc.)
      2. Activities of daily living are limited by the stress incontinence
   iv. Request for injection of periurethral bulking agents for UI is considered experimental and investigational for neurogenic bladder and all other indications
   v. Prior to collagen implant therapy, a skin test for collagen sensitivity must be administered and evaluated over a 4 week period. No skin test is required for the carbon-coated beads
   vi. Request is for 5 injection procedures only.
h. **Request for continuation of treatment** will be covered for **1 or more** of the following:
   i. **Posterior tibial nerve stimulation** will be covered when **All** of the following criteria are met:

1. Documentation of improvement of incontinence after 12 treatments

ii. Periurethral Injections of Bulking Agents will be covered when **All** of the following criteria are met:

1. Incontinence improves after 3 treatments with bulking agents

NOTE: If incontinence does not improve after 3 treatments with bulking agents, treatment is considered ineffective and further treatment with bulking agents is not considered medically necessary.

i. The requested procedure does **NOT** include **ALL** of the following as their effectiveness has not been established.

i. Radiofrequency energy (SURx, Renessa System, etc.) for the treatment of stress urinary incontinence.
ii. The Genityte procedure (laser therapy)
iii. Pudendal nerve stimulation
iv. Autologous myoblast transplantation
v. Autologous muscle-derived cell therapy
vi. Collagen porcine dermis mesh
vii. Stem cell therapy
viii. The extraurethral non-circumferential retropubic adjustable compression devices (ProACT Therapy System, Uromedica, Inc.)
ix. Radiofrequency micro-remodeling with SURs System (paraurethral or transvaginal)
x. The Neocontrol system, which uses extracorporeal magnetic innervation (ExMI)
xi. Additional treatments or systems not listed above that have not been proven to be effective in evidence-based literature.

III. Information Submitted with the Prior Authorization Request:

1. Chart notes from the treating physician documenting history of incontinence and treatments
2. For review of sacral nerve stimulators and PTNS, 12 months of chart notes from the treating physician are required, documenting that the above criteria are met.

IV. CPT or HCPC codes covered:

Codes	Description
64561	Percutaneous implantation of neurostimulator electrodes; sacral nerve
64566	Posterior tibial neurostimulation, percutaneous needle electrode, single treatment, includes programming
64581	Implantation neurostimulator electrodes; sacral nerve
A4290	Sacral nerve stimulation test lead, each
C1767	GENERATOR, NEUROSTIMULATOR (IMPLANTABLE), NON-RECHARGEABLE
C1778	LEAD, NEUROSTIMULATOR (IMPLANTABLE)
C1815	Prosthesis, urinary sphincter (implantable)
C1883	ADAPTOR/EXTENSION, PACING LEAD OR NEUROSTIMULATOR LEAD (IMPLANTABLE)
C1897	LEAD, NEUROSTIMULATOR TEST KIT (IMPLANTABLE)

L8603	Injectable bulking agent, collagen implant, urinary tract, 2.5 ml syringe, includes shipping and necessary supplies
L8604	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies
L8606	Injectable bulking agent, synthetic implant, urinary tract, 1 ml syringe, includes shipping and necessary supplies
L8680	IMPLANTABLE NEUROSTIMULATOR ELECTRODE, EACH

V. CPT or HCPC codes NOT covered:

Codes	Description
53860	Transurethral radiofrequency micro-remodeling of the female bladder neck and proximal urethra for stress urinary incontinence
E0740	Incontinence treatment system, pelvic floor stimulator, monitor, sensor, and/or trainer

VI. Annual Review History

Review Date	Revisions	Effective Date
02/2013	Annual Review: Added table with review date, revisions, and effective date. Added percutaneous tibial nerve stimulation criteria and description.	03/1/2013
02/2014	Annual Review: No changes	02/25/2014
09/2015	Annual Review: Added ICD-9, ICD-10, HCPC, CPT , Medicare references	09/2
03/2016	Annual Review: Deleted ICD-9 codes – updated Sacral nerve stimulation, updated Medicare references	03/23/2016
06/2017	Annual Review: Updated to new template	07/01/2017
8/2018	Annual Review: Changed percutaneous tibial nerve stimulation to posterior tibial nerve stimulation. Added description of PTNS	08/22/2018
03/2019	Annual Review: Clarified clinical requirements for sacral nerve stimulation, updated HCPC codes	04/01/2019

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15. Centers for Medicare & Medicaid Services; Local Coverage Determination (LCD): Wisconsin Physicians Service Insurance Corporation; Radiofrequency Treatment for Urinary Incontinence (L31615): effective date 06/15/2011; Revision Effective Date 4/1/2015; Updated 3/17/2015
16. Centers for Medicare & Medicaid Services; Local Coverage Article: Sacral Nervie Stimulation for Urinary and Fecal Incontinence R3 (A51543); Nordian Healthcare Solutions; effective date 04/20/2012; Revision Effective Date 09/01/2014; Updated 8/27/2014
17. Centers for Medicare & Medicaid Services; National Coverage Determination (NCD) for Biofeedback Therapy for the Treatment of Urinary Incontinence (30.1.1): effective date 7/01/2001; Implementation Date 7/1/2001
18. Physician Advisors

Appendix 1 – Applicable ICD-10 diagnosis codes:

Codes	Description
F98.0	Enuresis not due to a substance or known physiological condition
N30.10	Interstitial cystitis (chronic) without hematuria
N30.11	Interstitial cystitis (chronic) with hematuria
N31.2	Flaccid neuropathic bladder, not elsewhere classified
N31.8	Other neuromuscular dysfunction of bladder
N31.9	Neuromuscular dysfunction of bladder, unspecified

N32.81	Overactive bladder
N36.44	Muscular disorders of urethra
N39.3	Stress incontinence (female) (male)
N39.41	Urge incontinence
R32	Unspecified urinary incontinence
R33.9	Retention of urine, unspecified
R35.0	Frequency of micturition
R39.14	Feeling of incomplete bladder emptying
N39.42	Incontinence without sensory awareness
N39.43	Post-void dribbling
N39.45	Continuous leakage
N39.46	Mixed incontinence
N39.490	Overflow incontinence
N39.498	Other specified urinary incontinence
R39.15	Urgency of urination

Appendix 1 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD) and Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD):

Jurisdiction(s): 5, 8	**NCD/LCD Document (s):**
National Coverage Determination (NCD) 30.1.1 Biofeedback Therapy for the Treatment of Urinary Incontinence	
https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=42&ncdver=1&DocID=30.1.1&kq=true&bc=gAAAABAAAAAAAA%3d%3d&	
National Coverage Determination (NCD) 230.18 Sacral Nerve Stimulation for Urinary Incontinence	
https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=249&ncdver=1&DocID=230.18&kq=true&bc=gAAAABAAAAAAAA%3d%3d&	
National Coverage Determination (NCD) 230.10 Incontinence Control Devices	
https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=241&ncdver=1&DocID=230.10&kq=true&bc=gAAAABAAAAAAAA%3d%3d&	

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC

Periurethral Injection of Bulking Agents for Urinary Incontinence

Question: Should periurethral injection of bulking agents be paired with urinary incontinence?

Question source: HSD claims reconsideration

Issue: Intramural urethral bulking aims to augment the urethral wall and increase the urethral closure force. Various types of bulking agents are injected into the submucosa of the proximal urethra just distal to the bladder neck. The injections are usually administered under local anesthesia, either transurethrally or paraurethrally. It is used as a treatment for urinary incontinence.

Currently, CPT 51715 (Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck) is found on lines 87 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM, 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION and 432 HYPOSPADIAS AND EPISPADIAS.

The code was originally added as a biennial review change in 1995 with no prior review of this procedure found in old minutes.

Evidence

1) **Kirchin 2012**, Cochrane review of periurethral bulking agents for women with urinary incontinence
    a. N=14 trials (2004 women)
        i. Trials were small and generally of moderate quality.
    b. One trial of 45 women that compared injection therapy with conservative treatment showed early benefit for the injectable with respect to continence grade (risk ratio (RR) 0.7, 95% confidence interval (CI) 0.52 to 0.94) and quality of life (RR 0.54, 95%CI 0.16 to 0.92).
    c. Another, comparing injection of autologous fat with placebo terminated early because of safety concerns.
    d. Two trials that compared injection with surgical management found significantly better objective cure in the surgical group (RR 4.77, 95% CI 1.96 to 11.64; and RR 1.69, 95% CI 1.02 to 2.79), although the latter trial data did not reach statistical significance if an intention-to-treat analysis was used.
    e. One trial of 30 women showed a weak (but not clinically significant) advantage for patient satisfaction (data not suitable for analysis in Revman) after mid-urethral injection in comparison to bladder neck injection but with no demonstrable difference in continence levels.
    f. Authors' conclusions: The available evidence base remains insufficient to guide practice. In addition, the finding that placebo saline injection was followed by a similar symptomatic improvement to bulking agent injection raises questions about the mechanism of any beneficial effects. One small trial comparing silicone particles with pelvic floor muscle training was suggestive of benefit at three months but it is not known if this was sustained, and the treatment was associated with high levels of postoperative retention and dysuria. Greater symptomatic improvement was observed with surgical treatments, though the advantages need to be set against likely higher risks.

2) **NICE 2005** Intramural urethral bulking procedures for stress urinary incontinence in women
    a. Efficacy
        i. A small randomised controlled trial reported that 53% (34/64) of patients treated by urethral bulking with collagen had no incontinence at 12 months, compared with 72% (39/54) treated with conventional open surgery.
        ii. One case series of patients treated with collagen reported that, after 12 months, 42% (38/90) had either no incontinence or an improvement in symptoms, as measured objectively using cystometry and abdominal leak point pressure.
        iii. One case series of patients treated with silicone particles reported that 68% (69/102) had either no incontinence or marked improvement after a mean follow-up of 3 months. This proportion decreased to 48% (40/84) after a mean follow-up of 18 months.
    b. Safety
        i. Five case series reported safety data on a total of 389 patients. The most commonly reported adverse events were urinary tract infection, affecting 1% (1/102) to 12% (11/90) of patients, and urinary retention, affecting 0% (0/40) to 11% (10/90) of patients. Other reported complications included abscess at the injection site, urgency of micturition and prolonged pain.
        ii. The Specialist Advisors stated that migration of the bulking agent, voiding difficulties, urinary tract infection and allergic reaction are potential adverse events. Haemorrhage was listed as a rare potential adverse event.

<u>Trusted sources coverage recommendation</u>

1) **NICE 2019** Urinary incontinence and pelvic organ prolapse in women: management
    a. Consider intramural bulking agents to manage stress urinary incontinence if alternative surgical procedures are not suitable for or acceptable to the woman. Explain to the woman that:
        i. these are permanent injectable materials
        ii. repeat injections may be needed to achieve effectiveness
        iii. limited evidence suggests that they are less effective than the surgical procedures listed in recommendation 1.5.2 and the effects wear off over time
        iv. there is limited evidence on long-term effectiveness and adverse events

<u>Expert guidelines</u>

1) **American Urology Association 2017**: SURGICAL TREATMENT OF FEMALE STRESS URINARY INCONTINENCE
    a. In patients considering surgery for stress urinary incontinence, physicians may offer the following options: (Strong Recommendation; Evidence Level: Grade A)
        i. Bulking agents
            1. “The Panel believes that bulking agents are viable treatments for SUI; however, little long-term data exists for them.”
            2. Still, the role for bulking agents may best be considered in patients who wish to avoid more invasive surgical management or who are concerned with the lengthier recovery time after surgery or who experience

insufficient improvement following a previous anti-incontinence procedure.

b. In patients with stress urinary incontinence and a fixed, immobile urethra (often referred to as 'intrinsic sphincter deficiency') who wish to undergo treatment, physicians should offer pubovaginal slings, retropubic midurethral slings, or urethral bulking agents. (Expert Opinion)

2) **Syan 2016**, summary of guidelines for treatment of urinary incontinence
   a. Bulking agents are periurethral injections that allow for short term improvement in SUI symptoms. The European Association of Urology (EAU) determined that repeat injections are often required for therapeutic effect (level of evidence 2a); however, the benefit is low adverse risks compared with open surgery. The Canadian Urology Association (CUA) advises bulking agents for indications such as older age, patients opting for less invasive surgery, and patients with high anaesthetic risk. They give a Grade B recommendation to offer this treatment, although both CUA and NICE recommend that patients should be counselled on the likelihood of requiring repeat injections, that the efficacy is inferior to conventional surgical techniques, and that the efficacy decreases over time.

<u>Other payers</u>:

1) MODA 2019
   a. Periurethral Injections of bulking agents will be covered to plan limitations when all of the following criteria is met:
      i. The bulking agent is cleared by the FDA for urinary incontinence (e.g., Coaptite [calcium hydroxylapatite], Contigen [glutaraldehyde crossed-linked collagen], Durasphere [carbon-coated spheres/beads], Macroplastique [polydimethylsiloxane], Uryx [ethylene vinyl alcohol copolymer])
      ii. Patient has urinary incontinence resulting from intrinsic sphincter deficiency that is refractory to 12 months conservative management (e.g. Kegel exercises, biofeedback, electrical stimulation, and/or pharmacotherapies); or
      iii. The member has stress incontinence for six months and ALL of the following:
         1. No other causes of stress incontinence (urinary tract infection, etc.)
         2. Activities of daily living are limited by the stress incontinence
      iv. Request for injection of periurethral bulking agents for UI is considered experimental and investigational for neurogenic bladder and all other indications
      v. Request is for 5 injection procedures only.
   b. Request for continuation of treatment will be covered for 1 or more of the following:
      i. Periurethral Injections of Bulking Agents will be covered when…the following criteria are met:
         1. Incontinence improves after 3 treatments with bulking agents
      ii. NOTE**:** If incontinence does not improve after 3 treatments with bulking agents, treatment is considered ineffective and further treatment with bulking agents is not considered medically necessary.

2) **Aetna 2019**
   a. Periurethral Injections of Bulking Agents: Aetna considers periurethral injections of bulking agents that are cleared by the Food and Drug Administration (FDA) for urinary incontinence (UI) (e.g., Coaptite [calcium hydroxylapatite], Contigen [glutaraldehyde

crossed-linked collagen], Durasphere [carbon-coated spheres/beads], Macroplastique [polydimethylsiloxane], Uryx [ethylene vinyl alcohol copolymer]) medically necessary for the management of members with UI resulting from intrinsic sphincter deficiency that is refractory to conservative management (e.g., Kegel exercises, biofeedback, electrical stimulation, and/or pharmacotherapies).

Members whose incontinence does not improve after 3 treatments with bulking agents are considered treatment failures and are not likely to respond to this therapy. In such cases, further treatment with bulking agents is not considered medically necessary.

Aetna considers injection of periurethral bulking agents for UI experimental and investigational for neurogenic bladder and all other indications.

Periurethral injections of bulking agents have no proven value in any of the following circumstances:

i. Members undergoing or planning to undergo desensitization injections to meat products; *or*
ii. Members with an acute condition involving cystitis, urethritis, or infection; *or*
iii. Members with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies; *or*
iv. Previous pelvic radiation therapy; *or*
v. Unstable or noncompliant bladder.

Claims history

Review of claims data found one claim for CPT 51715 for 1 diagnosis that currently pairs with that code on line 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION; however, this diagnosis does not appear appropriate for periurethral bulking agents (ICD-10 N35.81 Other urethral stricture). Other diagnoses paired with CPT 51715 were on line 453 URINARY INCONTINENCE, line 464 UTERINE PROLAPSE; CYSTOCELE or line 529 CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA.

HERC staff summary: There is very little evidence available regarding periurethral injection of bulking agents for treatment of urinary incontinence. The low-quality evidence that is available indicates that these agents have little long term effectiveness, but may provide some short term benefits. There are adverse events associated with these injections. Other treatments for urinary incontinence that are currently covered on the Prioritized List are more effective than bulking agent therapy. However, bulking agents are recommended by expert groups and covered by other payers, due to the short term improvement in symptoms and the preference of some patients to avoid more invasive procedures.

Periurethral bulking agents are currently paired on the Prioritized List with a variety of diagnoses that are not indicated for this procedure.

HERC staff recommendations:

1) Remove CPT 51715 (Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck) from lines 87 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM, 327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION, 432 HYPOSPADIAS AND EPISPADIAS.
    a. No appropriate diagnoses on these lines for pairing

2) Add limited coverage of periurethral bulking agents based on expert opinion for those patients who are not surgical candidates or who choose not to have invasive surgery
    a. Add CPT 51715 to 453 URINARY INCONTINENCE
    b. Modify GN47 as shown below

GUIDELINE NOTE 47, URINARY INCONTINENCE

Line 453

Surgery for genuine stress urinary incontinence may be indicated when all of the following are documented (A-G):

A) Patient history of (1, 2, and 3):
    1) Involuntary loss of urine with exertion
    2) Identification and treatment of transient causes of urinary incontinence, if present (e.g., delirium, infection, pharmaceutical causes, psychological causes, excessive urine production, restricted mobility, and stool impaction)
    3) Involuntary loss of urine on examination during stress (provocative test with direct visualization of urine loss) and low or absent post void residual

B) Patient's voiding habits

C) Physical or laboratory examination evidence of either (1 or 2):
    1) Urethral hypermobility

2) Intrinsic sphincter deficiency

D) Diagnostic workup to rule out urgency incontinence

E) Negative preoperative pregnancy test result unless patient is postmenopausal or has been previously sterilized

F) Nonmalignant cervical cytology, if cervix is present

G) Patient required to have 3 months of alternative therapy (e.g., pessaries or physical therapy, including bladder training, pelvic floor exercises and/or biofeedback, as available). If limited coverage of physical therapy is available, patients should be taught pelvic floor exercises by their treating provider, physical therapist or trained staff, and have documented consistent practice of these techniques over the 3 month period.

H) Periurthral bulking agent injection is only covered for patients who otherwise meet the criteria for surgery for urinary incontinence above but who:

   i. Are not candidates for major surgery due to comorbidities OR

   ii. Choose not to have major surgery and are aware of the limited benefits of bulking agent injections and the need for repeat procedures.

Note: Patients whose incontinence does not improve after 3 treatments with bulking agents are considered treatment failures and no longer candidates for this procedure

Cochrane Library

Cochrane Database of Systematic Reviews

Urethral injection therapy for urinary incontinence in women (Review)

Kirchin V, Page T, Keegan PE, Atiemo K, Cody JD, McClinton S

Kirchin V, Page T, Keegan PE, Atiemo K, Cody JD, McClinton S.
Urethral injection therapy for urinary incontinence in women.
Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003881.
DOI: 10.1002/14651858.CD003881.pub3.

www.cochranelibrary.com

WILEY

[Intervention Review]

Urethral injection therapy for urinary incontinence in women

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Editorial group: Cochrane Incontinence Group.
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Citation: Kirchin V, Page T, Keegan PE, Atiemo K, Cody JD, McClinton S. Urethral injection therapy for urinary incontinence in women. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No.: CD003881. DOI: 10.1002/14651858.CD003881.pub3.

ABSTRACT

Background

Periurethral or transurethral injection of bulking agents is a minimally invasive surgical procedure used for the treatment of stress urinary incontinence in adult women.

Objectives

To assess the effects of periurethral or transurethral injection therapy on the cure or improvement of urinary incontinence in women.

Search methods

We searched the Cochrane Incontinence Group Specialised Trials Register (searched 8 November 2010) and the reference lists of relevant articles.

Selection criteria

All randomised or quasi-randomised controlled trials of treatment for urinary incontinence in which at least one management arm involved periurethral or transurethral injection therapy.

Data collection and analysis

Two review authors independently assessed methodological quality of each study using explicit criteria. Data extraction was undertaken independently and clarification concerning possible unreported data sought directly from the investigators.

Main results

Excluding duplicate reports, we identified 14 trials (excluding one that was subsequently withdrawn from publication and not included in this analysis) including 2004 women that met the inclusion criteria. The limited data available were not suitable for meta-analysis because they all came from separate trials. Trials were small and generally of moderate quality.

One trial of 45 women that compared injection therapy with conservative treatment showed early benefit for the injectable with respect to continence grade (risk ratio (RR) 0.7, 95% confidence interval (CI) 0.52 to 0.94) and quality of life (RR 0.54, 95% CI 0.16 to 0.92). Another, comparing Injection of autologous fat with placebo, terminated early because of safety concerns. Two trials that compared injection with surgical management found significantly better objective cure in the surgical group (RR 4.77, 95% CI 1.96 to 11.64;

and RR 1.69, 95% CI 1.02 to 2.79), although the latter trial data did not reach statistical significance if an intention-to-treat analysis was used.

Eight trials compared different agents and all results had wide confidence intervals. Silicone particles, calcium hydroxylapatite, ethylene vinyl alcohol, carbon spheres and dextranomer hyaluronic acid combination gave improvements which were not shown to be more or less efficacious than collagen. Dextranomer hyaluronic acid compound treated patients appeared to have significantly higher rates of injection site complications (16% with the hyaluronic acid compound versus none with collagen; RR 37.78, 95% CI 2.34 to 610) and this product has now been withdrawn from the market.

A comparison of periurethral and transurethral methods of injection found similar outcomes but a higher (though not statistically significant) rate of early complications in the periurethral group. One trial of 30 women showed a weak (but not clinically significant) advantage for patient satisfaction (data not suitable for analysis in Revman) after mid-urethral injection in comparison to bladder neck injection but with no demonstrable difference in continence levels.

Authors' conclusions

The available evidence base remains insufficient to guide practice. In addition, the finding that placebo saline injection was followed by a similar symptomatic improvement to bulking agent injection raises questions about the mechanism of any beneficial effects. One small trial comparing silicone particles with pelvic floor muscle training was suggestive of benefit at three months but it is not known if this was sustained, and the treatment was associated with high levels of postoperative retention and dysuria. Greater symptomatic improvement was observed with surgical treatments, though the advantages need to be set against likely higher risks. No clear-cut conclusions could be drawn from trials comparing alternative agents, although dextranomer hyaluronic acid was associated with more local side effects and is no longer commercially available for this indication. There is insufficient evidence to show superiority of mid-urethral or bladder neck injection. The single trial of autologous fat provides a reminder that periurethral injections can occasionally cause serious side effects.

PLAIN LANGUAGE SUMMARY

Injections of bulking agents for urinary incontinence in women

Stress incontinence is losing urine when coughing, laughing, sneezing or exercising. Usually muscles and tissue form a cushion supporting the base of the bladder and closing the urethra (the passage through which urine leaves the body). If they do not, artificial cushioning can be created by injecting bulking agents into the area around the urethra. The review of 14 trials, which included 2004 women, found some limited evidence that this can relieve stress incontinence in women. Other treatments such as surgery might be better. Using the women's own fat tissue as the agent injected can cause serious complications.

BACKGROUND

This review is part of a series of Cochrane reviews on the effects of surgical treatment for urinary incontinence. This is an update of a review on periurethral injection therapy previously published by the Cochrane Incontinence Group in 2007. The reader is referred to another review in the series by Glazener (Glazener 2004) for background information regarding the description of urinary incontinence, the principal categories of incontinence, and the broad options for management.

Surgical procedures designed to treat urinary incontinence generally aim to improve support to the vesico-urethral junction and correct deficient urethral closure. The precise mechanism whereby differing procedures improve continence continues to be a matter of debate, making selection of the most appropriate option for an individual difficult. The surgeon's preference, co-existing urogenital problems, anatomical features of the bladder outlet and co-morbidity suffered by the patient can all influence the choice of procedure. Numerous surgical methods have been described which can be subdivided into seven main categories:

1. open abdominal retropubic colposuspension (Lapitan 2005);

2. anterior vaginal repair (anterior colporrhaphy) (Glazener 2001);

NICE guidance

Intramural urethral bulking procedures for stress urinary incontinence in women

Interventional procedures guidance
Published: 23 November 2005
nice.org.uk/guidance/ipg138

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

1 Guidance

1.1 Current evidence on the safety and short-term efficacy of intramural urethral bulking procedures for stress urinary incontinence is adequate to support the use of these procedures provided that normal arrangements are in place for clinical governance and for audit or research.

1.2 Clinicians should ensure that patients understand that the benefits of the procedures diminish in the long term and provide them with clear written information. In addition, use of the Institute's information for the public is recommended.

1.3 Further publication of longer-term efficacy outcomes will be useful. Clinicians should submit data to the British Association of Urological Surgeons registry, or the British Society of Urogynaecologists registry (for further information contact the British Society of Urogynaecologists).

2 The procedure

2.1 Indications

2.1.1 Stress urinary incontinence is the involuntary leakage of urine during exercise or movements such as coughing, sneezing and laughing. It is usually caused by weak or damaged muscles and connective tissues of the pelvic floor, or by weakness of the urethral sphincter itself. It is estimated that 10–52% of adult women have some form of incontinence.

2.1.2 Typically, first-line treatment is conservative and includes pelvic floor muscle training, electrical stimulation and biofeedback. If the condition does not improve, surgical alternatives in women may include colposuspension, tension-free vaginal tape, transobturator foramen procedures or traditional suburethral slings.

2.2 Outline of the procedure

2.2.1 Intramural urethral bulking aims to augment the urethral wall and increase the urethral closure force. Several millilitres of bulking agent are injected into the submucosa of the proximal urethra just distal to the bladder neck. The injections are usually administered under local anaesthesia, either transurethrally or para-urethrally. Injections are undertaken either under vision using a cytoscope; or blindly, using a non-endoscopic implantation device.

2.2.2 A number of bulking agents are currently available.

2.3 Efficacy

2.3.1 A small randomised controlled trial reported that 53% (34/64) of patients treated by urethral bulking with collagen had no incontinence at 12 months, compared with 72% (39/54) treated with conventional open surgery.

2.3.2 One case series of patients treated with collagen reported that, after 12 months, 42% (38/90) had either no incontinence or an improvement in symptoms, as measured objectively using cystometry and abdominal leak point pressure. One case series of patients treated with silicone particles reported that 68% (69/102) had either no incontinence or marked improvement after a mean follow-up of 3 months. This proportion decreased to 48% (40/84) after a mean follow-up of 18 months. Four randomised controlled trials reported no difference in efficacy between different bulking agents. For more details, refer to the Sources of evidence.

2.3.3 The Specialist Advisors noted that efficacy may depend on patient selection, the bulking agent used and the injection technique.

2.4 Safety

2.4.1 Five case series reported safety data on a total of 389 patients. The most commonly reported adverse events were urinary tract infection, affecting 1% (1/102) to 12% (11/90) of patients, and urinary retention, affecting 0% (0/40) to 11% (10/90) of patients. Other reported complications included abscess at the injection site, urgency of micturition and prolonged pain. For more details, refer to the Sources of evidence.

2.4.2 The Specialist Advisors stated that migration of the bulking agent, voiding difficulties, urinary tract infection and allergic reaction are potential adverse events. Haemorrhage was listed as a rare potential adverse event.

2.5 Other comments

2.5.1 The Committee noted that a variety of bulking agents may be used for these procedures which may have different risk and benefit profiles.

2.5.2 The Committee particularly noted that the benefits of these procedures diminish with time but that the procedure can be repeated.

3 Further information

3.1 NICE has issued guidance on tension-free vaginal tape (replaced by NICE clinical guideline 40, 'Urinary incontinence: the management of urinary incontinence in women'), transobturator foramen procedures for stress urinary incontinence and insertion of extra-urethral (non-circumferential) retropubic adjustable compression devices. NICE is also producing guidance on insertion of biological slings for stress urinary incontinence [Now published as 'Insertion of biological slings for stress urinary incontinence'].

Andrew Dillon
Chief Executive
November 2005

Sources of evidence

The evidence considered by the Interventional Procedures Advisory Committee is described in the following document.

'Interventional procedure overview of intramural urethral bulking procedures for stress urinary incontinence in women', August 2004.

Information for patients

NICE has produced information describing its guidance on this procedure for patients, carers, and those with a wider interest in healthcare. It explains the nature of the procedure and the decision made, and has been written with patient consent in mind.

4 About this guidance

NICE interventional procedure guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS. It is for healthcare professionals and people

using the NHS in England, Wales, Scotland and Northern Ireland, and is endorsed by Healthcare Improvement Scotland for implementation by NHSScotland.

This guidance was developed using the NICE interventional procedure guidance process.

We have produced a summary of this guidance for patients and carers. Information about the evidence it is based on is also available.

Changes since publication

23 January 2012: minor maintenance.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

NICE National Institute for Health and Care Excellence

NICE guideline

Urinary incontinence and pelvic organ prolapse in women: management

NICE guideline

Published: 2 April 2019
nice.org.uk/guidance/ng123

unknown.

1.5.1 If a woman is thinking about a surgical procedure for stress urinary incontinence, use the NICE patient decision aid on surgery for stress urinary incontinence to promote informed preference and shared decision making. Discussion with the woman should include:

- the benefits and risks of all surgical treatment options for stress urinary incontinence that NICE recommends, whether or not they are available locally
- the uncertainties about the long-term adverse effects for all procedures, particularly those involving the implantation of mesh materials
- differences between procedures in the type of anaesthesia, expected length of hospital stay, surgical incisions and expected recovery period
- any social or psychological factors that may affect the woman's decision. [2013, amended 2019]

1.5.2 If non-surgical management for stress urinary incontinence has failed, and the woman wishes to think about a surgical procedure, offer her the choice of:

- colposuspension (open or laparoscopic) or
- an autologous rectus fascial sling.

Also include the option of a retropubic mid-urethral mesh sling in this choice but see recommendations 1.5.7 to 1.5.11 for additional guidance on the use of mid-urethral mesh sling procedures for stress urinary incontinence. [2019]

1.5.3 Consider intramural bulking agents to manage stress urinary incontinence if alternative surgical procedures are not suitable for or acceptable to the woman. Explain to the woman that:

- these are permanent injectable materials
- repeat injections may be needed to achieve effectiveness
- limited evidence suggests that they are less effective than the surgical procedures listed in recommendation 1.5.2 and the effects wear off over time

- there is limited evidence on long-term effectiveness and adverse events. [2019]

1.5.4 If an intramural bulking agent is injected, give the woman written information about the bulking agent, including its name, manufacturer, date of injection, and the injecting surgeon's name and contact details. [2019]

1.5.5 If the woman's chosen procedure for stress urinary incontinence is not available from the consulting surgeon, refer her to an alternative surgeon. [2019]

1.5.6 Providers must ensure that data on surgical procedures for stress urinary incontinence are recorded in a national registry, as outlined in the section on collecting data on surgery and surgical complications in this guideline. [2019]

Mid-urethral mesh sling procedures

1.5.7 When offering a retropubic mid-urethral mesh sling, advise the woman that it is a permanent implant and complete removal might not be possible. [2019]

1.5.8 If a retropubic mid-urethral mesh sling is inserted, give the woman written information about the implant, including its name, manufacturer, date of insertion, and the implanting surgeon's name and contact details. [2019]

1.5.9 When planning a retropubic mid-urethral mesh sling procedure, surgeons should:

- use a device manufactured from type 1 macroporous polypropylene mesh
- consider using a retropubic mid-urethral mesh sling coloured for high visibility, for ease of insertion and revision. [2013, amended 2019]

1.5.10 Do not offer a transobturator approach unless there are specific clinical circumstances (for example, previous pelvic procedures) in which the retropubic approach should be avoided. [2019]

1.5.11 Do not use the 'top-down' retropubic mid-urethral mesh sling approach or single-incision sub-urethral short mesh sling insertion except as part of a clinical trial. [2019]

Approved by the AUA Board of Directors March 2017

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

American Urological Association (AUA) /

Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU)

SURGICAL TREATMENT OF FEMALE STRESS URINARY INCONTINENCE: AUA/SUFU GUIDELINE

Kathleen C. Kobashi, MD, FACS, FPMRS; Michael E. Albo, MD; Roger R. Dmochowski, MD; David A. Ginsberg, MD; Howard B. Goldman, MD; Alexander Gomelsky, MD; Stephen R. Kraus, MD, FACS; Jaspreet S. Sandhu, MD; Tracy Shepler; Jonathan R. Treadwell, PhD; Sandip Vasavada, MD; Gary E. Lemack, MD

Purpose

Stress urinary incontinence (SUI) is a common problem experienced by many women. SUI can have a significant negative impact on the quality of life (QOL) of not only those who suffer from the condition, but also potentially on those friends and family members whose lives and activities may also be limited. The surgical options for the treatment of SUI continue to evolve; as such, this guideline and the associated algorithm aims to outline the currently available treatment techniques as well as the data associated with each treatment. It should be noted that some of the data included in the analysis involved techniques that are no longer commercially available for reasons not necessarily related to outcomes. Indeed, the panel recognizes that this guideline will require continued literature review and updating as further knowledge regarding current and future options continues to develop.

Methodology

A comprehensive search of the literature was performed by ECRI Institute. This search included articles published between January 1, 2005 and December 31, 2015. To focus the analysis on the most relevant evidence, analysts only considered articles published in full after January 1, 2005 in the English language and that reported SUI data for one or more of the Key Questions. An update abstract search was conducted through September 2016, which pulled in an additional 66 abstracts related to the key questions of interest. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate) or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

GUIDELINE STATEMENTS

PATIENT EVALUATION

1. In the initial evaluation of patients with stress urinary incontinence desiring to undergo surgical intervention, physicians should include the following components: (Clinical Principle)

    - History, including assessment of bother
    - Physical examination, including a pelvic examination
    - Objective demonstration of stress urinary incontinence with a comfortably full bladder (any method)
    - Assessment of post-void residual urine (any method)
    - Urinalysis

2. Physicians should perform additional evaluations in patients being considered

for surgical intervention who have the following conditions: (Expert Opinion)

- Inability to make definitive diagnosis based on symptoms and initial evaluation
- Inability to demonstrate stress urinary incontinence
- Known or suspected neurogenic lower urinary tract dysfunction
- Abnormal urinalysis, such as unexplained hematuria or pyuria
- Urgency-predominant mixed urinary incontinence
- Elevated post-void residual per clinician judgment
- High grade pelvic organ prolapse (POP-Q stage 3 or higher) if stress urinary incontinence not demonstrated with pelvic organ prolapse reduction
- Evidence of significant voiding dysfunction

3. Physicians may perform additional evaluations in patients with the following conditions: (Expert Opinion)

- Concomitant overactive bladder symptoms
- Failure of prior anti-incontinence surgery
- Prior pelvic prolapse surgery

CYSTOSCOPY AND URODYNAMICS TESTING

4. Physicians should not perform cystoscopy in index patients for the evaluation of stress urinary incontinence unless there is a concern for urinary tract abnormalities. (Clinical Principle)

5. Physicians may omit urodynamic testing for the index patient desiring treatment when stress urinary incontinence is clearly demonstrated. (Conditional Recommendation; Evidence Level: Grade B)

6. Physicians may perform urodynamic testing in non-index patients. (Expert Opinion)

PATIENT COUNSELING

7. In patients wishing to undergo treatment for stress urinary incontinence, the degree of bother that their symptoms are causing them should be considered in their decision for therapy. (Expert Opinion)

8. In patients with stress urinary incontinence or stress-predominant mixed urinary incontinence who wish to undergo treatment, physicians should counsel regarding the availability of the following treatment options: (Clinical Principle)

- Observation
- Pelvic floor muscle training (± biofeedback)
- Other non-surgical options (e.g., continence pessary)
- Surgical intervention

9. Physicians should counsel patients on potential complications specific to the treatment options. (Clinical Principle)

10. Prior to selecting midurethral synthetic sling procedures for the surgical treatment of stress urinary incontinence in women, physicians must discuss the specific risks and benefits of mesh as well as the alternatives to a mesh sling. (Clinical principle)

TREATMENT

11. In patients with stress urinary incontinence or stress-predominant mixed urinary incontinence, physicians may offer the following non-surgical treatment options: (Expert Opinion)

- Continence pessary
- Vaginal inserts
- Pelvic floor muscle exercises

12. In index patients considering surgery for stress urinary incontinence, physicians may offer the following options: (Strong Recommendation; Evidence Level: Grade A)

- Midurethral sling (synthetic)

- Autologous fascia pubovaginal sling
- Burch colposuspension
- Bulking agents

13. In index patients who select midurethral sling surgery, physicians may offer either the retropubic or transobturator midurethral sling. (Moderate Recommendation; Evidence Level: Grade A)
14. Physicians may offer single-incision slings to index patients undergoing midurethral sling surgery with the patient informed as to the immaturity of evidence regarding their efficacy and safety. (Conditional Recommendation; Evidence Level: Grade B)
15. Physicians should not place a mesh sling if the urethra is inadvertently injured at the time of planned midurethral sling procedure. (Clinical Principle)
16. Physicians should not offer stem cell therapy for stress incontinent patients outside of investigative protocols. (Expert Opinion)

SPECIAL CASES

17. In patients with stress urinary incontinence and a fixed, immobile urethra (often referred to as 'intrinsic sphincter deficiency') who wish to undergo treatment, physicians should offer pubovaginal slings, retropubic midurethral slings, or urethral bulking agents. (Expert Opinion)
18. Physicians should not utilize a synthetic midurethral sling in patients undergoing concomitant urethral diverticulectomy, repair of urethrovaginal fistula, or urethral mesh excision and stress incontinence surgery. (Clinical Principle)
19. Physicians should strongly consider avoiding the use of mesh in patients undergoing stress incontinence surgery who are at risk for poor wound healing (e.g., following radiation therapy, presence of significant scarring, poor tissue quality). (Expert Opinion)
20. In patients undergoing concomitant surgery for pelvic prolapse repair and stress urinary incontinence, physicians may perform any of the incontinence procedures (e.g., midurethral sling, pubovaginal sling, Burch colposuspension). (Conditional Recommendation; Evidence Level: Grade C)
21. Physicians may offer patients with stress urinary incontinence and concomitant neurologic disease affecting lower urinary tract function (neurogenic bladder) surgical treatment of stress urinary incontinence after appropriate evaluation and counseling have been performed. (Expert Opinion)
22. Physicians may offer synthetic midurethral slings, in addition to other sling types, to the following patient populations after appropriate evaluation and counseling have been performed: (Expert Opinion)

- Patients planning to bear children
- Diabetes
- Obesity
- Geriatric

OUTCOMES ASSESSMENT

23. Physicians or their designees should communicate with patients within the early postoperative period to assess if patients are having any significant voiding problems, pain, or other unanticipated events. If patients are experiencing any of these outcomes, they should be seen and examined. (Expert Opinion)
24. Patients should be seen and examined by their physicians or designees within six months post-operatively. Patients with unfavorable outcomes may require additional follow-up. (Expert Opinion)

- The subjective outcome of surgery as perceived by the patient should be assessed and documented.
- Patients should be asked about residual incontinence, ease of voiding/force of stream, recent urinary tract infection, pain, sexual function and new onset or worsened overactive bladder symptoms.
- A physical exam, including an examination of all surgical incision sites, should be performed to evaluate

healing, tenderness, mesh extrusion (in the case of synthetic slings), and any other potential abnormalities.

- A post-void residual should be obtained.

INTRODUCTION

PURPOSE

Stress urinary incontinence (SUI) is a common problem experienced by many women. SUI can have a significant negative impact on the quality of life (QOL) of not only those who suffer from the condition, but also potentially on those friends and family members whose lives and activities may also be limited. The surgical options for the treatment of SUI continue to evolve; as such, this guideline and the associated algorithm aims to outline the currently available treatment techniques as well as the data associated with each treatment. It should be noted that some of the data included in the analysis involved techniques that are no longer commercially available for reasons not necessarily related to outcomes. Indeed, the panel recognizes that this guideline will require continued literature review and updating as further knowledge regarding current and future options continues to develop.

METHODOLOGY

Systematic Review. A comprehensive search of the literature was performed by ECRI Institute. This search included articles published between January 1, 2005 and December 31, 2015. Study designs included systematic reviews, randomized controlled trials (RCTs), controlled clinical trials (CCTs), and observational studies (diagnostic accuracy studies, cohort with and without comparison group, case-control, case series). Three methodologic research analysts reviewed the abstracts identified in the literature search; each article was screened by at least two of the three analysts. Articles that potentially fulfilled the outlined inclusion criteria and potentially answered one or more of the questions specified by the panel were retrieved in full text for review by the team. For all excluded studies, analysts recorded the reason for exclusion as well as whether the exclusion was based on abstract review or full text review. To focus the analysis on the most relevant evidence, analysts only considered articles published in full after January 1, 2005 in the English language and that reported SUI data for one or more of the Key Questions. An update abstract search was conducted through September 2016, which pulled in an additional 66 abstracts related to the key questions of interest.

Included interventions: Included interventions were limited to those that were FDA-approved with adequate robust data. Injectable bulking agents (Macroplastique, Coaptite, Contigen [collagen], silicone, Durasphere [carbon coated zirconium beads]); retropubic bladder neck suspensions (Burch colposuspension); midurethral slings(MUS) (retropubic [SPARC, TVT, ALIGN, Supris, Advantage, Lynx, Desara, I-STOP, TFS], transobturator [TVT-O, Monarc, ALIGN TO, Obtryx, Aris], Prepubic, Adjustable [Remeex]); pubovaginal slings (PVS) (autologous, allograft, xenograft); artificial urinary sphincter; single incision (Altis, MiniArc, Ajust, Solyx, SIMS, TVT-Secure)

Excluded interventions: Laparoscopic colposuspension*, Obtape, ProteGen, Gore-Tex, bone-anchor, multifilament, In-Fast, anterior vaginal wall sling, Renessa, stem cell/tissue engineering, adjustable continence therapy, Bulkamid, MMK (Marshall-Marchetti-Krantz), needle suspensions (Stamey, Pereyra, Raz, Gittes), anterior colporrhaphy, Kelly plication.

*While the Panel acknowledges that a minimally invasive Burch colposuspension may be utilized by some individuals, neither laparoscopic nor robotic Burch colposuspension, specifically, were included due to the lack of sufficient data regarding these approaches in the literature.

Included comparisons: Any comparisons of two or more of the included interventions was incorporated, though not all comparisons within a given category (e.g., comparisons of two bulking agents, or comparisons of two retropubic midurethral slings [RMUS]) were included. Additionally, analysts compared bottom-up versus top-down RMUS, as well as outside-in versus inside-out transobturator midurethral slings (TMUS).

The following outcomes are included in this review: QOL questionnaires (symptom, QOL, sexual function, satisfaction, expectation, bother), voiding diaries, stress test, pad test, urodynamics, surgical complications/adverse events, need for retreatment, UITN-based criteria, and complications (e.g., erosion, extrusion, retention, voiding dysfunction, perforation, dyspareunia, obstruction, exposure, de novo urgency, recurrent urinary tract infection [UTI], bleeding, pain, neuropathy, neurovascular or visceral injury, hematoma, infection, hernia, seroma, slow stream). Many studies reported rates of "success" or "failure," which was defined differently by different studies. Generally, outcomes were based on a set of variables such as stress tests, patient reports, and the need for retreatment.

Of the 450 publications retrieved for full review, 256 were excluded. The most common reasons for exclusion were RCTs that were a part of already included systematic reviews to avoid duplication.

Data Extraction and Data Management. Information from each included article was extracted by one of three analysts using standard extraction forms. The team lead developed the forms and trained the extractors. The lead reviewed the work of the other extractors and searched for inconsistencies and missing information in the extracted data.

Assessment of Quality. Because different Key Questions involved different types of evidence, analysts tailored the quality assessments as follows:

- For systematic reviews, analysts rated quality based on the review authors' ratings of the quality of their included studies (if review authors did not rate quality, analysts extrapolated a rating based on their description of study limitations). For diagnostic cohort studies, analysts used the QUADAS-2 instrument.[1]
- In reviewing effectiveness, analysts judged the quality of systematic reviews and RCTs using the same processes as previously discussed.
- For complications, analysts divided the evidence into comparative data (comprising systematic reviews and RCTs) and non-comparative data (comprising individual groups from RCTs and non-randomized studies).
- For comparative data, analysts used the same processes as previously discussed. For non-comparative data, analysts considered three items: prospective design, consecutive enrollment, and objective measurement of outcome. If all three were clearly true, the study was high quality; if just one was false or unclear, the study was moderate quality. If two or three were false or unclear, the study was low quality.
- In reviewing contraindications for MUS and indications for injectables, analysts did not assess quality because those questions involve patient enrollment criteria.
- In reviewing preoperative cystoscopy, analysts identified no studies on the effect of preoperative cystoscopy, so no quality assessment was necessary.
- For urodynamics, analysts judged the quality of randomized trials using the Cochrane risk-of-bias instrument.[2]
- For patient factors predicting outcomes, analysts used the Quality in Prognostic Studies (QUIPS) tool.[3]
- In reviewing outcomes instruments, analysts did not assess quality since it is not clear what would constitute a high quality study of instruments utilized to assess such outcomes.
- In reviewing length of follow-up, analysts judged quality solely on the basis of the percentage of enrolled patients who provided data during follow-up. Studies for which all follow up time points had 85%+ completion were deemed high quality; studies for which any follow up time point had 60% or less completion were deemed low quality; all others were deemed moderate quality.

Determination of Evidence Strength. The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes not only individual study quality but consideration of study design, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings, and treatments for the purposes of the guideline. The AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.[4]

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (Table 1). ***Strong Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net

harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. ***Conditional Recommendations*** are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence *is likely to change confidence*. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

Where gaps in the evidence existed, the Panel provides guidance in the form of ***Clinical Principles*** or ***Expert Opinion*** with consensus achieved using a modified Delphi technique if differences of opinion emerged.[5] A *Clinical Principle* is a statement for which there may or may not be evidence in the medical literature and that is widely agreed upon by urologists or other clinicians. *Expert Opinion* refers to a statement for which there is no evidence and that is achieved by consensus of the Panel.

Process. The Surgical Management of Female Stress Urinary Incontinence Panel was created in 2014 by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair who in turn appointed the Vice Chair. In a collaborative process, additional Panel members, including additional members of the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) with specific expertise in this area, were then nominated and approved by the PGC. The AUA conducted a thorough peer review process. The draft guidelines document was distributed to 93 peer reviewers, 41 of which submitted comments. The Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the PGC and Science and Quality Council (S&Q). It was then submitted to the AUA and SUFU Boards of Directors for final approval. Panel members received no remuneration for their work.

BACKGROUND

SUI is a common problem experienced by women. The prevalence of SUI has been reported to be as high as 49%, depending on population and definition, and it can have a significant negative impact on an individual's QOL and on that of her family and friends.[6-8] While many women choose surgical management for their SUI, the specific options for surgical treatment have evolved over time.[9] The first AUA Female SUI Guidelines Panel reviewed available literature up to 1994 while the literature search for the SUI Guidelines Panel that directly preceded the present iteration concluded in June 2005.[10] Indeed, the Panel recognized that given the rapidly changing landscape, this guideline would require ongoing literature review and continual updates to keep up with further developments in the management of SUI.

INDEX PATIENT

The index patient for this guideline, as in the previous iterations of the SUI guidelines, is an otherwise healthy female who is considering surgical therapy for the correction of pure stress and/or stress-predominant mixed urinary incontinence (MUI) who has not undergone previous SUI surgery. Patients with low-grade pelvic organ prolapse were also considered to be index patients. However, while the stage of prolapse was often specified in more recent trials, it was not indicated in many of the earlier studies. Where evidence was available, the data is presented separately for index patients and non-index patients. The Panel recognizes that many women who seek surgical correction of SUI do not meet the definition of the index patient. In fact, most of the studies in the literature do not enroll patients based on this definition

TABLE 1: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

	Evidence Strength A (High Certainty)	**Evidence Strength B (Moderate Certainty)**	**Evidence Strength C (Low Certainty)**
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence		

of the index patient. Therefore, the Panel felt it was also important to review the literature regarding patients undergoing surgery for SUI that did not meet this definition of the index patient.

NON-INDEX PATIENT

Non-index patients reviewed in this analysis include women with SUI and pelvic prolapse (stage 3 or 4), MUI (non-stress-predominant), incomplete emptying/ elevated post-void residual (PVR) and/or other voiding dysfunction, prior surgical interventions for SUI, recurrent or persistent SUI, mesh complications, high body mass index (BMI), neurogenic lower urinary tract dysfunction and advanced age (geriatric). Finally, the Panel felt it was important to more fully understand the literature regarding the safety of mesh products used in the surgical treatment of SUI and, therefore, included studies of women who had undergone mesh procedures regardless of whether they were index or non-index patients. The Panel also acknowledges that persistent or recurrent SUI following any SUI treatment is not uncommon; however, there is a lack of robust data to substantiate any recommendation from the Panel regarding the management of these patients.

DEFINITIONS

SUI is the symptom of urinary leakage due to increased abdominal pressure, which can be caused by activities such as sneezing, coughing, exercise, lifting, and position change. Though the utility of urethral function assessment remains controversial, some clinicians utilize leak point pressure and others utilize urethral closure pressure. Intrinsic sphincter deficiency (ISD) is often defined as a leak point pressure of less than 60 cm H_20 or a maximal urethral closure pressure of less than 20 cm H_20, often in the face of minimal urethral mobility. Urgency urinary incontinence (UUI) is the symptom of urinary leakage that occurs in conjunction with the feeling of urgency and a sudden desire to urinate that cannot be deferred. Mixed incontinence refers to a combination of SUI and UUI.

GUIDELINE STATEMENTS

PATIENT EVALUATION

1. **In the initial evaluation of patients with stress urinary incontinence desiring to undergo surgical intervention, physicians should include the following components: (Clinical Principle)**
    - **Focused history, including assessment of bother**
    - **Focused physical examination, including a pelvic examination**
    - **Objective demonstration of stress urinary incontinence with a comfortably full bladder(any method)**
    - **Assessment of post-void residual urine (any method)**
    - **Urinalysis**
2. **Physicians should perform additional evaluations in patients being considered for surgical intervention who have the following conditions: (Expert Opinion)**
    - **Inability to make definitive diagnosis based on symptoms and initial evaluation**
    - **Inability to demonstrate stress urinary incontinence**
    - **Known or suspected neurogenic lower urinary tract dysfunction**
    - **Abnormal urinalysis, such as unexplained hematuria or pyuria**
    - **Urgency-predominant mixed urinary incontinence**
    - **Elevated post-void residual per clinician judgment**
    - **High grade pelvic organ prolapse (POP-Q stage 3 or higher) if stress urinary incontinence not demonstrated by pelvic organ prolapse reduction**
    - **Evidence of significant voiding dysfunction**
3. **Physicians may perform additional evaluations in patients with the following conditions: (Expert Opinion)**
    - **Concomitant overactive bladder symptoms**
    - **Failure of prior anti-incontinence surgery**
    - **Prior pelvic prolapse surgery**

The purpose of the diagnostic evaluation in the incontinent woman is to document, confirm, and characterize SUI; to assess the differential diagnosis and comorbidities; and to prognosticate and aid in the selection of treatment. The first goal of the diagnostic evaluation is to confirm the diagnosis of SUI and optimally characterize the incontinence. The literature search regarding the optimal evaluation for the index

patient yielded two systematic reviews[11,12] and four individual studies that addressed this issue.[13-16] The role of six variables was assessed: history, questionnaires/scales, stress test, Q-tip test, pad test, and urodynamics. Additional tests, including urinalysis, pelvic examination, prolapse assessment, cystoscopy, PVR volume, and voiding diary, yielded no additional meaningful evidence.

History. Holroyd-Leduc et al. performed a moderate-quality systematic review of various methods for diagnosing urinary incontinence during office assessment.[11] A meta-analysis of 10 cohort studies with 2,657 patients found that the presence of coughing, sneezing, lifting, walking, or running as initiators of incontinence increased the likelihood of SUI as the cause of urinary leakage, while their absence decreased the likelihood of SUI. Thus, a woman with a positive clinical history had a 74% chance of having SUI, whereas a woman with a negative clinical history had a 34% chance of having SUI. Likewise, in a systematic review by Martin et al. that combined data from 15 cohort studies with 3,545 patients, a woman with a positive clinical history had a 73% chance of having SUI, whereas a woman with a negative clinical history had a 16% chance of having SUI.[12] Thus, the evidence from two moderate-quality meta-analyses suggests that clinical history provides some diagnostic value for patients with signs/symptoms potentially caused by SUI; however, history alone, while helpful, does not definitively diagnose SUI in women.

Questionnaires. Eight questionnaires were assessed in the two systematic reviews for their ability to diagnose SUI.[11,12] While most questionnaires showed small positive and negative likelihood ratios (LRs) for diagnosing or ruling out SUI, the limited number of studies for each questionnaire resulted in an overall strength of evidence of low. It is important to note that an assessment of bother, regardless of method or questionnaire, is paramount to the decision to operate in the index patient. Since SUI is a condition that impacts QOL (rather than quantity of life), the treatment decisions should be closely linked to the ability to improve bother caused by the symptoms. If bother is minimal, then strong consideration should be given to non-surgical management.

Stress test. Two moderate-quality systematic reviews and one additional study evaluated stress tests for diagnosis of SUI using urodynamic evaluations as the reference standard. While stress tests were performed under different protocols (e.g. retrograde filling with 200 mL saline; 20 minutes after catheterization for PVR volume), a positive stress test had a high sensitivity and specificity for detecting SUI on urodynamics. Similar results were obtained in a single study that combined the supine and standing stress test.[17] However, since this combined test was evaluated in only one study, the strength of evidence supporting it is low. Additionally, in a secondary analysis of an RCT by Albo et al., the sensitivity and specificity of the supine empty bladder stress test to predict ISD were 49% and 60%, respectively, suggesting that the supine stress test did not identify ISD.[13]

Q-tip test. Holroyd-Leduc et al. included two studies with a total of 253 patients that evaluated the Q-tip test, with one study using a cutoff angle of 20° and the other 35°.[11] Both studies used urodynamic tests as the reference standard and the pooled positive LR was very small, suggesting that a positive test is unlikely to aid in the diagnosis of SUI. Intuitively, this makes sense, since SUI may exist without urethral hypermobility and vice versa. Thus, moderate strength evidence suggests that a positive Q-tip test has little value for diagnosis of SUI, and this test cannot be recommended by the panel to diagnose SUI. However, it can provide some potentially useful information regarding the degree of urethral mobility.

Pad test. The review by Holroyd-Leduc et al. included one study with 105 patients (Versi et al.)[18] that compared the 48-hour pad test to a reference standard of urodynamic findings. Women with a positive pad test had an 81% chance of having SUI, whereas women with a negative pad test had a 13% chance of having SUI. In this study, however, all patients had either SUI or no incontinence. Thus, the authors concluded that "the pad test confirms an incontinence problem, but its role in distinguishing the type of incontinence cannot be commented on."

Martin et al. included two studies in their analysis.[12] One of these was the Versi study, while the study by Jorgensen et al.[19] compared the one-hour pad test to a reference standard of urodynamic findings. The latter study showed a high sensitivity (94%) but low specificity (44%) for diagnosing SUI. These results correspond to women with a positive pad test having a 69% chance of having SUI, and women with a negative pad test having a 15% chance of having SUI. Since each test was evaluated by only one small study, the strength of evidence for both tests is low, and importantly, though a pad test may confirm the presence of incontinence, it does not distinguish the specific type of incontinence.

After performing a history and physical examination, including a pelvic examination with a comfortably full bladder, the diagnosis of SUI may be fairly straightforward in the index patient. The sine-qua-non for a definitive diagnosis is a positive stress test, or witnessing of involuntary urine loss from the urethral meatus coincident with increased abdominal pressure, such as occurs with coughing and Valsalva maneuver. If leakage is not witnessed in the supine position, the test may be repeated in the standing position to facilitate the diagnosis. Once the increase in abdominal pressure has subsided, flow through the urethra should subside as well. Rarely, one may witness urine loss after an increase in intra-abdominal pressure has subsided. In this scenario, the incontinence may be, at least in part, due to an involuntary detrusor contraction (stress-induced detrusor overactivity).

The Panel felt that physicians should obtain the following details from the history, bladder diary, questionnaires, and/or pad testing.

- Characterization of incontinence (stress, urgency, mixed, continuous, without sensory awareness)
- Chronicity of symptoms
- Frequency, bother, and severity of incontinence episodes
- Patient's expectations of treatment (patient-centered goals)
- Pad or protection use
- Concomitant urinary tract symptoms (e.g., urgency, frequency, nocturia, dysuria, hematuria, slow flow, hesitancy, incomplete emptying)
- Concomitant pelvic symptoms (e.g., pelvic pain, pressure, bulging, dyspareunia)
- Concomitant gastrointestinal symptoms (e.g., constipation, diarrhea, splinting to defecate)
- Obstetric history (e.g., gravity, parity, method of delivery)
- Previous treatments for incontinence (e.g., behavioral therapy, Kegel exercises/pelvic floor muscle training, pharmacotherapy, surgery)
- Previous pelvic surgeries
- Past medical history (e.g., hypertension, diabetes, history of pelvic radiation)
- Current and past medications
- Fluid, alcohol, and caffeine intake
- Menopausal status

Additionally, the physical examination of the index or non-index patient should include the following components:

- Focused abdominal examination
- Evaluation of urethral mobility (any method)
- Supine and/or standing stress test with comfortably full bladder
- Assessment of pelvic prolapse (any method)
- Assessment of vaginal atrophy/estrogenization status
- Focused neurologic examination

Diagnostic evaluations that should be performed in the index or non-index patient include the following:

- Urinalysis
- PVR

The presence of microscopic hematuria may warrant additional evaluation with upper tract imaging and cystoscopy. The assessment of PVR may alert the physician to the potential for incomplete bladder emptying. Several points deserve mention. First, the reliability of a single elevated PVR value for predicting emptying dysfunction remains in question, just as a single low PVR value does not rule out the presence of incomplete emptying. Second, the threshold value of a significant PVR is similarly undefined. Finally, a persistently elevated PVR does not characterize the cause of impaired emptying, but rather indicates the need for further evaluation. Additionally, an elevated PVR in the presence of SUI may impact patient counseling regarding surgical interventions and patient expectations. Elevated PVR may be an indication of hypocontractility of the bladder and may put a patient at risk for retention after treatment for SUI. Consideration of the relationship between incomplete bladder emptying and UTI should be considered, and a urinalysis with culture as indicated should be obtained in patients with elevated PVR in the face of symptoms of a UTI.

The second goal of a diagnostic evaluation in a woman with SUI is to assess the differential diagnosis of incontinence and evaluate the impact of coexisting conditions. The differential diagnosis of SUI includes other causes of urethral incontinence, such as overflow

incontinence (a clinical diagnosis) and detrusor overactivity incontinence, low bladder compliance, and stress-induced detrusor overactivity (urodynamic diagnoses). Other anatomic findings such as pelvic organ prolapse and number and location of ureteral orifices can be diagnosed by physical examination and cystoscopy, respectively. Similarly, additional functional conditions, such as urethral obstruction and impaired or absent contractility, can be identified via urodynamics testing, including cystometry, non-invasive uroflow, pressure-flow study, and PVR assessment. Urinary incontinence may also occur due to a urethral diverticulum, a urinary fistula, or an ectopic ureter. These entities are often suspected on the basis of history and examination, but generally require cystoscopy and other urinary tract imaging for confirmation.

Certain coexistent conditions may influence surgical technique, impact the outcomes of treatment, and influence the nuances of patient counseling. For example, a patient with MUI who has a large PVR volume and detrusor underactivity might be counseled that her urgency symptoms may persist and that there is a potential for urinary retention following surgical treatment of SUI. Furthermore, surgical technique might be tailored based on some anatomic features and the presence of concomitant urinary urgency and UUI.

The third goal of the diagnostic evaluation is to aid in prognosis and selection of treatment. There are few facts and many opinions about predicting the outcome of surgery based on the conditions described above. However few clinicians would disagree that operations for SUI should be confined to those who have demonstrable SUI, including occult SUI demonstrable only after reduction of pelvic organ prolapse. Nevertheless, an understanding of the specific concomitant conditions facilitates individualized treatment planning and informed consent. It also provides the surgeon information with which to formulate a sense regarding potential outcome and possible complications such as incomplete bladder emptying, persistent, worsened, or de novo urgency/ UUI, and recurrent sphincteric incontinence. Urodynamic evaluation may be of assistance in elucidating complex presentations of incontinence.

Additional evaluation should also be performed in women with suspected neurogenic etiology for their incontinence or in women with evidence of dysfunctional voiding. Women who present with persistent or recurrent SUI after previous definitive surgical intervention may also benefit from additional evaluation. Likewise, in select patients with symptomatic SUI in whom SUI cannot be demonstrated, additional evaluation may be beneficial. It must be mentioned that the need for further evaluation of any given patient depends upon a number of additional factors, including the physician's degree of certainty and comfort regarding the accuracy of the diagnosis, the degree of bother the symptoms are causing the patient, the impact that further studies will have on diagnosis, and treatment risks, options, and likely outcomes. The desire and willingness of the patient to undergo further studies should also be taken into consideration.

CYSTOSCOPY AND URODYNAMICS TESTING

4. **Physicians should not perform cystoscopy in index patients for the evaluation of stress urinary incontinence unless there is a concern for urinary tract abnormalities. (Clinical Principle)**

The consensus of the Panel is that there is no role for cystoscopy in the evaluation of patients considering surgical therapy for SUI who are otherwise healthy and have a normal urinalysis. However, if these patients elect surgical therapy, intraoperative cystoscopy should be performed with certain surgical procedures (e.g., midurethral or pubovaginal fascial slings) to confirm the integrity of the lower urinary tract and the absence of foreign body within the bladder or urethra.

Cystoscopy should be performed as indicated in patients in whom bladder pathology is suspected based on history or concerning findings on physical exam or urinalysis. In particular, cystoscopy should be performed in patients found to have microhematuria on urinalysis with microscopy. A cystoscopy should also be performed in patients in whom there is a concern for structural lower urinary tract abnormalities.

The consensus of panel members is that cystoscopy should be performed in patients who have a history of prior anti-incontinence surgery or pelvic floor reconstruction, particularly if mesh or suture perforation is suspected. This suspicion may be based upon new onset of lower urinary tract symptoms, hematuria, or recurrent UTI.

5. **Physicians may omit urodynamic testing for the index patient desiring treatment when stress urinary incontinence is clearly demonstrated. (Conditional Recommendation; Evidence Level: Grade B)**

Urodynamics testing is not necessary in otherwise healthy patients during initial patient evaluation or to determine outcomes after surgery. The role of

urodynamics in patients with uncomplicated SUI (pure SUI or stress-predominant MUI) undergoing surgery was evaluated in the Value of Urodynamic Evaluation (VALUE) trial.[15] The investigators in this large multicenter RCT compared office evaluation alone to urodynamics in addition to office evaluation in 630 patients and showed no difference in outcomes as measured by clinical reduction in complaints measured by the Urinary Distress Inventory and the Patient Global Impression of Improvement (PGI-I).

Another RCT did show that urodynamics in addition to office evaluation lead to better outcomes than office evaluation alone.[16] However, the conclusions of this study were weakened by the low enrollment of only 72 patients, 12 of whom were excluded from the urodynamics arm because of "unfavorable parameters" for surgery, including detrusor overactivity, and valsalva leak point pressure (VLPP) less than 60 cm H_2O.

6. Physicians may perform urodynamic testing in non-index patients. (Expert Opinion)

In certain patients, urodynamic testing should be considered. Urodynamic testing may be performed at the urologist's discretion in certain non-index patients, including but not limited to those patients listed below to facilitate diagnosis, treatment planning, and counseling:

- History of prior anti-incontinence surgery
- History of prior pelvic organ prolapse surgery
- Mismatch between subjective and objective measures
- Significant voiding dysfunction
- Significant urgency, UUI, overactive bladder (OAB)
- Elevated PVR per clinician judgment
- Unconfirmed SUI
- Neurogenic lower urinary tract dysfunction

PATIENT COUNSELING

7. In patients wishing to undergo treatment for stress urinary incontinence, the degree of bother that their symptoms are causing them should be considered in their decision for therapy. (Expert Opinion)

Since SUI is a condition that impacts QOL, treatment decisions should be closely linked to the ability of any intervention to improve the bother caused to the patient by her symptoms. If the patient expresses minimal subjective bother due to the SUI, then strong consideration should be given to conservative, non–surgical therapy. To this point, patients should be counseled on the risks, benefits, and alternatives to any intervention they may choose in addition to the concept that the primary goal of treatment is to improve QOL.

8. In patients with stress urinary incontinence or stress-predominant mixed urinary incontinence who wish to undergo treatment, physicians should counsel regarding the availability of the following treatment options: (Clinical Principle)

- **Observation**
- **Pelvic floor muscle training (± biofeedback)**
- **Other non-surgical options (e.g., continence pessary)**
- **Surgical intervention**

The Panel believes that patients should be offered all of the above-mentioned options before a treatment decision is made. There are a variety of factors that impact the patient's final decision with regard to treatment. Observation is appropriate for patients who are not bothered enough to pursue further therapy, not interested in further therapy, or who are not candidates for other forms of therapy. Pelvic floor muscle training and incontinence pessaries are appropriate for patients interested in pursuing therapy that is less invasive than surgical intervention. Pelvic floor physical therapy can be augmented with biofeedback in the appropriate patient. The patient must be willing and able to commit to regularly and consistently performing pelvic floor training for this to be successful.

Physicians should educate the patient regarding appropriate surgical options before treatment decisions are made. The primary categories of surgical options include bulking agents, colposuspension, and slings. Patients should be made aware that slings can be performed with or without the use of synthetic mesh.

Discussing these various treatment options and their potential risks and benefits allows the patient to combine this information with her own goals for treatment in order to make an informed decision.

9. Physicians should counsel patients on potential complications specific to the treatment options. (Clinical Principle)

The potential complications related to a given

intervention can play a significant role in the decision-making process for patients considering treatment for SUI. Accordingly, physicians need to educate and counsel patients regarding possible complications, some of which are non-specific and others that are unique to the various types of SUI surgery. Patients should be aware that with any intervention there is a risk of continued symptoms of SUI immediately after the procedure or recurrent SUI at a later time that may require further intervention.

Patients should be made aware of possible intra-operative risks that can occur with surgery to correct SUI. These risks include but are not limited to bleeding, bladder injury, and urethral injury, as well as inherent risks of anesthesia, and of the procedure itself.

Voiding dysfunction can be seen after any type of intervention for SUI and may involve both storage and emptying symptoms. There is a risk of *de novo* storage symptoms (urgency, frequency and/or UUI) or worsening of baseline OAB symptoms for patients with MUI or SUI with urinary urgency. Depending on the symptoms, this may require one of the many options available to treat OAB or, if the symptoms are thought to be related to post-operative obstruction, may require sling incision, sling loosening, or urethrolysis. Obstruction resulting in urinary retention is also a potential complication and would require intermittent catheterization, indwelling Foley catheter drainage, and possible sling incision, sling loosening, or urethrolysis if this does not resolve spontaneously.

Complaints of abdominal, pelvic, vaginal, groin, and thigh pain can be seen after sling placement. In addition to generalized pain, patients should be counseled about the risk of pain associated with sexual activity. Symptoms of dyspareunia can occur following pelvic floor reconstructive surgery.

In patients who are considering a synthetic mesh sling, counseling regarding the risk of transvaginal mesh placement is imperative. Risks include mesh exposure into the vagina and/or perforation into the lower urinary tract, either of which could require additional procedures for surgical removal of the involved mesh and, if necessary, repair of the lower urinary tract.

UTI can occur following any intervention for SUI, and the incidence appears to be highest in the immediate postoperative period (within three months). Patients undergoing autologous fascial sling have the additional risk of possible wound infection, seroma formation, or ventral incisional or leg hernia depending on the fascial harvest site (i.e. rectus fascia versus fascia lata, respectively), and pain at the harvesting site.

10. Prior to selecting midurethral synthetic sling procedures for the surgical treatment of stress urinary incontinence in women, physicians must discuss the specific risks and benefits of mesh as well as the alternatives to a mesh sling. (Clinical principle)

The Panel believes that patients considering surgical intervention should be counseled regarding the risks and benefits of the use of synthetic mesh to treat SUI. This detailed discussion should make clear to the patient the possible risks, benefits, and alternatives of MUS. The focus of the discussion should not be on the superiority of one technique over another; indeed, the literature does not definitively suggest that MUS is more or less effective to alternative interventions, such as PVS or colposuspension.

The focus should be on the benefits, the potential risks, and the FDA safety communication regarding MUS, thereby allowing the patient to make a goal-oriented, informed decision as to how she would like to approach her SUI treatment. MUS is the most studied surgical treatment for female SUI. Other than bulking agents, MUS is also the least invasive surgical options to treat SUI. Effectiveness is well documented in the short and medium term with increasing evidence supporting its effectiveness in the long-term as well.[20] This volume of literature and length of follow-up is not available for PVS or colposuspension; however, as mentioned above, there is no conclusive evidence that any one of the available sling procedures is superior or inferior to the others with regard to efficacy.

All surgical interventions (MUS, PVS, colposuspension) to treat SUI have potential adverse outcomes, such as continued incontinence, voiding dysfunction, urinary retention, pain, and dyspareunia. Clinical outcomes appear to be worse for patients who have had prior surgery for SUI, irrespective of the approach. Patients considering MUS should be made aware of the prior FDA public health notifications regarding the use of transvaginal mesh to treat SUI or pelvic organ prolapse (https://www.fda.gov/medicaldevices/safety/alertsandnotices/ucm262435.htm) and be advised of possible mesh-related risks, such as vaginal exposure (which can also be associated with dyspareunia) and perforation into the lower urinary tract or other neurovascular or visceral symptoms. There does appear to be a greater risk of mesh erosion associated with diabetes and a history of smoking;[21-23] Other factors that have been suggested to portend an increased risk of mesh erosion on multivariate analysis include older age, >2 cm vaginal incision length, and previous vaginal surgery.[24] However, a review of the literature did not find an association between obesity, parity,

menopausal status, or use of hormone replacement and mesh-related adverse events.

An additional important resource for patients and clinicians is the joint SUFU/American Urogynecologic Society (AUGS) position statement regarding mesh (http://sufuorg.com/docs/news/augs-sufu-mus-position-statement.aspx).

TREATMENT

11. **In patients with stress urinary incontinence or stress-predominant mixed urinary incontinence, physicians may offer the following non-surgical treatment options: (Expert Opinion)**

- **Continence pessary**
- **Vaginal inserts**
- **Pelvic floor muscle exercises**

Patients may opt for the use of conservative measures to treat stress or stress-predominant urinary incontinence. There are no comparative or direct observational data concerning the use of urethral plugs, continence pessaries, or vaginal inserts in the management of these patients. The Panel believes these are low-risk options to consider in the treatment of patients. Some basic maintenance should be followed with these devices, including regular visits to monitor time of use and tissue quality to minimize complications. The optimal patient for any of these treatment options is not currently established.

12. **In index patients considering surgery for stress urinary incontinence, physicians may offer the following options: (Strong Recommendation; Evidence Level: Grade A)**

- **Midurethral sling (synthetic)**
- **Autologous fascia pubovaginal sling**
- **Burch colposuspension**
- **Bulking agents**

Several surgical options exist for SUI. Choice of intervention should be individualized based upon the patient's symptoms, the degree of bother the symptoms cause the patient, patient goals and expectations, and the risks and benefits for a given patient. Although most of these procedures have been available for some time, very little comparative data between these broad treatment categories exists to assist the physician in choosing a therapy.

***Midurethral synthetic sling*.** MUS may be characterized as retropubic (top-down or bottom-up), transobturator (inside-out or outside-in), single incision sling (SIS) or adjustable sling types. Long-term data exists for several of the slings but vary in their duration of follow up, in both comparative and non-comparative analyses. Furthermore, it remains important to assess the manner in which success was defined in each of these studies, as definitions vary between series.

Retropubic midurethral synthetic sling (RMUS). Initially introduced as a bottom-up retropubic approach in the late 1990s, the TVT™ is arguably the most widely studied anti-incontinence procedure, with data that exceeds 15 years follow up.[20,25] Success rates are reported to be between 51 and 87%. The TVTä has also been the subject of numerous comparative studies. The retropubic top-down versus bottom-up approach was evaluated in two publications, one systematic review[20] and one additional study.[26] Ford et al. (2015) included five trials with a total of 631 women with SUI or stress-predominant MUI symptoms that compared these two procedures.[20] The average study quality was moderate. Definitive superiority for one approach over the other has not been found; however, results favored the bottom-up approach in some meta-analyses. In these studies, a significant reduction in bladder or urethral perforation, voiding dysfunction, and vaginal tape erosion was noted with the bottom-up approach. Meta-analyses regarding other adverse events (perioperative complications, *de novo* urgency or urgency incontinence, and detrusor overactivity) were inconclusive due to wide confidence intervals. Accordingly, the Panel does not support one retropubic method over another.

Transobturator midurethral synthetic sling (TMUS). The TMUS was developed in an effort to simplify and even minimize the complication profile realized with the retropubic approach. Single and multicenter prospective and retrospective studies have confirmed efficacy with success rates ranging between 43 and 92% in follow up of up to 5 years.[20] With the possibility that TMUS would have an improved safety profile over RMUS, it was natural to do comparative efficacy analyses between the sling types. Overall, in aggregate, most short-term analyses that compared RMUS and TMUS found them to be equivalent. However, long-term comparisons are relatively lacking. The Trial of Mid-urethral Slings (TOMUS) compared the short (one and two year) and long (five year) outcomes of RMUS and TMUS. Short-term analyses demonstrated statistical equivalence between the two procedures; however, slight

advantages towards the RMUS were seen with longer follow up (five years).[27]

The transobturator approaches have both outside-in and inside-out techniques. Evidence suggests that these approaches have similar effectiveness.

Single incision synthetic sling (SIS). In another development toward simplification of the synthetic sling, the SIS was introduced as a less invasive, lower morbidity surgery with the potential to maintain efficacy of the synthetic sling. It should be emphasized that no long-term data is available with the SIS, but more recent comparative analyses have become available. The SIS was compared with bottom-up RMUS. Overall evidence on effectiveness favors RMUS over SIS, but most of the SIS trials involved TVT-Secur, which is a device that has since been withdrawn from the market for poor results. The average study quality was moderate, and a five-study meta-analysis indicated a two-fold difference in success rates in favor of RMUS.[28] Comparison of SIS and TMUS have been studied with index and non-index patients. Taken in aggregate, the overall results show equivalence with the available SIS and TMUS with regard to effectiveness and sexual function, although the trials are primarily lower level evidence. Furthermore, there is a lack of long-term RCT data on SIS compared with other sling types. Accordingly, there is insufficient comparative data to favor a SIS over either RMUS or TMUS.

Autologous fascia pubovaginal sling (PVS). The autologous fascia PVS, which involves the placement of autologous fascia lata or rectus fascia beneath the urethra to provide support has been performed for many years. Using varying definitions, single center studies have confirmed between 87% and 92% success with 3-15 year follow up.[29-31] Still, comparative analyses of this time-tested technique have been lacking until the last decade. Well-controlled and appropriately blinded comparisons of fascia sling versus other anti-incontinence procedures is difficult due to the inherent differences in morbidity of the techniques. The SISTEr trial compared the fascial sling to the Burch colposuspension in a well-conducted RCT. Data suggested effectiveness and need for retreatment favoring the fascial sling over the Burch colposuspension (66% versus 49%). This trial used strict composite outcome criteria of no self-reported SUI on questionnaire, no need for retreatment, and a negative stress test. The Panel believes that the autologous fascia PVS is a viable option for the management of SUI. The added morbidity of the fascial harvest should be considered in the preoperative discussion when considering sling type (see complications section). Efforts to use other materials, such as porcine dermis and cadaveric fascia, as substitution for the autologous fascia have shown inferior results.[32]

Colposuspension. While largely supplanted by MUS, the suture-only based colposuspension still has a role in the management of SUI, although many would consider this primarily for patients concerned with the use of mesh or who are undergoing concomitant open or minimally invasive (laparoscopic or robotic) abdominal-pelvic surgery, such as hysterectomy. Comparative studies of the Burch colposuspension with the TVT™ showed essentially equivalent outcomes with the TVT™ in several RCTs. Despite the large number of trials, results were too sparse to indicate whether there is a difference between these two treatments. The SISTEr trial compared the Burch colposuspension with the autologous fascial PVS. This comparison had outcome data to five years and favored the autologous fascia PVS over the Burch colposuspension due to the lower retreatment rates (4% versus 13%). While no definitive selection criteria exist for this procedure over others, the Panel believes colposuspension is a viable approach for women with SUI who wish to avoid the morbidity of fascial harvest and also wish to avoid mesh, particularly if undergoing a simultaneous abdominal procedure, such as open or minimally invasive hysterectomy. One should realize that the colposuspension does carry some morbidity with its incision as shown in the SISTEr trial with over 20% of patients having wound related issues. The data also suggest that the colposuspension is likely inferior to fascial sling in most efficacy related outcomes.

Bulking agents. The Panel believes that bulking agents are viable treatments for SUI; however, little long-term data exists for them. Retreatment tends to be the norm for bulking agent therapy, and determination of absolute outcomes accordingly becomes challenging. There is inadequate data to allow the recommendation of one injectable agent over another. Still, the role for bulking agents may best be considered in patients who wish to avoid more invasive surgical management or who are concerned with the lengthier recovery time after surgery or who experience insufficient improvement following a previous anti-incontinence procedure. Patients should be counseled on the expected need for repeat injections.

13. **In index patients who select midurethral sling surgery, physicians may offer either the retropubic or transobturator midurethral**

sling. (Moderate Recommendation; Evidence Level: Grade A)

The selection of RMUS versus TMUS should be determined by the surgeon based on comfort or preference and degree of urethral mobility after discussion with the patient regarding the difference in risks of adverse events between each procedure.

Five systematic reviews[20,33-36] and 11 publications citing RCT trials were reviewed by the panel. Of the 11 RCTs, 4 enrolled only index patients,[37-40] and 7 enrolled patients with MUI or did not clearly define enrollment.[41-47]

The largest systematic review included 55 trials with a total of 8,652 patients with SUI or stress-predominant MUI.[20] The rates of subjective and objective cure were similar between TMUS and RMUS in the short-term (up to 1 year). There were fewer and less robust studies with medium term (1-5 years) and long-term (>5 years) follow-up with subjective cure rates ranging from 43-92% for TMUS and 51-88% for RMUS. The review by Sun et al.[33] used more stringent inclusion criteria than that performed by Ford et al.[20] and included 16 RCTs with a total of 2,646 women with SUI or MUI. The RCTs in that review included at least 40 patients, no more than 15% loss to follow-up, and objective cure as an outcome. They performed separate meta-analyses of studies that evaluated only patients with isolated SUI (7 trials; index patients) and studies that evaluated patients with either isolated SUI or MUI (9 trials; mixed index and non-index patients). The review was inconclusive with regard to efficacy.

Eleven RCTs investigated comparative efficacy between the TMUS and RMUS, and the balance of data suggests similar effectiveness. Four of the 11 RCTs looked specifically at index-patients: one indicated equivalence,[37] and three[38-40] were inconclusive. Of the remaining seven trials, two found equivalence,[41,44] four were inconclusive,[43,45-47] and one[42] indicated an advantage of RMUS. The latter trial, Schierlitz et al.,[42] reported that the risk of failure was 15 times greater (95% CI: 2 to 113) in women who underwent a TMUS procedure compared to women who underwent an RMUS procedure. However, it should be noted that all patients in this trial had ISD based on either VLPP or maximum urethral closure pressure, which may limit its applicability. The meta-analysis by Ford et al.[20] also demonstrated a significantly higher rate of repeat incontinence surgery within five years in the TMUS group.

Overall, however, some early short-term data suggested equivalence in incontinence rates after surgery when comparing TMUS to RMUS in both index and non-index patients. That being said, robust long-term data are lacking, and the data from increasing follow up appear to be demonstrating a lack of durability of TMUS versus RMUS.

Validated QOL and incontinence severity measures were assessed by Fan et al.[35] in seven RCTs that compared RMUS (TVT) and TMUS (TVT-O). A meta-analysis of six trials measuring Urogenital Distress Inventory scores found a statistically significant weighted mean difference favoring TMUS slings (2.28, 95% CI: 1.77 to 2.80). Meta-analyses of other instrument scores (IIQ, VAS, ICIQ-SF, and UISS) found no significant between-group differences, but the 95% confidence intervals were all too wide to rule out the possibility of a difference between treatments. Schimpf et al.[36] found no significant difference in patient satisfaction between TMUS or RMUS.

Significant differences in adverse events were identified in both the systematic review and in individual RCTs. While the systematic reviews did not provide enough information on patient characteristics to separate index from non-index patients, seven of the individual RCTs reviewed reported data on index patient's only.

Ford et al.[20] found more major vascular or visceral injuries, bladder or urethral perforations, voiding dysfunction, and suprapubic pain with the RMUS, while groin pain, repeat incontinence surgery between one and five years, and repeat incontinence surgery after more than five years were more likely to occur with the TMUS. Sun et al.[33] noted higher rates of bladder perforation, hematoma, and voiding dysfunction with the RMUS and higher rates of thigh/groin pain with the TMUS. While most other adverse events outcomes were inconclusive due to wide confidence intervals, *de novo* urgency or UUI were equivalent between the two procedures.

In summary, the balance of evidence suggests equivalence in efficacy, QOL improvement, and satisfaction between the TMUS and RMUS, particularly within the first few years after surgery. Longer-term data are less clear, with some studies showing lower likelihood of the need for repeat treatment after RMUS. Adverse events differed with the TMUS having a lower risk of intraoperative injury and voiding dysfunction, while the RMUS has lower rates of short-term groin pain and need for repeat stress incontinence surgery.

a. When performing TMUS in women with stress -predominant urinary incontinence surgeons

may perform either the in-to-out or out-to-in TMUS technique.

Data from 10 RCTs of both index and non-index patients are consistent in finding equivalence between the two approaches. Ford et al.[20] performed a meta-analysis that included 10 trials with a total of 1,463 women with SUI or MUI with stress- predominant symptoms that compared the outside-in and inside-out TMUS. Subjective and objective cure at various follow-up times indicated equivalence between the procedures. One trial demonstrated a significant mean difference of 16.54 (95% CI: 4.84 to 28.24) in IIQ-7 scores favoring the inside-out procedure. Adverse events were different with vaginal perforation occurring more frequently with the outside-in approach and voiding dysfunction occurring more frequently with the inside-out approach. Four additional RCTs of moderate and high quality were consistent with the conclusion of equivalence between the two approaches.[39,48-51]

b. When performing RMUS in women with stress-predominant urinary incontinence surgeons may perform either the bottom-up or the top-down approach.

Most studies comparing the top-down to the bottom-up technique demonstrated equivalence or were inconclusive. The systematic review by Ford et al.[20] detected a statistically significant difference in the subjective cure rates favoring the bottom-up approach; however, the relative risks for both the subjective and objective cure rates fell within the equivalence range. The top-down approach had higher rates of bladder and urethral perforation, voiding dysfunction, and vaginal tape erosion while an analysis of other adverse events such as perioperative complications, *de novo* urgency or urgency incontinence, and detrusor overactivity was inconclusive due to wide confidence intervals. Lord et al.[26] identified higher rates of urinary retention with the top-down approach (6.5%) versus the bottom-up approach (0%). Panelists felt that the limited evidence from one review demonstrating a small increase in adverse events with the top-down approach was insufficient to make a recommendation favoring the bottom-up approach over the top-down approach.

c. A MUS may be considered in the non-index patient or in the patient with intrinsic sphincter deficiency after appropriate evaluation and counseling.

Very few of the meta-analyses or individual studies restricted the enrollment to index patients. Studies that restricted to index patients had similar comparative outcomes to those studies that included some non-index patients. Therefore, while there are no evidence-based recommendations that the Panel can make regarding placement of a MUS in patients who do not fall into the definition of the index patient, the Panel feels that it is important to consider several factors when deciding whether or not to proceed with a MUS. Considerations may include prior pelvic floor reconstruction and technique, temporal relationship to any prior surgery, presence or absence of pelvic prolapse, degree of urethral mobility, concomitant and urinary urgency or urgency incontinence symptoms.

Regarding patients with ISD (typically defined as VLPP <60 cm water and/or minimal urethral hypermobility), one review evaluated the comparative efficacy of RMUS and TMUS in 8 RCTs with a total of 399 patients with ISD-associated SUI or MUI. A meta-analysis of subjective cure rate at up to 5 years follow up found a statistically significant difference favoring RMUS, although the effect size was quite small and the 95% confidence interval fell within the range of equivalence (RR 0.88, 95% CI: 0.80 to 0.96). A meta-analysis of objective cure rate at up to 5 years found no statistically significant between-group difference, but the effect size and 95% confidence interval was similar to that for subjective cure (RR 0.90, 95% CI: 0.79 to 1.03). They also meta-analyzed 2 RCTs with 183 patients with ISD-associated SUI or MUI that performed QOL assessment.[34] In general, this review found equivalent effectiveness between the two treatments. However, they found that repeat incontinence surgery within five years was significantly lower in the RMUS group**.** One RCT[42] confirmed the conclusion of Ford et al. (2015)[20] that the rate of repeat sling surgery within one to five years is lower (better) after RMUS than after TMUS.

14. Physicians may offer single-incision slings to index patients undergoing midurethral sling surgery with the patient informed as to the immaturity of evidence regarding their efficacy and safety. (Conditional Recommendation; Evidence Level: Grade B)

SIS products were introduced into the market since the last review and have continued to evolve over time leading to inconsistent evidence regarding their efficacy and safety. Some evidence has suggested that SIS are associated with low rates of postoperative groin pain, but higher rates of vaginal mesh exposure and mesh perforation into the bladder or urethra. However, these higher rates appeared predominantly in meta-analyses/ studies that included TVT-Secur, which has been

withdrawn from the market.

Three systematic reviews and 13 additional publications addressed the comparison of the transobturator midurethral sling with the single-incision sling. Most of the trials were of short duration, and a variety of SIS were used in the trials. Of the 13 individual RCTs that were reviewed, 4 utilized a non TVT-Secur SIS, and all showed similar effectiveness between the SIS and the TMUS. After removing the trials that included TVT-Secur, the remaining trials consistently suggest similar efficacy between the TMUS and a variety of currently marketed SIS.

Nambiar et al.[28] included 20 trials that compared adverse events between SIS and either inside-out or outside-in TMUS. After removing the 8 trials that utilized TVT-Secur as the SIS, the remaining 12 trials were inconclusive with regard to efficacy. While they did not show any differences in subjective or objective cure rates, the confidence intervals were too large to rule out a significant difference.

Zhang et al.[52] used more specific selection criteria, including five RCTs that compared the SIMS-AJUSTsling to TVT-O or TOT slings. They demonstrated equivalence in both objective and subjective cure rates.

Fan et al. (2015)[35] assessed the impact on validated incontinence impact instruments using eight RCTs that compared SIS (two used TVT-Secur) to TVT-O slings. A meta-analysis of five trials using the PISQ-12 found significantly higher sexual function scores in the SIS group. One trial using the KHQ found significantly greater improvement in the total KHQ score in the TMUS group, while the other instruments yielded inconclusive results, as they did not find a significant difference between treatments.

The literature regarding adverse events following SIS is inconsistent. In one study, data regarding four specific adverse events favored TMUS over SIS: less vaginal mesh exposure, less mesh perforation into the bladder or urethra, greater need for repeat SUI surgery, and greater need for any other additional or new surgical procedure. In contrast, meta-analyses of these same outcomes comparing TMUS and SIS were inconclusive. While both postoperative and long-term pain and discomfort favored SIS when compared to TMUS, all other outcomes, meta-analyses were inconclusive.

A meta-analysis of postoperative groin pain found a significant reduction favoring the SIMS-AJUST sling. Meta-analyses for other adverse events (including postoperative pain, lower urinary tract injuries, postoperative voiding difficulties, de novo urgency and/or worsening of preexisting surgery, vaginal tape erosion, and repeat continence surgery) were inconclusive.

Five additional publications compared SIS other than TVT-Secur with the TMUS. Franco et al.[53] found inconclusive results except that pain was less after Contasure Needless (C-NDL) when compared to TMUS. Foote[54] and Schellart et al.[55] also found less pain with the MiniArc SIS versus the TMUS and inconclusive results for other adverse events. Mostafa et al.[56] and Schweitzer et al.[57] compared TVT-O to SIMS-AJUST and found comparative adverse event rates to be inconclusive.

The Panel felt that longer-term data were necessary before being able to make a stronger statement regarding the SIS. The current data, while demonstrating similar efficacy to TMUS, are generally limited to short-term (12 months) trials involving substantially fewer patients than trials involving full length RMUS or TMUS.

15. **Physicians should not place a mesh sling if the urethra is inadvertently injured at the time of planned midurethral sling procedure. (Clinical Principle)**

Given the risks of mesh erosion the Panel felt that in cases where the urethra has been entered unintentionally, mesh procedures for SUI should be avoided. If the surgeon feels it is appropriate to proceed with sling placement in the face of an inadvertent entry into the urethra, then a non-synthetic sling should be utilized.

16. **Physicians should not offer stem cell therapy for stress incontinent patients outside of investigative protocols. (Expert Opinion)**

The Panel recognizes that stem cell therapy may be a future option for women with SUI; however, there is currently not enough data to support this treatment modality. Future studies are necessary to identify the best cell type and technique as well as patient characteristics to guide treatment decisions.

SPECIAL CASES

17. **In patients with stress urinary incontinence and a fixed, immobile urethra (often referred to as 'intrinsic sphincter deficiency') who wish to undergo treatment, physicians should offer pubovaginal slings, retropubic midurethral slings, or urethral bulking agents. (Expert Opinion)**

There are multiple deficiencies in the literature with regard to ISD, including the definition of ISD, the coexisting morbidities, the variable outcomes measures and the variability in the procedures that have been performed and evaluated in the literature.

While there are a number of trials that have compared one procedure to another in patients with ISD, they are usually subanalyses of larger trials. Some argue that a MUS should be avoided in a patient with an immobile urethra because the mechanism of action by which the MUS corrects incontinence is by compressing the urethral lumen as it moves into the sling with increased intraabdominal pressure. The immobile urethra may require additional tension on the sling, which should be avoided when using mesh slings. Nevertheless, in situations in which a MUS is being considered, there is some data suggesting that the RMUS is preferred over the TMUS.[58]

The Panel believes that in the case of a minimally mobile urethra, RMUS or PVS may a preferred option, and in the case of the non-mobile urethra, PVS may be the preferred option. Other techniques that have been used effectively in this scenario include the spiral (circumferential) sling using autologous fascia, and the artificial urinary sphincter.[59,60]

Bulking injections have been shown to be effective in this setting as well; however, the risk of SUI recurrence, and the likely need for future injections should be discussed with the patient.

Overall the consensus of the Panel was that while RMUS and bulking agents may be considered in these settings, the autologous PVS is a preferred approach based on the lack of robust evidence for RMUS in these patients, the suboptimal outcomes with bulking injections and the long track record of PVS.

18. **Physicians should not utilize a synthetic midurethral sling in patients undergoing concomitant urethral diverticulectomy, repair of urethrovaginal fistula, or urethral mesh excision and stress incontinence surgery. (Clinical Principle)**

It is a well-accepted principal that synthetic mesh should not electively be placed in close proximity to a fresh opening into the genitourinary tract. High level evidence supporting or refuting this is noticeably lacking given the extant case reports suggesting urethral erosion associated with mesh slings. Mesh placed in close proximity to a concurrent urethral incision can theoretically affect wound healing, potentially resulting in mesh perforation. Thus, a synthetic sling should not be placed concurrently with any procedure in which the urethra is opened in proximity to the sling position. Specifically, if a concurrent anti-incontinence procedure is necessary when performing a urethral diverticulectomy, urethrovaginal fistula repair, or removal of mesh from within the urethra, a synthetic sling should not be utilized. Instead, an anti-incontinence procedure that does not involve placement of synthetic material suburethrally, or use of a biologic material, preferably autologous fascia, should be considered.

19. **Physicians should strongly consider avoiding the use of mesh in patients undergoing stress incontinence surgery who are at risk for poor wound healing (e.g., following radiation therapy, presence of significant scarring, poor tissue quality). (Expert Opinion)**

Proper healing of the vaginal epithelium is critical in the prevention of mesh exposures. Compromised tissue may heal poorly, thereby increasing the risk for complications when mesh is placed. Patients with poor tissue characteristics (e.g., following radiation therapy, significant fibrosis from prior vaginal surgery, severe atrophy) are at increased risk for complications following synthetic mesh placement. Other chronic states that lead to impaired wound healing, such as long-term steroid use; impaired collagen associated with systemic autoimmune disorders, such as visceral Sjogren's disease or systemic lupus erythematosus; and immune suppression may also increase the risk of a mesh exposure. Physicians should consider the presence of other comorbid conditions and treatments that may affect wound healing (e.g., radiation therapy, presence of significant scarring, poor tissue quality) when selecting sling type in patients undergoing stress incontinence surgery. In such cases, alternatives to synthetic mesh should be considered, although there is no direct evidence that patients are at increased risk of urethral perforation in these circumstances.

20. **In patients undergoing concomitant surgery for pelvic prolapse repair and stress urinary incontinence, physicians may perform any of the incontinence procedures (e.g., midurethral sling, pubovaginal sling, Burch colposuspension). (Conditional Recommendation; Evidence Level: Grade C)**

SUI may coexist with pelvic organ prolapse in a significant number of patients. Women with preexisting SUI may have worsening of urinary incontinence, and some without any symptoms of SUI may develop stress leakage following reduction of the prolapse. Physicians

may choose to perform a concomitant incontinence procedure when repairing pelvic organ prolapse; however, they must balance the benefits with the potential for an unnecessary surgery and possible additional morbidity. Several caveats are important in the consideration of this clinical scenario. Three general approaches can be considered: (1) perform a concomitant incontinence procedure in all women undergoing prolapse surgery, (2) perform an incontinence procedure in none, and (3) selectively perform an anti-incontinence procedure based on the presence of preexisting SUI and/or the finding of occult SUI (SUI that only becomes apparent when the prolapse is reduced). Informed patient decision-making is critical in this situation. A nomogram has been developed that can help estimate the risk of developing SUI after vaginal prolapse surgery and can aid in the decision regarding whether or not to perform a concomitant anti-incontinence procedure.[61]

When specifically considering patients without SUI symptoms preoperatively, two important studies provide guidance. The CARE trial showed that women undergoing an abdominal sacrocolpopexy without preoperative complaints of SUI who had a concomitant Burch colposuspension had a lower rate of postoperative SUI than those who did not have a Burch colposuspension.[62] Even when occult SUI was not demonstrated preoperatively, those who had the Burch colposuspension had a lower chance of developing SUI postoperatively. The OPUS trial randomized patients undergoing a vaginal repair of stage 2 or greater anterior vaginal wall prolapse, without symptoms of SUI, to either undergo a concomitant RMUS or sham incision (i.e., no surgery for SUI).[63] At 12 month follow-up, those who had a concomitant sling had a lower rate of SUI than those who did not. However, it is important to recognize that the difference was not marked (27.3% SUI in those that had a sling and 43.0% in those that did not). Critically, the number of patients needed to treat with a sling to prevent one case of incontinence was 6.3. Thus, one could argue that 5 of 6 patients who had a sling placed had an unnecessary procedure with the additional (small but real) risk of increased morbidity.

Ultimately, the decision as to whether or not to perform a concomitant incontinence procedure at the time of prolapse surgery should be a product of a shared decision making process between the physician and patient after a review of the risks and benefits of this additional procedure.

21. Physicians may offer patients with stress urinary incontinence and concomitant neurologic disease affecting lower urinary tract function (neurogenic bladder) surgical treatment of stress urinary incontinence after appropriate evaluation and counseling have been performed. (Expert Opinion)

Patients with neurogenic lower urinary tract dysfunction may have straightforward SUI or SUI related to their neurologic process. In either event, patients with neurogenic lower urinary tract dysfunction do not fall into the category of the index patient, and a detailed evaluation should be performed. Other issues, such as incomplete emptying, detrusor overactivity, and impaired compliance, should be identified and in many cases treated prior to surgical intervention for SUI. In a patient who requires intermittent catheterization, one must be cognizant of possible complications with the use of a bulking agent (bulking effect may be attenuated by frequent catheter passage) or a synthetic sling (potential catheter trauma in the area of the sling could place the patient at risk for mesh erosion into the urethra). These concerns must be discussed relative to the overall risks and benefits of the procedure. Should the sling need to be placed under tension with the goal of planned permanent surgical retention, clinical judgement would suggest that the procedural choice should be a non-mesh sling. Lastly, patients with neurogenic lower urinary tract dysfunction who undergo sling procedures in particular should be followed long-term for changes in lower urinary tract function that could be either induced over time by the neurologic condition itself, or potentially by the sling procedure.

22. Physicians may offer synthetic midurethral slings, in addition to other sling types, to the following patient populations after appropriate evaluation and counseling have been performed: (Expert Opinion)

- **Patients planning to bear children**
- **Diabetes**
- **Obesity**
- **Geriatric**

The Panel believes that in most instances, placement of a sling should be postponed until child bearing is complete. Overall, there does appear to be a relatively high rate of SUI recurrence following delivery, independent of mode of delivery, among women with a history of MUS. In light of the elective nature of the surgery, the Panel suggests that in most instances, surgical treatment of SUI should be deferred until after

child bearing is complete.

Diabetic women planning to undergo sling surgery should be counseled regarding their higher risk for mesh erosion and reduced effectiveness compared with their non-diabetic counterparts. There is some overlap with obesity in this category; however, after controlling for obesity, diabetes was found to have a negative impact on outcomes.[21,22,64-67]

Obesity (defined as a BMI of > 30) has been well studied in several trials, and there appears to be a slight correlation suggesting worse clinical effectiveness of slings in obese patients compared with those with lower BMI. Increased risk of voiding dysfunction and mesh erosion were not found to be associated with obesity.[21,24,43,68,69]

Geriatric patients (defined as 65 years old or older in most studies) undergoing incontinence surgery should be counseled that they are at lower likelihood of successful clinical outcomes compared with younger patients. No clear association is noted between age and mesh erosion or voiding difficulty in patients undergoing MUS surgery.

Due to the lack of robust data regarding various patient populations, there are no evidence-based recommendations that the Panel can make regarding the use of MUS in non-index populations, such as those with high-grade prolapse, high BMI, advanced age, or recurrent or persistent SUI. However, the Panel does feel that there are a number of factors that should be considered when making the decision to proceed with a MUS in these patients. These may include the type of previous surgery, length of time since previous surgery, presence or absence of hypermobility, degree of urgency or urgency incontinence symptoms, and other potential contributing factors.

OUTCOMES ASSESSMENT

23. **Physicians or their designees should communicate with patients within the early postoperative period to assess if patients are having any significant voiding problems, pain, or other unanticipated events. If patients are experiencing any of these outcomes, they should be seen and examined. (Expert Opinion)**

Early intervention may ameliorate potential complications in patients who have had SUI surgery. Specifically, if there is evidence a patient has symptoms of obstruction, early intervention may be necessary to reduce patient bother and to prevent development of bladder dysfunction in the long-term. Other postoperative complications, such as dyspareunia, persistent pain, frequent UTI, and mesh-specific complications, such as vaginal extrusion and lower urinary tract erosion, might also be more expeditiously and effectively treated with early communication. Because patients may not recognize some of the potential adverse events that can occur, they may suffer unnecessarily if the appropriate questions and assessment are not performed. Though clearly this communication can be in person, there is no evidence that a phone discussion cannot provide the same information.[70] Recent evidence would suggest that verbal communication potentially supplemented by live internet-based communication (tele-medicine) of wounds can suffice for follow up evaluation in uncomplicated post-operative scenarios and can identify surgical complications expeditiously when present.[71] If patients are having voiding dysfunction, a decrease in the force of their urinary stream, unexpected pain, recurrent UTI, new onset dyspareunia, or other unanticipated symptoms, they should be evaluated in person by the physician or his/her designee. If appropriate, depending on the index surgery, the patient can be taught clean intermittent catheterization (CIC), a catheter can be placed, or surgical intervention may be necessary. Additionally, in circumstances of preoperative concern related to postoperative voiding dysfunction (e.g. poor quality bladder contraction identified on urodynamic evaluation), CIC instruction should be considered as a component of preoperative teaching.

24. **Patients should be seen and examined by their physicians or designees within six months post-operatively. Patients with unfavorable outcomes may require additional follow-up. (Expert Opinion)**

- **The subjective outcome of surgery as perceived by the patient should be assessed and documented.**
- **Patients should be asked about residual incontinence, ease of voiding/force of stream, recent urinary tract infection, pain, sexual function and new onset or worsened overactive bladder symptoms.**
- **A physical exam, including an examination of all surgical incision sites, should be performed to evaluate healing, tenderness, mesh extrusion (in the case of synthetic slings), and any other potential abnormalities.**

- **A post-void residual should be obtained.**
- **A standardized questionnaire (e.g. PGI-I) may be considered.**

At some point between six weeks and six months after surgery, the patient should be assessed and examined in person by the surgeon or his/her designee to evaluate the outcomes of surgery and to assess for any potential complications.

At the time of follow-up, the subjective outcome of surgery as perceived by the patient should be assessed and documented. Information related to resolution of SUI, need for pads and number used, presence or absence of OAB symptoms, ease of voiding/force of the urinary stream as well as other pertinent lower urinary tract symptoms should be elicited. New onset surgical site or pelvic pain and dyspareunia should also be explicitly queried.

Completion of a standardized questionnaire by the patient at this visit to assess her satisfaction may be considered. The PGI-I is an easy to use and responsive form that correlates well with other outcomes questionnaires and can be used to facilitate comparisons between centers. It is recommended, though several objective, validated incontinence questionnaires are also available for this purpose and can be utilized.[72-77] For physicians who utilize a validated lower urinary tract questionnaire in the initial evaluation of their patients with SUI, repeating the same questionnaire postoperatively is recommended.

Sexual function, including whether the patient or their partner is experiencing any pain during intercourse, should be assessed. Patients should also be asked about any UTIs since surgery.

A physical exam should be performed and a PVR should be measured.

A pelvic exam as well as an abdominal/thigh exam, depending on the surgery performed, should be performed to assess for wound healing at the surgical sites. Tenderness at any trocar sites (prepubic/thigh) or incisions should be evaluated, to rule out infection, hematoma, or extruded mesh and to document a baseline for longitudinal comparison. A vaginal exam should be performed to assess for any delay in healing, tenderness, potential wound disruption, and in the case of synthetic slings, mesh exposure. While exposure can be identified visually during a half-speculum exam palpation of the anterior vaginal wall may also identify mesh exposure that is not easily visible. If the index of suspicion is high in spite of inability to definitively identify extruded mesh, an examination under anesthesia can be considered. Wound complications specifically associated with autologous harvest sites (seroma, hernia) should also be assessed.

FUTURE DIRECTIONS

Continued emphasis on outcomes reporting has placed more focus on the importance of patient literacy in the informed consent process and the perioperative preparation schema. It is generally accepted that appropriate informed consent relies on adequate patient information and instruction. It is also clear that the complexity of functional urologic conditions such as female SUI provide unique and significant hurdles to patient understanding and appropriate determination of risk/benefit related to interventions for these conditions. Increased reliance on non-paper-based informational resources has evolved given the understanding that adult education requires repetitive delivery of information in discreet and discernable informatics groupings. Expanded use of tests of functional health literacy in adults (TOFHLA) may expedite literacy assessments in unique individuals.

Improving and honing a physician's ability to provide valuable and comprehensible education for patients regarding their condition and therapeutic options are of clear importance in accomplishing successful treatment. Patients who understand their condition and the rationale behind their treatment are more satisfied with their outcomes.[78] Accordingly, the development of ancillary tools that can supplement and move toward more effective and successful communication between patients and their surgeons would be of significant worth. Similarly, overcoming obstacles that result in disparities in healthcare, such as socioeconomic, language, and access barriers would provide great value to many.

The use of telemedicine in surgery is expanding rapidly and across multiple specialties within surgical disciplines. Telesurgery has been performed for the last several decades, but the use of telemedicine, from a standpoint of mentoring and consultation, has recently become more popular. Although not completely explored, some pelvic floor disorders would appear to be uniquely suited to teleconsultation and telefollow-up for purposes of managing chronic conditions, which these disorders represent.[79]

In considering new treatments, stem cell injection for the indication of SUI represents possibly one of the most compelling emerging therapies. Stem cell use for the treatment of SUI has been proposed for more than

ten years.[80-83] Different stem cell populations have been evaluated for this indication. The six cell types include embryonic, muscle-derived (satellite cells), bone marrow-derived,[84] mesenchymal, adipose, urinary, and human umbilical cord blood types. Human amniotic fluid stem cells (hAFSCs) have also been proposed.[85,86]

Autologous muscle-derived cells (AMDSC) have been evaluated for intrasphincteric injection for SUI.[87] The primary outcome was the incidence and severity of adverse events. Treatment related complications included minor events such as pain/bruising at the biopsy and injection sites. A higher percentage of patients receiving high doses (in terms of cell numbers) experienced a 50% or greater reduction in pad weight, had a 50% or greater reduction in diary-reported stress leaks and had zero to one leak during a three-day period at final follow-up.

Stem cell use for the indication of SUI continues to evolve. Current evidence is limited by a lack of active comparator arms and outcomes limitations. Additionally, the optimal cell type, injection method, and final administration characteristics for cell transfer (inclusive of volume of viable cells) remain areas for improvement and study.

It is anticipated that as materials science advances, the use of nanoparticulate technology expands, and improved understanding of wound healing evolves, other therapies will arise for SUI. These therapies will need to be carefully vetted and assessed for safety and efficacy, and it is hoped that enhanced collaboration between regulatory, academic, and patient outcomes groups will provide continued improvement in interventions for SUI.

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DISCLAIMER

This document was written by the Stress Urinary Incontinence Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2014. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology with specific expertise on this disorder. The mission of the Panel was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the treatment of stress urinary incontinence.

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (‘off label‘) that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

BJUI
BJU International

Guideline of guidelines: urinary incontinence

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The objective of the article is to review key guidelines on the management of urinary incontinence (UI) to guide clinical management in a practical way. Guidelines produced by the European Association of Urology (updated in 2014), the Canadian Urological Association (updated in 2012), the International Consultation on Incontinence (updated in 2012), and the National Collaborating Centre for Women's and Children's Health (updated in 2013) were examined and their recommendations compared. In addition, specialised guidelines produced by the collaboration between the American Urological Association and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction on overactive bladder and the use of urodynamics were reviewed. The Appraisal of Guidelines for Research and Evaluation II (AGREE) instrument was used to evaluate the quality of these guidelines. There is general agreement between the groups on the recommended initial evaluation and the use of conservative therapies for first-line treatment, with a limited role for imaging or invasive testing in the uncomplicated patient. These groups have greater variability in their recommendations for invasive procedures; however, generally the mid-urethral sling is recommended for uncomplicated stress UI, with different recommendations on the approach, as well as the comparability to other treatments, such as the autologous fascial sling. This 'Guideline of Guidelines' provides a summary of the salient similarities and differences between prominent groups on the management of UI.

Keywords

urinary incontinence, guidelines, urodynamics, anti-incontinence procedures

Introduction

Urinary incontinence (UI) is a common disease, with prevalence as high as 30% in women aged 30–60 years. About 50% of this UI is attributable to stress UI (SUI) [1]. Urgency UI (UUI) is another type of UI that contributes significantly. With myriad treatment options, both conservative and invasive, many professional organisations have created guidelines to help clinicians provide care for individual patients with UI.

These guidelines provide recommendations on the appropriate examinations and diagnostic testing for UI, as well as the role of conservative or invasive therapy. The methodologies upon which the guidelines are based are similar, starting with systematic reviews and grading of available literature (Table A1). Recommendations are then made with different definitions and strengths (Table A2) between the publications. Guidelines are not necessarily meant to be exhaustive, but act more as practical review of the evidence-based management of 'index patients'.

Guidelines Reviewed

The European Association of Urology (EAU) guidelines on UI, now in its third edition (2014) [2], initially utilised the first International Consultation on Incontinence (ICI) in 1998 [3] (Table 1). Subsequent updates have used both the International Consultation on Urologic Diseases [4] and the National Institute for Health and Care Excellence (NICE) [5] literature reviews to create an underlying framework to their guidelines. However, since 2012, editions have been written based on thorough literature review, integrating studies from databases such as MedLine with Cochrane Centre publications and meta-analyses, creating a completely new framework, Updates are now performed annually to include newer interventions, such as mirabegron or more current evaluation of drug options, and patient-reported outcomes, and provides grades of recommendations A–C (Table A2) [2].

The Canadian Urological Association (CUA) first published practical guidelines in 2005 and gave updated recommendations in 2012 based on a review of PubMed, MedLine, and The Cochrane Library database. They provided grades of recommendations that were defined similarly to the EAU guidelines, with the addition of a recommendation Grade D for inconsistent or inconclusive evidence [6].

The AUA focused on surgical management for female SUI and created a meta-analysis from literature review in 1997 [7], updated with current literature in 2009 [8] and again

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Table 1 Guidelines reviewed.

Guideline	Year of publication/ update
European Association of Urology (EAU)	2014
Canadian Urological Association (CUA)	2012
American Urologic Association (AUA)	2012
International Consultation on Incontinence (ICI)	2012
Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline	2012
Urodynamic Studies in Adults: AUA/SUFU Guideline	2012
National Institute for Health and Care Excellence (NICE)	2013

revised in 2012 [9]. Their goal was to provide standards, recommendations and options to guide clinicians on the management of SUI (Table 2). This will be referred to as the AUA guideline; however, this organisation also has a separate guideline in collaboration with the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) specifically on the diagnosis and treatment of overactive bladder (OAB), updated in 2014 [10] (referred to as the AUA/SUFU OAB guideline) and a 2012 guideline on the use of urodynamic studies (UDS) in adults (referred to as the AUA/SUFU UDS guideline). This UDS guideline, like the others mentioned, is based on a systematic review of articles from 2005 to 2011 [11].

Other guidelines exist, such as the continued work of the ICI, which collaborates with the International Scientific Committee (ISC) to produce clinical recommendations for practitioners. The ICI produced its fifth edition of recommendations in 2012 on a vast number of topics initially analysed by sub-committees, including evaluation and treatment of UI [4]. Recommendations were based of the on subjective opinion of their group of recognised experts in the field and a review of the available published literature (Table 2). The ICI also creates a separate grading for recommendations for diagnostic tests and studies (Table 3).

The NICE created an updated guideline on SUI, OAB, and mixed UI (MUI) in women in 2013 [5]. This group used literature from the Ovid platform and assessed guidelines provided by other groups to create their own evidence synthesis and recommendations.

Of necessity, these guidelines relied on expert opinion or consensus to generate recommendations when the data on topics were either limited or conflicting. Although this does limit the strength of the recommendation, all the guidelines reviewed clearly articulated when 'Expert Opinion' was relied upon. By providing the recommendations of all these organisations, this guideline of guidelines will hopefully help clinicians evaluate if a recommendation is varied, due to both known and unknown external influences, and determine a treatment pathway that is best for the patient and less affected by biases. It would be ideal for the clinician if a formalised collaborative effort could be made between these groups to create a singular guideline on management of UI. However, these organisations represent patient populations that are different and unique, and influenced by very different healthcare systems and, in some cases, external influences. Therefore, a uniform recommendation may not be applicable universally.

Prominent groups, such as the Royal Australian College of General Practitioners, have also produced guidelines on management of UI [12]; however, many groups, including this one, drew upon the previously mentioned guidelines to form their recommendations. In an effort to avoid redundancy and create a concise summary, these other guidelines are not specifically discussed.

We used the Appraisal of Guidelines for Research and Evaluation II (AGREE) instrument [13] to describe the

Table 2 Initial evaluation.

Recommendation	Guideline supporting recommendation (Grade included if specified)
Detailed history with emphasis on characterization of incontinence	EAU, AUA, CUA, NICE (Level 4), ICI (Level 5 – Grade D)
Detailed partum history	EAU
Exclude other disease processes (e.g. malignancy, ectopic ureter, etc.)	EAU
Physical examination	EAU, AUA, CUA, NICE, ICI
Pelvic examination	ICI, NICE (Level 4), CUA (Grade C)
Leakage of urine objectively observed in order to diagnose SUI	AUA (Standard)
Assess patient treatment expectations	CUA (Level 2 – Grade B)
Bladder/voiding diaries	NICE (Level 3)
3-day bladder diary	ICI (highly recommends)
3–7-day bladder diary	EAU (Level 2b – Grade A)
Voiding diary	AUA (Grade C), AUA/SUFU OAB
Questionnaires	EAU Grade B (for monitoring changes)
ICIQ for initial assessment	CUA and ICI (Grade A)

Table 3 Diagnostic tests.

Recommendation	Guideline supporting recommendation (Grade included if specified)
Urine analysis	EAU, AUA, CUA, ICI, NICE (Level 2)
Post-void residual urine volume measurement for symptoms of incomplete emptying or distended bladder on examination	EAU, AUA, CUA, ICI, NICE
Pad testing for quantifying UI	EAU (Grade C), AUA (Recommendation)
Pad testing for monitoring change after treatment	EAU (Grade C)
Routine imaging not recommended	EAU, AUA, CUA, ICI, NICE
Cystoscopy not recommended in uncomplicated UI	EAU, AUA, CUA, ICI, NICE
Cystoscopy when fistula suspected	CUA

quality of the guidelines examined. When provided, supplementary material was reviewed and included in our analysis. The present paper's authors found that all guidelines drew upon high quality literature and thus had high values for the 'Rigour of Development', and generally had excellent description of scope, purpose, and applicability, with clear presentation of topics. However, several of the guidelines were limited in describing contributing authors' conflicts and competing interests, and at times the intended user of the guideline was not clearly articulated. Scores were assigned based on careful review of the guidelines and material provided. Ultimately, the AGREE analysis is meant to comment on the reader's ease of ascertaining the topics the AGREE analysis touches upon. Low scores may therefore be given for difficulty determining the answers to these topics in the body of work, although the answers may be present. It is important to note that several of these guidelines were not intended as exhaustive review articles, but rather as an accessible and applicable resource for clinicians. As a result, although all these guidelines are excellent in many of the domains of the AGREE II analysis, they receive low scores in certain areas that may have been beyond the intent of their work. We think all these guidelines are robust, for which reason they were included in our present review. Lower scores on the AGREE II analysis should not be interpreted as less reliable recommendations, but instead as not adhering strictly to all factors considered as complete by the AGREE instrument.

Overall, all guidelines were assigned high scores, validating their high quality (Table A4).

Initial Evaluation

History and physical

The guidelines on UI agree that a detailed history is a requirement (Table 2). The consensus of these guidelines is a characterisation of the UI, focused on severity, degree of bother, timing, presence (or absence) of urgency, or mixed symptoms (EAU, AUA, NICE). The ICI makes recommendation as well but gives it the lowest level and quality of data (Level 5, Grade D) [14].

The guidelines on UI recommend considering other disease processes that can present as UI, but require further evaluation and a different management pathway. Emphasis varies based on the scope of the guideline (i.e. UI in general vs disease-specific guidelines – SUI).

The physical examination is appreciated as an important part of the evaluation and diagnosis of UI, but lacks high-quality data to prove its worth. The evaluation should include general status (mental status, obesity, mobility), an abdominal examination, and a pelvic examination. The CUA (Grade C) and ICI encourage specific evaluation of pelvic floor muscles. NICE gives 'Expert Opinion' that an assessment of the patient's pelvic floor should be evaluated to determine if pelvic floor muscle training (PFMT) would be therapeutic, although they acknowledge there is a lack of evidence to support this (level of evidence 4). The AUA provides a 'Standard' that, in order to diagnose SUI, a leakage of urine with increased abdominal pressure must be objectively shown on examination (positive stress test); otherwise the symptoms may represent an abnormal detrusor contraction. However, an opinion piece by Bhavin et al. [15] reviewing these guidelines questions this dogma, and counsels that, in their experience, patients with absent objective findings of SUI may still have subjective improvement in symptoms with therapy.

Questions and questionnaires

Assessment of patients' treatment expectations is given a Grade B recommendation (level of evidence 2) by the CUA as this guides treatment options. This sentiment is echoed by the AUA, making the assessment of patient expectations a 'Recommendation', here based on panel consensus. The EAU guideline specifically asked if assessment of patient perspective improved patient outcomes. They do not find evidence; therefore do not specially make a recommendation. There is a statement in the document that poor adherence to therapy may be related to unrealistic expectations.

The ICI highly recommends the use of a 3-day bladder diary for initial evaluation, while the EAU specifies a Grade A recommendation (level of evidence 2b) to use 3–7 day diaries if a patient with UI is having concurrent storage and voiding symptoms. The exact duration is not agreed upon based on the studies they reviewed [16,17]. Similar level of evidence existed for the diary to be used as a measure of outcome [18]. The AUA guideline for treatment of SUI also recommends the use of a voiding diary (Grade C, Panel Consensus), as does the AUA/SUFU OAB guideline. NICE cautions that the optimal duration of a voiding diary is unclear (level of evidence 4), and recommend a minimum of 3 days for initial assessment of OAB.

The scope and aim of the various guidelines may result in different conclusions about the utility and evidence behind the use of questionnaires, with some more highly recommended than others. The CUA and ICI give a Grade A recommendation to include the ICI Questionnaire (ICIQ) as part of initial assessment for specific clinical situations. However, the EAU guideline on UI states there is low level evidence of the increased sensitivity of tests such as the ICIQ or quality-of-life (QoL) questionnaires over bladder diaries [19], where no evidence was found to show that these questionnaires have an impact on outcome of treatment. In fact, many of the studies the EAU reviewed using patient-reported outcome measures were actually done in patients without UI [19,20]. The EAU gives a Grade B

recommendation for their use in standardised assessments, e.g. to monitor change after an intervention. NICE recommends the use of high-quality questionnaires for quantifying the impact of symptoms on QoL, and to use for assessing outcomes after treatment. Similar to other guidelines, they recommend the use of questionnaires such as the ICIQ, amongst others.

Initial Diagnostic Tests

Guidelines on UI agree upon a urine analysis as an initial diagnostic test and, if a patient is having symptoms of incomplete emptying or examination findings are concerning for a distended bladder, to measure post-void residual urine volume (PVR) (Table 3). Interpretation of this value must be done cautiously, as there is no consensus on an abnormal PVR [15].

The EAU (Grade C recommendation) and the AUA (Recommendation) supports pad testing when quantification of UI is required, as there is good evidence that pad tests can diagnose UI, as well as correlate the test to a patient's symptoms (Level 1b evidence by the EAU) [21,22]. In addition, studies support (level of evidence 1b) that changes in leaked urine volume in repeat pad testing has use in measuring treatment outcome [23,24], The EAU supports repeat pad testing for detecting change after treatment (Grade C). NICE agrees pad testing has utility in evaluating therapy; however, they caution that there is a lack of evidence of its use affecting outcome (Level 3).

Tests for urethral mobility or competence include the Q-tip test, Bonney, Marshall, and Fluid-Bridge tests. Based on a lack of evidence that these tests aid clinical assessment, NICE recommends against their use.

Guidelines agree with a high level of evidence that routine imaging is not recommended unless there is concern for other underlying pelvic disorders. There is agreement that routine cystoscopy should not be performed in the uncomplicated UI patient.

There are certain indications where the initial diagnostic testing is not sufficient. The AUA, for example, recommends further evaluation in the following circumstances: OAB symptoms, history of prior pelvic surgery (especially prior anti-UI procedures), neurogenic bladder, an elevated PVR, high-grade pelvic organ prolapse (POP), a negative stress test with SUI symptoms, an uncertain diagnosis, and, perhaps most importantly, the patient's willingness to undergo these studies. Further evaluation may include cystoscopy, UDS, imaging studies, pad testing, and voiding diaries. In some clinical scenarios, a fistula can be a cause of UI, and therefore test with dyes to stain urine can help. The use of dyes is also included in the appendix of the EAU guidelines, but no specific recommendation is made. The CUA recommends cystoscopy when a fistula is suspected [25].

Urodynamic Studies

UDS are a series of tests that can be invaluable for managing the lower urinary tract and LUTS (Table 4). The questions that arise surrounding UDS usually focus on the timing of this test during the management algorithm, patient populations in whom UDS are indicated, and in what situations do UDS help predict outcomes of interventions.

In neurologically intact adults with SUI, the EAU provides Level 1a evidence that although 'preliminary urodynamics' did influence choice of treatment, they did not alter the clinical outcome of conservative or drug therapy [26]. They cite Level 1b evidence that 'preliminary urodynamics' failed to improve outcome of SUI surgery in patients that have uncomplicated clinical SUI [27,28]. The EAU recommendation is to not perform UDS if conservative treatment is pursued (Grade B), and recommends advising patients that UDS is useful to discuss treatment options, but does not predict treatment outcome (Grade C). The AUA/SUFU UDS guideline [11] provides 'the option' to perform UDS in patients with UI if considering invasive treatment, and both the ICI and the EAU recommends UDS testing if the results will alter treatment recommendation and management. NICE recommends against UDS before initiating conservative treatment. All guidelines recommend UDS if there is recurrent UI after invasive treatments.

The AUA/SUFU guideline on UDS made a total of 19 statements about UDS on four disease states: SUI/POP, OAB UUI and MUI, neurogenic bladder, and LUTS. For example, if symptomatic SUI is not seen on UDS, it recommends repeat stress testing with urethral catheter removal. This is based on studies by Maniam et al. [29] and Huckabay et al. [30], which report that 50% of women with SUI will fail to

Table 4 Urodynamic studies.

Guideline	Recommendation
EAU	Do not perform if pursuing conservative treatment (Grade B) Counsel that UDS does not predict treatment outcome (Grade C) Use UDS if results will alter treatment recommendation and management
ICI	Use UDS if results will alter treatment recommendation and management
AUA/SUFU UDS guideline	Option: perform in patients with UUI if considering invasive treatment
NICE	Consider if diagnosis unclear, history of prior surgery for SUI, or for symptoms suspicious for detrusor overactivity or voiding dysfunction (Level 4)
All guidelines reviewed	Use UDS if there is recurrent UI after failure of invasive treatments

demonstrate SUI with a catheter in place; however, they will have objective SUI after the catheter is removed. It gives an 'Option' when stress-testing women with high-grade POP that the POP be reduced to assess for occult SUI [31]. Almost all of the statements made about UI are based on Grade C evidence strength or 'Expert Opinion'.

Conservative Management

All guidelines recommend a trial of conservative treatment before invasive therapy (Table 5). These conservative therapies include behavioural therapy, physical therapy, and scheduled voiding.

Behavioural therapy is recommended early in the treatment algorithm for both UUI and SUI. Scheduled voiding and restriction of fluid in women with excessive intake receives a Grade B recommendation from CUA, a well-validated recommendation by other groups such as the French College of Gynecologists and Obstetricians [32]. NICE recommends advising modification of overly high or overly low fluid intake in patients with OAB or UI symptoms. Smoking cessation receives a Grade C recommendation from the CUA, while the EAU gives a Grade A recommendation for cessation advice, consistent with good medical practice. However, the EAU acknowledges that smoking cessation does not have a definite effect on UI, based on a systematic review by Imamura et al. [33] providing only Level 4 evidence to support cessation.

Avoidance of caffeine is also recommended for the management of UI (Grade B from CUA and EAU). The EAU clarifies that caffeine reduction (Level 2 evidence) improves urgency and frequency, but not UI [34]. NICE gives a recommendation to encourage a trial of caffeine reduction in women with OAB. In obese women, the CUA gives a Grade A recommendation for weight loss as an intervention, and the EAU recommends >5% weight loss as a treatment plan (Grade A) [35]. Weight reduction evidence is cited in the AUA/SUFU OAB guidelines [36], included as one of the components of behavioural therapy. NICE recommends advising weight loss in women with a body mass index of >30 kg/m^2.

Table 5 Conservative management.

Recommendation	Guideline supporting recommendation (Grade included if specified)
Scheduled voiding	NICE (Level 3), CUA (Grade B)
Restriction of fluid	NICE (Level 1), CUA (Grade B)
Smoking cessation	CUA (Grade C), EAU (Grade A)
Avoidance of caffeine	NICE, CUA (Grade B), EAU (Level 2 – Grade B)
Weight loss >5% reduction	NICE (Level 3), CUA (Grade A) EAU (Grade A) AUA/SUFU OAB guideline
Treatment of constipation	EAU (Level 4 – Grade C)
Use of containment devices or disposable pads for light UI	EAU (Grade A)
Pads, external devices, and catheters for moderate-to-severe UI	EAU (Grade A)
PFMT	EAU (Level 1 – Grade A), CUA (Grade A)
Posterior tibial nerve stimulation (PTNS) for UUI	EAU for second-line treatment (Level 2b – Grade B) CUA (Grade B) AUA/SUFU OAB guidelines (use as third line)

Constipation is commonly treated in patients with UI; however, the EAU found no strong evidence that treating constipation will improve UI (level of evidence 4) and provide a Grade C recommendation to treat co-existing constipation in women with UI.

Bladder training (fluid intake, caffeine restriction, bowel habits, and voiding schedules) receives Grade A recommendations by both the CUA and the EAU as first-line therapies for UUI or MUI, although the EAU acknowledges Level 2 evidence that the effectiveness of this therapy diminishes when treatment is stopped. NICE recommends a trial of bladder training for a minimum of 6 weeks for OAB or MUI. The CUA provides Level 2 evidence that behavioural therapy improves symptoms at 3 months but is not sustained at 12 months [37].

The EAU supports the use of containment devices and recommends disposable pads for light UI (Grade A), and pads, external devices and catheters for moderate-to-severe UI (Grade A), with attention paid to balancing benefits and harms of each [38].

PFMT provides stabilisation of the urethra, and increases urethral closure pressures. The EAU reports Level 1 evidence that PFMT improves UI and QoL in both SUI and MUI as compared with no treatment [39], and both the CUA and EAU give Grade A recommendations for PFMT as first-line therapy for UUI [40]. However, the EAU reports Level 2 evidence that short-term benefits are not maintained at 15 years of follow-up [41]. NICE recommends a trial of supervised PFMT for a minimum of 3 months as a first-line treatment. If benefit is derived, they recommend continuing an exercise programme for these patients.

Posterior tibial nerve simulation (PTNS) is used in patients with UUI. Characterised as 'conservative therapy' in the EAU guideline, this therapy is considered in patients that have already tried antimuscarinic therapy. PTNS is also considered as a 'third line' in the AUA/SUFU OAB guidelines [10]. The EAU reports Level 2b evidence that PTNS is effective in patients who have failed antimuscarinic therapy, and give a Grade B recommendation to offer PTNS as a short-term option for improvement, although not cure, for these patients [42]. The CUA also gives a Grade B recommendation for its use, cautioning that maintenance is necessary to maintain efficacy [43]. However, NICE found that there was limited

evidence evaluating the effectiveness of PTNS over alternative treatments, with limited outcome evidence supporting its use. As a result, NICE recommends against PTNS unless conservative management has failed, and recommend counselling patients that there is insufficient evidence to recommend its use.

Drug Therapy

Antimuscarinics are recommended as first- or second-line treatment for UUI by the CUA (Grade B) (Table 6). The CUA and EAU provide Level 1a evidence that the antimuscarinics are superior to placebo [44], but do not provide recommendation on which medication to choose. Instead the CUA guideline encourages the choice to be based upon patient and physician preference, physician experience, and coverage. Similarly, the AUA/SUFU OAB guidelines counsel clinicians with a 'Standard' (evidence strength Grade B) that they should offer symptomatic patients medication, with similar efficacy noted between all these oral medications [10]. The EAU supports that there is no consistent evidence that one antimuscarinic is better than another for curing UUI or improving QoL (level of evidence 1a); however, they do provide some drug-specific recommendations, such as using the immediate release (IR) formulations of medications for initial drug therapy for UUI, and switching to extended release (ER) or long-acting formulations if IR is ineffective. (Grade A) [44,45]. NICE recommends initiating therapy at the lowest recommended dose. The AUA/SUFU OAB guidelines give a 'Standard' that ER formulations should be preferentially prescribed over IR formulations, if available, for lower rates of dry mouth. NICE recommend offering transdermal formulations in patients with inability to tolerate oral medications. The ICI and the CUA recommends a trial of 8–12 weeks to assess efficacy of drugs, with consideration of an alternative drug if initial therapy is poorly tolerated. The AUA/SUFU OAB guidelines support this idea with a 'Clinical Principle' to consider dose modification or trial of another antimuscarinic if symptoms are not controlled, or for significant adverse drug effects. NICE recommends counselling patients on common adverse effects and that full benefits may not be achieved until 4 weeks after initiation.

Table 6 Drug therapy.

Recommendation	Guideline supporting recommendation (Grade included if specified)
Antimuscarinics as first- or second-line treatment for UUI	NICE, CUA (Grade B), AUA/SUFU OAB guideline (Grade B; Standard)
Similar efficacy between oral antimuscarinics	EAU (Level 1a)
Use IR formulations for initial therapy, use ER if ineffective	EAU (Grade A)
ER preferential to IR due to lower rates of dry mouth	AUA/SUFU OAB guidelines (Standard)
Trial of 8–12 weeks to assess efficacy of drugs	ICI, CUA
Consider dose modification or trial of another antimuscarinic if ineffective or adverse drug effects	NICE, AUA/SUFU OAB guidelines (Clinical Principle)
Caution use in elderly	EAU, CUA, AUA/SUFU OAB guideline
Use non-pharmacological treatments first	EAU (Grade A)
Combine behavioural changes with drug therapy	EAU (Grade C)
Duloxetine use for SUI and MUI	EAU (level 1a), NICE (second line therapy; Level 1+)
Use for temporary improvement in UI symptoms	ICI (Grade B), EAU (Grade B)
Mirabegron as a second-line treatment for SUI	EAU (Level 1a-grade B), AUA/SUFU OAB guideline, ICI, NICE
Desmopressin for short-term relief	EAU (Level 1b – Grade B), NICE
Post-menopausal women	EAU (Grade A), NICE (Level 1+)
Offer topical hormonal therapy if vulvovaginal atrophy present	EAU (Level 1a – Grade A)
Use alternative HRT for women on oral conjugate equine oestrogens	

HRT, hormone replacement therapy.

The EAU, the CUA, and the AUA/SUFU OAB guidelines caution against antimuscarinic use for UUI treatment in the elderly, and the EAU gives Grade A recommendation to make every effort to use non-pharmacological treatments first, due to cumulative effects of drugs on cognition that increases with length of exposure, and to combine modifications with drug therapy to reduce drug load (Grade C recommendation). As a 'Clinical Principle', the AUA/SUFU OAB guidelines state that antimuscarinics should not be offered to patients with narrow angle glaucoma without approval from the patient's ophthalmologist, and also to use with caution in patients with impaired gastric emptying or history of urinary retention. NICE specifically states that oxybutynin should not be used in frail, older women, as its risk of impairment of daily functioning is common.

α-Adrenergic drugs have the potential to increase urethral closure pressure. The EAU guidelines echo the Cochrane review [46] that these drugs are not superior to placebo for SUI. β-adrenergic receptor agonists can stimulate detrusor relaxation and the EAU now recommends offering mirabegron for UUI, along with patient counselling that the long-term effects are as yet uncertain (Grade B, Level 1a evidence) [47,48]. The AUA/SUFU OAB guideline gives a 'Standard' that either oral antimuscarinics or β_3-adrenoceptor agonists should be offered as a second-line treatment, with a level of evidence of Grade B that mirabegron is as efficacious as antimuscarinic therapy, and may have lower rates of constipation and dry mouth. There is limited knowledge of potential long-term effects of mirabegron, and potential adverse effects on patients with other significant comorbidities [10].

Duloxetine is not curative, but there is Level 1a evidence demonstrated by the EAU that it improves SUI and MUI in women [49,50]. However, there are high rates of

discontinuation due to significant gastrointestinal and CNS side-effects. Both the ICI and the EAU give grade B recommendation to offer it for temporary improvement in UI symptoms.

The EAU found Level 1b evidence that desmopressin reduces UI within 4 h of administration; however, continuous use does not provide improvement or cure [51]. Therefore they gave a Grade B recommendation to offer its use to patients for short-term relief, not for long-term control, and that patients should be counselled that the European Union and the USA Food and Drug Administration does not license this medication for this purpose. NICE recommends desmopressin to reduce nocturia if that is the primary bothersome symptom, although caution for its use in women with cystic fibrosis and women aged >65 years with cardiovascular disease or hypertension.

The EAU (level of evidence 1a) and NICE (level of evidence 1+) found that oral conjugate equine oestrogens can increase the risk or worsen pre-existing UI in women [52]. They recommend topical hormonal therapy in postmenopausal women with UI and findings of vulvovaginal atrophy.

Surgical Management for SUI

The overall goal of surgical management should be to improve or cure UI (Table 7). An individual surgeon's experience factors into the type of surgical intervention offered. With this caveat in mind, the guidelines provide recommendations on how to counsel and decide between the various interventions. The guidelines reviewed cured/dry rates, as well as long-term cure rates for the different types of surgeries. Open colposuspension was historically considered the 'gold standard' surgical treatment for SUI, so a large body of research uses this technique as the comparator.

Open colposuspensions were compared with laparoscopic colposuspensions. The EAU and AUA found similar efficacy for SUI in terms of cured/dry rates, similar risks of voiding difficulties or *de novo* urgency, but found that laparoscopic surgery was associated with decreased length of hospital stay and lower risk of 'other complications' per the EAU [53]. The AUA described lower rates of febrile complications in laparoscopic vs open, based on their meta-analysis; however, they note higher rates of ureteric injury (4–11% vs 1% in open surgery) [9]. The CUA found comparable subjective outcomes, although poorer objective outcomes with laparoscopic colposuspension when compared with open colposuspension and mid-urethral slings (MUS) in the short- and medium-term for treatment of SUI (level of evidence 2). The CUA (Grade A) and NICE recommend against the use of laparoscopic colposuspension for routine surgical treatment of SUI, and the CUA gives a Grade D recommendation to consider this option if the patient is undergoing laparoscopic surgery for another intervention. The EAU and the AUA did not give specific recommendations about a choice between laparoscopic and open surgery.

Table 7 Surgical management for SUI.

Recommendation	Guideline supporting recommendation (Grade included if specified)
Open vs laparoscopic colposuspensions have comparable cured/dry rates	EAU, AUA
Due to poorer objective outcomes, recommend against laparoscopic technique	CUA (Grade A), NICE (Level 1)
Retropubic mid-urethral slings (MUS) is the preferred surgical treatment for uncomplicated SUI	EAU (Level 1a – Grade A)
MUS should be offered as preferred surgical treatment (retropubic, transobturator, or single incision)	AUA (Grade A)
Transobturator and retropubic approach for MUS have equivalent cure rates	EAU (Level 4), CUA
Counsel on higher risk of chronic pain and dyspareunia with transobturator approach, higher risk of perioperative complications with retropubic approach	EAU (Grade A)
Retropubic MUS as effective as autologous fascial sling	CUA (Level 2 – Grade A)
Autologous fascial sling more effective than biological or synthetic slings	CUA (Grade A)
Single-incision synthetic slings are less effective than conventional MUS techniques	EAU (Level 1b), CUA
Recommend against this approach for SUI treatment	CUA (Grade A)
Counsel that the efficacy of this approach is not yet determined	EAU (Grade A)
Concomitant SUI and prolapse surgical treatment can be performed	AUA (Recommendation), EAU (Grade A)
Tension the sling only after prolapse is repaired	AUA (Panel Consensus)
Benefit of prophylactic treatment of occult SUI is uncertain	AUA, EAU (Grade C)
Bulking agents provide short term improvement in SUI	CUA (Grade B), NICE (Level 3)
Do not offer to women seeking cure of SUI symptoms	EAU (Grade A)

MUS, mid-urethral slings.

The EAU, AUA and CUA found evidence that the retropubic MUS gave equivalent cure rates for SUI vs colposuspension, including a randomised comparative trial by Ward et al. [54] from the UK that revealed equivalent cure rates at 6 months between transvaginal tape and colposuspension for treatment of SUI. In addition, equivalent cure rates were noted between Burch colposuspension and the transobturator approach [55]. The EAU found a lower rate of *de novo* urgency symptoms and voiding dysfunction (level of evidence 1a) of the MUS vs colposuspension. The EAU made a Grade A recommendation that the MUS should be offered as the preferred surgical treatment when available for women with uncomplicated SUI.

NICE overall recommends offering MUS, open colposuspension or autologous rectus fascial sling to patients who fail conservative therapy, and does not recommend one over the others.

The EAU and the CUA compared the transobturator with the retropubic approach to the synthetic MUS and found equivalent cure rates at 12 months. However, the EAU cited lower rates of *de novo* urgency, voiding symptoms, and intraoperative bladder perforation, and higher rates of chronic pain at 12 months with the transobturator approach vs the retropubic approach (level of evidence 1a) [56]. Overall, the EAU determined no evidence to support one type of procedure over another (Level 4 evidence). The EAU gave a Grade A recommendation to counsel on higher risk of chronic pain and dyspareunia with the transobturator approach, and the higher risk of perioperative complications in the retropubic approach. NICE recommends counselling patients that long-term data on the transobturator approach are lacking long-term outcome data.

When comparing autologous fascial slings, the EAU determined a similar cure rate when compared with open colposuspension (Level 1b); however, autologous fascial slings had higher complication rates including voiding dysfunction and postoperative UTIs [57]. The CUA found the retropubic MUS is as effective as the autologous fascial sling (Level 2 evidence); however, the autologous fascial sling was associated with more *de novo* storage urinary symptoms than the retropubic MUS [58]. The CUA gave a Grade A recommendation that the autologous fascial sling may be more effective than biological or synthetic slings, but caution that there are higher rates of storage urinary tract symptoms postoperatively.

The EAU and CUA reviewed single-incision synthetic sling (SIS) operations; however, the EAU determined these approaches were less effective than conventional MUS, despite shorter operative times and less immediate postoperative pain (level of evidence 1b) [59]. The CUA published that SIS are not recommended for SUI (Grade A), while the EAU gave a Grade A recommendation to counsel that the efficacy of SIS is not yet determined. NICE recommends against the use of needle suspensions in treating SUI.

The AUA guideline issued a 'Standard' that the intervention choice should be based on the patient's preferences, as well as the surgeon's experience and judgment. However, they did make a Grade A recommendation that the MUS (retropubic, transobturator, or SIS) should be offered as the preferred surgical treatment when available, due to the shorter operative time and recovery time, and the lower short-term morbidity. If the MUS is not available, they recommend offering colposuspension or autologous fascial sling, with counselling that there is a higher risk of obstructive voiding symptoms with the latter (Grade C).

The AUA evaluated SUI outcomes when surgical treatments were performed concomitantly with POP repair and, based on their meta-analysis, the AUA made a recommendation that it is safe to perform concomitant SUI and POP surgery only after the completing the POP repair ('Panel Consensus'). The panel did not have an opinion on the role of a prophylactic UI surgery on women presenting with high-grade POP who are discovered to have occult UI. The EAU gave a Grade A recommendation to perform simultaneous surgery for treatment of POP and SUI, although patients should be counselled that there is an increased risk of adverse events with combined surgery as compared with POP repair alone (level 1b evidence) [60]. Similar to the AUA, they state that the benefit of prophylactic treatment of occult SUI for POP is uncertain (Grade C recommendation). NICE did not include patients with POP in their guideline recommendations.

Bulking agents are periurethral injections that allow for short-term improvement in SUI symptoms. The EAU determined that repeat injections are often required for therapeutic effect (level of evidence 2a); however, the benefit is low adverse risks compared with open surgery [61]. The CUA advises bulking agents for indications such as older age, patients opting for less invasive surgery, and patients with high anaesthetic risk. They give a Grade B recommendation to offer this treatment, although both CUA and NICE recommend that patients should be counselled on the likelihood of requiring repeat injections, that the efficacy is inferior to conventional surgical techniques, and that the efficacy decreases over time [50].

Mesh Complications

Given recent USA governmental regulatory statements and the medical legal ramifications, the AUA guideline directly addressed the use of synthetic slings. They acknowledge that there are unique complications related to mesh insertion; however, they determined that these risks are rare, and gave a standard of care statement that intraoperative cystoscopy should be performed on all sling surgeries to help minimise these risks.

The AUA encourages surgeons to have an open discussion about mesh-related complications and the benefits of synthetic slings compared with biological or autologous slings. The CUA also recommends counselling on the potential need for repeat surgical intervention should a mesh-related complication arise. The CUA and AUA guidelines outline contraindications to mesh surgery that raise the risk of mesh-related complications.

'Surgical' Management for UUI

For patients with UUI, after failure of conservative and medical therapy, surgical interventions can be offered. Botulinum toxin (BTX) injections result in variable continence rates, ranging from 29% to 87% [6]. Repeat injections maintain efficacy without increasing adverse events [62]. The CUA gives their

use a Grade B recommendation; however, notes that at the time of its guideline publication, it was not yet approved for use in idiopathic detrusor overactivity (DO) in Canada, although as of 2014 it has been approved for this indication. The ICI gives a Grade C recommendation for BTX use in treating symptomatic DO unresponsive to other therapies. Interestingly, the EAU gives a Grade A recommendation for BTX use in refractory UUI, although it recommends counselling patients on the limited duration of response, the risk of UTI, and the potential need to perform clean intermittent catheterisation (CIC). The AUA/SUFU OAB guidelines give clinicians a 'Standard' to offer BTX for patients who fail first- and second-line therapy, and cautions that this should only be offered to patients who agree to frequent visits to monitor for retention and are willing to catheterise if necessary. NICE states that this therapy should only be initiated if women have been sufficiently trained in CIC and are able to perform CIC if needed. They recommend starting with a dose of 200 units, although this should be reduced to 100 units if patients prefer a lower risk of catheterisation in exchange for potentially reduced chance of success.

Sacral neuromodulation (SNS) (Interstim®) has a cure rate of 39% for UUI and has approval for use in OAB, with numerous complications but low rates [63]. These include implantation site pain, lead migration, bowel dysfunction, infection, and generator problems. It is noted by the CUA to be an 'expensive treatment'. However, due to the efficacy of this treatment, both the EAU and CUA give a Grade A recommendation for use in refractory UUI. The AUA/SUFU OAB guideline makes the 'Recommendation' to offer SNS as a third-line treatment for refractory OAB symptoms. They counsel that, although SNS has been shown to offer subjective improvement, symptoms can return if treatment ceases. Because of the significant QoL improvements, they even state that the benefit for the appropriate patient outweighs the risks of the procedure. However, they give a recommendation Grade C on its use based on the lack of 'blinded' studies showing efficacy of SNS. NICE recommends counselling patients on long-term implications including the risk of failure, the long-term commitment required for efficacy, and adverse effects including potential need for surgical revision.

Augmentation cystoplasty is an intervention for refractory DO that is associated with high short- and long-term severe complications [64]. The CUA cites a 50% patient satisfaction rate with the outcome [65]. The EAU recommends offering this intervention only to patients with refractory DO who are not interested in BTX or SNS (Grade C). NICE, the EAU, and AUA/SUFU OAB guidelines advise counselling patients on the risks for CIC, the long- and short-term complications, and the possible small risk of malignancy (EAU Grade C). The AUA/SUFU OAB guidelines give the 'Expert Opinion' that this can be offered for rare cases of severe refractory OAB, with most of these cases related to neurogenic bladders. NICE discusses use of urinary diversion if patients fail conservative therapy and BTX, augmentation cystoplasty and SNS either fail or are unacceptable options.

Complicated UI

There are generally two broad categories for patients who have complicated UI: MUI and failed surgical therapy. For MUI, all guidelines recommend focusing on and treating the predominant symptom. The CUA recommends counselling patients that UUI may not improve with surgery for SUI (Grade B); however, there is a 50–74% chance of improvement or cure of OAB symptoms after sling procedures [66]. The EAU recommends counselling patients that the success of SUI surgery for MUI is decreased when compared with treating SUI alone (Grade A).

For patients who have failed prior surgery, the EAU found Level 2 evidence that SUI surgical options are less effective when they are performed as a second-line surgical therapy [67]. While autologous fascial slings were associated with improved cured/dry rates as compared with open colposuspension (level of evidence 2) [68], there is no evidence that one surgical option is better than another for second-line surgery (level of evidence 3). The EAU recommends basing surgical technique for recurrent SUI on careful evaluation of the patient and findings from UDS (Grade C). Patients should be counselled that second-line procedures have inferior outcomes, reduced efficacy, and a higher risk of complications when compared with first-line procedures (Grade C).

Conclusion

The topic of UI is vast and includes subtleties and intricacies regarding diagnosis, treatment, and varied patient populations and disease states. The guidelines that were discussed in the present review all have similar suggestions for the initial evaluation and use of conservative therapies. It is generally agreed that the initial evaluation should include a thorough history and tools to quantify and qualify the degree of UI. For the patients with uncomplicated SUI, invasive testing and imaging should be avoided, and UDS should be reserved for more complicated cases. Conservative therapy should be first line, including behavioural modifications.

As expected, there is more variability when it comes to recommendations for invasive measures. It is generally agreed upon that the MUS should be recommended for the patient with uncomplicated SUI, with different recommendations on the approach, as well as the comparability to other treatments such as the autologous fascial sling.

This is in no way a complete analysis of each guideline, but summarises some of the salient similarities and differences. As with any guideline or recommendation, if evidence is limited it does not necessarily imply that there is no role for

the test or intervention in question, but rather a recommendation cannot be made based on the available evidence. However, there are situations when evidenced-based medicine debunks myths or dogma and thus the efforts that have been put forth in these documents are critical to continue to advance the field of UI.

Reviewing multiple guidelines has also highlighted the considerable redundancy that exists. Organisations that conduct such systematic reviews and structuring of guidelines are often duplicating efforts. Although it is reassuring as a consumer of the guideline to know that independent efforts arrive at the same conclusions, in some cases more formalised collaboration could be argued as a more efficient methodology. Even here the quality of the data in some cases can limit or bias conclusions that are drawn. There are other factors that may motivate organisations to undertake the endeavour of creating their own 'guideline'. These may include things like differences in available devices or medications, different regulatory bodies, unique needs of their constituents or patient populations, and the ability to highlight options of those they consider 'expert'. Guidelines try to be evidence based when possible, but given some limitations the art of medicine still has a role.

Key points

- Guidelines are not exhaustive, but practical evidence based reviews of 'index patients'.
- Evaluation should include detailed history and characterisation of urinary incontinence (UI).
- Guidelines suggest a stepwise approach to treat both urgency UI and stress UI, starting with conservative therapy, advancing to more invasive procedures as needed.
- Urodynamics should be used if there is recurrent UI after failure of invasive treatments.
- Retropubic mid-urethral sling is the preferred surgical treatment for uncomplicated stress UI.

Conflicts of Interest

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Abbreviations: AGREE, Appraisal of Guidelines for Research and Evaluation II; BTX, Botulinum toxin; CIC, clean intermittent catheterisation; CUA, Canadian Urological Association; DO, detrusor overactivity; EAU, European Association of Urology; ER, extended release; ICI(Q), International Consultation on Incontinence (Questionnaire); IR, immediate release; MUS, mid-urethral slings; NICE, National Institute for Health and Care Excellence; OAB, overactive bladder; PFMT, pelvic floor muscle training; POP, pelvic organ prolapse; PTNS, posterior tibial nerve simulation; PVR, post-void residual urine volume; QoL, quality of life; (E)(I)R, (extended) (immediate) release; SIS, single-incision synthetic sling; SNS, sacral neuromodulation; SUFU, Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction; UDS, urodynamic studies; (M)(S)(U)UI, (mixed) (stress) (urgency) urinary incontinence.

Appendix

Table A1 Definitions used for level of evidence in clinical guidelines.

	EAU	CUA	AUA*	ICI	NICE
1	1a Evidence obtained from meta-analysis of randomised trials 1b Evidence obtained from at least one randomised trial	Meta-analysis of randomised trials or at least one randomised trial	A high quality evidence, well-conducted RCTs, exceptionally strong observational studies	Usually involves meta-analysis of trials (RCTs) or a good quality RCT, or 'all or none' studies in which no treatment is not an option	Meta-analyses or systematic reviews of RCTs with: 1++ very low risk of bias 1+ low risk bias 1– high risk of bias
2	2a Evidence obtained from one well-designed controlled study without randomisation 2b Evidence obtained from at least one other type of well-designed quasi-experimental study	One well-designed controlled study without randomisation or at least one other type of well-designed quasi-experimental study	B Moderate quality evidence; RCTs with weakness; generally strong observational studies	'Low' quality RCT or meta-analysis of good quality prospective 'cohort studies'	2++ systematic reviews of case-control or cohort studies 2+ well conducted case control or cohort studies 2– case control or cohort studies with risk of confounding or bias
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports	Well-designed non-experimental studies (comparative, correlation and case reports)	C low quality evidence; observational studies that provide conflicting information or design problems	Good quality retrospective 'case-control studies' or 'case series'	Non-analytical studies
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities	Expert committee reports or opinions or clinical experience of respected authorities	N/A	Expert opinion based not on evidence but on 'first principles' or bench research	Expert opinion or formal consensus

Nomenclature used by the AUA for all of its guidelines, including the three guidelines reviewed in the present paper. RCT, randomised controlled trial.

Table A2 Definitions used for clinical guidelines regarding grade of recommendation. The terms 'Standard', 'Recommendation' and 'Option', and the respective definition, are included in order of increasing degree of flexibility of the recommendation.

	EAU	CUA	AUA	ICI	NICE
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial	Clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial based on Level 1 evidence (recommended)	*Standard – benefits of taking a decisive action outweigh risks/ burdens OR risks/burdens outweigh benefits based on Grade A or B evidence; panel is making a directive statement to take or not to take a specific action	Depends on consistent Level 1 evidence, often means recommendations are effectively mandatory and placed within a clinical care pathway. May follow Level 2 evidence; however, needs a greater body of evidence if based on anything except Level 1 evidence	At least one meta-analysis, systematic review, or RCT where evidence level is 1++ or 1+ with consistent results, or evidence drawn from NICE technology appraisal
B	Based on well conducted clinical studies, but without randomised clinical trials	Well-conducted clinical studies, but without randomised clinical trials, consistent Level 2/3 evidence (recommended)	*Recommendation – if benefits outweigh risks/burdens OR risks/ burdens outweigh benefits based on Grade C evidence; panel is making a directive statement to take or not to take a specific action	Depends on consistent Level 2 and/or 3 studies, or 'majority evidence' from RCTs	Body of evidence includes 2++ studies with overall consistency of results or extrapolated from 1++ or 1+ studies
C	Made despite the absence of directly applicable clinical studies of good quality	Made despite the absence of directly applicable clinical studies of good quality, Level 4 studies or majority evidence (optional)	*Option – if benefits and risks/burdens are evenly balanced or unclear based on Grade A, B or C evidence; decision to take or not to take a specific action is up to practitioner and patient	Depends on Level 4 studies or 'majority evidence' from Level 2/ 3 studies or Delphi processed expert opinion	Body of evidence with 2+ studies or extrapolated from 2++ studies
D	N/A	Evidence inconsistent/ inconclusive (no recommendation possible) or the evidence indicates the drug should not be recommended	†Clinical Principle –statement about a component of clinical care that is widely agreed upon by urologists or other clinicians; may or may not be evidence in literature †Expert Opinion – statement achieved by consensus of the Panel based on members' clinical training, experience, knowledge and judgment; no published evidence	No recommendation possible: where evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Dephi	Evidence Level 3 or 4, or extrapolated from 2+ studies, or based on formal consensus *D (GPP): good practice point recommendation based on experience of guideline development group

*RCT, randomised controlled trial. *Nomenclature used by the AUA for all of its guidelines, including the three guidelines reviewed in this paper. †Used in the AUA/SUFU OAB guidelines and the AUA/SUFU UDS guidelines.*

Table A3 Definition of grades of recommendations used by the ICI for diagnostic tests and studies.

Highly recommended	A test that should be done on every patient
Recommended test	Test of proven value in evaluation of most patients, and its use is strongly encouraged during initial evaluation
Optional test	Test of proven value in evaluation of selected patients; its use is left to clinical judgment of the physician
Not recommended	A test of no proven value

Table A4 AGREE II instrument scores obtained from two reviewers.

	EAU	CUA	AUA	ICI	NICE
%:					
Domain 1: Scope and Purpose	100	78	100	100	100
Domain 2: Stakeholder Involvement	83	72	100	83	100
Domain 3: Rigour of Development	100	100	100	100	100
Domain 4: Clarity of Presentation	100	100	100	100	100
Domain 5: Applicability	68	75	75	83	83
Domain 6: Editorial independence	54	33	54	17	100
Overall	100	83	83	100	100%

Lower Extremity Chronic Venous Disease

Question: Should coverage of lower extremity chronic venous disease (e.g. varicose veins) on the Prioritized List be updated?

Question source: HERC Staff

Issue: This topic had been identified for an EbGS Coverage Guidance. However, it was felt more appropriate to go through VbBS for consideration of Prioritized List changes rather than requiring a full Coverage Guidance due to the availability of a recent high quality AHRQ evidence review of this topic.

Lower extremity chronic venous disease (LECVD) is a heterogeneous term that encompasses a variety of conditions. Patients with LECVD can be asymptomatic or symptomatic, and they can exhibit a myriad of signs including varicose veins, telangiectasias, LE edema, skin changes, and/or ulceration. The etiology of LECVD includes venous dilation, venous reflux, (venous) valvular incompetence, mechanical compression (e.g., May-Thurner syndrome), and post-thrombotic syndrome. While the majority of patients with LECVD are asymptomatic, serious complications can occur, including LE amputation, acute and chronic VTE, chronic thromboembolic pulmonary hypertension, and mortality. A serious and common issue with LECVD is the formation of venous leg ulceration. Uncomplicated LECVD can result in reduced quality of life, pain, and social isolation.

Currently, varicose veins that cause swelling or pain are including on line 637 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION, with various treatments pairing on that line. A similar condition to varicose veins, post-thrombotic syndrome, is included on line 517 POSTTHROMBOTIC SYNDROME. If a varicose vein is associated with an ulcer, treatment is paired on line 379 CHRONIC ULCER OF SKIN. If the varicose vein is causing inflammation (phlebitis), then the diagnosis is included on line 514 PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL.

The treatment of LECVD varies tremendously and can be divided into noninvasive and invasive therapies. Noninvasive approaches include therapies that improve venous circulation and reduce LE edema (e.g., compression devices, medical therapy [e.g., diuretics], and exercise), therapies that prevent thromboembolic complications (e.g., anticoagulation), and therapies that specifically address skin changes and ulceration (e.g., wound care). When these more conservative measures fail, invasive therapies are often recommended and include endovascular intervention (e.g., ablation, angioplasty) and/or surgical management (e.g., venous ligation, venous excision).

The providers who nominated this topic requested coverage for varicose veins and similar conditions that caused pain that interfered with ability to work, walk, etc., recurrent swelling despite conservative therapy such as compression garments, bleeding from a varicosity, or recurrent phlebitis.

The CCO medical directors felt strongly that pain should not be a criterion for coverage, as it is not a criterion for coverage of uncomplicated hernias or similar conditions.

Recurrent phlebitis involves a redness or warmth along the vein, and pain in the area. It is usually treated conservatively. In rare cases, it can progress to cellulitis or DVT.

VBBS/HERC history

May 2015

Coverage of various treatment options for varicose veins was broadened to include many of the minimally invasive modalities. There was some discussion that there was no evidence to support broadening the complications that would allow coverage of varicose veins. The current coverage of varicose veins only being treated if they caused ulceration or infection was felt to encompass the major complications that require treatment of the varicosities. The addition of additional types of treatments based on good efficacy and lower cost was thought to be an excellent idea.

September 24, 2004

Varicose veins of lower extremities with edema, pain and swelling were moved from a covered line to an uncovered line. Coverage for severe venous stasis dermatitis without an ulcer to prevent ulceration was added to the cellulitis line.

Current Prioritized List status--procedures

CPT Code	Code Description	Line(s)
36465-36466	Injection of non-compounded foam sclerosant … (eg, great saphenous vein, accessory saphenous vein)	379 CHRONIC ULCER OF SKIN 514 PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL 517 POSTTHROMBOTIC SYNDROME 637 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION
36470-36471	Injection of sclerosant; single incompetent vein (other than telangiectasia)	379,514,517,545 SUBLINGUAL, SCROTAL, AND PELVIC VARICES, 637
36473-36479	Endovenous ablation therapy of incompetent vein, extremity, percutaneous (mechanochemical, radiofrequency, laser) (first or subsequent vein)	379,514,517,637
36482-36483	Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate)	660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
37700 37718 37722 37735 37760-37766 37780 37785	Vein ligation (various veins of lower extremity)	379,514,517,637 Limited number on line 79 PHLEBITIS AND THROMBOPHLEBITIS, DEEP

Current Prioritized List status: diagnoses

ICD-10 code	Code description	Current line(s)
I83.0	Varicose veins of unspecified lower extremity with ulcer	379 CHRONIC ULCER OF SKIN
I83.1	Varicose veins of lower extremity with inflammation	514 PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL
I83.2	Varicose veins of unspecified lower extremity with both ulcer and inflammation	379
I83.81	Varicose veins of lower extremity with pain	637 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION
I83.89	Varicose veins of lower extremities with other complications	637
I86.8	Varicose veins of other specified sites	Undefined Diagnosis File
I83.9	Asymptomatic varicose veins of lower	637

	extremity	
I87.00	Postthrombotic syndrome without complications of lower extremity	517 POSTTHROMBOTIC SYNDROME 637
I87.01	Postthrombotic syndrome with ulcer of lower extremity	379
I87.02	Postthrombotic syndrome with inflammation of lower extremity	514,517
I87.03	Postthrombotic syndrome with ulcer and inflammation of lower extremity	379
I87.09	Postthrombotic syndrome with other complications of lower extremity	517,637
I87.2	Venous insufficiency (chronic) (peripheral)	637
I87.8	Other specified disorders of veins	637
I87.9	Disorder of vein, unspecified	637

Evidence Summary

AHRQ, 2017 Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD); Technology Assessment Report

1) Systematic review
2) Treatment of lower extremity chronic venous insufficiency/incompetence/reflux
    a) N=93 studies on treatment effectiveness (87 RCTs, 6 observational)
    b) Modalities: exercise training, medical therapy, weight reduction, mechanical compression therapy, surgical intervention, and endovenous intervention
    c) Effectiveness
        i. Among patients undergoing endovenous interventions, radiofrequency ablation (RFA), endovenous laser ablation (EVLA), and sclerotherapy, improvement demonstrated in quality-of-life scores and standardized symptom scores.
        ii. When compared with patients treated with placebo, those treated with foam sclerotherapy had statistically significant improvement in standardized symptom scores, occlusion rates, and quality of life.
        iii. There was no difference in effectiveness between sclerotherapy and surgery (SOE=low).
        iv. Meta-analysis of any surgery vs compression therapy on wound healing: the summary effect of these studies was a non-statistically significant OR of 1.24 (95% CI, 0.83 to 1.84) favoring surgery
        v. Reported harms of surgical interventions included infection, bleeding, skin burns and thromboembolism
        vi. KQ3a: The comparative effectiveness of exercise, medical therapy, mechanical compression therapy, and invasive procedures on health outcomes
            - insufficient strength of evidence limits ability to make any conclusions regarding effectiveness of any of the studied interventions
3) Treatment of lower extremity chronic venous obstruction/thrombosis
    a) N= 8 studies (3 randomized controlled trials, 5 observational)
        i. Modalities: exercise training, medical therapy, weight reduction, mechanical compression therapy, surgical intervention, and endovenous intervention
    b) In patients with post-thrombotic syndrome, exercise training plus patient education and monthly phone follow-up resulted in improved quality of life but not improved symptom severity when compared with patient education and monthly phone follow-up. In patients with both May-Thurner Syndrome and superficial venous reflux who were treated with EVLA (with or without stent placement), there were fewer recurrent ulcerations, improvement in reflux severity and symptoms, and improvement in quality of life in long-term follow-up.
4) **Conclusions.** The available evidence for treatment of patients with LECVD is limited by heterogeneous studies that compared multiple treatment options, measured varied outcomes, and assessed disparate outcome timepoints. When compared with patients' baseline measures, endovenous interventions (e.g. EVLA, sclerotherapy, and RFA) and surgical ligation demonstrated improvement in quality-of-life scores and Venous Clinical Severity Score at various timepoints after treatment; however, there were no

statistically significant differences in outcomes between treatment groups (e.g. endovenous vs. endovenous; endovenous vs. surgical). Several advances in care in endovenous interventional therapy have not yet been rigorously tested, and there are very few studies on conservative measures (e.g., lifestyle modification, compression therapy, exercise training) in the literature published since 2000. Additionally, the potential additive effects of many of these therapies are unknown. The presence of significant clinical heterogeneity of these results makes conclusions for clinical outcomes uncertain and provides an impetus for further research to improve the care of patients with LECVD.

Other payer policies

1) **Noridian (CMS) 2017**
    - **a.** Indications for surgical treatment (CPT codes: 37700, 37718, 37722, 37735, 37760, 37761, 37765, 37766, 37780, 37785) and sclerotherapy (CPT codes: 36470, 36471) [similar guidance for endovascular therapies]:
        - **i.** A 3-month trial of conservative therapy such as exercise, periodic leg elevation, weight loss, compressive therapy, and avoidance of prolonged immobility where appropriate, has failed, AND
        - **ii.** The patient is symptomatic and has one, or more, of the following:
            1. **1.** Pain or burning in the extremity severe enough to impair mobility
            2. **2.** Recurrent episodes of superficial phlebitis
            3. **3.** Non-healing skin ulceration
            4. **4.** Bleeding from a varicosity
            5. **5.** Stasis dermatitis
            6. **6.** Refractory dependent edema
2) **Aetna 2018**
    - a. Aetna considers the following procedures medically necessary for treatment of varicose veins when the following criteria are met: great saphenous vein or small saphenous vein ligation / division / stripping, radiofrequency endovenous occlusion (VNUS procedure), and endovenous laser ablation of the saphenous vein (ELAS) (also known as endovenous laser treatment (EVLT)).
    - b. Incompetence at the saphenofemoral junction or saphenopopliteal junction is documented by recent (performed within the past 6 months) Doppler or duplex ultrasound scanning, and all of the following criteria are met:
        - i. Ultrasound documented junctional reflux duration of 500 milliseconds (ms) or greater in the saphenofemoral or saphenopopliteal vein to be treated; *and*
        - ii. Vein size is 4.5 mm or greater in diameter measured by ultrasound below the saphenofemoral or saphenopopliteal junction (not valve diameter at junction); *and*
        - iii. Saphenous varicosities result in *any* of the following:
            1. Intractable ulceration secondary to venous stasis; *or*
            2. More than 1 episode of minor hemorrhage from a ruptured superficial varicosity; or a single significant hemorrhage from a

ruptured superficial varicosity, especially if transfusion of blood is required; *or*

3. Saphenous varicosities result in *either* of the following, and symptoms persist despite a 3-month trial of conservative management (including analgesics and prescription gradient support compression stockings):
    a. Recurrent superficial thrombophlebitis; *or*
    b. Severe and persistent pain and swelling interfering with activities of daily living and requiring chronic analgesic medication.

Disposition of submitted literature

1) Morrison 2018: comparison of different treatment techniques, no conservative therapy control
2) Eberhardt 2014: non-systematic review
3) Ragu 2016: retrospective cohort study, higher level evidence available
4) Lee 2015: cohort study, higher level evidence available
5) Pannier 2015: non-systematic review
6) Puleo 2013: cohort study, higher level evidence available

HERC staff summary:

Currently, chronic lower extremity venous insufficiency is only on a covered line on the Prioritized List if there is associated ulceration. There is insufficient evidence to determine if treatment of chronic lower extremity venous disease with surgery or minimally invasive treatments results in improved outcomes (pain, quality of life, symptom scores) compared to placebo or usual (non-surgical) care. Most major insurers cover therapies for varicose veins when there are complications such as ulceration or bleeding. However, most major insurers also cover therapy for complications which are "below the line" such as recurrent superficial thrombophlebitis, severe and persistent pain interfering with activities of daily living, and stasis dermatitis. It does not appear that the prior intent of the HSC/HERC to cover varicose veins with cellulitis is currently possible with the pairings on the Prioritized List. Based on discussions with the CCO medical directors, recurrent thrombophlebitis would be a more accurate description than cellulitis for the condition intended for coverage.

HERC staff recommendations:

1) Add coverage of chronic lower extremity venous disease for patients with recurrent thrombophlebitis, consistent with prior HSC/HERC intent to cover with "cellulitis"
    a. Add varicose veins with other complications to line 379 CHRONIC ULCER OF SKIN and keep on line 517 POSTTHROMBOTIC SYNDROME/637 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION
        i. ICD10 I83.89 (Varicose veins of lower extremities with other complications)
        ii. ICD10 I87.09 (Postthrombotic syndrome with other complications of lower extremity)
    b. Adopt a new guideline note to line 379 as shown below
2) Clarify when ulceration is an indication for varicose vein treatment in the new guideline
3) Modify the line title of line 379 to CHRONIC ULCER OF SKIN; VARICOSE VEINS WITH MAJOR COMPLICATIONS

GUIDELINE NOTE XXX, TREATMENT OF CHRONIC LOWER EXTREMITY VENOUS DISEASE

Lines 379,517,637

Treatment of chronic lower extremity venous disease is only included on line 379 when

1) The patient has had an adequate 3-month trial of conservative therapy and failed; AND
2) The patient has one of the following:
    a. Non-healing skin ulceration in the area of the varicose vein(s), OR
    b. Recurrent episodes of superficial thrombophlebitis.

Otherwise, these diagnoses are included on lines 517 or 637.

Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD)

Technology Assessment Report
Project ID: DVTT0515

April 6, 2017

Duke University Evidence-based Practice Center

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Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD)

Structured Abstract

Objectives. For patients with lower extremity chronic venous disease (LECVD), the optimal diagnostic testing and treatment for symptom relief, preservation of limb function, and improvement in quality of life is not known. This systematic review included a narrative review of diagnostic testing modalities and assessed the comparative effectiveness of exercise training, medical therapy, weight reduction, mechanical compression therapy, and invasive procedures (i.e., surgical and endovascular procedures) in patients with LECVD.

Data sources. We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews for relevant English-language studies published from January 1, 2000 to June 30, 2016.

Review methods. Two investigators screened each abstract and full-text article for inclusion, abstracted the data, and performed quality ratings and evidence grading. Random-effects models were used to compute summary estimates of effects.

Results. A total of 111 studies contributed evidence, as follows:

Diagnosis of LECVD: A narrative review was conducted due to the scant literature and availability of only 10 observational studies evaluating the comparative effectiveness of diagnostic testing modalities in a heterogeneous population of patients with LECVD. In addition to the history and physical exam, multiple physiologic and imaging modalities (plethysmography, duplex ultrasound, intravascular ultrasonography, magnetic resonance venography, computed tomography venography, and invasive venography) are useful to confirm LECVD and/or localize the disease and guide therapy. There was insufficient evidence to support or refute the recommendations from current clinical guidelines that duplex ultrasound should be used as the firstline diagnostic test for patients being evaluated for LECVD or for those for whom invasive treatment is planned.

Treatment of lower extremity chronic venous insufficiency/incompetence/reflux: Ninety-three studies (87 randomized controlled trials, 6 observational) evaluated the comparative effectiveness of exercise training, medical therapy, weight reduction, mechanical compression therapy, surgical intervention, and endovenous intervention in patients with lower extremity chronic venous insufficiency/incompetence/reflux. There was no long-term difference in effectiveness between radiofrequency ablation (RFA) and high ligation plus stripping, but RFA was associated with less periprocedural pain, faster improvement in symptom scores and quality of life, and fewer adverse events.

Among patients undergoing endovenous interventions, RFA, endovenous laser ablation (EVLA), and sclerotherapy demonstrated improvement in quality-of-life scores and standardized symptom scores. When compared with patients treated with EVLA, those treated with foam sclerotherapy had significantly less periprocedural pain but lower rates of vein occlusion and higher rates of repeat intervention, and patients treated with RFA had significantly less periprocedural pain but

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Varicose Veins

- Clinical Policy Bulletins
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Policy

I. Aetna considers the following procedures medically necessary for treatment of varicose veins when the following criteria are met: great saphenous vein or small saphenous vein ligation / division / stripping, radiofrequency endovenous occlusion (VNUS procedure), and endovenous laser ablation of the saphenous vein (ELAS) (also known as endovenous laser treatment (EVLT)).

A. Incompetence at the saphenofemoral junction or saphenopopliteal junction is documented by recent (performed within the past 6 months) Doppler or duplex ultrasound scanning, and all of the following criteria are met:

1. Ultrasound documented junctional reflux duration of 500 milliseconds (ms) or greater in the saphenofemoral or saphenopopliteal vein to be treated; *and*
2. Vein size is 4.5 mm or greater in diameter measured by ultrasound below the saphenofemoral or saphenopopliteal junction (not valve diameter at junction); *and*
3. Saphenous varicosities result in *any* of the following:

a. Intractable ulceration secondary to venous stasis; *or*
b. More than 1 episode of minor hemorrhage from a ruptured superficial varicosity; or a single significant hemorrhage from a ruptured superficial varicosity, especially if transfusion of blood is required; *or*
c. Saphenous varicosities result in *either* of the following, and symptoms persist despite a 3-month trial of conservative managementFootnotes* (including analgesics and prescription gradient support compression stockings):

i. Recurrent superficial thrombophlebitis; *or*
ii. Severe and persistent pain and swelling interfering with activities of daily living and requiring chronic analgesic medication.

Footnotes* **Note**: A trial of conservative management is not required for persons with persistent or recurrent varicosities who have undergone prior endovenous catheter ablation procedures or stripping/division/ligation in the same leg because conservative management is unlikely to be successful in this situation.

B. Surgical ligation (including subfascial endoscopic perforator vein surgery (SEPS)) or endovenous ablation

procedures are considered medically necessary for the treatment of incompetent perforating veins with vein diameter measured by recent ultrasound of 3.5 mm or greater with outward flow duration of 500 milliseconds duration or more, located underneath an active or healed venous stasis ulcer (also known as CEAP C5 or C6) (see Appendix).

C. Endovenous ablation procedures are considered medically necessary adjunctive treatment of symptomatic accessory saphenous veins for persons who meet medical necessity criteria for endovenous ablation above and who are being treated or have previously been treated by one of the procedures listed above for incompetence (i.e., reflux) at the saphenofemoral junction or saphenopopliteal junction and anatomically related persistent junctional reflux is demonstrated after the great or small saphenous veins have been removed or ablated.

Note: Initially, endovenous ablation therapy of the first vein and of the second and subsequent veins in each affected extremity is considered medically necessary when criteria are met. (**Note**: Thus one primary code and one secondary code for each affected leg are considered medically necessary for initial endovenous ablation treatment.) Additional endovenous ablation therapy is considered medically necessary for persons with persistent or recurrent junctional reflux of the greater saphenous vein, lesser saphenous vein following initial endovenous ablation therapy. (In order to authorize additional endovenous ablation, there should be documentation that the member continues to have symptoms and ultrasound showing persistent junctional reflux.) Additional endovenous ablation therapy may also be necessary for treatment of accessory saphenous veins as noted above. These procedures are considered experimental and investigational for treatment of varicose tributaries and accessory veins other than the accessory saphenous vein. These procedures are considered cosmetic for all other indications.

Note: Doppler or duplex ultrasound studies are considered necessary prior to varicose vein treatment to assess the anatomy and to determine whether there is significant reflux at the saphenofemoral or saphenopopliteal junction requiring surgical repair, and after completion of the treatment to determine the success of the procedure and detect thrombosis. Ultrasound guidance is inclusive of the VNUS or ELAS procedures.

Note: The term endovenous catheter ablation (EVCA) is a non-specific term that refers to the several catheter based minimally invasive alternatives to surgical stripping such as radiofrequency endovenous occlusion (VNUS procedure) and endovenous laser ablation of the saphenous vein (ELAS). In assessing the medical necessity of EVCA, reference should be made to the specific technique that is being employed.

II. Aetna considers liquid or foam sclerotherapy (endovenous chemical ablation) (e.g., Varithena) medically necessary adjunctive treatment of symptomatic saphenous veins, varicose tributaries, accessory, and perforator veins 2.5 mm or greater in diameter, measured by recent ultrasound, for persons who meet medical necessity criteria for varicose vein treatment in section I above and are being treated or have previously been treated by one or more of the procedures noted in section I above for incompetence (i.e., reflux) at the saphenofemoral junction or saphenopopliteal junction. Varithena has not been proven to be more effective than other methods of foam sclerotherapy.

Sclerotherapy is considered experimental and investigational for treatment of reflux of the saphenofemoral junction or saphenopopliteal junction the because sclerotherapy has not been proven to be effective for treatment of junctional reflux. Sclerotherapy alone has not been shown to be effective for persons with reflux at the saphenofemoral or saphenopopliteal junctions; under established guidelines, individuals with reflux should also be treated with endovenous ablation, ligation or division of the junction to reduce the risk of varicose vein recurrence. Sclerotherapy is considered cosmetic for treatment of veins less than 2.5 mm in diameter and for all other indications.

Note: Since ultrasound-monitored or duplex-guided techniques for sclerotherapy have not been shown to definitively increase the effectiveness or safety of this procedure, these tests are only considered medically necessary when initially performed to determine the extent and configuration of varicose veins. Ultrasound- or radiologically guided or monitoring techniques are of no proven value when performed solely to guide the needle

or introduce the sclerosant into the varicose veins.

Note: The number of medically necessary sclerotherapy injection sessions varies with the number of anatomical areas that have to be injected, as well as the response to each injection. Usually 1 to 3 injections are necessary to obliterate any vessel, and 10 to 40 vessels, or a set of up to 20 injections in each leg, may be treated during one treatment session. Initially, up to two sets of injections of sclerosing solution in multiple veins in each affected leg (i.e., a total of four sets of injections if both legs are affected) are considered medically necessary when criteria are met. (**Note**: A set of injections is defined as multiple sclerotherapy injections during a treatment session.) Additional sets of injections of sclerosing solution are considered medically necessary for persons with persistent or recurrent symptoms.

III. Aetna considers ambulatory phlebectomy or transilluminated powered phlebectomy (TriVex System) medically necessary adjunctive treatment of symptomatic saphenous veins, varicose tributaries, accessory, and perforator veins 2.5 mm or greater in diameter for persons who meet the medical necessity criteria for varicose vein treatment in section I above and who are being treated or have previously been treated by one or more of the procedures noted in section I above for incompetence (i.e., reflux) at the saphenofemoral junction or saphenopopliteal junction. Ambulatory phlebectomy or transilluminated powered phlebectomy is considered experimental and investigational for treatment of junctional reflux as these procedures have not been proven to be effective for these indications. Ambulatory phlebectomy and the TriVex system is considered cosmetic for veins less than 2.5 mm in diameter and all other indications. **Note**: Transilluminated powered phlebectomy has not been proven to be superior to other methods of varicose vein removal. Therefore, the TriVex procedure should be billed as any other varicose vein removal procedure.

Note: Initially, up to two multiple stab phlebectomy incisions in each affected extremity (i.e., a total of four multiple stab incisions if both legs are affected) are considered medically necessary when criteria are met. Additional multiple stab phlebectomy incisions are considered medically necessary for persons with persistent or recurrent symptoms. (**Note**: A set of stab phlebectomy incisions is defined as multiple stab phlebectomy incisions during a treatment session.)

IV. Aetna considers photothermal sclerosis (also referred to as an intense pulsed light source, e.g., the PhotoDerm VascuLight, VeinLase), which is used to treat small veins such as small varicose veins and spider veins, cosmetic because such small veins are cosmetic problems and do not cause pain, bleeding, ulceration, or other medical problems.

V. Aetna considers transdermal laser treatment experimental and investigational for the treatment of large varicose veins because it has not been proven in direct comparative studies to be as effective as sclerotherapy and/or ligation and vein stripping in the treatment of the larger varicose veins associated with significant symptoms (pain, ulceration, inflammation). **Note**: Although transdermal Nd:YAG laser has been shown to be effective for the treatment of telangiectasias and reticular veins, treatment of these small veins is considered cosmetic.

VI. Aetna considers endomechanical or mechanicochemical ablation (MOCA) (e.g., ClariVein) experimental and investigational for varicose veins because it has not been proven to be as effective as established alternatives.

VII. Aetna considers Asclera polidocanol injection as cosmetic; although Asclera has been approved by the Food and Drug Administration (FDA) for the treatment of telangiectasias and reticular veins less than 3 mm in diameter, treatment of these small veins is considered cosmetic.

VIII. Aetna considers valvular reconstruction medically necessary for chronic venous insufficiency.

IX. Aetna considers micronized purified flavonoid fraction for the treatment of varicose veins experimental and investigational because its effectiveness has not been established.

X. Aetna considers the VeinGogh Ohmic Thermolysis System experimental and investigational because of insufficient evidence of its effectiveness.

XI. Aetna considers the use of medical adhesive (also referred to as cyanoacrylate superglue, n-butyl-cyanoacrylate) (e.g., VariClose Vein Sealing System, VenaSeal Closure System) for the treatment of varicose veins experimental and investigational because its effectiveness has not been established.

XII. Aetna considers polymorphism genotyping of matrix metalloproteinases genes (e.g., MMP1, MMP2, MMP3, and MMP7) as markers of predisposition to varicose veins experimental and investigational because the effectiveness of this approach has not been established.

XIII. Aetna considers synthetic matrix metalloproteinases inhibitors for the treatment of varicose veins experimental and investigational because its effectiveness has not been established.

For endoluminal cryoablation (also referred to as cryofreezing, cryostripping, cryosurgery, cryotherapy) for varicose veins, see CPB 0100 - Cryoablation.

Background

Varicose veins are a common condition. In adult western populations visible varicose veins are present in 20 to 25 % of women and 10 to 15 % of men. In most persons, varicose veins do not cause symptoms other than poor cosmesis. Varicose vein surgery is one of the most commonly performed cosmetic procedures in the United States.

Most varicose veins do not require medical treatment (Tapley et al, 2003). In some cases, however, the circulation may be hindered enough to cause swelling of the foot and ankle, discomfort, a tingling sensation, or a feeling of heaviness. For most people with varicose veins, wearing specially fitted elastic stockings is all that is needed. The stockings should be carefully fitted to the individual, providing the most pressure in the lowest part of the leg. The stockings should be put on when first arising in the morning, preferably before getting out of bed. Exercise such as walking or cycling also helps promote better circulation from the lower part of the body. Resting with the legs elevated will help promote circulation; in contrast, sitting with the legs crossed can aggravate the condition. Authorities have recommended 6 or more months as a reasonable duration for a trial conservative management (NHS, 2005).

A substantial proportion of varicose vein symptoms respond to conservative management. A randomized controlled clinical trial compared surgery (n = 124) to conservative management (n = 122) of varicose veins (Michaels et al, 2006). Conservative management consisted of lifestyle advice relating to exercise, leg elevation, management of weight and diet, and the use of compression hosiery. In the surgical arm of the trial patients received the same lifestyle advice but also underwent surgical treatment, consisting of flush ligation of sites of reflux, stripping of the long saphenous vein and multiple phlebectomies, as appropriate. Although a greater proportion of patients assigned to surgery plus lifestyle advice at relieving symptoms at 1 year, approximately one-third of subjects assigned to conservative management reported some relief from conservative management with compression hosiery. At 2 years, there was no significant difference in symptom improvement between groups assigned to conservative management versus surgery. The authors posited that the lack of significant difference in symptomatology between groups at 2 years may have been due to cross-overs, with 7 patients in the conservative management group opting for surgery in year 1 and 37 patients opting for surgery in year 2. The study also found that persons assigned to surgery plus lifestyle advice had a greater improvement in cosmesis and quality of life than persons assigned to lifestyle advice alone, although it is not known whether improvements in quality of life were primarily related to improvements in cosmesis versus reductions in symptomatology. Weaknesses of the study included a substantial loss to follow-up in all groups. Fifteen of the 124 patients assigned to surgery either refused surgery in favor of conservative management or declined surgery due to fitness. Of the remaining 109 patients who underwent surgery, 43 were lost to follow up by the first year. Of subjects assigned to conservative treatment, 21 were lost to follow-up by the first year. The authors observed that, although surgery was more effective at improving symptomatology at 1 year, a substantial proportion of patients assigned to conservative treatment reported resolution or improvements in aching (26 %), heaviness (46 %), itching (56 %), and swelling (68 %). In addition, a substantial proportion of persons assigned to conservative management reported improvements in cosmesis. "Indeed, 22 % of the latter reported that they no longer had cosmetic concerns. These

observations suggest a substantial benefit from surgery but perhaps support the case for careful evaluation of patients' symptoms and problems when considering surgical treatment."

An editorialist noted that the short follow-up of subjects assigned to surgery may result in an underestimate of the costs and an exaggeration of the benefits of surgery (van Rij, 2006). By the third year, only 40 % of subjects in the study by Michaels et al assigned to surgery were assessed. The editorialist noted, however, that most recurrences are diagnosed later than 3 years. Focusing on the short-term may lead to an under-estimate of cost and an over-estimate of benefit. The editorialist stated that prospective comparisons of durability up to 5 years and longer are infrequent and yet by this time the recurrence rate may be as high as 50 %.

In patients with varicose veins, leg pain may be associated with superficial thrombophlebitis or venous leg ulcers. In evaluating the role of varicose vein surgery in treatment of these conditions, the effectiveness of varicose vein surgery must be compared to conservative management.

If the patient is suffering from superficial thrombophlebitis, conservative management is indicated. According to available guidelines, uncomplicated superficial thrombophlebitis is usually treated symptomatically with heat, simple analgesia, non-steroidal anti-inflammatory drugs (NSAIDs), and compression stockings (SCHIN, 2002). Treatment should continue until symptoms have completely subsided (usually 2 to 6 weeks to subside but the thrombosed vein may be palpable and tender for months). More severe thrombophlebitis, as indicated by the degree of pain and redness and the extent of abnormality, should be treated by bed rest with elevation of the extremity and application of hot, wet compresses.

Leg ulcers arising from venous problems are called venous (varicose or stasis) ulcers. The main conservative treatment has been to apply a firm compression garment (bandage or stocking) to the lower leg in order to help the blood return back up the leg. Cullum et al (2002) conducted a meta-analysis of the literature on the effectiveness of compression bandaging and stockings in the treatment of varicose leg ulcers. The authors concluded that compression increases ulcer-healing rates compared with no compression. The authors also found that multi-layered systems are more effective than single-layered systems. High compression is more effective than low compression but there are no clear differences in the effectiveness of different types of high compression. In a meta-analysis, Nelson et al (2002) found circumstantial evidence of the benefit of compression in reducing recurrence of varicose ulcers. The authors also noted that recurrence rates may be lower in high compression hosiery than in medium compression hosiery and therefore patients should be offered the strongest compression with which they can comply.

According to a systematic review of the evidence, pentoxifilline has also been shown to be effective for treatment of venous leg ulcers (Nelson et al, 2002). According to the systematic evidence review, compression has been shown to prevent venous leg ulcers. The effectiveness of vein surgery for prevention or treatment of venous ulcers is "unknown" (Nelson et al, 2002).

Beyond conservative therapy, the treatment of varicose veins in the lower legs includes injection/compression sclerotherapy and surgical stripping or ligation or a combination of these approaches depending upon the severity of the condition. Despite many years of experience, there is still a disappointingly high recurrence rate of varices because many patients are inadequately investigated before treatment. As it has been shown that physical examination alone is unreliable, pre-treatment Doppler or Duplex ultrasound examination must be performed for localization of the sites of incompetence to allow the individualization of the treatment strategy for each patient. Photographs or office diagrams may be helpful in assessing the size and extent of the varices.

Under established guidelines, the basic tenet of successful treatment is to eliminate the primary and secondary sources of the reflux. These sources are usually a nearby perforator, or most often a major junction that causes redirected venous return through veins with intact valves.

Sclerotherapy has been found to be more effective in patients with dilated superficial or residual varicose veins, recurrent varicosities or incompetent perforating veins of small to moderate size (less than 6 mm) without vein reflux. Large varicosities do not respond as well as small varicosities to sclerotherapy (Rosenberg, 2006; MSAC, 2011; MAS, 2011). Inadvertent intra-arterial injection has been an untoward sequela of sclerotherapy. Almost all cases of painful varicosities are associated with junctional reflux. When reflux at the saphenofemoral and/or saphenopopliteal

junctions is present, accepted guidelines provide that sclerotherapy should not be performed until surgical ligation and division of the junction has been done. The junctions themselves can not be adequately treated by sclerotherapy as junctional reflux must be addressed by endovenous ablation methods or surgical ligation or stripping (Jakobsen, 1979; MSAC, 2008; MSAC, 2011). Although varicosities can occasionally be present in the absence or reflux, there is a lack of evidence from reliable clinical studies of the effectiveness of sclerotherapy in relieving symptomatic varicosities not associated with junctional reflux. The sole randomized controlled clinical trial (n = 25) to address the efficacy of sclerotherapy in varicosities not associated with junctional reflux (Kalhe and Leng, 2004) evaluated sclerotherapy efficacy in obliterating varicosities, but did not address its effectiveness at relieving pain. Although sclerotherapy can be used to treat visible subcuticular veins (i.e., spider angiomas, and telangiectasias) less than 2.5 mm in size, these small veins do not cause symptoms and their treatment is purely cosmetic (MSAC, 2011).

Doppler ultrasound is often used in conjunction with other non-invasive physiologic testing to characterize the anatomy and physiology of the varicose vein network prior to injection or surgical intervention. However, duplex scans are also sometimes utilized during the sclerotherapy procedure itself. Their purported usefulness in this regard includes the localization of deep or inaccessible injection sites, such as when there are extensive networks of large deep varicosities, areas of significant reflux between superficial and deep systems, or risks to arterial structures. Ultrasound has also been used to monitor the effectiveness of compressive sclerotherapy in obliterating the lumen of the target vein and reducing reflux/retrograde flow. However, these indications have not been scientifically validated. There is little evidence, in the form of randomized prospective clinical trials, to support that ultrasound makes a significant difference in optimizing outcome or decreasing complications, from sclerotherapy for varicose veins, when compared to non-ultrasound-guided techniques. A structured evidence review conducted by the Alberta Heritage Foundation for Medical Research (AHFMR) (2003) concluded that “the reviewed evidence does not adequately address the questions; which sclerosant is superior and which technique with or without ultrasound guidance is most efficacious.”

Venous reflux can be elicited manually by calf muscle compression and release, by the Valsava maneuver, or by pneumatic tourniquet release (Markovic & Shortell, 2014). If saphenofemoral reflux lasting longer than 500 ms is present, the diameter of the great saphenous veins (GSV) is recorded 2.5 cm distal to the saphenofemoral junction. The size of the vein has been correlated with the presence of significant saphenous reflux. The compliant GSV adjusts its luminal size to the level of transmural pressure, and measurement of its diameter has been shown to reflect the severity of hemodynamic compromise in limbs with GSV reflux. In a cohort study, Navarro, et al. (2002) evaluated the relationship of GSV diameter determined in the thigh and calf to clinical severity of reflux in 112 legs in 85 consecutive patients with saphenofemoral junction and truncal GSV incompetence. The authors stated that they found that the GSV diameter proved to be a relatively accurate measure of hemodynamic impairment and clinical severity in a model of saphenofemoral junction and GSV incompete ce, predicting not only the absence of abnormal reflux, but also the presence of critical venous incompetence. A GSV diameter of 5.5 mm or less predicted the absence of abnormal reflux, with a sensitivity of 78 %, a specificity of 87 %, positive and negative predictive values of 78 %, and an accuracy of 82 %.

Ligation and division of the saphenofemoral and/or saphenopopliteal junction is indicated in patients with symptomatic varicose veins who have failed conservative management, when reflux of greater than 0.5 seconds is demonstrated by Doppler examination or Duplex scanning. The literature states that operative excision of varicose veins in the leg(s) should be reserved for those that are very large (greater than 6 mm), extensive in distribution, or occur in large clusters. Ligation alone usually results in a high recurrence rate of the varicose vein, which may then require sclerotherapy treatment (MSAC, 2008). Stripping of the greater and/or lesser saphenous vein, performed in conjunction with ligation and division of their respective junctions, is indicated when the saphenous veins themselves show varicose changes (usually greater than 1 cm in diameter). Varicose vein surgery and/or sclerotherapy during pregnancy is not appropriate because dilatation of veins in the legs is physiologic and will revert to normal after delivery, at which time a more accurate appraisal can be made. Visible subcuticular veins (i.e., spider angiomas, and telangiectasias) less than 2.5 mm in size do not cause symptoms and their treatment is purely cosmetic.

Ambulatory phlebectomy (AP) (also known as microphlebectomy) is a minimally invasive procedure performed under local anesthesia, and is an accepted outpatient therapy for the removal of varicose veins. This treatment allows excision of almost all of the large varicose veins except the proximal long saphenous vein, which is better-managed by stripping.

Non-refluxing varicose veins on the surface of the leg, not including the saphenous veins, may be treated as an outpatient procedure under local anaesthetic using ambulatory phlebectomy (MSAC, 2011). However, recurrence rates can be high if the source of the reflux is not treated (MSAC, 2011). The junctions themselves can not be treated with simple phlebectomy as junctional reflux must be addressed by endovenous ablation methods or rarely by surgical ligation and stripping (MSAC, 2011; Weiss, 2007). Patients can ambulate immediately after AP. Complications associated with AP include blister formation, localized thrombophlebitis, skin necrosis, hemorrhage, and persistent edema. The use of broad compression pads following AP reduces hemorrhage and enhances resorption.

The TriVex System (transilluminated powered phlebectomy) is an alternative method of providing ambulatory phlebectomy. This entails endoscopic resection and ablation of the superficial veins using an illuminator and a "powered vein rejector", a small powered surgical device. In this procedure, veins are marked with a magic marker. In order to enhance visualization of the veins, a bright light is introduced into the leg through a tiny incision. The powered vein rejector, which has a powered oscillating end, is then introduced to cut and dislodge the veins. The pieces of vein are then gently retrieved by suction down a tube. Transilluminated powered phlebectomy is usually performed in the hospital on an outpatient basis and under general anesthesia or using local anesthesia with sedation.

The manufacturer of the TriVex System states that the unique illumination feature allows the surgeon to quickly and accurately target and remove the vein and then visually confirm its complete extraction. The manufacturer claims that this new process makes varicose vein removal more effective, complete and less traumatic for patients, by reducing the number of incisions required to perform the procedure and the duration of surgery. The manufacturer also claims that this method not only reduces the pain associated with varicose vein removal but also reduces the potential for post-operative infection. There is inadequate evidence, however, in the published peer-reviewed medical literature substantiating these claims. The potential advantages of the TriVex System over standard ambulatory phlebectomy have not been proven. Therefore, the TriVex procedure should be billed as any other varicose vein removal procedure.

The term endovenous catheter ablation (EVCA) has been used to refer to the several new catheter based minimally invasive alternatives to surgical stripping, including laser ablation and radiofrequency ablation. Endovenous catheter ablation and surgical ligation/stripping are indicated for treatment of the same general population: patients in whom the great and/or small saphenous veins have reflux or incompetence of 0.5 seconds or longer demonstrated on duplex scanning, and varicose vein symptoms significantly impinge on quality of life (MSAC, 2011). These patients have exhausted conservative treatment measures, and sclerotherapy is considered unlikely to provide successful results. Endovenous laser ablation and radiofrequency ablation are essentially identical except for the use of different specialized equipment and catheters, with thermal energy delivered through either a radiofrequency catheter or laser fiber (MSAC, 2011). The objectives of the two treatments are the same, being the destruction or ablation of a refluxing vein or segment of vein via application of thermal energy. The procedure to place the catheter within the vein is the same for radiofrequency ablation and endovenous laser ablation, also both procedures are conducted under duplex ultrasonography guidance (MSAC, 2011). The physiological mechanism of vein ablation is also the same, with thermal energy producing endothelial and vein wall damage, denaturing and occluding the vein to close the vein, abolishing venous reflux and visible varicosities (MSAC, 2011).

ECVA is performed with tumescent anesthesia (Markovic & Shortell, 2014). Tumescent anesthesia allows physicians to use large volumes (500 ml) of dilute (0.1%) lidocaine in a single session while achieving anesthesia levels equivalent to those achieved with 1% lidocaine. In this way, the entire thigh portion of the GSV can be safely anesthetized (and consequently obliterated) at one time. Epinephrine can be added to the solution to improve postoperative hemostasis, increase venous contraction around the heat-generating catheter, and lengthen the duration of postprocedural analgesia. A common formula for the tumescent anesthesia solution is 450 ml of normal saline mixed with 50 ml of 1% lidocaine with epinephrine (1:100,000 dilution) and 10 ml of sodium bicarbonate to buffer the acidity of the lidocaine.

Endovenous laser ablation of saphenous vein (ELAS) is a treatment alternative to surgical ligation and stripping of the greater saphenous vein. Endovenous laser therapy for varicose veins is indicated for patients with clinically documented primary venous reflux, confirmed by duplex ultrasound, of the great or small saphenous veins (MSAC, 2008). Endovenous laser ablation is only suitable for patients with large, saphenous varicose veins, as the catheter requires saphenous veins with a minimum 4.5mm in diameter.These patients have exhausted other conservative treatment measures and sclerotherapy is considered unlikely to be successful (MSAC, 2008). After ultrasound

examination to confirm the site and extent of saphenous reflux, a catheter is introduced into the damaged vein along a guide wire via percutaneous puncture at the distal extent of the diseased saphenous vein (MSAC, 2008). Perivascular infiltration of dilute local anesthetic along the length of the vein is then performed under ultrasound guidance to collapse the lumen and compress the vein onto the catheter, to dissipate heat generated during the procedure so as to prevent tissue damage, and to anesthetise the vein (MSAC). The guide wire is replaced with a laser probe introduced through the catheter to just below the saphenofemoral or saphenopopliteal junction, with positioning confirmed by ultrasound. Laser energy is then applied as the fiber and catheter are slowly withdrawn so as to close the vein and abolish venous reflux. Pulses of laser light are emitted inside the vein, and the vein collapses, and seals shut. This procedure may be performed in the office under local anesthesia. A bandage or compression hose is placed on the treated leg following the treatment. The procedure is performed on an outpatient basis.

Endovenous laser treatment can only be used for large veins, as a catheter must be inserted into the lumen of the vein to be treated (MSAC, 2008).. Endovenous laser treatment is not viable on saphenous veins smaller than 4.5 mm in diameter, and cannot be used for the treatment of small veins or telangiectases. Smaller veins may be treated with sclerotherapy or ambulatory phlebectomy.

A range of laser wavelengths can be used to achieve occlusion; there is no strong evidence to indicate that any particular wavelength is superior to any other (MSAC, 2008). One systematic evidence review reported that the short term (within 6 months) reported occlusion rates of the GSV and small saphenous vein (SSV) found in studies of endovenous laser therapy were all greater than 90%.

Absolute contraindications to ELAS treatment include occlusive deep venous thrombosis and pregnancy. Relative contraindications include occlusive arterial disease, hypercoabulability, tortuous veins, and inability to ambulate (MSAC, 2008).

Endoluminal radiofrequency thermal heating (VNUS Closure Procedure) has been used with or without ligation and division for treatment of incompetence of the saphenofemoral and saphenopopliteal junction. To perform the radiofrequency ablation (RFA) procedure, the affected leg is prepared and draped, and a superficial local anaesthetic agent is used to anesthetize the site of cannulation. A radiofrequency catheter is inserted into the lumen of the greater saphenous vein, starting at its junction with the femoral vein. Under some protocols, the placement of the catheter is guided by duplex ultrasonography. The radiofrequency catheter heats the inner lumen of the vein to 85°C, with subsequent scarring and closure of the treated vein. The procedure is performed in an office setting without general anesthesia; treatment time averages 20 mins. Adverse sequelae include purpura, erythema and pain, which generally resolve days or weeks after treatment, and indurated fibrous cords that may remain for several months.

Upon completion of the RFA procedure, the site of venous puncture is dressed, and compression stockings and/or bandages are applied as appropriate to reduce the risk of venous thromboembolism and to reduce postoperative bruising and tenderness (MSAC, 2011). Non-steroidal anti-inflammatory drugs are commonly used for post-procedural pain relief. For most patients additional procedures such as sclerotherapy or phlebectomy are required for the treatment of superficial veins below the knee, any tributary varicose veins, and telangiectases. These procedures may be performed during the RFA or endovenous laser treatment procedure, or over one or two follow-up visits.

Radiofrequency ablation is designed as a single-use therapeutic intervention, delivered as a single course of treatment per affected leg to obliterate the great or small saphenous veins through the application of thermal energy (MSAC, 2011). While generally indicated for primary varicose veins, re-treatment of varicose veins with RFA may be possible in some patients where neovascularisation or revascularisation has occurred. However, revascularization in the short term following treatment is uncommon. Studies reporting on radiofrequency ablation with the more efficient second generation catheters report ablation rates close to 100% at 6-month follow-up with no major adverse events (MAS, 2011).

Prospective case series extending to 24 months have shown success rates with RFA similar to those reported for vein ligation and stripping. Weiss and Weiss (2002) reported complete disappearance of the treated saphenous vein in 90 % of 21 patients followed for 24 months. Endothermal radiofrequency thermal heating may be performed with or without high ligation of the greater saphenous vein. Chandler et al (2000) found no statistically significant difference in 1-year

success rates from endovenous radiofrequency catheter ablation in 120 limbs treated without saphenofemoral ligation and 60 limbs treated with saphenofemoral ligation. The authors concluded that "these early results suggest that extended sapheno-femoral junction (SFJ) ligation may add little to effective GSV [greater saphenous vein] obliteration, but our findings are not sufficiently robust to warrant abandonment of SFJ ligation as currently practiced in the management of primary varicose veins associated with GSV reflux."

Pivotal studies of endovenous catheter ablation (endovenous laser ablation and endovenous radiofrequency ablation) procedures have focused on junctional incompetence. There is a lack of evidence of the effectiveness of endovenous catheter ablation procedures for treatment of varicose tributaries and perforator veins. In addition, there are no studies comparing endovenous catheter ablation procedures to standard methods of treating varicose tributaries and perforator veins with sclerotherapy and ambulatory phlebectomy.

The Society for Interventional Radiologists (2003) has a position statement on VNUS that states that “(d)uplex ultrasound is necessary to map the anatomy of the venous system prior to the procedure, and imperative during the procedure for correct catheter placement and for proper tumescent anesthetic administration to minimize potential complications. Duplex ultrasound also is necessary for follow-up after endovenous ablation.”

Sadick (2000) has noted that the new less-invasive technologies for treatment of varicose veins must be evaluated with caution. "Long-term studies with other technologies must be compared with surgical ligation of the incompetent SFJ (saphenofemoral junction). Six-month and 5-year follow-ups are two different end points. The latter is a more accurate time interval of therapeutic efficacy."

Subfascial endoscopic perforator vein surgery (SEPS) is a minimally invasive endoscopic procedure that eliminates the need for a large incision in the leg. It has been explored as an alternative to the traditional open surgical treatment of chronic venous insufficiency. The aim of the procedure is to interrupt incompetent medial calf perforating veins to reduce venous reflux and decrease ambulatory venous hypertension in critical areas above the ankle where venous ulcers most frequently develop. Kalra and Gloviczki (2002) stated that available evidence confirmed the superiority of SEPS over open perforator ligation, but do not address its role in the surgical treatment of advanced chronic venous insufficiency (CVI) and venous ulceration. Ablation of superficial reflux by high ligation and stripping of the greater saphenous vein with avulsion of branch varicosities is concomitantly performed in the majority of patients undergoing SEPS. The clinical and hemodynamic improvements attributable to SEPS thus are difficult to ascertain. As with open perforator ligation, clinical and hemodynamic results are better in patients with primary valvular incompetence (PVI) than in those with the post-thrombotic (PT) syndrome. Until prospective, randomized, multicenter clinical studies are performed to address lingering questions regarding the effectiveness of SEPS, the procedure is recommended in patients with advanced CVI secondary to PVI of superficial and perforating veins, with or without deep venous incompetence. The performance of SEPS in patients with PT syndrome remains controversial.

Contraindications for SEPS include associated arterial occlusive disease, infected ulcer, a non-ambulatory patient, and a medically high-risk patient. Diabetes, renal failure, liver failure, morbid obesity, ulcers in patients with rheumatoid arthritis, or scleroderma, and presence of deep vein obstruction at the level of the popliteal vein or higher on pre-operative imaging are relative contraindications. Patients with extensive skin changes, circumferential large ulcers, recent deep vein thrombosis, severe lymphedema, or large legs may not be suitable candidates (Kalra and Gloviczki, 2002).

McDonagh et al (2002, 2003) has reported on the effectiveness of ultrasound-guided foam sclerotherapy (comprehensive objective mapping, precise image-guided injection, anti-reflux positioning and sequential sclerotherapy (COMPASS) technique) in the treatment persons with varicosities of the greater saphenous vein with saphenous vein reflux. Published studies of the COMPASS technique involve relatively short-term follow up. Study subjects were followed for 3 years, and for only 2 years after completion of a series of repeat sclerotherapy injections that were administered over 1 year. In addition, these studies do not include a comparable group of subjects treated with surgery, which has been the primary method of treating incompetent long saphenous veins. Thus, it is not possible to reach definitive conclusions about the durability of results of the COMPASS technique or its effectiveness compared with surgery for treatment of greater saphenous vein varicosities and saphenofemoral incompetence. In addition, published studies of the COMPASS technique come from a single group of investigators. In reviewing the study by McDonagh

(2002), Allegra (2003) commented: “Surgical treatment has a long history with 5-20 year follow-ups being routine. The 3 year follow-up in the present study is certainly not comparable …. This study does not answer questions raised against ultrasound guided sclerotherapy. It would be important to have the relevant aspects of this study duplicated, reproduced, and verified.”

Published long-term randomized controlled clinical studies have demonstrated that surgery plus sclerotherapy is more effective than surgery alone for treatment of varicosities associated with incompetence of the saphenofemoral junction. Belcaro et al (2003) reported on the results from the Venous Disease International Control (VEDICO) trial, the first long-term randomized controlled clinical trial of foam sclerotherapy. The VEDICO trial involved 749 patients with varicose veins and saphenous vein incompetence who were randomly treated by six different approaches: standard sclerotherapy, high-dose sclerotherapy, surgical ligation, stab avulsion, foam sclerotherapy, and combined surgery (ligation or stab avulsion) and high dose sclerotherapy. At 10 years, the occurrence of new veins was 56 % for standard sclerotherapy, 51 % for foam sclerotherapy, 49 % for high-dose sclerotherapy, 41 % for stab avulsion, 38 % for ligation, and 27 % for combined surgery and sclerotherapy.

Belcaro et al (2000) reported on the results of a randomized controlled clinical study comparing ultrasound-guided sclerotherapy with surgery alone or surgery combined with sclerotherapy in 96 patients with varicose veins and superficial venous incompetence. Although all approaches were reported to be effective in controlling the progression of venous incompetence, surgery appeared to be the most effective method on a long-term basis, and that surgery combined with sclerotherapy may be more effective than surgery alone. After 10 years follow-up, no incompetence of the saphenofemoral junction was observed in both groups assigned to surgery, compared to 18.8 % of limbs of subjects assigned to ultrasound-guided sclerotherapy. Of limbs treated with ultrasound-guided sclerotherapy, 43.8 % of the distal venous systems were incompetent, compared to 36 % of limbs of subjects treated with surgery alone, and 16.1 % of limbs of subjects treated with surgery plus sclerotherapy.

The L'Agence Nationale d' Accreditation et d'Evaluation en Sante (l'ANAES) (Grange et al, 1998) conducted a systematic review of the literature on the indications of surgery for varicose veins of the legs. Given the lack of good scientific evidence on the various treatments for primary varicose veins, the working group made recommendations based on professional agreement. They concluded that surgery is the treatment of choice for saphenous veins with reflux. An evidence review of surgical treatments for deep venous incompetence by the Alberta Heritage Foundation for Medical Research (Scott and Corabain, 2003) stated that "(s)clerotherapy is particularly effective in superficial venous incompetence when there is a large vein located in close proximity to the ulcer. However, surgery is indicated when there is substantial proximal incompetence in a saphenous vein."

A comprehensive evidence review of sclerotherapy for varicose veins conducted by the Alberta Heritage Foundation for Medical Research (2003) concluded that "the reviewed evidence does not adequately address the questions; which sclerosant is superior and which technique with or without ultrasound guidance is most efficacious … In recent years, new methods such as ES (endovascular sclerotherapy) and foam sclerotherapy (using ultrasound guidance) have been developed and proposed to improve the safety and efficacy of sclerotherapy for various types of varicose veins. Evidence about these new techniques for treating patients with incompetence of the long saphenous vein is limited." The assessment concluded that although "(s)clerotherapy appears to be the treatment of choice for reticular varicosities, telangiectasia and other small, unsightly blood vessels … (t)he place of sclerotherapy as the first treatment for larger varicose veins (saphenous or non-saphenous) remains controversial."

There is a lack of reliable evidence that one type of sclerosant is significantly better than any other (Tisi 2007; Jia et al, 2006). Jia and colleagues (2007) evaluated the safety and effectiveness of foam sclerotherapy for varicose veins. The authors concluded that serious adverse events associated with foam sclerotherapy are rare. However, there is insufficient evidence to allow a meaningful comparison of the effectiveness of this treatment with that of other minimally invasive therapies or surgery.

Kendler and associates (2007) noted that "(r)ecently the use of foam sclerotherapy had a renaissance. Several studies have documented the efficacy of foam sclerotherapy in selected patients. The possibility of treating patients in an outpatient setting, with low costs and rapidly, makes foam sclerotherapy very attractive compared to invasive and minimally invasive methods. However long-term follow-ups in properly controlled randomized trials are needed before

foam sclerotherapy can be recommended as a routine procedure".

The FDA has approved Asclera (polidocanol) injection (BioForm Medical Inc., Franksville, WI) to close spider veins (tiny varicose veins less than 1 millimeter in diameter) and reticular veins (those that are 1 to 3 millimeters in diameter). As these small veins have not been demonstrated to cause symptoms, treatment of these small veins is considered cosmetic.

There is emerging evidence for the Ambulatory Conservative Hemodynamic Management of Varicose Veins (CHIVA) method. In an open-label, randomized controlled trial, Pares and colleagues (2010) compared the effectiveness of the Ambulatory Conservative Hemodynamic Management of Varicose Veins (CHIVA) method for the treatment of varicose veins with respect to the standard treatment of stripping. According to the authors, CHIVA consists of minimally invasive surgical procedures under local anesthesia that are based on hemodynamic analysis of the legs with pulsed Doppler ultrasound. A total of 501 adult patients with primary varicose veins were treated in a single center. They were assigned to an experimental group, the CHIVA method (n = 167) and 2 control groups: stripping with clinic marking (n = 167) and stripping with Duplex marking (n = 167). The outcome measure was clinical recurrence within 5 years, assessed clinically by previously trained independent observers. Duplex ultrasonography was also used to assess recurrences and causes. In an intention-to-treat analysis, clinical outcomes in the CHIVA group were better (44.3 % cure, 24.6 % improvement, 31.1 % failure) than in both the stripping with clinic marking (21.0 % cure, 26.3 % improvement, 52.7 % failure) and stripping with Duplex marking (29.3 % cure, 22.8 % improvement, 47.9 % failure) groups. The ordinal odds ratio between the stripping with clinic marking and CHIVA groups, of recurrence at 5- year follow-up, was 2.64, (95 % confidence interval (CI): 1.76 to 3.97, $p < 0.001$). The ordinal odds ratio of recurrence at 5-year follow-up, between the stripping with Duplex marking and CHIVA group, was 2.01 (95 % CI: 1.34 to 3.00, $p < 0.001$). The authors concluded that these findings indicated that the CHIVA method is more effective than stripping with clinical marking or stripping with Duplex marking to treat varicose veins. Furthermore, when carrying out a stripping intervention, Duplex marking does not improve the clinical results of this ablative technique.

In a randomized study, Rasmussen et al (2011) compared 4 treatments for varicose GSVs. A total of 500 consecutive patients (580 legs) with GSV reflux were randomized to endovenous laser ablation (EVLT, 980 and 1,470 nm, bare fiber), radiofrequency ablation (RFA), ultrasound-guided foam sclerotherapy (USGFS) or surgical stripping using tumescent local anesthesia with light sedation. Mini-phlebectomies were also performed. Patients were examined with duplex imaging before surgery, and after 3 days, 1 month and 1 year. At 1 year, 7 (5.8 %), 6 (4.8 %), 20 (16.3 %) and 4 (4.8 %) of the GSVs were patent and refluxing in the laser, radiofrequency, foam and stripping groups respectively ($p < 0.001$). One patient developed a pulmonary embolus after foam sclerotherapy and 1 a deep vein thrombosis after surgical stripping. No other major complications were recorded. The mean (S.D.) post-intervention pain scores (scale 0 to 10) were 2.58 (2.41), 1.21 (1.72), 1.60 (2.04) and 2.25 (2.23), respectively ($p < 0.001$). The median (range) time to return to normal function was 2 (0 to 25), 1 (0 to 30), 1 (0 to 30) and 4 (0 to 30) days, respectively ($p < 0.001$). The time off work, corrected for weekends, was 3.6 (0 to 46), 2.9 (0 to 14), 2.9 (0 to 33) and 4.3 (0 to 42) days, respectively ($p < 0.001$). Disease-specific quality-of-life and Short Form 36 (SF-36) scores had improved in all groups by 1-year follow-up. In the SF-36 domains bodily pain and physical functioning, the radiofrequency and foam groups performed better in the short-term than the others. The authors concluded that all treatments were efficacious. The technical failure rate was highest after foam sclerotherapy, but both RFA and foam were associated with a faster recovery and less post-operative pain than EVLT and stripping.

In a Cochrane review, Nesbitt et al (2011) reviewed available randomized controlled trial (RCT) data comparing USGFS, RFA and EVLT to conventional surgery (high ligation and stripping (HL/S)) for the treatment of great saphenous varicose veins. The Cochrane Peripheral Vascular Diseases (PVD) Group searched their Specialised Register (July 2010) and CENTRAL (The Cochrane Library 2010, Issue 3). In addition the authors performed a search of EMBASE (July 2010). Manufacturers of EVLT, RFA and sclerosant equipment were contacted for trial data. All RCTs of EVLT, RFA, USGFS and HL/S were considered for inclusion. Primary outcomes were recurrent varicosities, re-canalization, neovascularization, technical procedure failure or need for re-intervention, patient quality of life (QoL) scores and associated complications. Secondary outcomes were type of anesthetic, procedure duration, hospital stay and cost. A total of 13 reports from 5 studies with a combined total of 450 patients were included. Rates of re-canalization were higher following EVLT compared with HL/S, both early (within four months) (5/149 versus 0/100; odds ratio (OR) 3.83, 95 % CI: 0.45 to 32.64) and late re-canalization (after 4 months) (9/118 versus 1/80; OR 2.97 95 % CI: 0.52

to 16.98), although these results were not statistically significant. Technical failure rates favored EVLT over HL/S (1/149 versus 6/100; OR 0.12, 95 % CI: 0.02 to 0.75). Recurrence following RFA showed no difference when compared with surgery. Re-canalization within 4 months was observed more frequently following RFA compared with HL/S although not statistically significant (4/105 versus 0/88; OR 7.86, 95 % CI: 0.41 to 151.28); after 4 months no difference was observed. Neovascularization was observed more frequently following HL/S compared with RFA, but again this was not statistically significant (3/42 versus 8/51; OR 0.39, 95 % CI: 0.09 to 1.63). Technical failure was observed less frequently following RFA compared with HL/S although this was not statistically significant (2/106 versus 7/96; OR 0.48, 95 % CI: 0.01 to 34.25). No RCTs comparing HL/S versus USGFS met the study inclusion criteria. QoL scores and operative complications were not amenable to meta-analysis. The authors concluded that currently available clinical trial evidence suggests RFA and EVLT are at least as effective as surgery in the treatment of great saphenous varicose veins. There are insufficient data to comment on USGFS. They stated that further randomized trials are needed; and they should aim to report and analyze results in a congruent manner to facilitate future meta-analysis.

Mueller and Raines (2013) stated that the ClariVein system is the first venous ablation technique to employ a hybrid (dual-injury) technique built into 1 catheter-based delivery system. Endo-mechanical abrasion is produced by the tip of the catheter's rotating wire (mechanical component); and EVCA is via simultaneous injection of sclerosant over the rotating wire (chemical component). The author was an early adopter of this technique and via experience has developed a detailed step-by-step protocol. To date, there have been 2 pivotal clinical studies published using the ClariVein system. These data were compared with the results using other methods of endovenous ablation. The authors concluded that the ClariVein system has the potential to become a first-line treatment.

Lawson et al (2013) noted that less invasive endovenous techniques have been shown to be as effective as open surgery in the treatment of varicose veins. Furthermore, they cause less post-operative bruising and pain and enable early return to normal activities and work. Tumescent anesthesia is safe and obviates complications of general or spinal anesthesia. Drawbacks are a steep learning curve and painful administration during treatment. Tumescentless techniques like ClariVein or VenaSeal Sapheon Closure System are recently under investigation. Short-term results of VenaSeal are comparable with thermal ablation. The procedure is safe without serious adverse events. Peri-operative pain and patient discomfort with this tumescentless approach is minimal but post-operative recovery is temporarily hindered by thrombophlebitis in 14 to 15 % of patients. One-year results in a small feasibility study has demonstrated durable closure at this end-point. No longer-term results are available. A randomized control trial between VenaSeal and Covidien ClosureFast is in a preparatory phase.

A randomized controlled trial comparing foam sclerotherapy to laser ablation and surgery found that laser ablation and surgery had better outcomes, and that laser had the fewest procedural complications. Brittenden et al (2014) stated that ultrasound-guided foam sclerotherapy and endovenous laser ablation are widely used alternatives to surgery for the treatment of varicose veins, but their comparative effectiveness and safety remain uncertain. In a randomized trial involving 798 participants with primary varicose veins at 11 centers in the United Kingdom, these researchers compared the outcomes of foam, laser (laser ablation of truncal saphenous veins, followed if needed by foam sclerotherapy) and surgical treatments (proximal ligation and stripping of the great saphenous vein with concurrent phlebectomy). Study participants had varicose veins larger than 3 mm in diameter and reflux of the saphenous veins of more than 1 second by duplex ultrasound. The participants mean age was 49 years, 57% were women, and approximately 30% had bilateral varicose veins. Those with recurrent varicose veins after previous treatment were excluded. Primary outcomes at 6 months were disease-specific quality of life and generic quality of life, as measured on several scales. Secondary outcomes included complications and measures of clinical success. After adjustment for baseline scores and other covariates, the mean disease-specific quality of life was worse after treatment with foam than after surgery ($p = 0.006$) but was similar in the laser and surgery groups. There were no significant differences between the surgery group and the foam or the laser group in measures of generic quality of life. At 6 months, approximately 80% of patients in the laser and surgery groups showed complete ablation of the great saphenous vein on duplex ultrasound, compared with only 43% in the foam group ($p < 0.001$). The frequency of procedural complications was similar in the foam group (6 %) and the surgery group (7 %); but was lower in the laser group (1 %) than in the surgery group ($p < 0.001$); the frequency of serious adverse events (approximately 3 %) was similar among the groups. At 6 months, lumpiness and staining of the skin were somewhat more common in the foam group.

On November 26, 2013, the FDA approved Varithena (polidocanol injectable foam) for the treatment of patients with incompetent veins and visible varicosities of the great saphenous vein (GSV) system. The prescribing information states: "Varithena (polidocanol injectable foam) is indicated for the treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein (GSV) system above and below the knee. Varithena improves the symptoms of superficial venous incompetence and the appearance of visible varicosities." Although the FDA approval does not exclude use of Varithena foam sclerotherapy for treatment of SF or SP ; junctional reflux, there are a lack of studies comparing Varithena to endovenous ablation procedures for SF or SP junctional reflux. In addition, there is a paucity of evidence examining the long-term durability of results of Varithena treatment of junctional reflux.

Todd et al (2014) reported on a RCT to determine efficacy and safety of polidocanol endovenous microfoam in treatment of symptoms and appearance in patients with saphenofemoral junction incompetence due to reflux of the great saphenous vein or major accessory veins. Patients were randomized equally to receive polidocanol endovenous microfoam 0.5 %, polidocanol endovenous microfoam 1.0 % or placebo. The primary efficacy end-point was patient-reported improvement in symptoms, as measured by the change from baseline to Week 8 in the 7-day average electronic daily diary VVSymQ™ score. The co-secondary end-points were the improvement in appearance of visible varicosities from baseline to Week 8, as measured by patients and by an independent physician review panel. In 232 treated patients, polidocanol endovenous microfoam 0.5 % and polidocanol endovenous microfoam 1.0 % were superior to placebo, with a larger improvement in symptoms (VVSymQ (-6.01 and-5.06, respectively, versus -2.00; $p < 0.0001$) and greater improvements in physician and patient assessments of appearance ($p < 0.0001$). These findings were supported by the results of duplex ultrasound and other clinical measures. Of the 230 polidocanol endovenous microfoam-treated patients (including open-label patients), 60 % had an adverse event compared with 39 % of placebo; 95 % were mild or moderate. No pulmonary emboli were detected and no clinically important neurologic or visual adverse events were reported. The most common adverse events in patients treated with polidocanol endovenous microfoam were retained coagulum, leg pain and superficial thrombophlebitis; most were related to treatment and resolved without sequelae.

Brittenden and colleagues (2015) stated that foam sclerotherapy (foam) and endo-venous laser ablation (EVLA) have emerged as alternative treatments to surgery for patients with varicose veins (VV), but uncertainty exists regarding their effectiveness in the medium to longer term. These investigators evaluated the clinical effectiveness and cost-effectiveness of foam, EVLA and surgery for the treatment of VV. A total of 798 patients with primary VV (foam, $n = 292$; surgery, $n = 294$; EVLA, $n = 212$) were included in this study. Patients were randomized between all 3 treatment options (8 centers) or between foam and surgery (3 centers). Primary outcome measures included disease-specific [Aberdeen Varicose Vein Questionnaire (AVVQ)] and generic [European Quality of Life-5 Dimensions (EQ-5D), Short Form questionnaire-36 items (SF-36) physical and mental component scores] quality of life (QoL) at 6 months. Cost-effectiveness as cost per quality-adjusted life-year (QALY) gained. Secondary outcome measures entailed QoL at 6 weeks; residual VV; Venous Clinical Severity Score (VCSS); complication rates; return to normal activity; truncal vein ablation rates; and costs. The results appeared generalizable in that participants' baseline characteristics (apart from a lower-than-expected proportion of females) and post-treatment improvement in outcomes were comparable with those in other RCTs. The health gain achieved in the AVVQ with foam was significantly lower than with surgery at 6 months [effect size -1.74, 95 % CI: -2.97 to -0.50; $p = 0.006$], but was similar to that achieved with EVLA. The health gain in SF-36 mental component score for foam was worse than that for EVLA (effect size 1.54, 95 % CI: 0.01 to 3.06; $p = 0.048$) but similar to that for surgery. There were no differences in EQ-5D or SF-36 component scores in the surgery versus foam or surgery versus EVLA comparisons at 6 months. The trial-based cost-effectiveness analysis showed that, at 6 months, foam had the highest probability of being considered cost-effective at a ceiling willingness-to-pay ratio of £20,000 per QALY. EVLA was found to cost £26,107 per QALY gained versus foam, and was less costly and generated slightly more QALYs than surgery. Markov modelling using trial costs and the limited recurrence data available suggested that, at 5 years, EVLA had the highest probability (approximately 79 %) of being cost-effective at conventional thresholds, followed by foam (approximately 17 %) and surgery (approximately 5 %). With regard to secondary outcomes, health gains at 6 weeks ($p < 0.005$) were greater for EVLA than for foam (EQ-5D, $p = 0.004$). There were fewer procedural complications in the EVLA group (1 %) than after foam (7 %) and surgery (8 %) ($p < 0.001$). Participants returned to a wide range of behaviors more quickly following foam or EVLA than following surgery ($p < 0.05$). There were no differences in VCSS between the 3 treatments. Truncal ablation rates were higher for surgery ($p < 0.001$) and EVLA ($p < 0.001$) than for foam, and were similar for surgery and EVLA. The authors concluded that considerations of both the 6-month clinical outcomes and the estimated 5-year cost-effectiveness

suggested that EVLA should be considered as the treatment of choice for suitable patients.

Marsden et al (2015) investigated the cost-effectiveness of interventional treatment for VV in the United Kingdom National Health Service (UK NHS), and informed the national clinical guideline on VV, published by the National Institute of Health and Care Excellence (NICE). An economic analysis was constructed to compare the cost-effectiveness of surgery, endo-thermal ablation (ETA), ultrasound-guided foam sclerotherapy (UGFS), and compression stockings (CS). The analysis was based on a Markov decision model, which was developed in consultation with members of the NICE guideline development group (GDG). The model had a 5-year time horizon, and took the perspective of the UK NHS. Clinical inputs were based on a network meta-analysis (NMA), informed by a systematic review of the clinical literature. Outcomes were expressed as costs and quality-adjusted life years (QALYs). All interventional treatments were found to be cost-effective compared with CS at a cost-effectiveness threshold of £20,000 per QALY gained; ETA was found to be the most cost-effective strategy overall, with an incremental cost-effectiveness ratio of £3,161 per QALY gained compared with UGFS. Surgery and CS were dominated by ETA. The authors concluded that interventional treatment for VV is cost-effective in the UK NHS. Specifically, based on current data, ETA is the most cost-effective treatment in people for whom it is suitable. The results of this research were used to inform recommendations within the NICE guideline on VV.

Compression Following Treatment for Varicose Veins

El-Sheikha et al (2015) stated that consensus regarding compression following treatment of VV has yet to be reached. This systematic review aimed to establish the optimal compression regimen after venous treatment. A systematic review of MEDLINE, Embase and CENTRAL was performed to identify RCTs investigating different compression strategies following treatment for superficial venous insufficiency. A total of 7 RCTs comparing different durations and methods of compression fulfilled the inclusion criteria. The treatment modality was open surgery in 3 trials, foam sclerotherapy in 2 and EVLA in 2 trials. The quality of the studies was variable, and significant sources of potential bias were present. Both the studies and compression regimens used were heterogeneous; 10 products were used in 6 general regimens for a duration of 0 to 42 days. One study suggested that 7 days rather than 2 days of stockings following EVLA was associated with superior QoL and less pain at 1 week. Another study reported that, following surgery, application of a compression stocking after 3 days of bandaging was associated with a slightly longer recovery than no compression after 3 days. One study recorded compliance clearly, finding it to be only 40 %. The quality and heterogeneity of the studies precluded meta-analysis. The authors concluded that there is currently little quality evidence upon which to base any recommendations concerning compression following treatment for VV.

Micronized Purified Flavonoid Fraction Therapy

Pietrzycka and colleagues (2015) stated that the etiology of VV involves various factors and pathomechanisms including endothelial cell activation or dysfunction, venous hypertension, vein wall hypoxia, shear stress disturbances, inflammatory reaction activation or free radical production. To improve the understanding of the mechanisms of potential pharmacological interventions for chronic venous disease, these researchers evaluated the influence of micronized purified flavonoid fraction (MPFF) on the relationship between antioxidant enzyme balance, endothelin-1 (ET-1) and tumor necrosis factor-alpha (TNF-α) levels. Blood samples were obtained from 89 women with primary VV; 34 were treated with MPFF and 55 did not receive any phlebotropic drug treatment. For the evaluation of the blood antioxidant enzyme balance, catalase (CAT) and superoxide dismutase (SOD) activity was assessed and the CAT/SOD ratio was calculated. Patients taking MPFF had significantly lower ET-1 levels than those not taking MPFF [median (25 to 75th quartile): 24.2 (22.30 to 27.87) versus 37.62 (24.9 to 44.58) pg/ml; $p < 0.05$]. In those taking MPFF, a higher CAT/SOD ratio [39.8 (24.7 to 72.6) versus 28.8 (16.3 to 57.7); $p < 0.05$] and a lower TNF-α concentration [6.82 (4.42 to 13.39) versus 12.94 (6.01 to 27.33) pg/ml; $p < 0.05$] was also observed. In women not taking MPFF, ET-1 levels increased with the CAT/SOD ratio. In those taking MPFF, the ET-1 level was stable at about 25.0 pg/ml; up to a CAT/SOD ratio of 100. TNF-α level increased continuously with an increasing CAT/SOD ratio; however, the highest levels of TNF-α were observed in women not taking MPFF. The authors concluded that they demonstrated the ability of MPFF to effectively lower the levels of ET-1 and TNF-α in patients with chronic venous disease. They sated that further investigations are needed to define the therapeutic potential of MPFF including the potential effect on chronic subclinical inflammation, antioxidant imbalance and vascular dysfunction during the development of chronic venous

disease.

Cyanoacrylate Tissue Adhesive (e.g., the VariClose Vein Sealing System and the VenaSeal Closure System

The VenaSeal Closure System:

The VenaSeal Closure System (Sapheon Inc., Morrisville, NC) is a minimally invasive, non-tumescent, non-thermal and non-sclerosant procedure that uses a medical adhesive to close the diseased vein in patients with symptomatic venous reflux disease. Unlike other treatments, the VenaSeal Closure System does not require tumescent anesthesia, allowing patients to return to their normal activities following the procedure; it also eliminates the risk of nerve or other heat-related injuries associated with thermal-based procedures, and thus may reduce the need for compression stockings post-procedure.

Toonder et al (2014) noted that percutaneous thermo-ablation techniques are still being used today and seem more effective than non-thermal techniques. However, thermal techniques require anesthesia and potentially may cause inadvertent damage to surrounding tissues such as nerves. Cyanoacrylate adhesive has a proven record, but not for the treatment of chronic venous disease of the leg. Innovation has led to the development of the VenaSeal Sapheon Closure System, which has been designed to use a modified cyanoacrylate glue as a new therapy for truncal vein incompetence. These researchers examined the feasibility of ultrasound-guided cyanoacrylate adhesive perforator embolization (CAPE). The authors stated that results of this feasibility study showed a 76 % occlusion rate of incompetent perforating veins without serious complications; further investigation with a dedicated delivery device in a larger patient population is needed.

McHugh and Leahy (2014) stated that endothermal treatment of the great saphenous vein has become the first line of treatment for superficial venous reflux. Newer treatments, especially non-thermal ablation have potential benefits both for patient acceptability and decreased risk of nerve injury. These researchers described the current non-thermal options available including advantages and disadvantages. Ultrasound-guided foam sclerotherapy avoids the risk of nerve injury, however it is not as effective as endothermal ablation. Mechano-chemical endovenous ablation combines mechanical endothelial damage using a rotating wire, with the infusion of a liquid sclerosant (the ClariVein System). Reports suggested that this system is safe and effective, eliminating the need for tumescent anesthesia with no reported case of nerve injury. Finally the VenaSeal Closure System comprises the endovenous delivery of cyanoacrylate tissue adhesive to the vein causing fibrosis. Peri-operative discomfort seems to be minimal but the complication of thrombophlebitis has been reported in up to 15 % of patients. The authors concluded that non-thermal options promise comparable treatment efficacy without the added morbidity associated with high thermal energies. They stated that the potential of treating venous reflux without the risk of nerve damage may change how surgeons approach venous disease.

On February 20, 2015, the FDA granted pre-market approval of the VenaSeal Closure System to treat superficial varicosities of the legs through endovascular embolization and is intended for adults with clinically symptomatic venous reflux diagnosed by duplex ultrasound. The FDA approval was based on a multi-center, RCT by Morrison et al (2015)

Morrison and colleagues (2015) noted that preliminary evidence suggests that CAPE may be effective in the treatment of incompetent GSVs. These investigators reported early results of a RCT of CAPE versus RFA for the treatment of symptomatic incompetent GSVs. A total of 222 subjects with symptomatic GSV incompetence were randomly assigned to receive either CAPE (n = 108) with the VenaSeal Closure System or RFA (n = 114) with the ClosureFast System. After discharge, subjects returned to the clinic on day 3 and again at months 1 and 3. The study's primary end-point was closure of the target vein at month 3 as assessed by duplex ultrasound and adjudicated by an independent vascular ultrasound core laboratory. Statistical testing focused on showing non-inferiority with a 10 % delta conditionally followed by superiority testing. No adjunctive procedures were allowed until after the month 3 visit, and missing month 3 data were imputed by various methods. Secondary end-points included patient-reported pain during vein treatment and extent of ecchymosis at day 3. Additional assessments included general and disease-specific quality of life surveys and adverse event rates. All subjects received the assigned intervention. By use of the predictive method for imputing missing data, 3-month closure rates were 99 % for CAE and 96 % for RFA. All primary end-point analyses, which used

various methods to account for the missing data rate (14 %), showed evidence to support the study's non-inferiority hypothesis (all $p < 0.01$); some of these analyses supported a trend toward superiority ($p = 0.07$ in the predictive model). Pain experienced during the procedure was mild and similar between treatment groups (2.2 and 2.4 for CAPE and RFA, respectively, on a 10-point scale; $p = 0.11$). At day 3, less ecchymosis in the treated region was present after CAPE compared with RFA ($p < 0.01$). Other adverse events occurred at a similar rate between groups and were generally mild and well-tolerated. The authors concluded that CAPE was proven to be non-inferior to RFA for the treatment of incompetent GSVs at month 3 after the procedure. Both treatment methods showed good safety profiles; CAPE does not require tumescent anesthesia and is associated with less post-procedure ecchymosis. While these findings supported non-inferiority, the reliability of this approach is unclear. These early results need to be validated by well-designed studies with lower rates of data loss and longer follow-up.

Furthermore, an UpToDate review on "Overview and management of lower extremity chronic venous disease" (Alguire and Scovell, 2015) does not mention VenaSeal/non-thermal ablation as a therapeutic option.

Proebstle et al (2015) noted that cyanoacrylate (CA) embolization of refluxing GSVs has been previously described. The outcomes from a multi-center study are still lacking. A prospective, multi-center study was conducted in 7 centers in 4European countries to abolish GSV reflux by endovenous CA embolization. Neither tumescent anesthesia (Ta) nor post-interventional compression stockings were used. Varicose tributaries remained untreated until at least 3 months after the index treatment. Clinical examination, quality of life assessment, and duplex US evaluation were performed at 2 days and after 1, 3, 6, and 12 months. In 70 patients, of whom 68 (97.1%) were available for 12-month follow-up, 70 GSVs were treated. Two-day follow-up showed 1 proximal and 1 distal partial re-canalization; 3 additional proximal re-canalizations were observed at 3-month ($n = 2$) and 6-month ($n = 1$) follow-up. Cumulative 12-month survival free from re-canalization was 92.9 % (95 % CI: 87.0 % to 99.1 %). Mean (standard deviation) Venous Clinical Severity Score improved from 4.3 ± 2.3 at baseline to 1.1 ± 1.3 at 12 months. Aberdeen Varicose Vein Questionnaire score showed an improvement from 16.3 at baseline to 6.7 at 12 months ($p < 0.0001$). Side effects were generally mild; a phlebitic reaction occurred in 8 cases (11.4 %) with a median duration of 6.5 days (range of 2 to 12 days). Pain without a phlebitic reaction was observed in 5 patients (8.6 %) for a median duration of 1 day (range of 0 to 12 days). No serious AEs occurred; and paresthesia was not observed. The authors concluded that endovenous CA embolization of refluxing GSVs was safe and effective without the use of TA or compression stockings. Moreover, they stated that further work is needed to compare CA against endothermal ablation in RCTs.

Lam and colleagues (2017) stated that the treatment of incompetent truncal veins has been innovated by the introduction of minimally invasive non-thermal non-tumescent (NTNT) techniques. One of these consists of the use of cyanoacrylate glue to occlude the vein lumen by means of the VenaSeal device. These investigators evaluated NTNT ablation of incompetent saphenous trunks using the VenaSeal device. They concluded that cyanoacrylate adhesive embolization of incompetent truncal veins using the VenaSeal device is a safe and effective innovative technique. Moreover, they stated that further studies are needed to evaluate anatomical and clinical outcomes at long-term.

Morrison et al (2017) noted that endovenous CA closure (CAC) is a new FDA-approved therapy for treatment of clinically symptomatic venous reflux in saphenous veins. The device is indicated for the permanent closure of lower extremity superficial truncal veins, such as the GSV. Early results from a randomized trial of CAC have been reported previously. These investigators reported 1-year outcomes. There were 222 subjects with symptomatic GSV incompetence randomly assigned to receive either CAC ($n = 108$) or RFA ($n = 114$). After the month 3 visit, subjects could receive adjunctive therapies aimed at treating visible varicosities and incompetent tributaries. Vein closure was assessed at day 3 and months 1, 3, 6, and 12 using duplex US. Additional study visit assessments included the Venous Clinical Severity Score; Clinical, Etiology, Anatomy, and Pathophysiology classification; EuroQol-5 Dimension; and Aberdeen Varicose Vein Questionnaire. Both time to closure and time to first re-opening of the target vein were evaluated using survival curve analysis; AEs were evaluated at each visit. Of 222 enrolled and randomized subjects, a 12-month follow-up was obtained for 192 (95 CAC and 97 RFA; total follow-up rate, 192/222 [86.5 %]). By month 1, 100 % of CAC subjects and 87 % of RFA subjects demonstrated complete occlusion of the target vein. By month 12, the complete occlusion rate was nearly identical in both groups (97.2 % in the CAC group and 97.0 % in the RFA group); 12-month freedom from re-canalization was similar in the CAC and RFA groups, although there was a trend toward greater freedom from re-canalization in the CAC group ($p = 0.08$). Symptoms and quality of life improved equally in both groups. Most AEs were mild-to-moderate and not related to the device or procedure. The authors

concluded that in patients with incompetent GSVs, treatment with both CAC and RFA resulted in high occlusion rates. Time to complete occlusion was faster with CAC, and freedom from re-opening was higher after CAC; quality of life scores improved equally with both therapies.

This study had several drawbacks:

I. this trial included a modest drop-out rate, with month 12 data unavailable for 13 of 108 (12.0 %) subjects in the CAC group (9 withdrawn and 4 visits not done) and 19 of 114 (16.6 %) subjects in the RFA group (8 withdrawn and 11 visits not done),
II. blinding, although potentially advantageous, was not feasible because RFA requires TA administration, and CAC has characteristic findings on ultrasound. However, the primary study outcome (anatomic closure) was easily judged with ultrasound and is objective,
III. ultrasound interpretations performed by study investigators could have introduced bias; however, the core laboratory had no knowledge of the sites' findings at the time of the readings, and their findings agreed with those of the investigators (there was 100 % agreement between investigator reads and core laboratory reads; k statistic was 1.0), and
IV. to minimize confounding due to non-device-related post-intervention factors, subjects in both groups were asked to use compression stockings after the index procedure for 7 days.

This was done solely for the trial, but it was not done for 2 prior studies of CAC. Whether compression stockings improve complete occlusion rates could be the subject of further study.

In a prospective, single-arm, single-center, feasibility study, Almeida et al (2017) evaluated the long-term safety and effectiveness of endovenous cyanoacrylate (CA)-based closure of incompetent GSV. This trial was conducted at the Canela Clinic (La Romana, Dominican Republic) to assess the effectiveness and safety of a CA-based adhesive for GSV closure at 36 months after treatment. A total of 38 subjects were treated by injection of small boluses of CA under US guidance and without the use of peri-venous TA or post-procedure graduated compression stockings. Periodic scheduled follow-up was performed during 36 months. At month 36, there were 29 subjects who were available for follow-up. Complete occlusion of the treated veins was confirmed by duplex US in all subjects with the exception of 2 subjects showing re-canalization at month 1 and month 3. Kaplan-Meier analysis revealed an occlusion rate at month 36 of 94.7 % (95 % CI: 87.9 % to 100 %). The mean Venous Clinical Severity Score (VCSS) improved from 6.1 ± 2.7 at baseline to 2.2 ± 0.4 at month 36 ($p < 0.0001$). Pain, edema, and varicosities (VCSS subdomains) improved in 75.9 %, 62.1 %, and 41.4 % of subjects, respectively, at month 36. Overall AEs were mild or moderate and self-limited. The authors concluded that CA adhesive appeared to be an effective and safe treatment for saphenous vein closure, with long-term occlusion rates comparable to those of other thermal and non-thermal methods and with no reported serious AEs. This was a small study (n = 38) with a rather high drop-out rate (23.7 %; 9 out of 38).

Gibson and Ferris (2017) noted that CA closure of the GSV with the VenaSeal Closure System is a relatively new modality. Studies have been limited to moderate-sized GSV and some have mandated post-operative compression stockings. These investigators reported the results of a prospective study of CA closure for the treatment of GSV, SSV, and/or accessory saphenous veins (ASV) up to 20 mm in diameter. A total of 50 subjects with symptomatic GSV, SSV, and/or ASV incompetence were each treated at a single session. Compression stockings were not used post-procedure. Subjects returned to clinic at week 1 and again at 1 month. Post-procedure evaluations were performed at 7 days and 1 month and included numerical pain rating score, revised venous clinical severity score, the Aberdeen Varicose Vein Questionnaire score, and time to return to work and normal activities. Duplex US was performed at each visit. Procedural pain was mild (numerical pain rating scale 2.2 ± 1.8). All treated veins (48 GSV vein, 14 ASV, and 8 SSV) had complete closure by duplex US at 7 days and 1 month. Mean time to return to work and normal activities was 0.2 ± 1.1 and 2.4 ± 4.1 days, respectively. The revised venous clinical severity score was improved to 1.8 ± 1.4 ($p < 0.001$) and Aberdeen Varicose Vein Questionnaire score to 8.9 ± 6.6 ($p < 0.001$) at 1 month. Phlebitis in the treatment area or side branches occurred in 10 subjects (20 %) and completely resolved in all but 1 subject (2 %) by 1 month; 98 % of subjects were "completely" or "somewhat" satisfied, and 2 % "unsatisfied" with the procedure at 1 month, despite the protocol disallowance of concomitant side branch treatment. The authors concluded that CA closure was safe and effective for the treatment of 1 or more incompetent saphenous or accessory saphenous veins. Closure rates were high

even in the absence of the use of compression stockings or side branch treatment. Time back to work or normal activities was short and improvements in venous severity scores and QOL were significant, comparing favorably with alternative treatment methods.

The drawbacks of this study included:

I. its single-arm design,
II. relatively small sample size (n = 50) at a single center,
III. some end-points may be biased positively or negatively by the absence of a concurrent comparator group, and both the patients and physicians were aware that CA closure is a relatively novel procedure, and
IV. the short-term follow-up (1 month).

The VariClose Vein Sealing System:

Bozkurt and Yılmaz (2016) stated that cyanoacrylate ablation is the newest non-thermal vein ablation technique. In a prospective comparative study, these investigators presented the 1-year results of a new cyanoacrylate glue versus endovenous laser ablation for the treatment of venous insufficiency. A total of 310 adult subjects were treated with cyanoacrylate ablation or endovenous laser ablation. The primary end-point of this study was complete occlusion of the great saphenous vein; secondary end-points were procedure time, procedural pain, ecchymosis at day 3, adverse events (AEs), changes from baseline in VCSS, and AVVQ. Operative time was shorter (15 ± 2.5 versus 33.2 ± 5.7, $p < 0.001$), and peri-procedural pain was less (3.1 ± 1.6 versus 6.5 ± 2.3, $p < 0.001$) in cyanoacrylate ablation group compared to the endovenous laser ablation group. Ecchymosis on the 3rd day was also significantly less in cyanoacrylate ablation group ($p < 0.001$). Temporary or permanent paresthesia developed in 7 patients in endovenous laser ablation group and none in cyanoacrylate ablation group ($p = 0.015$). Closure rates at 1, 3, and 12 months were 87.1, 91.7, and 92.2 % for endovenous laser ablation and 96.7, 96.6, and 95.8 % for cyanoacrylate ablation groups, respectively. Closure rate at 1st month was significantly better in cyanoacrylate ablation group ($p < 0.001$). Although there was a trend of better closure rates in cyanoacrylate ablation patients, this difference did not reach to the statistical difference at 6th and 12th month ($p = 0.127$ and 0.138, respectively). Both groups had significant improvement in VCSS and AVVQ post-operatively ($p < 0.001$), but there was no significant difference in VCSS and AVVQ scores between the groups at 1st, 6th, and 12 months. Only a slightly better well-being trend was noted in cyanoacrylate ablation group in terms of AVVQ scores ($p = 0.062$). The authors concluded that the safety and effectiveness analysis showed that cyanoacrylate ablation is a safe, simple method that can be recommended as an effective endovenous ablation technique. Moreover, they stated that the follow-up data more than 1 year will clarify the future role of cyanoacrylate ablation for the treatment incompetent great saphenous veins.

Tekin and colleagues (2016) noted that endothermal treatment of the great saphenous vein has become the 1st line of treatment for superficial venous reflux. A new technique for venous insufficiency is non-thermal ablation with vein sealing system that comprises the endovenous delivery of cyanoacrylate tissue adhesive to the vein causing fibrosis. In a single-center, prospective study, these researchers examined the effectiveness of treatment of great saphenous vein incompetence in 62 patients with vein sealing system (VariClose). All cases were implemented under local anesthesia. Tumescent anesthesia was not required. Patients were not given any NSAID post-operatively; advised to wear elastic bandages for 1 day; and compression stockings were not offered. Treatment success was defined as complete occlusion of treated vein or re-canalized segment shorter than 5 cm. Subtotal re-canalization was defined as great saphenous vein flow containing 5 to 10 cm segment of treated vein. A re-canalized great saphenous vein or treatment failure was defined as an open part of the treated vein segment more than 10 cm in length. At 1 week and 1 month control, duplex scans showed total occlusion for all patients (100 %), total occlusion for 58 patients (93.5 %), and subtotal occlusion for 4 patients (6.5 %) at 3rd month. At the end of 6 months, total occlusion 56 patients (90.3 %) and subtotal occlusion for 2 patients (3.2 %). For 4 (6.5 %) patients, no occlusion was observed, and the diameter was greater than 11 mm. Embolization of great saphenous vein with cyanoacrylate has been performed since the beginning of this decade. Combined chemical and physical mechanism of action resulted in permanent vein closure. In a recently published study, a 24-month occlusion rate of 92 % was demonstrated. The most commonly reported complications of cyanoacrylate use for the treatment of varicose vein disease, so far, include ecchymosis and phlebitis. Almeida et al. reported that phlebitis is the most frequent side effect at a rate of 16 %. In this study, phlebitis rate was not as high as

reported. It may be caused due to shorter time of follow-up in the hospital. The authors concluded that endovenous ablation of incompetent great saphenous vein with cyanoacrylate-based glue is feasible. Operation time is short, and tumescent anesthesia is unnecessary as post-procedure compression stockings; lack of significant side effects and an yearly success rate of 100 % are benefits of the system. These findings need to be validated by well-designed studies with larger sample size and longer follow-up.

In a retrospective study, Yasim and associates (2017) presented the early results of the use of N-butyl cyanoacrylate (VariClose)-based non-tumescent endovenous ablation for the treatment of patients with varicose veins. A total of 180 patients with varicose veins due to incompetent saphenous veins were treated with the VariClose endovenous ablation method between May 2014 and November 2014. Participants consisted of 86 men and 94 women, with a mean age of 47.7 ± 11.7 years; they had a great saphenous vein diameter greater than 5.5 mm and a small saphenous vein diameter greater than 4 mm in conjunction with reflux for more than 0.5 s. Patients with varicose veins were evaluated with venous duplex examination, CEAP, and their VCSS were recorded. The median CEAP score of patients was 3, and the saphenous vein diameters were between 5.5 and 14 mm (mean of 7.7 ± 2.1 mm). A percutaneous entry was made under local anesthesia to the great saphenous vein in 169 patients and to the small saphenous vein in 11 patients. Duplex examination immediately after the procedure showed closure of the treated vein in 100 % of the treated segment. No complications were observed. The mean follow-up time was 5.5 months (ranging from 3 to 7). Re-canalization was not observed in any of the patients during follow-up. The average VCSS was 10.2 before the procedure and decreased to 3.9 after 3 months ($p < 0.001$). The authors concluded that the application of N-butyl cyanoacrylate (VariClose) is an effective method for treating varicose veins; it yielded a high endovenous closure rate, with no need for tumescent anesthesia. However, long-term results are currently unknown.

Furthermore, Bootun and colleagues (2016b) stated that the early results of 2 recently launched non-thermal, non-tumescent methods, mechanochemical endovenous ablation (MOCA) and cyanoacrylate glue, are promising.

Koramaz and associates (2017) retrospectively compared an n-butyl cyanoacrylate (NBCA)-based ablation method with EVLA for the management of incompetent GSV. Between May 2013 and August 2014, there were 339 patients with incompetent varicose veins who were treated with either the endovenous application of NBCA (VariClose Vein Sealing System [VVSS]; Biolas, Ankara, Turkey) or EVLA. The pre-procedural, intra-procedural, post-procedural, and follow-up data of the patients were collected and retrospectively compared. The mean age was 45.09 ± 12 years in the VVSS group and 47.08 ± 11 years in the EVLA group ($p = 0.113$). The average ablated vein length was 31.97 ± 6.83 cm in the VVSS group and 31.65 ± 6.25 cm in the EVLA group ($p = 0.97$). The average tumescent anesthesia use was 300 ml (range of 60 to 600 ml) in the EVLA group. The average procedure time was 7 minutes (range of 4 to 11 minutes) in the VVSS group and 18 minutes (range of 14 to 25 minutes) in the EVLA group ($p < 0.01$). On the basis of US examinations performed at the end of the procedure, all procedures in both groups were successful, and the target vein segments were fully occluded. The 12-month total occlusion rates in the VVSS and EVLA groups were 98.6 % and 97.3 %, respectively ($p = 0.65$). In both the VVSS and EVLA groups, the VCSS declined significantly with no difference between groups. There were fewer AEs after VVSS treatment compared with EVLA treatment (pigmentation, $p \leq 0.002$; phlebitis, $p \leq 0.015$). There was no need for tumescent anesthesia in the VVSS group. The authors concluded that the NBCA-based vein sealing system was a fast and effective therapeutic option for the management of incompetent saphenous veins that did not involve tumescent anesthesia, compression stockings, paresthesia, burn marks, or pigmentation. Moreover, they stated that further large-scale studies with long-term outcomes are needed to identify the optimal treatment modalities for patients with SVI.

Vos and co-workers (2017) performed a systematic review and meta-analysis to evaluate the effectiveness of MOCA and cyanoacrylate vein ablation (CAVA) for GSV incompetence. Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, and Cochrane databases were searched for papers published between January 1966 and December 2016. Eligible articles were prospective studies that included patients treated for GSV incompetence and described the primary outcome. Exclusion criteria were full text not available, case reports, retrospective studies, small series (n less than 10), reviews, abstracts, animal studies, studies of SSV incompetence, and recurrent GSV incompetence. Primary outcome was anatomic success; secondary outcomes were initial technical success, VCSS, AVVQ score, and complications. A total of 15 articles met the inclusion criteria. Pooled anatomic success for MOCA and CAVA was 94.7 % and 94.8 % at 6 months and 94.1 % and 89.0 % at 1 year, respectively; VCSS and AVVQ score significantly improved after treatment with MOCA and CAVA. The authors concluded that these findings were

promising for these novel techniques that could serve as alternatives for thermal ablation techniques. However, they stated that to determine their exact role in clinical practice, high-quality RCTs comparing these novel modalities with well-established techniques are needed.

Eroglu and colleagues (2017) presented mid-term results of patients with varicose veins treated with N-butyl cyanoacrylate (VariClose), a non-tumescent endovenous ablation technique. Endovenous ablation was performed on 180 patients with saphenous vein incompetence between May and October 2014. A total of 168 subjects capable of being followed-up for 30 months were included. Patients' pre- and post-operative data were recorded. Procedures were performed on the GSV in 159 patients and on the SSV in 9 patients. Saphenous vein diameters ranged between 5.5 mm and 14 mm. Full ablation was achieved in all patients following the procedure. No complications were encountered. Patients were monitored for 30 months. Ablation rates were 100 % at the 3rd month, 98.3 % at the 6th month, 96.6 % at 1 year, and 94.1 % at 30 months. Mean VCSS was 10.2 before procedures, decreasing to 3.9 at 3 months, 4.2 at 6 months, 2.9 at 12 months, and 2.7 at 30 months ($p = 0.000$). The authors concluded that d to its high success rate, absence of complications, no tumescent anesthesia requirement and high patient satisfaction, endovenous ablation with N-butyl cyanoacrylate is a good method. However, they stated that long-term follow-up results are needed.

Prasad and associates (2017) noted that recurrent lower limb venous insufficiency is often a challenge in clinical practice and is most commonly due to incompetent perforators. Many of these patients do not have adequate symptom relief with compression and require some form of treatment for incompetent perforator interruption. Various methods have been tried with different efficiencies. These investigators evaluated the feasibility, safety and effectiveness of an out-patient combined cyanoacrylate adhesion-sodium tetradecyl sulphate sclerotherapy for the treatment of patients with symptoms of persistent or recurrent lower limb venous insufficiency secondary to incompetent perforators. A total of 83 limbs of 69 patients with symptoms of persistent or recurrent lower limb venous insufficiency secondary to incompetent perforators were treated with cyanoacrylate embolization of incompetent perforators and sclerotherapy of dilated collateral veins (surface branch varicose veins). Technical success, procedural pain, perforator occlusion, venous occlusion, clinical improvement and ulcer healing were assessed. Follow-up was done 3- and 6-month post-procedure. Procedure could be successfully performed in all patients; a total of 191 perforators were treated. Perforator and varicose veins occlusion rate was 100 %. Deep venous extension of cyanoacrylate occurred in 4 (4.8 %) patients, with no adverse clinical outcome. Venous clinical severity score improved from a baseline of 8.18 ± 3.60 to 4.30 ± 2.48 on 3-month follow-up and 2.42 ± 1.52 on 6-month follow-up ($p < 0.0001$). All ulcers showed complete healing within 3 months. Significant prolonged thrombophlebitis occurred in 38.5 % of limbs. The authors concluded that combined cyanoacrylate adhesion and sodium tetradecyl sulphate sclerotherapy was technically easy, had a lot of advantages including being an out-patient procedure and highly effective but with a guarded safety profile. The main drawbacks of this study were its relatively small sample size ($n = 69$) and short-term follow-up (6 months); and the findings were confounded by the combined use of cyanoacrylate adhesion and sodium tetradecyl sulphate sclerotherapy.

ClariVein:

Witte et al (2015) noted that endovenous mechano-chemical occlusion using the ClariVein catheter is a new technique combining mechanical injury to the venous endothelium coupled with simultaneous catheter-guided infusion of a liquid sclerosant. This produces irreversible damage to the endothelium resulting in fibrosis of the vein. The technique is related to a low complication rate and a success rate of 96 % at 2 years and sustained quality of life improvement. This closure rate is comparable to endothermal techniques, but significantly less post-operative pain and earlier return to normal activities and work has been reported with endovenous mechano-chemical occlusion. The authors concluded that mechano-chemical occlusion using ClariVein has proven to be safe and effective and has several advantages compared to endothermal techniques. The possibility of retrograde ablation of distal SSV insufficiency in C6 ulceration is considered a significant advantage. Moreover, they stated that randomized comparative studies with long-term follow-up will continue to define the definite place of mechano-chemical occlusion.

Deijen et al (2016) stated that mechano-chemical endovenous ablation is a novel technique for the treatment of GSV and SSV incompetence which combines mechanical injury of the endothelium with simultaneous infusion of liquid sclerosant. The main objective of this study was to evaluate early occlusion. All consecutive patients who were eligible for the treatment with mechano-chemical endovenous ablation were included. Inclusion period was from the introduction of the device in the hospitals (September 2011 and December 2011) until December 2012. A total of 449

patients were included representing 570 incompetent veins. In 506 treated veins, duplex ultrasonography was performed at follow-up: 457 veins (90 %) were occluded at a follow-up of 6 to 12 weeks. In univariate and multivariate analysis, failure of treated GSV was associated with sapheno-femoral junction incompetence (OR 4; 95 % CI: 1.0 to 17.1, p = 0.049). The authors concluded that the ClariVein device appeared to be safe and had a high short-term technical effectiveness. Long-term clinical outcomes are needed to ascertain the clinical value of the ClariVein.

In a RCT, Lam et al (2016) identified the ideal polidocanol dosage and form for mechano-chemical ablation in order to occlude the GSV. When adhering to safe dosage levels, sclerosants with higher concentrations potentially limit the extent of treatment. It has been demonstrated that this problem may be overcome by using polidocanol as a microfoam. This paper was established on findings of a preliminary analysis. The initial study was a single-blinded multi-center RCT where patients are allocated to 3 treatment arms. Group 1 consisted of mechano-chemical ablation + 2 % polidocanol liquid, group 2: mechano-chemical ablation + 3 % polidocanol liquid, and group 3: mechano-chemical ablation + 1 % polidocanol foam. A total of 87 (34 males and 53 females (60.9 %)), mean age of 55 years; S.D. 16.0 (range of 24 to 84), were enrolled in the study. Treatment length was 30 cm (range of 10 to 30) for 95.2 % of the patients. Mean operating time was 16 minutes (range of 5 to 70). The mean sapheno-femoral junction diameter (7.7 mm) was similar in all 3 groups. At 6 weeks post-treatment duplex ultrasound showed that 25 out of 25 (100 %), 27 out of 28 (96.4 %) and 13 out of 23 (56.5 %) were occluded in the mechano-chemical ablation + 2 % polidocanol liquid, mechano-chemical ablation + 3 % polidocanol liquid and mechano-chemical ablation + 1 % polidocanol microfoam respectively ($p < 0.001$). However, stricter scrutiny showed that the anatomical success rate defined as occlusion of at least 85 % of the treated length to be 88.0 %, 85.7 % and 30.4 % respectively ($p < 0.001$). The authors concluded that mechano-chemical ablation using ClariVein combined with 1 % polidocanol microfoam is significantly less effective and should not be considered as a treatment option of incompetent truncal veins. They stated that further investigation to determine the ideal polidocanol liquid dosage with mechano-chemical ablation is advocated and is being conducted accordingly.

Vun and colleagues (2015) evaluated the effectiveness of the ClariVein system of MOCA of superficial vein incompetence. ClariVein treatment uses a micro-puncture technique and a 4-Fr sheath to allow a catheter to be placed 1.5 cm from the SFJ. Unlike EVLT or RFA, no tumescence is required. The technique depends on a wire rotating at 3,500 r/min causing endothelial damage while liquid sclerosant (1.5 % sodium tetradecyl sulphate) is infused. The wire is pulled back while continuously infusing sclerosant along the target vessel's length. Initially, 8 ml of dilute sclerosant was used, but this was subsequently increased to 12 ml. No routine post-op analgesia was prescribed and specifically no NSAIDs. Procedure times and pain scores (visual analog scale [VAS]) were recorded and compared to EVLT and RFA. All patients were invited for duplex post-procedure. A total of 51 GSV and 6 SSV were treated and followed-up with duplex in the 10 months from July 2011. No major complications or deep vein thrombosis were reported. Duplex showed patency of 3 treated veins with 2 more veins having only a short length of occlusion, giving a technical success rate of 91 %. Comparison with 50 RFA and 40 EVLT showed procedure times were significantly less for ClariVein (23.0 ± 8.3 mins) than for either RFA (37.9 ± 8.3 mins) or EVLT (44.1 ± 11.4 mins). Median pain scores were significantly lower for ClariVein than RFA and EVLT (1 versus 5 versus 6, $p < 0.01$). The authors concluded that MOCA with the ClariVein system is safe and effective. After some initial failures, the use of 12 ml of dilute sclerosant resulted in a very high technical success rate greater than 90 % which accorded with the limited published literature; and procedure times and pain scores were significantly better than for RFA and EVLT. These researchers stated that they await the long-term clinical outcomes.

Bootun and associates (2016a) noted that endovenous techniques are, at present, the recommended choice for truncal vein treatment. However, the thermal techniques require tumescent anesthesia, which can be uncomfortable during administration. Non-tumescent, non-thermal techniques would, therefore, have potential benefits. In a RCT, these investigators compared the degree of pain that patients experience while receiving MOCA or RFA. The early results of this RCT were reported here. Patients attending for the treatment of primary varicose veins were randomized to receive MOCA (ClariVein) or RFA (Covidien Venefit). The most symptomatic limb was randomized. The primary outcome measure was intra-procedural pain using a validated VAS. The secondary outcome measures were change in quality of life and clinical scores, time to return to normal activities and work as well as the occlusion rate. A total of 119 patients were randomized (60 in the MOCA group). Baseline characteristics were similar. Maximum pain score was significantly lower in the MOCA group (19.3 mm, SD ± 19 mm) compared to the RFA group ($34.5 \text{ mm} \pm 23 \text{ mm}$; $p < 0.001$). Average VAS was also significantly lower in the MOCA group ($13.4 \text{ mm} \pm 16 \text{ mm}$) compared to the RFA

(24.4 mm ± 18 mm; p = 0.001); 66 % attended follow-up at 1 month, and the complete or proximal occlusion rates were 92 % for both groups. At 1 month, the clinical and quality of life scores for both groups had similar improvements. The authors concluded that early results showed that MOCA is less painful than the RFA procedure, and clinical as well as quality of life scores were similarly improved at 1 month. The long-term data including occlusion rates at 6 months and quality of life scores are being collected. Furthermore, Bootun and colleagues (2016b) stated that the early results of 2 recently launched non-thermal, non-tumescent methods, MOCA and cyanoacrylate glue, are promising.

Lam and colleagues (2016) noted that the ClariVein system is an endovenous technique that uses MOCA to treat incompetent truncal veins. This study was conducted to identify the ideal Polidocanol dosage and form for MOCA in order to occlude the GSV. When adhering to safe dosage levels, sclerosants with higher concentrations potentially limit the extent of treatment. It has been demonstrated that this problem may be overcome by using Polidocanol as a microfoam. This paper was established on findings of a preliminary analysis. The initial study was a single-blinded, multi-center RCT where patients were allocated to 3 treatment arms:

I. group 1 consisted of MOCA + 2 % Polidocanol liquid,
II. group 2: consisted of MOCA + 3 % Polidocanol liquid, and
III. group 3: consisted of MOCA + 1 % Polidocanol foam.

A total of 87 patients (34 males and 53 females, mean age of 55 years [SD 16.0 and range of 24 to 84]) were enrolled in the study. Treatment length was 30 cm (range of 10 to 30) for 95.2 % of the patients. Mean operating time was 16 minutes (range of 5 to 70). The mean SFJ diameter (7.7 mm) was similar in all 3 groups. At 6 weeks post-treatment duplex ultrasound showed that 25 out of 25 (100 %), 27 out of 28 (96.4 %) and 13 out of 23 (56.5 %) were occluded in the MOCA + 2 % Polidocanol liquid, MOCA + 3 % Polidocanol liquid, and MOCA + 1 % Polidocanol microfoam respectively ($p < 0.001$). However, stricter scrutiny showed that the anatomical success rate defined as occlusion of at least 85 % of the treated length to be 88.0 %, 85.7 % and 30.4 % respectively ($p < 0.001$). The authors concluded that MOCA using ClariVein combined with 1 % Polidocanol microfoam was significantly less effective and should not be considered as a therapeutic option of incompetent truncal veins. They stated that further investigation to determine the ideal Polidocanol liquid dosage with MOCA is advocated and is being conducted accordingly.

Leung and colleagues (2016) stated that endovenous thermal techniques, such as EVLA, are the recommended treatment for truncal varicose veins. However, a disadvantage of thermal techniques is that it requires the administration of tumescent anesthesia, which can be uncomfortable. Non-thermal, non-tumescent techniques, such as MOCA have potential benefits; MOCA combines physical damage to endothelium using a rotating wire, with the infusion of a liquid sclerosant. Preliminary experiences with MOCA showed good results and less post-procedural pain. The Laser Ablation versus Mechanochemical Ablation (LAMA) trial is a single-center RCT in which 140 patients will be randomly allocated to EVLA or MOCA. All patients with primary truncal superficial venous insufficiency (SVI) who meet the eligibility criteria will be invited to participate in this trial. The primary outcomes are intra-procedural pain and technical efficacy at 1 year, defined as complete occlusion of target vein segment and assessed using duplex ultrasound. Secondary outcomes are post-procedural pain, analgesia use, procedure time, clinical severity, generic and disease-specific quality of life, bruising, complications, satisfaction, cosmesis, time taken to return to daily activities and/or work, and cost-effectiveness analysis following EVLA or MOCA. Both groups will be evaluated on an intention-to-treat basis. The aim of the LAMA trial is to establish whether MOCA is superior to the current first-line treatment, EVLA. The 2 main hypotheses are:

I. MOCA may cause less initial pain and disability allowing a more acceptable treatment with an enhanced recovery, and
II. this may come at a cost of decreased efficacy, which may lead to increased recurrence and affect longer term quality of life, increasing the requirement for secondary procedures.

In a large, single-center study, Tang and co-workers (2017) examined the effectiveness and patient experience of the ClariVein® endovenous occlusion catheter for varicose veins. A total of 300 patients (371 legs) underwent ClariVein treatment for their varicose veins; 184 for GSV incompetence, 62 bilateral GSV, 23 SSV, 6 bilateral SSV and 25 combined unilateral GSV and SSV. Patients were reviewed at an interval of 2 months post-procedure and underwent

Duplex ultrasound assessment. Post-operative complications were recorded along with patient satisfaction. All 393 procedures were completed successfully under local anesthetic. Complete occlusion of the treated vein was initially achieved in all the patients, but at 8 weeks' follow-up, there was only partial obliteration in 13/393 (3.3 %) veins. These were all successfully treated with ultrasound-guided foam sclerotherapy. Procedures were well-tolerated with a mean pain score of 0.8 (0 to 10), and no significant complications were reported. The authors concluded that ClariVein can be used to ablate long and short saphenous varicose veins on a walk-in-walk-out basis. Bilateral procedures can be successfully performed, and these were well-tolerated as can multiple veins in the same leg. They stated that early results are promising but further evaluation and longer term follow-up are needed.

Witte and colleagues (2016) reported the midterm results of mechanochemical ablation (MOCA) for treating GSV insufficiency. In a 1-year period, 85 consecutive patients (median age of 51.4 years; 71 women) undergoing MOCA with polidocanol in 104 limbs were enrolled in a prospective registry. Patients were evaluated at baseline and during follow-up (4 weeks and 1, 2, and 3 years) using duplex ultrasound, the CEAP (clinical, etiologic, anatomic and pathophysiologic) classification, the Venous Clinical Severity Score (VCSS), the RAND Short Form 36-Item Health Survey (RAND-SF36), and the Aberdeen Varicose Vein Questionnaire (AVVQ). Primary outcome measures were clinical and anatomic success; secondary outcome measures included general and disease-specific quality of life and re-interventions. Technical success (99 %) was achieved in all but 1 patient in whom technical problems with the device led to conversion to another method for treatment of 2 limbs. After a median follow-up of 36 months (interquartile range {IQR] 12.5, 46.3), re-canalization occurred in 15 (15 %) of 102 successfully treated vein segments. Anatomic success was 92 %, 90 %, and 87 % after 1, 2, and 3 years, respectively. The VCSS improved at all time-intervals compared to the pre-procedure median. The clinical success at 3 years was 83 %. The AVVQ and RAND-SF36 scores showed an improvement at all time-intervals compared to baseline values. Between 12 and 36 months, however, a significant deterioration was observed in VCSS, which was accompanied by worsening of disease-specific and general quality of life. The authors concluded that in the longest follow-up of MOCA to-date, this study showed MOCA to be an effective treatment modality for GSV insufficiency at midterm follow-up, but clinical results appeared to drop over time. The major drawbacks of this study were:

I. the results were affected by the chosen definitions of success. Although the definition used is in accordance with previous landmark trials, heterogeneity in the definition among studies was a major problem in comparing results and emphasized the need for standardization of outcome measures, and
II. follow-up was not completed for every patient, and questionnaires were not always complete.

Lane and associates (2017) noted that endovenous thermal ablation has revolutionized varicose vein treatment. New non-thermal techniques such as MOCA allow treatment of entire trunks with single anesthetic injections. Previous non-randomized work has shown reduced pain post-operatively with MOCA. This study presented a multi-center, RCT assessing the difference in pain during truncal ablation using MOCA and radiofrequency endovenous ablation (RFA) with 6 months' follow-up. Patients undergoing local anesthetic endovenous ablation for primary varicose veins were randomized to either MOCA or RFA. Pain scores using VAS and number scale (0 to 10) during truncal ablation were recorded. Adjunctive procedures were completed subsequently. Pain after phlebectomy was not assessed. Patients were reviewed at 1 and 6 months with clinical scores, quality of life scores and duplex ultrasound assessment of the treated leg. A total of 170 patients were recruited over a 21-month period from 240 screened. Patients in the MOCA group experienced significantly less maximum pain during the procedure by VAS (MOCA median of 15 mm (IQR 7 to 36 mm) versus RFA 34 mm (IQR 16 to 53 mm), $p = 0.003$) and number scale (MOCA median of 3 (IQR 1 to 5) versus RFA 4 mm (IQR 3 to 6.5), $p = 0.002$). “Average” pain scores were also significantly less in the MOCA group; 74 % underwent simultaneous phlebectomy. Occlusion rates, clinical severity scores, disease specific and generic quality of life scores were similar between groups at 1 and 6 months. There were 2 deep vein thromboses, 1 in each group. The authors concluded that pain secondary to truncal ablation was less painful with MOCA than RFA with similar short-term technical, quality of life and safety outcomes. They stated that further work with larger studies and extended follow-up is needed to evaluate the long-term outcomes and recurrence rates.

The authors noted that “This study was limited by lack of treatment blinding for the patients and interventional clinicians. This was due to the technical differences between devices, i.e., tumescent injections in the RFA group and device vibration in the MOCA group. Follow-up appointments and ultrasound scanning were treatment blind. A further limitation of this study is the lack of long-term follow-up -- only short-term occlusion rates are assessed in this study,

with the primary outcome obtained at the time of procedure. Operating time was not recorded in this study; however, all cases were performed in standardized theatre sessions in single slots with one surgeon performing all tasks, and 74 % of patients also underwent simultaneous phlebectomy. A major limitation of all tumescentless techniques is how to treat varicosities left after truncal ablation, with level one evidence now supporting combined treatment with phlebectomies. This study was designed and commenced prior to the completion of latest trial, but took into consideration the fact that phlebectomies cause pain, and so pain scores taken after truncal ablation but before any phlebectomies were completed. This, therefore, represents a significant limitation to the outcomes of this trial, as the pain scores reported above do not assess the complete treatment, except for those patients who did not undergo phlebectomy". Also, this study did not assess pain scores after phlebectomy or after the peri-procedural period.

National Institute for Health and Care Excellence's guideline on "Endovenous mechanochemical ablation for varicose veins" (2016) stated that " Current evidence on the safety and efficacy of endovenous mechanochemical ablation for varicose veins appears adequate to support the use of this procedure provided that standard arrangements are in place for consent, audit and clinical governance. Clinicians are encouraged to collect longer-term follow-up data".

Elias and Raines (2012) evaluated the safety and efficacy of the ClariVein system that employs mechanochemical ablation (MOCA) of the great saphenous vein (GSV). Patients eligible for ablation of the GSV underwent micro-puncture access with only local anesthesia to insert a 4 or 5 Fr sheath. The ClariVein catheter was placed through the sheath, the wire was extruded, and the distal tip of the wire positioned 2 cm from the sapheno-femoral junction under ultrasound (US) guidance. Catheter wire rotation was then activated for 2 to 3 seconds at approximately 3,500 rpm. With the wire rotating, infusion of the sclerosant was started simultaneously with catheter pullback. The sclerosant used was 1.5 % liquid sodium tetradecyl sulphate. A total of 30 GSVs in 29 patients were treated. All patients have reached 6-month follow-up; the average number of post-operative days was 260. No adverse events (AERs) have been reported; the primary closure rate was 96.7 %. The authors concluded that MOCA appeared to be safe and efficacious. The ClariVein technique eliminated the need for tumescent anesthesia. The great majority of incompetent GSVs can be treated with this technique. (This was a small study (n= 29) with short-term follow-up (6 months))

In a prospective cohort study, Boersma and associates (2013) evaluated the feasibility, safety and 1-year results of MOCA of small saphenous vein (SSV) insufficiency. A total of 50 consecutive patients were treated for primary SSV insufficiency with MOCA using the ClariVein device and polidocanol. Initial technical success, complications, patient satisfaction and visual analogue scale (VAS) pain score were assessed. Anatomic and clinical success was assessed at 6 weeks and at 1 year. Initial technical success of MOCA was 100 %. At the 6-week assessment, all treated veins were occluded. The 1-year follow-up duplex showed anatomic success in 94 % (95 % confidence interval [CI]:, 0.87 to 1). Venous clinical severity score (VCSS) decreased significantly from 3.0 (interquartile range (IQR) 2 to 5) before treatment to 1.0 (IQR 1 to 3, $p < 0.001$) at 6 weeks and to 1.0 (IQR 1 to 2, $p < 0.001$) at 1 year. Median procedural VAS score for pain was 2 (IQR 2 to 4). No major complications were observed, especially no nerve injury. The authors concluded that MOCA was a safe, feasible and efficacious technique for treatment of SSV insufficiency. One-year follow-up showed a 94 % anatomic success rate and no major complications.

One of the drawbacks of this study was that the maximum diameter of treated SSVs was 11 mm. The technical and clinical success of MOCA in larger-diameter varicose veins was still unknown. Pain scores during MOCA were very low. Post-procedural pain scores were not measured. The authors stated that further controlled studies are needed to compare pain with other techniques in SSV ablation. Patients on oral anti-coagulants were excluded; thus, these researchers could not provide data on the effect of anti-coagulant therapy on MOCA. In contrast to endothermal therapy, anti-coagulants might influence clot formation and lead to increased re-canalization.

In a prospective, observational, multi-center report, Bishawi and colleagues (2014) evaluated the efficacy of a tumescent-free technique using MOCA in selected patients with lower extremity chronic venous disease. Demographic information, clinical and procedural data were collected on a customized database. The distribution and extent of venous reflux and the closure rate of the treated veins were assessed with duplex US. Pain was evaluated during the procedure and post-operatively using an analog scale. The presence and severity of complications were recorded. Patient improvement was assessed by clinical-etiology-anatomy-pathophysiology (CEAP) class and venous clinical severity score (VCSS). There were 126 patients that were included at baseline, 81 % females, with a mean age of 65.5 ± 14 years. The average BMI was 30.5 ± 6. The mean diameter of the great saphenous vein in the upper thigh was

7.3 mm and the mean treatment length was 38 cm. Adjunctive treatment of the varicosities was performed in 11 % of patients during the procedure. Closure rates were 100 % at 1 week, 98 % at 3 months, and 94 % at 6 months. Post-procedure complications included hematoma 1 %, ecchymosis 9 %, and thrombophlebitis 10 %. There were no cases of venous thromboembolism. There was significant improvement in VCSS ($p < 0.001$) for all time intervals. The authors concluded that MOCA of the saphenous veins had the advantage of endovenous ablation without tumescent anesthesia, making it an almost pain-free procedure. High occlusion rates with significant clinical improvement can be achieved with this method at short-term.

Ozen et al (2014) evaluated the reliability and 2-year results of ClariVein device used in MOCA of GSV. In the authors' clinic, a total of 63 patients with GSV insufficiency had been treated using ClariVein device and polidocanol for 2 years. Both legs were treated in 10 of these patients. The anatomical and clinic success were assessed by Doppler US 6 months, 1 year, and 2 years later. The implementation success rate of the technique was 98 %. The anatomical success was found as 94 % at the end of 6 months, 95 % at the end of 1 year, and 95 % at the end of 2 years. The venous clinic severity score was found as 3.2 (IQR: IQR: 2 to 6) after 6 months, 1.2 (IQR: 1 to 3, $p < 0.001$) after 1 year, and 1.1 (IQR: 1 to 2, $p < 0.001$) after 2 years. No complications developed in any of the patients. The authors concluded that ClariVein was a simple, reliable, and efficient treatment method for GSV insufficiency. In 2-year follow-up, the anatomical success rate was found as 95 %, and no major complications were observed.

Stanisic et al (2016) stated that MOCA of the GSV and the SSV is an alternative to thermal ablation for the treatment of superficial venous reflux. These researchers evaluated the efficacy of MOCA for the treatment of incompetent GSV and SSV. They included 50 patients (60 legs) with incompetent GSV or SSV. Patients were aged 22 to 71 years, with median age of 41 years. Diameters of the saphenous veins treated were 4 to 16 mm, with median diameter 9 mm. Lengths of incompetent segments of the GSVs were 20 to 45 cm, with median length 36 cm. Lengths of incompetent segments of the SSVs were 12 to 25 cm, with median length of 17 cm. These investigators performed venous ablation using the ClariVein device with simultaneous injection of 2 % polidocanol in the dose of 0.2 ml/cm of the treated vein. All patients completed 12 months follow-up. In all patients the procedure resulted in complete occlusion of the incompetent segment of the saphenous vein. Additional foam sclerotherapy was needed in 41 legs (68.3 %). After 12 months partial or complete re-canalization was revealed in 1 GSV and 3 SSVs. The remaining veins (93.3 %) were completely occluded. During the procedure these researchers observed transient signs of polidocanol toxicity in 2 patients. The authors concluded that MOCA using the ClariVein device was a safe method for ablation of incompetent truncal veins in patients who prefer to be managed quickly, without pain and with satisfactory results after 1 year.

In a 2-year follow-up on the efficacy of MOCA in patients with symptomatic C2 or more advanced chronic venous disease, Kim and co-workers (2017) reported if early efficacy was maintained at 24 months. Patients with reflux in the great saphenous vein involving the sapheno-femoral junction and no previous venous interventions were included. Demographic information, clinical, and procedural data were collected. The occlusion rate of treated veins was assessed with duplex US. Patient clinical improvement was assessed by CEAP class and venous clinical severity score. Of the initial 126 patients, there were 65 patients with 24 month follow-up. Of these 65 patients, 70 % were women, with a mean age of 70 ± 14 years and an average BMI of 30.5 ± 6. The mean great saphenous vein diameter in the upper thigh was 7.6 mm and the mean treatment length was 39 cm. Adjunctive treatment of the varicosities was performed in 14 % of patients during the procedure. Closure rates were 100 % at 1 week, 98 % at 3 months, 95 % at 12 months, and 92 % at 24 months. There was 1 patient with complete and 4 with partial re-canalization ranging from 7 to 12 cm (mean length 9 cm). There was significant improvement in CEAP and venous clinical severity score ($p < 0.001$) for all time intervals. The authors concluded that early high occlusion rate with MOCA was associated with significant clinical improvement which was maintained at 24 months, making it a very good option for the treatment of great saphenous vein incompetence.

Whiteley et al (2017) examined the effects of MOCA using ClariVein on ex-vivo GSV with histology and immunofluorescent staining. Extra-fascial GSVs were harvested during surgery for varicose veins and were treated ex-vivo for 10 to 11 minutes with either liquid sclerotherapy or the use of ClariVein, with and without 3 % sodium tetradecyl sulfate. Veins were sectioned and subjected to hematoxylin and eosin staining and immunofluorescent staining for endothelial and smooth muscle cell markers (CD31 and α-actin) to assess overall damage and cell death in the vein wall compared with control sections. Histologic observations confirmed intimal damage from ClariVein, as has been previously shown; however, medial damage was also evident, which was not observed in control or liquid

sclerotherapy sections. Immunofluorescent staining in the 3 sections studied showed a 42 % decrease in CD31 staining and 27 % mean reduction in α-actin staining up to a depth of 300 μm with liquid sclerotherapy. This cytotoxic effect was significantly enhanced by MOCA with a reduction in CD31 staining just above 60 % and a 46 % mean decrease in α-actin staining noted up to a depth of 300 μm. Far greater reductions in staining compared with sclerotherapy were observed up to a depth of 600 μm. The authors concluded that MOCA using 3 % sodium tetradecyl sulfate increased the penetration of the sclerosant and its effect into the vein wall and showed superior rates of tissue destruction compared with liquid sclerotherapy alone. In this model, it appeared not solely to damage the endothelium but also to shear the medial layer, creating small lesions into which sclerosant can flow and exert its cytotoxic effect. These investigators stated that short-term follow-up studies of MOCA showed results that were comparable to those of RFA or EVLA. Initial investigations into the short- to medium-term success rates of ClariVein for treating reflux in the GSV reported excellent closure rates that stand above 95 % up to 1 year after the procedure, with the longest follow-up of 2 years showing 92 % closure. Separate analyses also showed significantly less post-operative pain and faster recovery of the patient with MOCA compared with RFA. This showed a considerable advantage over US-guided foam sclerotherapy, which was associated with a high risk of re-canalization and recurrent reflux even as early as 1 year after the procedure. These researchers noted that as time progresses, the medium- and long-term success rates of MOCA will need to be evaluated and compared with existing treatment modalities.

Witte et al (2017) reported the mid-term results of MOCA for treating GSV insufficiency. In a 1-year period, 85 consecutive patients (median age of 51.4 years; 71 women) undergoing MOCA with polidocanol in 104 limbs were enrolled in a prospective registry. The patients were evaluated at baseline and during follow-up (4 weeks and 1, 2, and 3 years) using duplex US, the CEAP (clinical, etiologic, anatomic and pathophysiologic) classification, the Venous Clinical Severity Score (VCSS), the RAND Short Form 36-Item Health Survey (RAND-SF36), and the Aberdeen Varicose Vein Questionnaire (AVVQ). Primary outcome measures were clinical and anatomic success. Secondary outcome measures included general and disease-specific QOL and re-interventions. Technical success (99 %) was achieved in all but 1 patient in whom technical problems with the device led to conversion to another method for treatment of 2 limbs. After a median follow-up of 36 months (IQR 12.5 to 46.3), re-canalization occurred in 15 (15 %) of 102 successfully treated vein segments. Anatomic success was 92 %, 90 %, and 87 % after 1, 2, and 3 years, respectively. The VCSS improved at all time intervals compared to the pre-procedure median. The clinical success at 3 years was 83 %. The AVVQ and RAND-SF36 scores showed an improvement at all time intervals compared to baseline values. Between 12 and 36 months, however, a significant deterioration was observed in VCSS, which was accompanied by worsening of disease-specific and general QOL. The authors concluded that in the longest follow-up of MOCA to-date, this study showed MOCA to be an effective treatment modality for GSV insufficiency at mid-term follow-up, but clinical results appeared to drop over time. The authors stated that the results of the present study were affected by the chosen definitions of success. Although the definition used was in accord with previous landmark trials, heterogeneity in the definition among studies was a major problem in comparing results and emphasized the need for standardization of outcome measures. Furthermore, follow-up was not completed for every patient, and questionnaires were not always complete.

While a Cochrane review on “Endovenous ablation therapy (laser or radiofrequency) or foam sclerotherapy versus conventional surgical repair for short saphenous varicose veins” (Paravastu et al, 2016) did not address the use of MOCA, it is interesting to note that the authors stated that “Further RCTs for all comparisons are required with longer follow-up (at least 5 years). In addition, measurement of outcomes such as recurrence of reflux, time taken to return to work, duration of procedure, pain, etc., and choice of time points during follow-up should be standardised such that future trials evaluating newer technologies can be compared efficiently”.

Polymorphism Genotyping of Matrix Metalloproteinases Genes (e.g., MMP1, MMP2, MMP3, and MMP7) as Markers of Predisposition to Varicose Veins

Kurzawski and associates (2009) noted that several risk factors for varicose veins have been identified: female gender, combined with obesity and pregnancy, occupations requiring standing for long periods, sedentary lifestyle, history of deep-vein thrombosis (DVT) and family history. However, no specific gene variants related to a wide prevalence of varicosities in general population have been identified. Extracellular matrix composition, predominantly maintained by matrix metalloproteinases (MMPs), may affect the vein-wall structure, which may lead to dilation of vessels and cause

varicosities. MMP-1 (tissue collagenase I) and MMP-3 (stromelysin I) expression was found to be raised in varicose veins compared with normal vessels. Thus, these investigators carried out a study to evaluate a potential association between MMP1 and MMP3 promoter polymorphisms and a risk of varicose veins. Genotyping for the presence of the polymorphisms -1607dupG (rs1799750) in MMP1 and -1171dupA (rs3025058) in the MMP3 promoter region was performed using polymerase chain reaction (PCR) and restriction-fragment length polymorphism assays in a group of 109 patients diagnosed with varicose veins and 112 healthy controls. The frequencies of the MMP1 and MMP3 alleles (minor allele frequency 0.440 in patients versus 0.451 in the controls for MMP1-1607*G and 0.514 versus 0.469 for MMP3-1171*dupA, respectively) and of genotypes did not differ significantly between patients and controls. The authors concluded that MMP1-1607dupG and MMP3-1171dupA promoter polymorphisms were not valuable markers of susceptibility for varicose veins.

Shadrina and colleagues (2017) examined the effects of single nucleotide polymorphisms (SNPs) in the promoter regions of MMP genes rs1799750 (-1607dupG) MMP1, rs243865 (C-1306T) MMP2, rs3025058 (-1171dupA) MMP3, and rs11568818 (A-181G) MMP7 on the risk of varicose vein of the lower extremities in ethnical Russians, residents of the Russian Federation. These researchers genotyped 536 patients with this pathology and 273 healthy participants without history of chronic venous disease. Association was examined using logistic regression analysis. None of the studied polymorphisms showed statistically significant association with the risk of varicose veins of the lower extremities. The authors concluded that these findings provided evidence that these polymorphisms are not involved in the pathogenesis of varicose veins and cannot serve as markers of predisposition to this pathology.

Matrix Metalloproteinases Inhibitors for the Treatment of Varicose Veins

Chen and colleagues (2017) noted that the veins of the lower extremity are equipped with efficient wall, contractile vascular smooth muscle (VSM), and competent valves in order to withstand the high venous hydrostatic pressure in the lower limb and allow unidirectional movement of deoxygenated blood toward the heart. The vein wall structure and function are in part regulated by MMPs, which are zinc-dependent endopeptidases that are secreted as inactive pro-MMPs by different cells in the venous wall including fibroblasts, VSM, and leukocytes. Pro-MMPs are activated by other MMPs, proteinases, and other endogenous and exogenous activators. Matrix metalloproteinases degrade various extracellular matrix (ECM) proteins including collagen and elastin, and could affect other cellular processes including endothelium-mediated dilation, VSM cell migration, and proliferation as well as modulation of calcium ion (Ca^{2+}) signaling and contraction in VSM. It is believed that increased lower limb venous hydrostatic pressure increases hypoxia-inducible factors and other MMP inducers such as extracellular MMP inducer, leading to increased MMP expression/activity, ECM protein degradation, vein wall relaxation, and venous dilation. Vein wall inflammation and leukocyte infiltration cause additional increases in MMPs, and further vein wall dilation and valve degradation, that could lead to chronic venous disease and VVs, which are often presented as vein wall dilation and tortuosity, incompetent venous valves, and venous reflux. Different regions of VVs show different MMP levels and ECM proteins with atrophic regions showing high MMP levels/activity and little ECM compared to hypertrophic regions with little or inactive MMPs and abundant ECM. Treatment of VVs includes compression stockings, venotonics, sclerotherapy, or surgical removal. However, these approaches do not treat the cause of VVs, and other lines of treatment may be needed. The authors stated that modulation of endogenous tissue inhibitors of metalloproteinases (TIMPs), and exogenous synthetic MMP inhibitors may provide new approaches in the management of VVs.

Appendix

List: Clinical, Etiological, Anatomical and Pathophysiological classification (CEAP) Classification

Clinical Classification

- C0 No visible or palpable signs of venous disease
- C1 Telangiectasias, reticular veins, malleolar flares

- C2 Varicose veins
- C3 Edema without skin changes
- C4 Skin changes ascribed to venous disease (eg, pigmentation, venous eczema, lipodermatosclerosis)
- C4a Pigmentation or eczema
- C4b Lipodermatosclerosis or atrophie blanche
- C5 Skin changes as defined above with healed ulceration
- C6 Skin changes as defined above with active ulceration

Source: Gloviczki et al, 2011.

Table: CPT Codes / HCPCS Codes / ICD-10 Codes

Code	Code Description

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

CPT codes covered if selection criteria are met:

Stab phlebectomy of varicose veins, 1-9 incisions, ambulatory - No specific code:

36465 - 36466	Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring
36470	Injection of sclerosant; single incompetent vein (other than telangiectasia)
36471	multiple incompetent veins (other than telangiectasia), same leg
36475	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; first vein treated
+ 36476	second and subsequent veins treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
36478	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated
+ 36479	second and subsequent veins treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
37500	Vascular endoscopy, surgical, with ligation of perforator veins, subfascial (SEPS)
37700	Ligation and division of long saphenous vein at saphenofemoral junction, or distal interruptions
37718	Ligation, division, and stripping, short saphenous vein
37722	Ligation, division, and stripping, long (greater) saphenous veins from saphenofemoral junction to knee or below
37735	Ligation and division and complete stripping of long or short saphenous veins with radical excision of ulcer and skin graft and/or interruption of communicating veins of lower leg, with excision of deep fascia
37760	Ligation of perforator veins, subfascial, radical (Linton type), including skin graft, when performed, open, 1 leg
37761	Ligation of perforator vein(s), subfascial, open, including ultrasound guidance, when performed, 1 leg
37765	Stab phlebectomy of varicose veins, one extremity; 10-20 stab incisions [ambulatory]

37766	more than 20 incisions [ambulatory]
37780	Ligation and division of short saphenous vein at saphenopopliteal junction (separate procedure)
37785	Ligation, division, and/or excision of varicose vein cluster(s), one leg

CPT codes not covered for indications listed in the CPB:

Polymorphism genotyping of matrix metalloproteinases genes, Synthetic matrix metalloproteinases inhibitors - no specific code:

36011	Selective catheter placement, venous system; first order branch (e.g., renal vein, jugular vein)
36468	Single or multiple injections of sclerosing solutions, spider veins (telangiectasia); limb or trunk
36473	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; first vein treated
36474	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
36482 - 36483	Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate) remote from the access site, inclusive of all imaging guidance and monitoring, percutaneous
37204	Transcatheter occlusion or embolization (eg, for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck
37241	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; venous, other than hemorrhage (eg, congenital or acquired venous malformations, venous and capillary hemangiomas, varices, varicoceles)
37244	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for arterial or venous hemorrhage or lymphatic extravasation
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
76942	Ultrasonic guidance for needle placement (eg, biopsy, aspiration, injection, localization device), imaging supervision and interpretation [not covered when performed solely to guide the needle or introduce the sclerosant into the varicose veins]
76998	Ultrasonic guidance, intraoperative [not covered when performed solely to guide the needle or introduce the sclerosant into the varicose veins]

Other CPT codes related to the CPB:

37252	Intravascular ultrasound (noncoronary vessel) during diagnostic evaluation and/or therapeutic intervention, including radiological supervision and interpretation; initial noncoronary vessel (List separately in addition to code for primary procedure)
75820, 75822	Venography, extremity, unilateral or bilateral, radiological supervision and interpretation
93922	Limited bilateral non-invasive physiologic studies of upper or lower extremity arteries, (eg, for lower extremity: ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus bidirectional, Doppler waveform recording and analysis at 1-2 levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus

	volume plethysmography at 1-2 levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries with transcutaneous oxygen tension measurements at 1-2 levels)
93923	Complete bilateral non-invasive physiologic studies of upper or lower extremity arteries, 3 or more levels (eg, for lower extremity: ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental blood pressure measurements with bidirectional Doppler waveform recording and analysis at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental volume plethysmography at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental transcutaneous oxygen tension measurements at 3 or more level(s), or single level study with provocative functional maneuvers (eg, measurements with postural provocative tests or measurements with reactive hyperemial)
93924	Non-invasive physiologic studies of lower extremity arteries, at rest and following treadmill stress testing, (ie, bidirectional Doppler waveform or volume plethysmography recording and analysis at rest with ankle/brachial indices immediately after and at timed intervals following performance of a standardized protocol on a motorized treadmill plus recording of time of onset of claudication or other symptoms, maximal walking time, and time to recovery) complete bilateral study
93970	Duplex scan of extremity veins including responses to compression and other maneuvers; complete bilateral study
93971	unilateral or limited study

HCPCS codes covered if selection criteria are met:

S2202	Echosclerotherapy

Other HCPCS codes related to the CPB:

A6530 - A6549	Compression stockings

ICD-10 codes covered if selection criteria are met:

I80.00 - I80.03	Phlebitis and thrombophlebitis of superficial vessels of lower extremities
I82.401 - I82.499	Acute embolism and thrombosis of deep veins of lower extremity
I82.501 - I82.599	Chronic embolism and thrombosis of deep veins of lower extremity
I83.001 - I83.899	Varicose veins of lower extremities
I87.001 - I87.09	Postthrombotic syndrome
I87.2	Venous insufficiency (chronic) (peripheral) [not covered for saphenopopliteal reflux]

ICD-10 codes not covered for indications listed in the CPB:

I83.90 - I83.93	Asymptomatic varicose veins of lower extremities
O22.00 - O22.03	Varicose veins of lower extremity in pregnancy
O22.20 - O22.23	Superficial thrombophlebitis in pregnancy
O22.90 - O22.93	Venous complication in pregnancy, unspecified
O87.0	Superficial thrombophlebitis in the puerperium
O87.4	Varicose veins of lower extremity in the puerperium
O87.9	Venous complication in the puerperium, unspecified

The above policy is based on the following references:

1. Dixon PM. Duplex ultrasound in the pre-operative assessment of varicose veins. Australas Radiol. 1996;40(4):416-421.
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Policy History

- Last Review 12/21/2018

  Effective: 11/20/1995

  Next Review: 01/10/2019

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes

Lead Screening and Lead Investigation

Question: How can the Prioritized List best be modified to assist in statewide public health efforts to improve lead screening and investigations?

Question source: Public Health Division, HSD

Issue: Oregon has a very low rate of serum lead testing for Medicaid children, despite a federal mandate to screen all Medicaid children prior to age 2 with serum testing (not just risk questionnaires). If a child's blood lead level is elevated over 5 µg/dL, the local public health office can go out to the home and look for sources of lead contamination and assist the family in reducing future lead exposures, as recommended by the CDC. These home investigations are also being done at very low rates. The public health division is working to increase lead screening rates and the number of home lead investigations. It has come to light that there are certain non-pairings on the Prioritized List that need correction to allow these statewide public health initiatives to move forward.

From the Oregon Public Health Division:

> The goal of lead screening is to identify children who have been exposed to lead, provide appropriate interventions and reduce the risk of exposure…The single most important factor in managing childhood lead poisoning is identifying and reducing the child's exposure to lead.
>
> Blood lead testing is the only acceptable laboratory test for screening and confirming lead poisoning. Venipuncture is preferred for specimen collection, but capillary testing is acceptable if care is taken to properly clean and prepare the finger…All capillary BLLs of 5 µg/dL or higher must be followed with a confirmatory venous test.

Very high lead levels (>45 µg/dL) are treated with chelation therapy. Lead levels above 5ug/dL require investigation into possible sources of lead exposure, abatement of the exposure source if possible, education of the family, and monitoring lead serum levels.

Currently, chelation HCPCS and CPT codes will pair with lead poisoning (ICD10 T56.0X). However, home visits for lead abatement (HCPCS T1029 Comprehensive environmental lead investigation, not including laboratory analysis, per dwelling) does not pair with elevated lead level diagnoses or with lead poisoning.

The AAP recommends using ICD-10 Z13.88 (Encounter for screening for disorder due to exposure to contaminants) for lead screening; however, Z77.011 (Contact with and (suspected) exposure to lead) is frequently used in practice. Providers can also pair lead screening with a well child check diagnosis code.

Lead screening is occasionally used in the work up of dementia in older adults.

Lead Screening and Lead Investigation

Current Prioritized List status

ICD-10 Code	**Code description**	**Current placement**
R78.71	Abnormal lead level in blood	Diagnostic Workup File (DWF)
T56.0X	Toxic effect of lead and its compounds	103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS
Z00.12	Encounter for routine child health examination	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
Z13.88	Encounter for screening for disorder due to exposure to contaminants	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
Z77.011	Contact with and (suspected) exposure to lead	Diagnostic Workup File (DWF)
CPT code		
83655	Lead (serum level)	Diagnostic Procedures File
96365 - 96368	Intravenous infusion, for therapy (used for chelation)	Ancillary Procedures File
HCPCS code		
S9355	Home infusion therapy, chelation therapy	103,151,158,194,295,339
T1029	Comprehensive environmental lead investigation, not including laboratory analysis, per dwelling	Never Reviewed HSD has in Ancillary File

HERC staff recommendations:

1) Add ICD-10 R78.71 (Abnormal lead level in blood) to lines 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS and 103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS
    a. Advise HSD to remove ICD-10 R78.71 from the Diagnostic Workup File
2) Add HCPCS T1029 (Comprehensive environmental lead investigation, not including laboratory analysis, per dwelling) to lines 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS, and 103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS
    a. Advise HSD to remove HCPCS T1029 from the Ancillary File

Vestibular Rehabilitation

Question: Should coverage of vestibular rehabilitation be modified on the Prioritized List?

Question source: Physical therapists at Providence

Issue: As part of the HERC Coverage Guidance topic nomination process, HERC staff received multiple nominations from Providence physical therapists about coverage of vestibular rehabilitation for vestibular disorders.

The submitters identified a number of codes that are repeatedly denied for coverage by OHP and are requesting reconsidering of coverage of vestibular rehabilitation for OHP patients.

Codes raised by stakeholders

Code	Code Description	Current Prioritized List Placement
R29.6	Repeated falls	Diagnostic Workup File (DWF)
Z91.81	History of falling	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
W19.XXD	Unspecified fall, subsequent encounter	Informational Diagnosis File
H81.X	Benign paroxysmal vertigo, vestibular neuronitis	510 VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM
H81.9X	Unspecified disorder of vestibular function	510 VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM
H83.0X	Labrynthitis	572 ACUTE NON-SUPPURATIVE LABYRINTHITIS
G43.109	Migraine with aura, not intractable, without status migrainosus	409 MIGRAINE HEADACHES
95992	Canalith repositioning procedure(s) (eg, Epley maneuver, Semont maneuver), per day	510 VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM
97110	Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop	31,46,57,68,71,72,74,81 and 56 other lines (not

	strength and endurance, range of motion and flexibility	including 510)
97112	Therapeutic procedure, 1 or more areas, each 15 minutes; neuromuscular reeducation of movement, balance, coordination, kinesthetic sense, posture, and/or proprioception for sitting and/or standing activities	31,46,57,68,71,72,81,91 and 51 other lines (not including 510)
97530	Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes	31,46,57,68,71,72,81,91 and 52 other lines (not including 510)

Other relevant codes currently placed on Prioritized List

Code	Code Description	Current Prioritized List Placement
92531	Spontaneous nystagmus, including gaze	292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS 416 MENIERE'S DISEASE 510 VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM
92532	Positional nystagmus test	292,416,510
92533	Caloric vestibular test, each irrigation (binaural, bithermal stimulation constitutes 4 tests)	292,416,510
92534	Optokinetic nystagmus test	292,416,510
92537	Caloric vestibular test with recording, bilateral; bithermal (ie, one warm and one cool irrigation in each ear for a total of four irrigations)	292,416,510
92538	Caloric vestibular test with recording, bilateral; monothermal (ie, one irrigation in each ear for a total of two irrigations)	292,416,510
92540	Basic vestibular evaluation, includes spontaneous nystagmus test with eccentric gaze fixation nystagmus, with recording, positional nystagmus test, minimum of 4 positions, with recording, optokinetic nystagmus test, bidirectional foveal and peripheral stimulation, with recording, and oscillating tracking test, with recording	292,416,510

Code	Code Description	Current Prioritized List Placement
92541	Spontaneous nystagmus test, including gaze and fixation nystagmus, with recording	292,416,510
92542	Positional nystagmus test, minimum of 4 positions, with recording	292,416,510
92544	Optokinetic nystagmus test, bidirectional, foveal or peripheral stimulation, with recording	292,416,510
92545	Oscillating tracking test, with recording	292,416,510
92546	Sinusoidal vertical axis rotational testing	292,416,510
92547	Use of vertical electrodes (List separately in addition to code for primary procedure)	292,416,510
92548	Computerized dynamic posturography	292,416,510
S9476	Vestibular rehabilitation program, non-physician provider, per diem	Never Reviewed

Evidence Summary

USPSTF, 2018

https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/falls-prevention-in-older-adults-interventions1

Population	Recommendation	Grade (What's This?)
Adults 65 years or older	The USPSTF recommends exercise interventions to prevent falls in community-dwelling adults 65 years or older who are at increased risk for falls.	B
Adults 65 years or older	The USPSTF recommends that clinicians selectively offer multifactorial interventions to prevent falls to community-dwelling adults 65 years or older who are at increased risk for falls. Existing evidence indicates that the overall net benefit of routinely offering multifactorial interventions to prevent falls is small. When determining whether this service is appropriate for an individual, patients and clinicians should consider the balance of benefits and harms based on the circumstances of prior falls, presence of comorbid medical conditions, and the patient's values and preferences.	C

Kundakci, 2018

- Systematic review of vestibular rehabilitation for chronic dizziness in adults
- 4 trials included
- Comparison to usual medical care (3 studies) or placebo eye exercise (1 study).
    - Hall
        - 3 times a day vestibular exercises, comparison placebo eye exercises. Both groups received a balance and gait home exercise program.
        - There were no significant differences between the intervention and comparison group with the exception of Dynamic Gait Index (4 other scales had no difference). The intervention group showed a significant decrease in fall risk. While 90% of the intervention group showed an improvement in fall risk, in the comparison group it was 50%.
    - Yardley
        - Booklet based vestibular rehabilitation (VR) only and booklet based VR with telephone support. Daily exercises at home for up to twelve weeks. Telephone support, up to three brief sessions from a vestibular therapist.
        - At 12 weeks, the treatment and comparison groups did not show any significant difference on the vertigo symptom scale. After one year follow-up there was a significant improvement in the intervention groups compared to the comparison group.
    - Yardley
        - 30–40 minute Vestibular Compensation Exercises after assessment at baseline and 6-week follow-up. Eight sets of standard head and body movements performed twice daily. Comparison standard medical care.
        - The intervention group improved on all measures (Vertigo symptom scale, Hospital Anxiety and Depression Scale, Vertigo Handicap Questionnaire, Provocative movements, and Sharpened Romberg Tests), while the comparison group demonstrated no improvement.
    - Yardley
        - Nurse-delivered VR exercises. Patients were seen individually for 30 to 40 minutes to take them the booklet and additional support, after first session advice by telephone at one and three weeks. Comparison of usual medical care.
        - There was a greater improvement on all primary outcome measures (series of subjective scales) in the treatment group compared to the usual medical care.

- **Author Conclusions:** This review suggests that exercise-based vestibular rehabilitation shows benefits for adult patients with chronic dizziness with

regard to improvement in the vertigo symptom scale, fall risk, balance and emotional status.

McDonnell, 2015
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005397.pub4/full

- Cochrane systematic review of vestibular rehabilitation for unilateral peripheral vestibular dysfunction
- 39 studies involving 2441 participants with unilateral peripheral vestibular disorders
- Individual and pooled analyses of the primary outcome, frequency of dizziness, showed a statistically significant effect in favour of vestibular rehabilitation over control or no intervention (odds ratio (OR) 2.67, 95% confidence interval (CI) 1.85 to 3.86; four studies, 565 participants).
- Secondary outcomes measures related to levels of activity or participation measured, for example, with the Dizziness Handicap Inventory, which also showed a strong trend towards significant differences between the groups (standardised mean difference (SMD) -0.83, 95% CI -1.02 to -0.64). The exception to this was when movement-based vestibular rehabilitation was compared to physical manoeuvres for benign paroxysmal positional vertigo (BPPV), where the latter was shown to be superior in cure rate in the short term (OR 0.19, 95% CI 0.07 to 0.49). There were no reported adverse effects.
- Author conclusions: There is moderate to strong evidence that vestibular rehabilitation is a safe, effective management for unilateral peripheral vestibular dysfunction, based on a number of high-quality randomised controlled trials. There is moderate evidence that vestibular rehabilitation resolves symptoms and improves functioning in the medium term. However, there is evidence that for the specific diagnostic group of BPPV, physical (repositioning) manoeuvres are more effective in the short-term than exercise-based vestibular rehabilitation; although a combination of the two is effective for longer-term functional recovery. There is insufficient evidence to discriminate between differing forms of vestibular rehabilitation.

Others policies
Aetna, 2019
http://www.aetna.com/cpb/medical/data/200_299/0238.html

Aetna considers vestibular rehabilitation for chronic vertigo medically necessary when all of the following criteria are met:

1. Symptoms (e.g., vertigo and imbalance) have existed for more than 6 months; *and*

2. The member has confirmed diagnosis of a vestibular disorder or has undergone ablative vestibular surgery; *and*
3. The member has failed medical management (e.g., use of vestibular suppressant medications to reduce symptoms).

Aetna considers vestibular rehabilitation experimental and investigational for all other indications because its effectiveness for indications other than the one listed above has not been established.

Note: Up to 12 visits (generally given 2 times a week for 6 weeks) are considered medically necessary initially. Up to 12 additional visits are considered medically necessary if, upon medical review, there is evidence of clinically significant improvement. If there is no evidence of improvement after 12 visits, additional visits are not considered medically necessary.

Excerpt from evidence summary

The literature indicates that the following groups of patients are generally not good candidates for vestibular rehabilitation:

- Patients with an unstable lesion, usually indicative of a progressive degenerative process (e.g., autoimmune inner ear disease);
- Patients with endolymphatic hydrops, Meniere's disease, or perilymphatic fistula;
- Patients with vertiginous symptoms from a demyelinating disease, epilepsy, or migraine.

HERC Staff Summary

Most of the concerns about non-pairing relate to the prioritization of vertiginous syndromes on Line 510, below the funding line. There is evidence of the efficacy of vestibular rehabilitation for a variety of vertiginous conditions.

The Prioritized List needs updating to enable intended coverage for fall prevention in alignment with the USPSTF recommendation. Currently "history of falling" is on Line 3, but there are no exercise therapy interventions that pair on this line.

Recommendations:

1. Add the following codes to Line 510 VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM

97110	Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility
97112	Therapeutic procedure, 1 or more areas, each 15 minutes;

	neuromuscular reeducation of movement, balance, coordination, kinesthetic sense, posture, and/or proprioception for sitting and/or standing activities
97530	Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes

2. Add Z91.81 *History of falling* to Line 292 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
    a. Delete from Line 3
    b. Rationale: Pairing on the dysfunction line rather than Line 3 seems most appropriate as PT/OT codes are here already. Placing all the PT codes on line 3 could result in unintended consequences.
3. Modify guideline note 106 as follows:

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,619

Included on Line 3 are the following preventive services:

A) US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2017.
    1) http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
        a. Treatment of falls prevention with exercise interventions is included on Line 292.
    2) USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.

B) American Academy of Pediatrics (AAP) Bright Futures Guidelines:
    1) http://brightfutures.aap.org. Periodicity schedule available at http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity Schedule_FINAL.pdf.
    2) Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.

C) Health Resources and Services Administration (HRSA) Women's Preventive Services-Required Health Plan Coverage Guidelines as retrieved from http://www.hrsa.gov/womensguidelines/ on 1/1/2017.

D) Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP): http://www.cdc.gov/vaccines/schedules/hcp/index.html or approved for the Oregon Immunization Program: https://public.health.oregon.gov/PreventionWellness/VaccinesImmunization/ImmunizationProviderResources/Documents/DMAPvactable.pdf

Colorectal cancer screening is included on Line 3 for average-risk adults aged 50 to 75, using one of the following screening programs:

A) Colonoscopy every 10 years
B) Flexible sigmoidoscopy every 5 years
C) Fecal immunochemical test (FIT) every year
D) Guaiac-based fecal occult blood test (gFOBT) every year

Colorectal cancer screening for average-risk adults aged 76 to 85 is covered only for those who

A) Are healthy enough to undergo treatment if colorectal cancer is detected, and
B) Do not have comorbid conditions that would significantly limit their life expectancy.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.

4. Add S9476 *Vestibular rehabilitation program, non-physician provider, per diem* to Line 510 VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM

5. If vertigo is the cause of recurrent falls, then the comorbidity rule could be used to allow coverage of vestibular rehabilitation for vertigo-associated “history of falling” on Line 292.

JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Interventions to Prevent Falls in Older Adults
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Janelle M. Guirguis-Blake, MD; Yvonne L. Michael, ScD, SM; Leslie A. Perdue, MPH; Erin L. Coppola, MPH; Tracy L. Beil, MS

IMPORTANCE Falls are the most common cause of injury-related morbidity and mortality among older adults.

OBJECTIVE To systematically review literature on the effectiveness and harms of fall prevention interventions in community-dwelling older adults to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed, Cumulative Index for Nursing and Allied Health Literature, and Cochrane Central Register of Controlled Trials for relevant English-language literature published through August 2016, with ongoing surveillance through February 7, 2018.

STUDY SELECTION Randomized clinical trials of interventions to prevent falls in community-dwelling adults 65 years and older.

DATA EXTRACTION AND SYNTHESIS Independent critical appraisal and data abstraction by 2 reviewers. Random-effects meta-analyses using the method of DerSimonian and Laird.

MAIN OUTCOMES AND MEASURES Number of falls (number of unexpected events in which a person comes to rest on the ground, floor, or lower level), people experiencing 1 or more falls, injurious falls, people experiencing injurious falls, fractures, people experiencing fractures, mortality, hospitalizations, institutionalizations, changes in disability, and treatment harms.

RESULTS Sixty-two randomized clinical trials (N = 35 058) examining 7 fall prevention intervention types were identified. This article focused on the 3 most commonly studied intervention types: multifactorial (customized interventions based on initial comprehensive individualized falls risk assessment) (26 trials [n = 15 506]), exercise (21 trials [n = 7297]), and vitamin D supplementation (7 trials [n = 7531]). Multifactorial intervention trials were associated with a reduction in falls (incidence rate ratio [IRR], 0.79 [95% CI, 0.68-0.91]) but were not associated with a reduction in other fall-related morbidity and mortality outcomes. Exercise trials were associated with statistically significant reductions in people experiencing a fall (relative risk, 0.89 [95% 13 CI, 0.81-0.97]) and injurious falls (IRR, 0.81 [95% CI, 0.73-0.90]) and with a statistically nonsignificant reduction in falls (IRR, 0.87 [95% CI, 0.75-1.00]) but showed no association with mortality. Few exercise trials reported fall-related fractures. Seven heterogeneous trials of vitamin D formulations (with or without calcium) showed mixed results. One trial of annual high-dose cholecalciferol (500 000 IU), which has not been replicated, showed an increase in falls, people experiencing a fall, and injuries, while 1 trial of calcitriol showed a reduction in falls and people experiencing a fall; the remaining 5 trials showed no significant difference in falls, people experiencing a fall, or injuries. Harms of multifactorial and exercise trials were rarely reported but generally included minor musculoskeletal injuries.

CONCLUSIONS AND RELEVANCE Multifactorial and exercise interventions were associated with fall-related benefit, but evidence was most consistent across multiple fall-related outcomes for exercise. Vitamin D supplementation interventions had mixed results, with a high dose being associated with higher rates of fall-related outcomes.

JAMA. 2018;319(16):1705-1716. doi:10.1001/jama.2017.21962
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Related article page 1696 and JAMA Patient Page page 1734

Supplemental content

Related article at jamainternalmedicine.com

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SYSTEMATIC REVIEW

The effectiveness of exercise-based vestibular rehabilitation in adult patients with chronic dizziness: A systematic review [version 1; referees: 2 approved]

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Latest published: 05 Mar 2018, **7**:276 (doi: 10.12688/f1000research.14089.1)

Abstract

Background: Dizziness is a non-specific term used by patients to describe several symptoms ranging from true vertigo, light headedness, disorientation or sense of imbalance. Vestibular rehabilitation (VR) is a specific form of exercise-based therapy programme aimed at alleviating the primary and secondary problems of a vestibular pathology. The aim of this study was to investigate the effectiveness of exercise-based vestibular rehabilitation in adult patients with chronic dizziness.

Methods: The following five databases were searched: the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE, PubMed, the Physiotherapy Evidence Database (PEDro) and Scopus (Elsevier). Two investigators independently reviewed all articles and a systematic review of literature was performed using the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The articles were included if they met the following inclusion criteria: (1) randomised controlled trial, (2) people with chronic dizziness, (3) adults aged 18 or over, (4) exercise-based VR, (5) VR exercises compared with sham or usual care, non-treatment or placebo and (6) only studies published full text in English.

Results: The initial search identified 304 articles, four of which met the criteria for analysis. All studies involved some form of vestibular rehabilitation, including vestibular compensation, vestibular adaptation and substitution exercises. These exercises were compared with usual medical care (three studies) or placebo eye exercise (one study). The Vertigo Symptom Scale was the most commonly used outcome measure to assess subjective perception of symptoms of dizziness (three studies). According to the PEDro scale, three studies were considered to be of high quality, and one was rated as fair.

Conclusions: This review suggests that exercise-based vestibular rehabilitation shows benefits for adult patients with chronic dizziness with regard to improvement in the vertigo symptom scale, fall risk, balance and emotional status.

Keywords

Vestibular Rehabilitation, Exercise, Physiotherapy, Chronic Dizziness, Vertigo, Balance

Open Peer Review

Referee Status: ✓ ✓

	Invited Referees 1	2
version 1 published 05 Mar 2018	✓ report	✓ report

1 **Shamekh Mohamed El-Shamy**, Cairo University, Egypt

2 **Alia Alghwiri**, The University of Jordan, Jordan

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Comments (0)

[Intervention Review]

Vestibular rehabilitation for unilateral peripheral vestibular dysfunction

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Editorial group: Cochrane ENT Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2015.

Citation: McDonnell MN, Hillier SL. Vestibular rehabilitation for unilateral peripheral vestibular dysfunction. *Cochrane Database of Systematic Reviews* 2015, Issue 1. Art. No.: CD005397. DOI: 10.1002/14651858.CD005397.pub4.

ABSTRACT

Background

This is an update of a Cochrane review first published in *The Cochrane Library* in Issue 4, 2007 and previously updated in 2011.

Unilateral peripheral vestibular dysfunction (UPVD) can occur as a result of disease, trauma or postoperatively. The dysfunction is characterised by complaints of dizziness, visual or gaze disturbances and balance impairment. Current management includes medication, physical manoeuvres and exercise regimes, the latter known collectively as vestibular rehabilitation.

Objectives

To assess the effectiveness of vestibular rehabilitation in the adult, community-dwelling population of people with symptomatic unilateral peripheral vestibular dysfunction.

Search methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ISRCTN and additional sources for published and unpublished trials. The most recent search was 18 January 2014.

Selection criteria

Randomised controlled trials of adults living in the community, diagnosed with symptomatic unilateral peripheral vestibular dysfunction. We sought comparisons of vestibular rehabilitation versus control (e.g. placebo), other treatment (non-vestibular rehabilitation, e.g. pharmacological) or another form of vestibular rehabilitation. Our primary outcome measure was change in the specified symptomatology (for example, proportion with dizziness resolved, frequency or severity of dizziness). Secondary outcomes were measures of function, quality of life and/or measure(s) of physiological status, where reproducibility has been confirmed and shown to be relevant or related to health status (for example, posturography), and adverse effects

Data collection and analysis

We used the standard methodological procedures expected by The Cochrane Collaboration.

Prolotherapy

Question: Should noncoverage of prolotherapy be clarified on the Prioritized List?

Question source: Indian Health Service is seeking clarification of HERC intended coverage.

Issue: There is no specific CPT code for prolotherapy. HERC has current coverage recommendations for back pain and for knee arthritis to not cover prolotherapy and platelet-rich plasma injections, respectively.

There is a new HCPCS code specific to prolotherapy which has not been reviewed by HERC.

Clinical Background:
From United, 2019

Prolotherapy is an injection-based complementary and alternative medical therapy for chronic musculoskeletal pain. Its core principle is that a relatively small volume of an irritant or sclerosing solution is injected at sites on painful ligament and tendon insertions, and in adjacent joint space over the course of several treatment sessions. It has been assessed as a treatment for a wide variety of painful chronic musculoskeletal conditions which are refractory to "standard of care" therapies. The three most commonly used prolotherapy solutions are hypertonic dextrose, phenol-glycerine-glucose, and morrhuate sodium.

Code	Code Description	Prioritized List Placement
M0076	Prolotherapy	Never Reviewed
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed	Temporary code
0481T	Injection(s), autologous white blood cell concentrate (autologous protein solution), any site, including image guidance, harvesting and preparation, when performed	Temporary code

Evidence summary

Prior HERC reviews:
HERC Coverage Guidance, Newer interventions for osteoarthritis of the knee, 2019.

- Platelet-rich plasma is not recommended for coverage (*weak recommendation*) for osteoarthritis of the knee
- Guideline Note 104 excludes platelet-rich plasma for osteoarthritis of the knee

HERC Coverage Guidance, Low back pain: minimally invasive and non-corticosteroid percutaneous interventions, 2018

- Prolotherapy is not included on back lines due to lack of evidence of effectiveness for the treatment of conditions on these lines, including cervical, thoracic, lumbar, and sacral conditions in Guideline Note 37 SURGICAL INTERVENTIONS FOR CONDITIONS OF THE BACK AND SPINE OTHER THAN SCOLIOSIS

Other Payers
United Healthcare, 2019
https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/prolotherapy-musculoskeletal-indications.pdf

Evidence review for
- Knee arthritis
- Fingers
- Lateral epicondylosis
- Rotator cuff tendinopathies
- Groin pain
- Temporal mandibular joint hypermobility
- Lower limb tendinopathies
- Low back pain
- Chronic pain

Coverage Rationale - Prolotherapy is unproven and not medically necessary due to insufficient evidence of efficacy.

Aetna, 2019
http://www.aetna.com/cpb/medical/data/200_299/0207.html
Aetna considers prolotherapy (also known as proliferant therapy, proliferation therapy, joint sclerotherapy, or reconstructive ligament therapy) experimental and investigational for all indications, including the following (not an all-inclusive list), because there is inadequate evidence of its effectiveness:

- Achilles tendinosis
- Back pain
- Coccynodynia
- Epicondylitis
- Hand osteoarthritis
- Iliotibial band syndrome
- Ischio-femoral impingement
- Knee ligament instability
- Knee osteoarthritis
- Metatarso-phalangeal joint instability
- Myofascial pain
- Neuropathic pain
- Osgood-Schlatter disease
- Osteomyelitis pubis
- Plantar fasciopathy
- Rotator cuff disease
- Sacroiliac joint pain / instability

- Shoulder pain
- Temporomandibular joint syndrome/Temporomandibular joint hypermobility
- Tendinopathies.

Aetna considers neural prolotherapy (low dose dextrose) experimental and investigational for neurogenic inflammatory pain and all other indications.

Aetna considers prolozone therapy experimental and investigational for any diagnosis because there is no peer-reviewed published clinical literature regarding its effectiveness.

Aetna considers Sarapin, an herbal extract that has been used as a sclerosant in prolotherapy, experimental and investigational for all indications because there is inadequate evidence of its effectiveness.

Cigna, 2019 https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/CMM-204_Prolotherapy.pdf

Prolotherapy performed for the treatment of musculoskeletal pain and/or instability (e.g., laxity, weakness) is considered **experimental, investigational or unproven**.

Premera Blue Cross, 2019
https://www.premera.com/medicalpolicies/2.01.26.pdf
Prolotherapy is considered investigational as a treatment of musculoskeletal pain.

HERC Staff Summary
Prolotherapy has been previously reviewed for some indications and not found to have sufficient evidence to warrant inclusion on the Prioritized List. Major commercial payers consider prolotherapy experimental for all indications. There is a lack of clarity about general coverage intent on the Prioritized List.

HERC Staff Recommendations:
1) Place M0076 *Prolotherapy* on Line 660
2) Add to guideline note 173

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review

M0076	Prolotherapy	Insufficient evidence of effectiveness	August, 2019

3) Modify Guideline Note 37 to remove prolotherapy, since it will be on 660
GUIDELINE NOTE 37, SURGICAL INTERVENTIONS FOR CONDITIONS OF THE BACK AND SPINE OTHER THAN SCOLIOSIS

Lines 346,527

Spine surgery is included on Line 346 only in the following circumstances:

A) Decompressive surgery is included on Line 346 to treat debilitating symptoms due to central or foraminal spinal stenosis, and only when the patient meets the following criteria:
   1) Has MRI evidence of moderate or severe central or foraminal spinal stenosis AND
   2) Has neurogenic claudication OR
   3) Has objective neurologic impairment consistent with the MRI findings. Neurologic impairment is defined as objective evidence of one or more of the following:
      a) Markedly abnormal reflexes
      b) Segmental muscle weakness
      c) Segmental sensory loss
      d) EMG or NCV evidence of nerve root impingement
      e) Cauda equina syndrome
      f) Neurogenic bowel or bladder
      g) Long tract abnormalities

   Foraminal or central spinal stenosis causing only radiating pain (e.g. radiculopathic pain) is included only on Line 527.

B) Spinal fusion procedures are included on Line 346 for patients with MRI evidence of moderate or severe central spinal stenosis only when one of the following conditions are met:
   1) spinal stenosis in the cervical spine (with or without spondylolisthesis) which results in objective neurologic impairment as defined above OR
   2) spinal stenosis in the thoracic or lumbar spine caused by spondylolisthesis resulting in signs and symptoms of neurogenic claudication and which correlate with xray flexion/extension films showing at least a 5 mm translation OR
   3) pre-existing or expected post-surgical spinal instability (e.g. degenerative scoliosis >10 deg, >50% of facet joints per level expected to be resected)

For all other indications, spine surgery is included on Line 527.

The following interventions are not included on these lines due to lack of evidence of effectiveness for the treatment of conditions on these lines, including cervical, thoracic, lumbar, and sacral conditions:

- ~~prolotherapy~~
- local injections (including ozone therapy injections)
- botulinum toxin injection

- intradiscal electrothermal therapy
- therapeutic medial branch block
- coblation nucleoplasty
- percutaneous intradiscal radiofrequency thermocoagulation
- percutaneous laser disc decompression
- radiofrequency denervation
- corticosteroid injections for cervical pain

Corticosteroid injections for low back pain with or without radiculopathy are only included on Line 527.

The development of this guideline note was informed by HERC coverage guidances on Percutaneous Interventions for Low Back Pain, Percutaneous Interventions for Cervical Spine Pain, Low Back Pain: Corticosteroid Injections and Low Back Pain: Minimally Invasive and Non-Cordicosteroid Percutaneous Interventions. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.

4) Make no change to Guideline Note 104. It specifically considers platelet rich plasma and not broader prolotherapy. Terminology around this may be changing as well.

GUIDELINE NOTE 104, NEWER INTERVENTIONS FOR OSTEOARTHRITIS OF THE KNEE

Lines 430,461

The following treatments are not included on this line for osteoarthritis of the knee:

· Whole body vibration
· Glucosamine/chondroitin (alone, or in combination)
· Platelet rich plasma
· Viscosupplementation
· Transcutaneous electrical stimulation (TENS)

CPT 20610 and 20611 are included on these lines only for interventions other than viscosupplementation for osteoarthritis of the knee.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.

Opportunistic Salpingectomy Guideline Clarification

Question: Should the opportunistic salpingectomy guideline and code placement be modified?

Question source: HSD Medicaid unit, RHEA staff

Issue: There is still ongoing confusion about the intent of the opportunistic salpingectomy guideline and concern about a need to modify the current pairing of salpingectomy codes. Due to coding and billing practices, opportunistic salpingectomy needs to be available on lines with the co-occurring gynecological surgeries. There is a request to clarify the definition of opportunistic salpingectomy.

Prioritized List Status

Code	Code Description	Current Prioritized List Placement
Z40.03	Encounter for prophylactic removal of fallopian tube(s)	6 REPRODUCTIVE SERVICES 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
58700	Salpingectomy, complete or partial, unilateral or bilateral (separate procedure)	6,37,51,61,428,529,578
58260	Vaginal hysterectomy, for uterus 250 g or less;	1,25,37,51,133,209,239,286 and 7 other lines.
58262	Vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s), and/or ovary(s)	1,25,51,209,312,395,403,420 and 2 other lines.
58290	Vaginal hysterectomy, for uterus greater than 250 g;	1,25,51,209,286,312,395,403 and 4 other lines.
58291	Vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)	1,25,51,209,312,395,403,420 and 2 other lines.
58661	Laparoscopy, surgical; with removal of adnexal structures (partial or total oophorectomy and/or salpingectomy)	6,37,51,61,191,239,286,312 and 6 other lines.

GUIDELINE NOTE 176, OPPORTUNISTIC SALPINGECTOMY

Line 6

Opportunistic salpingectomy during gynecologic procedures is included on Line 6, when it does not involve an increased payment (i.e., using a form of reference-based pricing) or require a change in the setting in which the procedure would be performed (e.g. necessitate a hospital setting instead of an ambulatory surgical center.)

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.

Gynecology lines

Line	Condition	Treatment	HERC Staff Recommendation
1	PREGNANCY	MATERNITY CARE	Add opportunistic salpingectomy
6	REPRODUCTIVE SERVICES	CONTRACEPTION MANAGEMENT; STERILIZATION	Add opportunistic salpingectomy
25	DYSPLASIA OF CERVIX AND CERVICAL CARCINOMA IN SITU, CERVICAL CONDYLOMA	MEDICAL AND SURGICAL TREATMENT	Add opportunistic salpingectomy
35	TERMINATION OF PREGNANCY	INDUCED ABORTION	Do not add
37	ECTOPIC PREGNANCY; HYDATIDIFORM MOLE; CHORIOCARCINOMA	MEDICAL AND SURGICAL TREATMENT	Add opportunistic salpingectomy
51	ACUTE PELVIC INFLAMMATORY DISEASE	MEDICAL AND SURGICAL TREATMENT	Add opportunistic salpingectomy
52	GONOCOCCAL INFECTIONS AND OTHER SEXUALLY TRANSMITTED DISEASES OF THE ORAL, ANAL AND GENITOURINARY TRACT	MEDICAL THERAPY	Do not add
61	TORSION OF OVARY	OOPHORECTOMY, OVARIAN CYSTECTOMY	Add opportunistic salpingectomy
63	SPONTANEOUS ABORTION; MISSED ABORTION	MEDICAL AND SURGICAL TREATMENT	Add opportunistic salpingectomy
133	CANCER OF CERVIX	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY	Add opportunistic salpingectomy
239	CANCER OF OVARY	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY	Add opportunistic salpingectomy
285	COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT	MEDICAL AND SURGICAL TREATMENT	Do not add
286	CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY	Add opportunistic salpingectomy
298	FISTULA INVOLVING FEMALE GENITAL TRACT	CLOSURE OF FISTULA	Add opportunistic salpingectomy
353	STRUCTURAL CAUSES OF AMENORRHEA	SURGICAL TREATMENT	Add opportunistic salpingectomy
395	ENDOMETRIOSIS AND ADENOMYOSIS	MEDICAL AND SURGICAL TREATMENT	Add opportunistic salpingectomy

403	UTERINE LEIOMYOMA AND POLYPS	SURGICAL TREATMENT	Add opportunistic salpingectomy
420	MENSTRUAL BLEEDING DISORDERS	MEDICAL AND SURGICAL TREATMENT	Add opportunistic salpingectomy
427	VAGINITIS AND CERVICITIS	MEDICAL THERAPY	Do not add
428	NONINFLAMMATORY DISORDERS AND BENIGN NEOPLASMS OF OVARY, FALLOPIAN TUBES AND UTERUS; OVARIAN CYSTS; GONADAL DYSGENISIS	MEDICAL AND SURGICAL TREATMENT	Add opportunistic salpingectomy
434	PRECANCEROUS VULVAR CONDITIONS	MEDICAL THERAPY	Do not add
437	FOREIGN BODY IN UTERUS, VULVA AND VAGINA	MEDICAL AND SURGICAL TREATMENT	Do not add
453	URINARY INCONTINENCE	MEDICAL AND SURGICAL TREATMENT	Add opportunistic salpingectomy
464	UTERINE PROLAPSE; CYSTOCELE	MEDICAL AND SURGICAL TREATMENT	Add opportunistic salpingectomy
467	GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT	OOPHORECTOMY, ORCHIECTOMY, HORMONAL REPLACEMENT FOR PURPOSES OTHER THAN INFERTILITY	Add opportunistic salpingectomy
478	BREAST CYSTS AND OTHER DISORDERS OF THE BREAST	MEDICAL AND SURGICAL TREATMENT	Do not add
479	CYSTS OF BARTHOLIN'S GLAND AND VULVA	INCISION AND DRAINAGE, MEDICAL THERAPY	Do not add
521	SEXUAL DYSFUNCTION	PSYCHOTHERAPY, MEDICAL AND SURGICAL TREATMENT	Do not add
529	CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA	MEDICAL AND SURGICAL TREATMENT	Add opportunistic salpingectomy
555	DYSMENORRHEA	MEDICAL AND SURGICAL TREATMENT	Add opportunistic salpingectomy
561	BENIGN NEOPLASM AND CONDITIONS OF EXTERNAL FEMALE GENITAL ORGANS	EXCISION	Do not add
569	OTHER COMPLICATIONS OF A PROCEDURE	MEDICAL AND SURGICAL TREATMENT	Do not add
578	CONGENITAL ANOMALIES OF FEMALE GENITAL ORGANS EXCLUDING VAGINA	SURGICAL TREATMENT	Add opportunistic salpingectomy
627	BENIGN CERVICAL CONDITIONS	MEDICAL THERAPY	Do not add

634	GALACTORRHEA, MASTODYNIA, ATROPHY, BENIGN NEOPLASMS AND UNSPECIFIED DISORDERS OF THE BREAST	MEDICAL AND SURGICAL TREATMENT	Do not add
656	GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY	EVALUATION	Do not add

HERC Staff Recommendations:

1) Add the following ICD-10-CM and CPT codes to multiple surgical OB/GYN lines (1, 25, 37, 51, 61, 63, 133, 239, 286, 298, 353, 395, 403, 420, 428, 453, 464, 467, 529, 555, 578):
    a. Z40.03 Encounter for prophylactic removal of fallopian tube(s)
    b. 58700 Salpingectomy, complete or partial, unilateral or bilateral (separate procedure)
2) Make no change to 58661 Laparoscopy, surgical; with removal of adnexal structures (partial or total oophorectomy and/or salpingectomy)
3) Add CPT code 58262 (Vaginal hysterectomy, for uterus 250 g or less with removal of tubes(s), and/or ovary(s)) to surgical OB/GYN lines 37, 133, 239, 286 and 555, where it does not appear, but which do include 58260 (Vaginal hysterectomy, for uterus 250 g or less)
4) Add CPT code 58291 (Vaginal hysterectomy, for uterus greater than 250 g with removal of tube(s) and/or ovary(s)) to surgical OB/GYN lines 286 and 420, where it does not appear, but which do include 58290 (Vaginal hysterectomy, for uterus greater than 250 g)
5) Modify Guideline Note 176 as follows:

GUIDELINE NOTE 176, OPPORTUNISTIC SALPINGECTOMY

Lines 1, 6, 25, 37, 51, 61, 63, 133, 239, 286, 298, 353, 395, 403, 420, 428, 453, 464, 467, 529, 555, 578

~~Opportunistic salpingectomy during gynecologic procedures is included on Line 6, when it does not involve an increased payment (i.e., using a form of reference-based pricing) or require a change in the setting in which the procedure would be performed (e.g. necessitate a hospital setting instead of an ambulatory surgical center.)~~

Opportunistic salpingectomy is defined as the prophylactic removal of the fallopian tubes for the primary prevention of ovarian cancer when a woman is undergoing pelvic surgery for another indication, or instead of a bilateral tubal ligation (BTL) for the purpose of sterilization. It is included on these lines when used for these purposes, however, no additional payment is intended beyond the cost of the indicated pelvic surgery (e.g. using reference-based pricing) or the cost of the BTL and as long as the addition of the opportunistic salpingectomy does not result in a change in setting (for example requiring a hospital setting versus ambulatory surgery center).

Opportunistic salpingectomy should be paired with Z40.03 *Encounter for prophylactic removal of fallopian tube(s) or Z30.2 Encounter for sterilization.*

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx.

Surgical Treatment for Chronic Pancreatitis Including Pancreatectomy with Autologous Islet Cell Transplant

Questions:

1) Is there any intention to cover islet cell transplant for type 1 diabetes on the Prioritized List?
2) Should partial and total pancreatectomy without autologous islet cell transplant be added to the surgical line for chronic pancreatitis?
3) Should total pancreatectomy with autologous islet cell transplant be added to the surgical line for chronic pancreatitis?

Question sources: California Medicaid; HERC staff

Issue:

Chronic pancreatitis is long-term inflammation of the pancreas characterized by an irreversible, permanent and progressive destruction of the pancreatic tissue. Chronic pancreatitis may be either hereditary, with a genetic cause often presenting in childhood or young adulthood, or acquired, which usually presents in adulthood. Alcohol is the most frequent cause of acquired chronic pancreatitis. Chronic pancreatitis is a disabling condition with a number of symptoms, of which the most debilitating is severe abdominal pain. Long-term pancreatitis may also interfere with insulin production and lead to diabetes. Current treatment is mainly symptom control, including opioid therapy. Some patients may benefit from surgical procedures; these may include drainage procedures in patients where there is dilatation of the main pancreatic duct and/or segmental resection of the pancreas where appropriate. Patients may also benefit from nerve block type procedures. The primary goal of surgery is to remove the cause of the symptoms by removing the pancreas (total pancreatectomy), with an aim to control pain resistant to other therapies; islet auto transplantation (a procedure where the patient's own islet cells are isolated and infused into their liver) is intended to prevent or lessen the very brittle diabetes mellitus which is an inevitable result of total pancreatectomy. Patients will also need lifelong oral replacement therapy of the digestive enzymes produced by the pancreas.

Islet cell transplant has been proposed as a treatment of type 1 diabetes. In this case, the transplanted cells can come from a cadaveric donor (allogenic). Such a transplant requires lifelong immunosuppression and is considered experimental by the FDA.

California Medicaid is looking at coverage of islet cell transplants and contacted Oregon to clarify coverage for OHP. Pancreatic islet cell transplant from cadaveric donors for treatment of type 1 diabetes has not been reviewed in detail in many years and has previously been considered experimental. There is currently one ambiguous code that could include pancreatic islet transplantation that is in the funded region and creates a lack of clarity as to HERC coverage intent. Pancreatectomy with autologous islet cell transplant has never been reviewed.

Currently, there are two lines for chronic pancreatitis, 251 CHRONIC PANCREATITIS/MEDICAL THERAPY and 596 CHRONIC PANCREATITIS/SURGICAL TREATMENT. Line 596 does not have the CPT codes for pancreatectomy, however. Searches through old minutes could not find any reference to why pancreatectomy was not included on the surgical treatment line. If the patient has a pancreatic pseudocyst, which is a complication of acute and chronic pancreatitis, then the patient could be treated with a partial or total pancreatectomy on line 363 CYST AND PSEUDOCYST OF PANCREAS.

Surgical Treatment for Chronic Pancreatitis Including Pancreatectomy with Autologous Islet Cell Transplant

Current Prioritized List Status:

Code	Code Description	Current Prioritized List Status
48150-48154	Subtotal pancreatectomy	47 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS 316 CANCER OF PANCREAS 363 CYST AND PSEUDOCYST OF PANCREAS 433 CANCER OF GALLBLADDER AND OTHER BILIARY
48155	Pancreatectomy, total	27 TYPE 2 DIABETES MELLITUS 156 ACROMEGALY AND GIGANTISM 316 342 OTHER AND UNSPECIFIED ANTERIOR PITUITARY HYPERFUNCTION, BENIGN NEOPLASM OF THYROID GLAND AND OTHER ENDOCRINE GLANDS 433
48160	Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells	84 DIABETES MELLITUS WITH END STAGE RENAL DISEASE Tx SIMULTANEOUS PANCREAS/KIDNEY (SPK) TRANSPLANT, PANCREAS AFTER KIDNEY (PAK) TRANSPLANT
G0341	Percutaneous islet cell transplant, includes portal vein catheterization and infusion	Never Reviewed
G0342	Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion	Never Reviewed
G0343	Laparotomy for islet cell transplant, includes portal vein catheterization and infusion	Never Reviewed
S2102	Islet cell tissue transplant from pancreas; allogeneic	Excluded File

Transplant services OARs
https://secure.sos.state.or.us/oard/viewSingleRule.action?ruleVrsnRsn=84704

Surgical Treatment for Chronic Pancreatitis Including Pancreatectomy with Autologous Islet Cell Transplant

Evidence for pancreatic surgery for chronic pancreatitis

1) **Ahmed 2015**, Cochrane review of endoscopic vs surgical intervention for painful obstructive chronic pancreatitis
    a. N=2 trials of endoscopic vs surgical intervention (N=111 patients, 55 endoscopic and 56 surgical)
        i. Compared with the endoscopic group, the surgical group had a higher proportion of participants with pain relief, both at middle/long-term follow-up (two to five years: risk ratio (RR) 1.62, 95% confidence interval (CI) 1.22 to 2.15) and long-term follow-up (≥ five years, RR 1.56, 95% CI 1.18 to 2.05). Surgical intervention resulted in improved quality of life and improved preservation of exocrine pancreatic function at middle/long-term follow-up (two to five years), but not at long-term follow-up (≥ 5 years). No differences were found in terms of major post-interventional complications or mortality, although the number of participants did not allow for this to be reliably evaluated.
    b. N=1 trial (N=32 patients, 17 surgical and 15 conservative) of surgical intervention vs conservative therapy.
    c. The trial showed that surgical intervention resulted in a higher percentage of participants with pain relief and better preservation of pancreatic function. The trial had methodological limitations, and the number of participants was relatively small.
    d. Authors' conclusions: For patients with obstructive chronic pancreatitis and dilated pancreatic duct, this review shows that surgery is superior to endoscopy in terms of pain relief. Morbidity and mortality seem not to differ between the two intervention modalities, but the small trials identified do not provide sufficient power to detect the small differences expected in this outcome. Regarding the comparison of surgical intervention versus conservative treatment, this review has shown that surgical intervention in an early stage of chronic pancreatitis is a promising approach in terms of pain relief and pancreatic function. Other trials need to confirm these results because of the methodological limitations and limited number of participants assessed in the present evidence.
2) **Yang 2014**, systematic review of early surgery for chronic pancreatitis
    a. N=11 studies
        i. Seven studies examined pain, three studies examined pancreatic function, and three studies examined rates of re-intervention.
    b. Meta-analysis of the three studies with comparative raw data regarding complete pain relief showed that early surgery compared to late surgery was associated with an increased likelihood of complete postoperative pain relief (RR=1.67, 95 % CI 1.09–2.56, p=0.02). Early surgery was also associated with reduced risk of pancreatic insufficiency and low re-intervention rates.
    c. Conclusions: Data from this study supports considering early surgery for pain management in patients with chronic pancreatitis, with the potential of a reduced risk of pancreatic insufficiency and the need for further intervention. Further prospective randomized studies are warranted comparing early surgery against conservative step-up approaches.
3) **Hartmann 2016**, review of surgery for chronic pancreatitis

   a. In general, several randomized controlled trials provide strong evidence that surgical therapy for painful obstructive chronic pancreatitis leads to significantly better long-term results than endoscopic interventions and that early surgical intervention is associated with improved postoperative pain relief, reduced risk of pancreatic insufficiency and decreased re-intervention rates in comparison with conservative 'step-up approaches.'

4) **Branganza 2011**, review of chronic pancreatitis
   a. Pancreatectomy is the last step in their algorithm for treatment
   b. Duodenum-preserving head resection combined, when appropriate, with lateral pancreaticojejunostomy, has been a major advance: only 8.7% of patients continued to have pancreatic pain at a median of 5-7 years follow-up, whereas 93% of patients had pancreatic pain preoperatively.

<u>Evidence for total pancreatectomy with islet cell autotransplantation for chronic pancreatitis</u>

1) **NHS 2018:** evidence review of total pancreatectomy and islet cell autotransplantation (TP IAT) for chronic pancreatitis
   a. N=15 studies
      i. three systematic reviews (Wu et al 2015, Bramis et al 2012, Dong et al 2011)
      ii. four uncontrolled studies of TP IAT (Fazlalizadeh et al 2016, Morgan et al 2015, Chinnakotla et al 2014a, Wilson et al 2014)
      iii. one comparative study (Bhayani et al 2014)
      iv. five uncontrolled studies conducted in paediatric patients only (Bellin et al 2017, Chinnakotla et al 2014b, Wilson et al 2013, Bellin et al 2011, Bellin et al 2008).
      v. There was one cost study of TP IAT based on a small comparative study.
   b. *Question 1: What is the clinical effectiveness and cost effectiveness of TP IAT in the management of uncontrolled pain caused by small duct chronic pancreatitis and resistant to other forms of treatment in patients of all ages?*
      i. One systematic review (Bramis et al 2012) included two studies which report post-operative reduction of 116mg and 55mg daily respectively in the use of morphine. One case series reported narcotic independence rate of 55% at one year and 73% at five years (Wilson 2014).
      ii. Two systematic reviews which carried out meta-analyses reported pooled insulin independence rates of 27% (95% CI: 21-33%) and 28.4% (95% CI: 15.7-46.0) at one year and 21% (95% CI: 16-27%) and 19.7% (95% CI: 5.1-52.6%) at two years respectively (Dong et al 2011, Wu et al 2015).
   c. *Question 4: Evidence for improvement of QoL*
      i. One study reported significant improvements in PhysQoL relative to baseline at one, two, and three years' post-surgery of 7.1, 5.8, and

7.8 and in PsychQoL relative to baseline at one year, two years, and three years' post-surgery of 3.9, 4.9, and 6.6 ($p < 0.001$ for all) (Morgan et al 2015). Another study reported MCS and PCS scale scores statistically improved over time ($p<0.001$).

ii. In one study, 92% of patients reported overall improvement in their health at one year and 85% at 5 years follow-up (Wilson et al 2014).

d. Conclusion: NHS England has concluded that there is sufficient evidence to support the routine commissioning of this treatment for the indication. Therefore, total pancreatectomy (for the indication of chronic pancreatitis) cannot be offered to patients if the option of islet auto transplant is not available (except in patients who already have no functioning islet cells).

e. Guideline:
   i. TP IAT will be reserved for patients with acquired intractable chronic pancreatitis who:
      1. have intractable abdominal pain despite regular opiate analgesia
      2. are receiving care guided by a pain control team
      3. have not responded to more conservative surgery including endoscopic pancreatic decompression or in whom such surgery is not clinically indicated
      4. have not responded to nerve block procedures or in whom these interventions are not clinically indicated
      5. are assessed by the multidisciplinary team as suffering from pain of an organic nature and are thought likely to achieve significant pain reduction from TP IAT
   ii. Exclusions
      1. TP IAT will not be performed:
         a. in patients with C-peptide negative diabetes, type 1 diabetes, known pancreatic cancer and any other condition that would prevent isolation of islet cells for auto transplant. These patients maybe suitable for pancreatectomy alone.
         b. where the risk associated with major surgery (pancreatectomy) is high
         c. where islet cell transplant risks are high including portal vein thrombosis, and significant parenchymal liver disease (e.g. cirrhosis of the liver)
         d. in patients considered by the MDT assessment to be unable to adhere to the complex medical management required following TP IAT

2) **Bramis 2012**, systematic review of total pancreatectomy and islet autotransplantation for chronic pancreatitis
    a. N=5 studies (n=296 patients)
        i. 4 case series, 1 retrospective cohort
    b. 2 studies reported post-operative morphine usage and found a reduction of 55mg and 116 mg in mean morphine dosage compared to pre-operative dosage
    c. The insulin independence rate ranged from 46 percent of patients at a mean follow-up of 5 years to 10 percent at 8 years.
    d. The impact on quality of life was poorly reported.
    e. Conclusion: This systematic review showed that TP/IAT had favorable outcomes with regard to pain reduction. Concurrent IAT enabled a significant proportion of patients to remain independent of insulin supplementation.
2) **Dong 2011**, systematic review and meta-analysis of islet autotransplantation after pancreatectomy for minimizing diabetes
    a. N=15 studies, (n=384 patients)—included 3 of the studies in Bramis 2012 above
        i. all single center case series
        ii. The overall quality of the included studies was suboptimal
    b. The rate of insulin independence at last follow-up was reported in all included studies except one. The pooled rate was 4.62 per 100 person-years (95% CI: 1.53–7.72; I2 = 97%).
    c. Insulin independence at 1 year was 27% (95% CI: 21– 33%) in 221 patients from five studies, and at 2 years 21% (95% CI: 16–27%) in 201 patients from three studies.
    d. The 30-day mortality was 5% (95% CI: 2–10%, I2 = 0%), whereas the mortality rate at last follow-up was 1.38 per 100 person-years (95% CI: 0.66–2.11; I2 = 0%). The cumulative mortality at 1 year (reported by ten studies including 321 patients) was 4.9% (95% CI: 2.6–7.3%) and at 2 years (reported by five studies including 254 patients), it was 6.2% (95% CI: 3.3–9.2%).
    e. Conclusions: islet cell autotransplantation postpancreatectomy offers some patients a chance for insulin independence. Better data reporting is essential to establish the risks and benefits of IAT after pancreatic surgery.

<u>Other payer policies</u>:

1) Aetna (2019) and Cigna (2019) and BCBS (2019) and Wellmark (2019) cover autologous islet cell transplantation for patients undergoing total or near total pancreatectomy, but consider allogenic (cadaveric) transplant for type 1 diabetes to be experimental
2) No insurer surveyed had a policy about partial or total pancreatectomy without islet cell autotransplantation for chronic pancreatitis; presumably all were covering this intervention

Surgical Treatment for Chronic Pancreatitis Including Pancreatectomy with Autologous Islet Cell Transplant

HERC staff summary

Allogenic (cadaveric) islet cell transplantation for treatment of type 1 diabetes is considered experimental by the FDA and all private insurers queried; it is appropriately on the Excluded File.

Partial pancreatectomy appears, based on limited data, to result in significant pain relief and improved quality of life for patients with chronic pancreatitis, particularly that caused by chronic duct obstruction. Partial or total pancreatectomy is the end step in standard treatment algorithms for chronic pancreatitis. Meta-analyses indicate that surgery has better pain reduction outcomes than the endoscopic procedures which are currently included on the medical chronic pancreatitis line.

The effectiveness of autologous islet cell transplantation after total or near total pancreatectomy for chronic pancreatitis on the reduction for the need for insulin is difficult to determine based on the current evidence base, which consists of nearly all poor-quality case series. The limited evidence base finds that only a minority (approximately 20%) of patients will avoid insulin 1 to 2 years after islet cell autologous transplantation. However, NHS/NICE, one of our trusted sources, has reviewed the evidence and found it sufficient to recommend coverage. All major insurers appear to cover this procedure.

HERC staff recommendations:

1) Add allogenic islet cell transplantation HCPCS S2012 (Islet cell tissue transplant from pancreas; allogeneic) to line 660/GN173
    a. Makes more visible the current placement on the Excluded File
    b. Not FDA approved; cannot be covered by Medicaid

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
S2012	Islet cell tissue transplant from pancreas; allogeneic	Insufficient evidence of effectiveness	August 2019

2) Add partial and total pancreatectomy CPT codes to line 596 CHRONIC PANCREATITIS Treatment: SURGICAL TREATMENT
    a. CPT 48150-48154 (Subtotal pancreatectomy)
    b. CPT 48155 (Pancreatectomy, total)

3) Add autologous islet cell transplantation after total pancreatectomy to line 596 CHRONIC PANCREATITIS Treatment: SURGICAL TREATMENT
    a. Add CPT 48160 and HCPCS G0341-G0343 to line 596
        i. 48160 Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells
        ii. G0341 Percutaneous islet cell transplant, includes portal vein catheterization and infusion
        iii. G0342 Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
        iv. G0343 Laparotomy for islet cell transplant, includes portal vein catheterization and infusion
    b. Remove CPT 48160 from line 84 DIABETES MELLITUS WITH END STAGE RENAL DISEASE Tx SIMULTANEOUS PANCREAS/KIDNEY (SPK) TRANSPLANT, PANCREAS AFTER KIDNEY (PAK) TRANSPLANT
        i. Not a treatment for diabetes mellitus
    c. Add a new guideline to line 596
        i. Based on NHS/NICE guideline

GUIDELINE NOTE XXX, TOTAL PANCREATECTOMY WITH ISLET CELL AUTOTRANSPLANT

Line 596

Total pancreatectomy with islet cell autotransplant (TP IAT) is only included on this line when the patient meets all of the following criteria:

1) Has acquired intractable chronic pancreatitis
2) Has intractable abdominal pain despite optimal medical therapy
3) Has not responded to more conservative surgery including endoscopic pancreatic decompression or in whom such surgery is not clinically indicated
4) Has not responded to nerve block procedures or in whom these interventions are not clinically indicated
5) Has been assessed by the multidisciplinary team and determined to have pain of an organic nature and are thought likely to achieve significant pain reduction from TP IAT
6) Is an appropriate candidate for major surgery
7) Is able to adhere to the complex medical management required following TP IAT
8) Does not have type 1 diabetes, known pancreatic cancer or any other condition that would prevent isolation of islet cells for autotransplant
9) Does not have a high risk of islet cell transplant including portal vein thrombosis, and significant parenchymal liver disease (e.g. cirrhosis of the liver)

Endoscopic or surgical intervention for painful obstructive chronic pancreatitis (Review)

Ahmed Ali U, Pahlplatz JM, Nealon WH, van Goor H, Gooszen HG, Boermeester MA

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 3

http://www.thecochranelibrary.com

WILEY

[Intervention Review]

Endoscopic or surgical intervention for painful obstructive chronic pancreatitis

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ABSTRACT

Background

Endoscopy and surgery are the treatment modalities of choice for patients with chronic pancreatitis and dilated pancreatic duct (obstructive chronic pancreatitis). Physicians face, without clear consensus, the choice between endoscopy or surgery for this group of patients.

Objectives

To assess and compare the effects and complications of surgical and endoscopic interventions in the management of pain for obstructive chronic pancreatitis.

Search methods

We searched the following databases in *The Cochrane Library*: CENTRAL (2014, Issue 2), the Cochrane Database of Systematic Reviews (2014, Issue 2), and DARE (2014, Issue 2). We also searched the following databases up to 25 March 2014: MEDLINE (from 1950), Embase (from 1980), and the Conference Proceedings Citation Index - Science (CPCI-S) (from 1990). We performed a cross-reference search. Two review authors independently performed the selection of trials.

Selection criteria

All randomised controlled trials (RCTs) of endoscopic or surgical interventions in obstructive chronic pancreatitis. We included trials comparing endoscopic versus surgical interventions as well as trials comparing either endoscopic or surgical interventions to conservative treatment (i.e. non-invasive treatment modalities). We included relevant trials irrespective of blinding, the number of participants randomised, and the language of the article.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration. Two authors independently extracted data from the articles. We evaluated the methodological quality of the included trials and requested additional information from study authors in the case of missing data.

Main results

We identified three eligible trials. Two trials compared endoscopic intervention with surgical intervention and included a total of 111 participants: 55 in the endoscopic group and 56 in the surgical group. Compared with the endoscopic group, the surgical group had a higher proportion of participants with pain relief, both at middle/long-term follow-up (two to five years: risk ratio (RR) 1.62, 95% confidence interval (CI) 1.22 to 2.15) and long-term follow-up (≥ five years, RR 1.56, 95% CI 1.18 to 2.05). Surgical intervention resulted in improved quality of life and improved preservation of exocrine pancreatic function at middle/long-term follow-up (two to five years), but not at long-term follow-up (≥ 5 years). No differences were found in terms of major post-interventional complications or mortality, although the number of participants did not allow for this to be reliably evaluated. One trial, including 32 participants, compared surgical intervention with conservative treatment: 17 in the surgical group and 15 in the conservative group. The trial showed that surgical intervention resulted in a higher percentage of participants with pain relief and better preservation of pancreatic function. The trial had methodological limitations, and the number of participants was relatively small.

Authors' conclusions

For patients with obstructive chronic pancreatitis and dilated pancreatic duct, this review shows that surgery is superior to endoscopy in terms of pain relief. Morbidity and mortality seem not to differ between the two intervention modalities, but the small trials identified do not provide sufficient power to detect the small differences expected in this outcome.

Regarding the comparison of surgical intervention versus conservative treatment, this review has shown that surgical intervention in an early stage of chronic pancreatitis is a promising approach in terms of pain relief and pancreatic function. Other trials need to confirm these results because of the methodological limitations and limited number of participants assessed in the present evidence.

PLAIN LANGUAGE SUMMARY

Endoscopy or surgery for patients with chronic pancreatitis and dilated pancreatic duct

Background

Endoscopy and surgery are the treatments of choice in patients with chronic pancreatitis and a dilated pancreatic duct. Pain is the most important symptom in this disease and can be severely debilitating. In addition, chronic pancreatitis can result in malabsorption and/or diabetes due to failure of the gland function of the pancreas.

Question

In this review, we compare endoscopy versus surgery in terms of pain relief, complications and mortality in patients with chronic pancreatitis with a dilated pancreatic duct.

Study characteristics

We performed a search in March 2014 and found three relevant randomised trials. Two comparing endoscopic versus surgical interventions (111 patients with durations of two and three years), while the third compared surgery to conservative treatment (i.e. no intervention) (32 patients with a duration of 16 months).

Key results

We found that surgery achieved pain relief in a higher proportion of participants than endoscopy. Surgery also had other advantages like improved quality of life for the first two years after intervention, although this difference disappeared with time. Similarly, surgery reduced the risk of developing malabsorption due to failure of the pancreas, but with longer follow-up this advantage became smaller. The studies seemingly showed no difference between endoscopy and surgery in complications after interventions. We also compared surgery with conservative treatment. The results of one trial suggested that surgery early in the condition achieved better pain relief and preservation of pancreatic function.

Quality of evidence

For endoscopy versus surgery, the quality of the evidence for pain relief, quality of life and pancreatic function was moderate (according to GRADE). For both complications and mortality this was low, since the two trials were too small to make reliable conclusions. The quality of evidence regarding surgery versus conservative treatment was low, since the trial was small, which precluded drawing reliable conclusions regarding all outcomes.

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REVIEW ARTICLE

Systematic Review of Early Surgery for Chronic Pancreatitis: Impact on Pain, Pancreatic Function, and Re-intervention

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Abstract
Background Surgical intervention has traditionally been reserved as the last management option for pain in chronic pancreatitis. Recently, there has been a call for surgery to be offered earlier in the disease process. The objectives of this review were to evaluate the effect of early surgery on postoperative pain, pancreatic function, and re-intervention rates in chronic pancreatitis.
Methods A systematic literature search through EMBASE, Cochrane Review, and PubMed from January 1950 to January 2014 was conducted. Citations found in relevant papers are hand-searched. Data which could be pooled were analyzed using Revman (v5.2). Risk of bias analysis was conducted.
Results Of the 2,886 potentially eligible studies identified, 11 studies met the inclusion criteria. There was large heterogeneity in the study designs, and studies were conducted over a lengthy time span. Seven studies examined pain, three studies examined pancreatic function, and three studies examined rates of re-intervention. Meta-analysis of the three studies with comparative raw data regarding complete pain relief showed that early surgery was associated with an increased likelihood of complete postoperative pain relief (RR=1.67, 95 % CI 1.09–2.56, p=0.02). Early surgery was also associated with reduced risk of pancreatic insufficiency and low re-intervention rates.
Conclusions Data from this study supports considering early surgery for pain management in patients with chronic pancreatitis, with the potential of a reduced risk of pancreatic insufficiency and the need for further intervention. Further prospective randomized studies are warranted comparing early surgery against conservative step-up approaches.

Keywords Surgery · Surgical management · Chronic pancreatitis · Pain · Pain management · Pancreatic function · Diabetes · Steatorrhea · Re-intervention

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Introduction

Chronic pancreatitis (CP) is a debilitating inflammatory disease characterized by recurrent episodes of pain, progression to pancreatic insufficiency, and increased risk of pancreatic cancer.[1,2] Most patients are eventually incapacitated by unrelenting pain and become heavy opioid users without satisfactory pain relief.[3] Achieving satisfactory pain relief in patients with chronic pancreatitis remains a challenge.[4]

Current management strategies have been based on a step-up approach, where conservative management, lifestyle modifications, and endoscopy are offered prior to surgery. Surgery, which has recognized morbidity and mortality, has been reserved as a last resort in this schema. Several, newer recent theories have been proposed describing the mechanisms of pain in chronic pancreatitis. These include ductal hypertension and the ensuing changes to peripancreatic nerves and cortical

Surgery for pancreatic disease

Daniel Hartmann, Benedikt Kaufmann, and Helmut Friess

Purpose of review
Surgery for pancreatic diseases is one of the most studied fields in general surgery and continues to evolve. This review focuses on recent advances in pancreatic surgery and summarizes the published research.

Recent findings
Surgery for pancreatic diseases is an evolving field with a wide range of innovations. Especially, contributions by high-volume pancreas centers have greatly improved outcomes in pancreatic surgery. In chronic pancreatitis, recent studies demonstrate that early surgical treatment should be favored over repeated endoscopic interventions, and local organ-preserving resection techniques should be preferred over classic Whipple resection. Major advances have also been made on the diagnosis of pancreatic cystic lesions; however, the assessment of the current guidelines is still evolving. In pancreatic cancer, neoadjuvant treatment regimens appear to be promising, and extended pancreatic resections with vascular resection can now be offered with lower mortality and morbidity rates. Minimal-invasive laparoscopic and robotic surgical techniques are being used more frequently for the resection of pancreatic tumors and have seen major progress.

Summary
In recent years, the outcome of patients undergoing pancreatic surgery improved due to better knowledge about the biology of the disease, more accurate diagnostic modalities, the application of organ-preserving surgical techniques in benign disorders and new advances in management strategies.

Keywords
acute pancreatitis, chronic pancreatitis, pancreatic cancer, pancreatic cystic neoplasms, pancreatic surgery

INTRODUCTION

In the past months, several interesting studies on surgery for pancreatic disease have been published and have led to major improvements. Nevertheless, even in high-volume centers pancreatic surgery is associated with a considerable postoperative morbidity and mortality, which is why the prevention and management of postoperative complications is an important factor. In April 2016, a case vignette, followed by two short essays in the *New England Journal of Medicine*, started a discussion on the clinical effect of surgical volume for pancreatic head resections [1▪▪]. Even though there is strong evidence in the literature that surgery in high-volume centers by high-volume surgeons is associated with a significantly lower mortality, more than one-third of participants of the poll favored a Whipple operation at low-volume centers [1▪▪]. This article aims at addressing the knowledge gaps, such as the strong inverse association between hospital volume and mortality [2]. In addition, this review highlights recent publications from basic and clinical research with an impact on surgical strategies for pancreatic diseases, such as acute and chronic pancreatitis, endocrine neoplasms, cystic lesions, and pancreatic cancer. Moreover, this article calls for a critical assessment of new developments, such as the application of alternative treatment strategies. Due to improved interventional and endoscopic techniques some indications for surgical intervention have changed and led to similar outcomes with less operative trauma. However, these developments must be critically evaluated, as these interventions could also lead to a prolonged disease state with worse outcomes such as pseudocyst formation, duodenum, and bile duct obstruction. In addition, some minimal-invasive and robotic approaches become more and more popular. This review highlights some of the recent studies in pancreatic surgery,

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Chronic pancreatitis

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Chronic pancreatitis is a progressive fibroinflammatory disease that exists in large-duct (often with intraductal calculi) or small-duct form. In many patients this disease results from a complex mix of environmental (eg, alcohol, cigarettes, and occupational chemicals) and genetic factors (eg, mutation in a trypsin-controlling gene or the cystic fibrosis transmembrane conductance regulator); a few patients have hereditary or autoimmune disease. Pain in the form of recurrent attacks of pancreatitis (representing paralysis of apical exocytosis in acinar cells) or constant and disabling pain is usually the main symptom. Management of the pain is mainly empirical, involving potent analgesics, duct drainage by endoscopic or surgical means, and partial or total pancreatectomy. However, steroids rapidly reduce symptoms in patients with autoimmune pancreatitis, and micronutrient therapy to correct electrophilic stress is emerging as a promising treatment in the other patients. Steatorrhoea, diabetes, local complications, and psychosocial issues associated with the disease are additional therapeutic challenges.

Introduction

Chronic pancreatitis is a progressive inflammatory disorder in which pancreatic secretory parenchyma is destroyed and replaced by fibrous tissue, eventually leading to malnutrition and diabetes. Two forms are recognised—a large-duct calcifying type[1] and a small-duct variant.[2–4] The disease is uncommon in Europe and the USA; its prevalence in France is 26 per 100 000 people.[5] This prevalence is not dissimilar to the middle of three estimates from Japan,[6,7] but considerably lower than the figure of 114–200 per 100 000 in south India.[7]

The main symptom of chronic pancreatitis is usually pain, which occurs as attacks that mimic acute pancreatitis or as constant and disabling pain. Despite decades of research, treatment of chronic pancreatitis remains mostly empirical, and thus patients are repeatedly admitted to hospital and have interventional procedures, which strains medical resources.[8] This absence of progress in treatment is a sign of uncertainty about how the identified causative factors lead to the disease. Therefore, in this Seminar we focus on the pathophysiology and pathology of chronic pancreatitis before describing clinical management.

Search strategy and selection criteria

We searched PubMed and the Cochrane library (to August, 2010) for reviews on chronic pancreatitis. We used Google scholar for specific searches, with "chronic pancreatitis" as the key phrase combined with "epidemiology", "pathology", "aetiology", "gene mutations", "pathogenesis", "classification", "diagnosis", "pancreatic function tests", "pancreatic imaging tests", "treatment of pain", "pancreatic enzyme therapy", "micronutrient therapy", "antioxidant therapy", "endoscopic treatment", or "surgical treatment". We selected the most up-to-date articles but did not disregard commonly referenced older publications. We also examined the reference lists of identified papers and selected those that we judged to be relevant. Review articles and book chapters are cited to give readers more details and references than this Seminar can accommodate.

Definition

Traditionally, chronic pancreatitis has been classed as fundamentally different from acute pancreatitis—the latter is usually characterised by restoration of normal pancreatic histology after full clinical recovery.[1] However, acute, recurrent acute, and chronic pancreatitis are now regarded as a disease continuum.[9,10] There are several reasons for this change: recurrent acute pancreatitis can develop into chronic pancreatitis;[10–12] there is an overlap in causative factors, both genetic and environmental;[10,13] experimental protocols can be modified to induce each condition;[14] and the pancreatitis attack is stereotyped—patients have severe abdominal pain and increased blood amylase, lipase, and trypsinogen.

Pathophysiology and pathology

Experimental studies since the 1950s have shown that an attack of pancreatitis begins as pancreastasis,[13] prevention of apical exocytosis in the pancreatic acinar cell (figure 1).[15] The acinar cell quickly releases newly synthesised enzyme via the basolateral membrane into lymphatics, by way of the interstitium, and directly into the bloodstream.[16] Some zymogen granules also release their stored enzyme basolaterally.[15] These events result in inflammation.[17] Findings from prospective clinical studies concur with this pancreastasis–pancreatitis sequence.[13,17]

Experimental work has pinpointed a burst of reactive oxygen species (ROS) as the trigger of so-called pancreastasis[18] and as the potentiator of inflammation by activating signalling cascades that convert the damaged acinar cell into a factory for chemokines and cytokines.[19,20] ROS serve several physiological roles, including in signal transduction,[13,21] but an excess of ROS compared with antioxidant capacity (electrophilic stress) is potentially very damaging. The exocytosis blockade seems to be caused by disruption of the methionine trans-sulphuration pathway that produces essential methyl and thiol (principally glutathione) moieties.[17,22] This problem also occurs in clinical acute or acute-on-chronic pancreatitis.[23–25]

In patients who develop large-duct chronic pancreatitis, studies in the quiescent phase of the disease show that the composition of pancreatic fluid changes in a manner

NHS England

Clinical Commissioning Policy: Total pancreatectomy with islet auto transplant for chronic pancreatitis (adults)

NHS England Reference: 170058P

Policy Statement

NHS England will commission total pancreatectomy with islet auto transplant for chronic pancreatitis in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About chronic pancreatitis

Chronic pancreatitis (CP) is long term (chronic) inflammation of the pancreas (pancreatitis) characterised by an irreversible, permanent and progressive destruction of the pancreatic tissue. Chronic pancreatitis maybe either hereditary,

with a genetic cause often presenting in childhood or young adulthood or acquired which usually presents in adulthood. Alcohol is the most frequent cause of acquired CP worldwide. After alcohol, the next largest sub-group are patients in whom no specific cause has been identified, called idiopathic CP. The fraction of patients with idiopathic disease varies from 10-30%. In recent years there has been a growing recognition of genetic factors causing pancreatitis, such as anatomic abnormalities; susceptibility with smoking; autoimmune factors; and several genetic susceptibility factors, of which mutations in four genes (*PRSS1, SPINK1, CFTR, CTRC*) are the most common. This latter form is termed hereditary chronic pancreatitis and is relatively uncommon but these patients have an increased risk of developing pancreatic cancer.

The pancreas is an organ in the abdomen which produces digestive juices, and also the hormone insulin from within islets. CP is a disabling condition with a number of symptoms, of which the most debilitating is severe abdominal pain. Long term pancreatitis may also interfere with insulin production and lead to diabetes. The pain has been described as a burning or shooting pain which can last for several hours or days in some cases and may eventually become persistent. Some people also experience symptoms of nausea and vomiting during the pain. As chronic pancreatitis progresses, the painful episodes may become more frequent and severe. Some patients may have 50-100 hospital admissions a year to manage their pain.

About current treatments

Current treatment options are based on symptom control, especially of abdominal pain and vomiting, which usually requires the use of opiate (containing opium) painkillers such as morphine. These treatments do not cure the underlying problem in the pancreas. The abdominal pain is often so severe patients require large doses of morphine which are given over long periods of time until a definitive treatment is recommended. Unfortunately high dose opiates have a number of significant adverse effects, including drug dependence which leads to a rapid deterioration in quality of life. Patients should be managed with input from chronic pain services to ensure that their pain management is optimised. Some patients may benefit from

surgical procedures; these may include drainage procedures in patients where there is dilatation of the main pancreatic duct and/or segmental resection of the pancreas where appropriate. Patients may also benefit from nerve block type procedures that include endoscopic ultrasound guided coeliac plexus block or thorascopic splanchnicectomy. Over time, with on–going damage to the pancreas the patient will develop diabetes and problems with gut malabsorption due to lack of digestive enzymes from the pancreas.

About the new treatment

The primary goal of surgery is to remove the cause of the symptoms, the pancreas (total pancreatectomy) with an aim to control pain resistant to other therapies; islet auto transplantation (a procedure where the patient's own islet cells are isolated and infused into their liver) is intended to prevent or lessen the very brittle (hard to control) diabetes mellitus which is an inevitable result of total pancreatectomy. Patients will also need lifelong oral replacement therapy of the digestive enzymes produced by the pancreas.

What we have decided

NHS England has carefully reviewed the evidence to treat chronic pancreatitis with total pancreatectomy with islet auto transplant. We have concluded that there is enough evidence to make the treatment available.

Systematic review

Systematic review of total pancreatectomy and islet autotransplantation for chronic pancreatitis

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Background: **Total pancreatectomy and islet autotransplantation (TP/IAT) is a treatment option in a subset of patients with chronic pancreatitis. A systematic review of the literature was performed to evaluate the outcome of this procedure, with an attempt to ascertain when it is indicated.**

Methods: **MEDLINE (1950 to present), Embase (1980 to present) and the Cochrane Library were searched to identify studies of outcomes in patients undergoing TP/IAT. Cohort studies that reported the outcomes following the procedure were included. The MOOSE guidelines were used as a basis for this review.**

Results: **Five studies met the inclusion criteria. The techniques reported for pancreatectomy and islet cell isolation varied between studies. TP/IAT was successful in reducing pain in patients with chronic pancreatitis. Comparing morphine requirements before and after the procedure, two studies recorded significant reductions. Concurrent IAT reduced the insulin requirement after TP; the rate of insulin independence ranged from 46 per cent of patients at 5 years' mean follow-up to 10 per cent at 8 years. The impact on quality of life was poorly reported. The studies reviewed did not provide evidence for optimal timing of TP/IAT in relation to the evolution of chronic pancreatitis.**

Conclusion: **This systematic review showed that TP/IAT had favourable outcomes with regard to pain reduction. Concurrent IAT enabled a significant proportion of patients to remain independent of insulin supplementation.**

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Introduction

Chronic pancreatitis is characterized by irreversible morphological and functional abnormalities due to long-standing inflammation and fibrosis of the pancreatic parenchyma. This is associated with intractable pain, malabsorption and diabetes mellitus. Although there is significant aetiological variation worldwide, the most common predisposing factor in the UK is alcohol excess[1]. Less common causes include biliary disease, hyperlipidaemia, hyperparathyroidism, and autoimmune and familial pancreatitis.

Chronic pain is the most debilitating symptom of chronic pancreatitis and often more difficult to manage than its associated endocrine or exocrine dysfunction. Evidence suggests that duct obstruction with resulting raised intraductal pressure[2], pancreatic ischaemia[3], neuronal injury and neuroimmune interaction[4] contribute to pain in pancreatitis. Furthermore, long-term morphine use can result in morphine-induced hyperalgesia characterized by reduced cold-induced pain tolerance[5].

A carefully managed progression from non-opioid to opioid analgesia is appropriate in the management of chronic pancreatitis. Interventional procedures such as coeliac plexus block may be considered[6], whereas early involvement of a chronic pain team ensures treatment tailored to the needs of the patient and maintenance of quality of life. When these measures fail, and in a carefully selected subset of patients in whom substance abuse is not

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ORIGINAL ARTICLE

Systematic review and meta-analysis: islet autotransplantation after pancreatectomy for minimizing diabetes

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Summary

Objective Islet autotransplantation (IAT) may decrease the morbidity and mortality of postpancreatectomy diabetes mellitus. The current systematic review and meta-analysis examined the rate of insulin independence (II) and mortality after IAT post-total (TP) or partial pancreatectomy (PP).

Methods Ovid MEDLINE, EMBASE, Web of Science, SCOPUS and reference lists were searched until 31 January 2011. Eligible studies enrolled adult patients with IAT post-TP or PP, regardless of study design, sample size and language. Two investigators identified eligible studies and extracted data independently. From each study, 95% confidence intervals (CIs) were estimated and pooled using random effects meta-analysis.

Results Fifteen observational studies were eligible (11 IAT post-TP, two post-PP and two including both). The II rates for IAT post-TP at last follow-up and transiently during the study were 4·62 per 100 person-years (95% CI: 1·53–7·72) and 8·34 per 100 person-years (95% CI: 3·32–13·37), respectively. In the later group, patients achieved transient II lasting 15·57 months (95% CI: 10·35–20·79). The II rate at last follow-up for IAT post-PP was 24·28 per 100 person-years (95% CI: 0·00–48·96). Whereas the 30-day mortality for IAT post-TP and post-PP was 5% (95% CI: 2–10%) and 0, respectively, the long-term mortality was 1·38 per 100 person-years (95% CI: 0·66–2·11) and 0·70 per 100 person-years (95% CI: 0·00–1·80) respectively.

Conclusions IAT postpancreatectomy offers some patients a chance for insulin independence. Better data reporting are essential to establish the risks and benefits of IAT after pancreatic surgery.

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Introduction

Islet autotransplantation (IAT) is a well-known procedure to decrease the morbidity related to diabetes mellitus (DM) after extensive pancreatic resection for chronic pancreatitis (CP). It is estimated that <50% of patients with CP eventually require operative intervention as a means of treating severe abdominal pain or other CP-related complications.[1] Total pancreatectomy (TP) is usually performed as a last resort for CP with persistent or recurrent pain following less-extensive procedures. However, TP alone always results in brittle DM contributing to morbidity and mortality of this procedure. The advent of IAT provides patients post-TP a chance of pain relief, without complete loss of pancreatic endocrine function.[2] Furthermore, in addition to end-stage CP with disabling pain, IAT post-TP or partial pancreatectomy (PP) has been utilized for an expanded series of benign pancreatic diseases including pancreatic pseudocysts, cystic neoplasms, insulinomas and neuroendocrine tumour.[2]

To our knowledge, the world's first IAT was performed at the University of Minnesota in 1977.[3] A woman with CP underwent IAT post near-TP and subsequently remained insulin independent and pain free until death 6 years later as a result of a cause unrelated to IAT.[4] However, early attempts at islet isolation were limited by the lack of standardization in collagenase preparations (an essential component of success in islet isolation), equipment and isolation procedures. The development of Liberase in 1995 resulted in the availability of better reagents and standardization of islet isolation, thus leading to specialized islet isolation techniques utilizing reliable reagents.[5,6] These technologies and procedures were developed for islet lo-transplantation, but the deployment of these programs for islet auto-transplantation was a natural next step. The number of centres doing islet autografts has increased during the past decade based on the literature. Up to now, IAT has been implemented at more than 20 centres worldwide.

However, published literature regarding variables relevant to glycemic status, mortality and follow-up is limited and heterogenous. Therefore, we performed a systematic review and meta-analysis of human IAT studies to summarize the rate of insulin

Breast Reconstruction with Acellular Matrix

Question: Should acellular matrix be added to the breast cancer line for post-mastectomy breast reconstruction?

Question sources: multiple CCOs, multiple providers

Issue: Acellular dermal matrix (ADM) is an implant material used in breast reconstruction after mastectomy. ADMs are soft tissue matrix grafts created by a process that results in decellularization but leaves the extracellular matrix intact. This matrix provides a scaffold upon and within which the patient's own cells can repopulate and revascularize the implanted tissue. Several products are currently on the market/FDA approved.

Acellular matrix for breast reconstruction was reviewed as a new CPT code in 2011. At that time, this type of implant for reconstruction was found to have a 12% risk of complications and HERC decided not to cover this procedure due to increased risk versus usual reconstruction techniques. This lack of coverage was affirmed in March, 2015.

This material is also listed by the manufacturer as being used in tympanoplasty, parotidectomy, facial soft tissue defects, fascial sling, lower eyelid reconstruction, nasal reconstruction, nasal septal perforation, cleft palate repair, oral resurfacing, vestibuloplasty, radial forearm freeflap repair, abdominal wall repair, and for burn therapy. Major insurers only appear to be covering for breast reconstruction after mastectomy.

Multiple CCOs have contacted HERC staff for clarification and re-evaluation of the policy of non-coverage for ADM. The surgeons in many of their communities are insisting that use of ADM is standard of care for post-mastectomy breast reconstruction.

The most recent American Society of Plastic Surgeons (2015) data estimate that acellular dermal matrices were used in 65 percent of nonautologous breast reconstructions in the United States (Lennox 2017).

From CareOregon

> Based on conversations…with Juliana Hansen at OHSU and Bruce Weber at Good Samaritan, these tissue expanders are the current standard of care, and are needed to complete breast reconstruction in 50-90% of cases, depending on the surgeon.
>
> It appears that the older plastic surgeons are the only ones trained to do recon breast surgery [without] using the matrix and as they are retiring only the younger plastic surgeons are available for the surgeries but they are not trained to do the reconstruction without using matrix. So this has become a problem with nobody trained to do the surgery the older way (without using matrix).
>
> …the decision to use this material is often made intraoperatively, if the patient lacks sufficient tissue of her own to achieve an optimal reconstruction result. I don't think a formal review of the literature is needed in this case, as apparently the benefits sufficiently exceed the risks that it has become standard practice, particularly among more recently trained plastic surgeons.

From Samaritan Health:

> One of our in-network plastic surgeons is questioning the placement of CPT 15777 (acellular dermal matrix) on line 660 stating that to his knowledge there are no other effective therapies for breast reconstruction and that the use of acellular dermal matrix is the current standard of care in non-autologous breast reconstruction used in over 80% of implant-based breast reconstructions in the US. He is asking me to advise him how to proceed surgically to treat his patients.

Plastic surgeons contacted as part of this review felt that cellular dermal matrix was generally standard of care and felt that the complications rate was similar to other techniques. Specific feedback from surgeons:

From Dr. Mark Jewell:

> Your records review is very outdated regarding the safety profile of ADM. ADM is a necessary part of contemporary breast reconstruction and unless OHP will pay for it in primary and secondary cases, I will not accept OHP covered patients.
>
> One additional topic is the use of ADM to address capsular contracture in breast reconstruction. ADM seems to be effective in treating capsular contracture versus ordinary capsulectomy procedures. I would argue that by not offering coverage for ADM during the initial breast reconstruction procedure, OHP is subjecting its covered to an increased risk of capsular contracture and reoperation along with risk of unsuccessful revisionary surgery.

From Dr. Dann Leonard

> I too have a large breast cancer reconstruction practice and use ADM regularly. The use of a dual plane pocket with supplement using ADM inferiorly, is now standard of care, and Medicaid patients are receiving inferior treatment under the current rules. I am sure that none of us want to give the poor of our state a lesser set of medical care standards.

Current code status

15777 (Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (eg, breast, trunk)) is on line 660/GN173.

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
15777	Acellular dermal matrix for soft tissue reinforcement (eg, breast, trunk)	Greater harms than other effective therapies	March, 2015

Evidence

Systematic reviews

1) **Hallberg 2018**, systematic review and meta-analysis of use of ADM for immediate breast reconstruction
    a. N=51 studies (28 non-randomized controlled studies and 23 case series)
        i. Inclusion criteria were all randomised and non-randomised controlled trials, and case series comprising > 200 patients reconstructed with AlloDermVR or > 20 with any other ADM or matrices/meshes
        ii. CEbP rated this review as fair to good quality
    a. The certainty of evidence for overall complication rate and implant loss is low
        iii. Overall complication rate (17 cohort studies and 18 case series)
            1. All the cohort studies had severe study limitations and a meta-analysis demonstrated high heterogeneity.
            2. The pooled relative risk ratio for the ten studies using biological matrix (ADM) compared with no matrix, including 6122 breasts, was 1.31 with a 95% confidence interval (CI) of 0.94–1.81.
            3. In summary, the use of matrices in breast reconstruction may result in little or no difference in the rate of complications compared without the use of matrices in women operated on for breast cancer. The certainty of evidence is low.
        iv. Implant loss (16 cohort studies, 21 case series), all with severe study limitations.
            1. A meta-analysis of studies that used biological matrix (ADM) demonstrated a high heterogeneity. The pooled relative risk ratio was 1.02 with a 95% CI of 0.65–1.58, including 16,830 breasts.
            2. A meta-analysis of studies that used synthetic meshes did not reveal a significant difference between the study groups either.
            3. Four studies, with severe limitations, reported implant loss per patient. The pooled relative risk ratio was 1.33 with a 95% confidence interval of 0.73–2.43, including 1307 patients.
            4. The case series reported implant loss at frequencies varying from 0% to 17%.
            5. In summary, it is uncertain whether there is little or no difference in the incidence of implant loss after breast reconstruction with matrix compared with no matrix in women with surgery for breast cancer. The certainty of evidence is very low.
    a. The certainty of evidence for delay of adjuvant treatment, implant loss, infection, capsular contraction and aesthetic outcome is very low
        a. Infection (21 cohort studies, 20 case series)
            i. All the cohort studies had severe study limitations.
            ii. A meta-analysis of studies that used biological matrix (ADM), including 8144 breasts, demonstrated an increased risk of infection with a relative risk ratio of 1.61 and a 95% CI of 1.20–2.15.

iii. The pooled relative risk ratio was 1.30 with a 95% confidence interval of 1.14–1.48 for the four studies using biological matrix (ADM) compared with no matrix.
iv. It is uncertain whether the use of matrices in breast reconstruction increases the risk of infection. The certainty of evidence is very low.

b. Capsular contraction (5 cohort studies, 5 case series)
i. All the cohort studies had severe study limitations and a meta-analysis demonstrated moderate heterogeneity.
ii. The pooled relative risk ratio using biological matrix (ADM) compared with no matrix, including 1645 breasts was 0.55 with a 95% confidence interval of 0.38–1.69.
iii. The case series reported capsular contraction at various frequencies; 0.4–13%.
iv. It is uncertain whether there is little or no difference in the incidence of capsular contraction after breast reconstruction with matrix compared with no matrix in women operated for breast cancer. The certainty of evidence is very low.

c. Aesthetic outcome (3 studies)
i. A total of 328 breasts were reconstructed with matrix, and 307 breasts were reconstructed without matrix. Evaluators who were unaware of the surgical method scored the aesthetic results. Three studies reported different results with regard to the overall aesthetic outcome, in one of them a statistically significant improved aesthetic score could be seen, while the opposite was reported in the other. The third study only reported five different sub-scores, with no consistent results in favor of either of the two methods. None of the studies used validated scales. It is uncertain whether there is little or no difference in aesthetic outcome following the use of matrix in patients with surgery for breast cancer. The certainty of evidence is very low.

b. In conclusion, there is a lack of high-quality studies that compare the use of matrix with no matrix in immediate breast reconstruction. Specifically, there are no data on risk of recurrence of cancer, delay of adjuvant treatment and health related quality of life (HRQoL). In addition, there is a risk of bias in many studies. It is often unclear what complications have been included and how they have been diagnosed, and how and when capsular contracture and aesthetic outcome have been evaluated. Controlled trials that further analyze the impact of radiotherapy, type of matrix and type of procedure (one or two stages) are necessary.

2) **Smith 2018**, meta-analysis of risks of human acellular dermal matrix (HADM) for breast reconstruction
a. Update of Kim 2012
b. N=13 studies
c. Complication rates were higher in HADM patients compared to submuscular reconstruction: total complications, 17.7% versus 6.1%; seroma, 8.3% versus 5.4%; infection, 7.2% versus 5.9%; and flap necrosis, 14.7% versus 7.1%. Meta-analysis revealed a statistically significant increased risk of total complications in patients who underwent reconstruction with HADM when compared with their submuscular reconstruction cohort (p = 0.03; relative risk (RR) = 1.46; confidence interval (CI): 1.04–2.04). Patients who underwent reconstruction with HADM demonstrated a significantly

increased risk of flap necrosis ($p < 0.01$; RR = 2.39; CI: 1.8–3.16) and infection ($p = 0.02$; RR = 1.5; CI: 1.07–2.09) when compared with those who underwent submuscular reconstruction. There was no significant difference in seroma, hematoma, or implant explantation between these two groups.

d. *Conclusions:* This study suggests an increased risk of overall complications, specifically infection and flap necrosis, in patients who underwent tissue expander/implant breast reconstruction with HADM when compared with those who underwent submuscular placement.

3) **Lee 2016**, meta-analysis of ADM for implant-based breast reconstruction
   a. N=23 studies (6199 patients)
      i. 1 RCT
      ii. 2 prospective cohort studies
      iii. Majority were retrospective cohort studies (range 32-628 patients)
      iv. 3 studies included in Hallberg above
   b. Increased risks: The use of ADM significantly elevated the risks of infection, seroma, and mastectomy flap necrosis, but did not affect the risks of implant loss, unplanned reoperation, and total complications.
      i. Infection: risk ratio 1.42 [1.02,1.99]
      ii. Seroma: risk ratio 1.41 [1.12, 1.78]
      iii. Mastectomy flap necrosis: risk ratio 1.44 [1.11, 1.87]
   c. No difference in risk:
      i. Unplanned return to OR: risk ratio 1.09 [0.63, 1.90]
      ii. Implant loss: risk ratio 1.00 [0.68, 1.48]
      iii. Total complications: risk ratio 1.08 [0.87, 1.34]
   d. Reduced risks: The risks of capsular contracture and implant malposition were significantly reduced by the application of ADM. The ADM allows for significantly greater intraoperative expansion and reduced frequency of injection to complete expansion.
      i. Capsular contracture: risk ratio 0.26 [0.15, 0.47]
      ii. Implant malrotation: risk ratio 0.21 [0.07, 0.59]
      iii. Injection frequency: risk ratio -1.56 [2.77, 0.35]
      iv. Time to complete expansion: risk ratio -17.73 [-40.36, 4.91]
   e. Conclusions. According to this meta-analysis, the increasing risks for serious complication and overall morbidity related to ADM use might not be remarkable, while its benefits for preventing late complications and improving expander dynamics might be appreciable. Although future well-controlled studies would be required, the implant-based breast reconstruction using ADM may be reliable and advantageous.

4) **Potter 2015**, systematic review of ADM for implant-based breast reconstruction
   f. N=69 articles (8 systematic reviews, 1 RCT, 40 comparative studies and 20 case series)
      i. All at high risk of bias
      ii. ADM was most commonly used for immediate (40) two-stage implant-based breast reconstruction (IBBR; 36) using human ADM (47), with few studies evaluating ADM-assisted single-stage procedures (10). Heterogeneity between study design and, especially, outcome measurement precluded meaningful data synthesis.
      iii. Conclusion: Current evidence for the value of ADMs in IBBR is limited. Use in practice should therefore be considered experimental, and evaluation within registries or well designed and conducted studies, ideally RCTs, is recommended to prevent widespread adoption of a potentially inferior intervention.

5) **Krisnan 2013**, cost-effectiveness evaluation for acellular dermal matrix for immediate breast reconstruction
    a. The overall complication rates were 30% and 34.5% with and without ADM. The decision model revealed a baseline cost increase of $361.96 when acellular dermal matrix is used. The increase in Quality-Adjusted Life Years (QALYs) is 1.37 in the population with acellular dermal matrix. This yields a cost-effective incremental cost-utility ratio (ICUR) of $264.20/QALY. Univariate sensitivity analysis confirmed that using acellular dermal matrix is cost-effective even when using retail costs for unilateral and bilateral reconstructions.
6) **Maxwell 2014**, systematic review of ADM for breast revision surgery
    a. N=7 studies (570 patients/736 breasts)
        i. All case series
    b. The recurrence rate for capsular contracture was 1.1 percent to 4.3 percent over an average follow-up period of 17 months to 3.1 years. By comparison, the 3-year cumulative incidence of capsular contracture in the Mentor Core study was 19 percent in the revision augmentation cohort.

RCTs not included in above systematic reviews

1) **Lohmander 2019**, RCT of acullular breast matrix
    a. N=135 women (64 with ADM, 65 without ADM)
    b. Four patients (6%) in each group had reconstructive failure with implant loss, but IBBR with ADM exhibited a trend of more overall complications and reoperations (difference 0.16, 95% CI, -0.01 to 0.32, P = 0.070), and with higher risk of wound healing problems (P = 0.013).
    c. Conclusions: With 6-months follow-up for all participants, immediate IBBR with ADM carried a risk of implant loss equal to conventional IBBR without ADM, but was associated with more adverse outcomes requiring surgical intervention. Further investigation of risk factors and patient selection in a long-term follow-up is warranted.
1) **Dikmans 2017**, RCT of one stage vs two stage breast reconstruction
    a. N=142 women (59 one stage implant-based breast reconstruction (IBBR) with ADM; 62 with two stage reconstruction without ADM)
    b. One-stage IBBR with ADM was associated with significantly higher risk per breast of surgical complications (crude odds ratio 3·81, 95% CI 2.67–5.43, p<0·001), reoperation (3.38, 2.10–5.45, p<0·001), and removal of implant, ADM, or both (8.80, 8.24–9.40, p<0·001) than two-stage IBBR. Severe (grade 3) adverse events occurred in 26 (29%) of 91 breasts in the one-stage IBBR with ADM group and in five (5%) of 92 in the two-stage IBBR group. The frequency of mild to moderate adverse events was similar in the two groups.
    c. Interpretation: Immediate one-stage IBBR with ADM was associated with adverse events and should be considered very carefully. Understanding of selection of patients, risk factors, and surgical and postsurgical procedures needs to be improved.

Submitted literature:

1) **Basu 2012,** non-systematic review of ADM for prevention of capsular contracture in breast reconstruction
    a. Note: lead author is a consultant for Lifecell Corp.

   b. N=15 articles (886 women/1,381 breasts)
      i. 1 prospective cohort, 13 retrospective cohort, 1 case series
   c. Rate of capsular contracture: 0-4%
   d. 1 study compared ADM against non-ADM reconstruction
      i. N=123 patients (208 breasts) with immediate two-stage construction with AlloDerm
      ii. N=80 patients (129 breasts) no ADM reconstruction
      iii. Capsular contracture was observed in eight out of 208 breasts in the acellular dermal matrix group (3.8 percent) and 25 out of 129 breasts in the nonmatrix group (19.4 percent).
   e. although the level of evidence remains III or lower and the studies are limited by duration of follow-up or by small sample size (low power), we did find that all the clinical studies revealed capsular contracture rates ranging between 0 percent and 4 percent.
   f. While the evidence for capsular contracture is suggestive, especially in postmastectomy breast reconstruction, the level of evidence should improve through better controlled studies with higher power, longer follow-up, and attention to the use of acellular dermal matrix and capsular contracture rates in revisionary breast surgery.
2) **Jansen 2011**, systematic review of AlloDerm for breast reconstruction
   a. N=14 studies (3 prospective cohort, 11 retrospective cohort)
      i. N=417 patients (623 breasts)
      ii. No comparison groups
   b. Complication rates were as follows: infection, 0 to 11 percent; hematoma, 0 to 6.7 percent; seroma, 0 to 9 percent; partial flap necrosis, 0 to 25 percent; implant exposure with removal, 0 to 14 percent; implant exposure with salvage, 0 to 4 percent; capsular contracture, 0 to 8 percent; and rippling, 0 to 6 percent.
   c. **Conclusions:** Complications using AlloDerm are comparable to those of non- AlloDerm alloplastic reconstructions. AlloDerm appears to confer a low rate of capsular contracture.

Disposition of other submitted literature:
1) Spear 2011: case series of 52 patients; higher level evidence available
2) Moyer 2014: case series of 9 patients; higher level evidence available

Future research:
1) Potter 2016
   a. Pragmatic RCT to evaluate the relative risks and benefits of ADMs in breast reconstruction
   b. Protocol published 2016, unclear when any results will be published

Expert society recommendations:
1) American Society of Plastic Surgeons 2013
   a. Recommendation: Evidence on acellular dermal matrix (ADM) in post-mastectomy expander/implant breast reconstruction is varied and conflicting. Surgeons should evaluate each clinical case individually and objectively determine the use of ADM.
   b. Level III Evidence; Recommendation Grade: C.

2) **Association of Breast Surgery and the British Association of Plastic, Reconstructive and Aesthetic Surgeons 2013**
    a. Recommends use only in a selected population

Other payer policies:
Most major insurers cover acellular dermal matrix for breast reconstruction, but only specific products.

HERC staff summary

Overall, the evidence regarding acellular dermal matrix (ADM) for breast reconstruction mainly relies on small cohort and case series studies and the level of evidence is judged to be low to very low for various outcomes. Three RCTs were identified examining ADM for primary reconstruction vs conventional reconstruction, which found increased risk of adverse events and reoperation and implant loss with ADM.

The systematic reviews for acellular dermal matrix use in breast reconstruction with implants or tissue expanders after mastectomy finds conflicting conclusions regarding complication rates and benefits. One systematic review and meta-analysis found significantly higher complication rates (infection, seroma, flap necrosis) with ADM compared to other reconstruction techniques not using ADM, while another systematic review and meta-analysis found no significant difference in complication rates. This difference might be explained by the inclusion of different types of complications or different definitions of a complication. Similarly, a reduction in rate of capsular contracture is seen in one systematic review and meta-analysis, but not in another. However, patient satisfaction is the same with both techniques. There is also increased rates of reoperation with ADM, which may counteract any improvement in capsular contracture. In general, the literature indicates limited, if any, benefit with use of ADMs but risk of increased complications. The major plastic surgery specialty society in the US expresses caution on use of ADMs due to varied and conflicting evidence.

The evidence on the use of ADM for revision of breast reconstruction consists solely of case series.

Many CCOs are indicating that they cannot contract with surgeons who do not use ADM. All major insurers cover ADM for breast reconstruction, although they limit the brands they include in coverage.

CEbP secondary review

Conclusions:

1. Of the recently published systematic reviews, the review by Hallberg and colleagues appears to be the most comprehensive (k=51). There is generally poor overlap of included studies among the recent systematic reviews published on this topic. It is likely that many of the studies included in other reviews did not meet criteria for inclusion in the Hallberg review because they did not report on a sufficient number of reconstructions. Center staff assessed the methodologic quality of the Hallberg review as good.
2. An additional systematic review focused on harms and adverse events reported in comparative cohort studies of ADM-assisted reconstruction and submuscular reconstructions found that ADM-assisted procedures were associated with a greater risk of complications including flap necrosis and infection.
3. Two randomized controlled open-label trials (reported in 3 manuscripts) were published between 2017 and 2019.
    a. The BRIOS study, which compared 1-stage implant-based breast reconstruction with ADM to 2-stage implant-based breast reconstruction, found that 1-stage procedures with ADM did not improve patient reported quality of life or aesthetic outcomes and were associated with a higher rate of adverse events.

b. A second trial reporting 6-month safety outcomes between IBBR with ADM and IBBR without ADM found that while implant loss was similar between the two groups, the rate of adverse events was greater in the group treated with IBBR with ADM.

HERC staff recommendation:

1) Do not add coverage for acellular dermal matrix for breast reconstruction
    a. Evidence to date is varied and conflicting regarding complication rates, as well as conflicting findings on benefits such as reduced contracture rates compared to other breast reconstruction techniques
2) Move acellular dermal matrix form line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS to line 500 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS
    a. Unclear if any difference in benefits or harms compared to other techniques
    b. Modify GN172 as shown below
    c. Modify GN173 as shown below

GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 500

The following interventions are prioritized on Line 500 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
15777	Acellular dermal matrix for soft tissue reinforcement (eg, breast, trunk)	Unclear benefits versus other effective therapies; increased risk of adverse events	May 2019

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
~~15777~~	~~Acellular dermal matrix for soft tissue reinforcement (eg, breast, trunk)~~	~~Greater harms than other effective therapies~~	~~March 2019~~

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REVIEW ARTICLE

Benefits and risks with acellular dermal matrix (ADM) and mesh support in immediate breast reconstruction: a systematic review and meta-analysis

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ABSTRACT

In modern implant-based immediate breast reconstruction, it has become common to use biological acellular dermal and synthetic matrices in combination with a tissue expander or an implant. The aim of this systematic review was to examine differences in recurrence of cancer, impact on oncological treatment, health related quality of life, complications and aesthetic outcome between matrix and no matrix in immediate breast reconstruction. Systematic searches, data extraction and assessment of methodological quality were performed according to predetermined criteria. Fifty-one studies were eligible and included in the review. The certainty of evidence for overall complication rate and implant loss is low (GRADE ⊕⊕□□). The certainty of evidence for delay of adjuvant treatment, implant loss, infection, capsular contraction and aesthetic outcome is very low (GRADE ⊕□□□). No study reported data on recurrence of cancer or health related quality of life. In conclusion, there is a lack of high quality studies that compare the use of matrix with no matrix in immediate breast reconstruction. Specifically, there are no data on risk of recurrence of cancer, delay of adjuvant treatment and Health related quality of life (HRQoL). In addition, there is a risk of bias in many studies. It is often unclear what complications have been included and how they have been diagnosed, and how and when capsular contracture and aesthetic outcome have been evaluated. Controlled trials that further analyse the impact of radiotherapy, type of matrix and type of procedure (one or two stages) are necessary.

ARTICLE HISTORY
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KEYWORDS
Breast reconstruction; aceullar dermal matrix; ADM; mesh; matrix; systematic review; implant; tissue expander

Introduction

In modern implant-based immediate breast reconstruction it has become common to use matrices in combination with a tissue expander or an implant. The usage of matrices in breast surgery was first reported in revisional aesthetic breast surgery in 2003 [1] and in breast reconstruction in 2005 [2]. Matrices can be divided into biological acellular dermal matrices (ADM) and synthetic meshes. ADMs are soft tissue grafts created by decellularisation of tissue, leaving the extracellular matrix. The matrix becomes a scaffold on which the patient's own cells can grow and thereby revascularise the graft and create an extra tissue layer. There are many different ADMs currently on the market, including, human-derived (e.g. AlloDerm®), porcine-derived (e.g. Permacol™, Strattice®) and bovine-derived (e.g. Veritas®). Synthetic meshes are knitted from permanent or absorbable fibres, work like an internal supporting bra, and are widely used in different surgical procedures. Examples include Vicryl®, TIGR® and TiLOOP® [3].

Often stated advantages [4] of using matrices include a better control and definition of the implant pocket and inframammary fold, the possibility to use a dual plane technique and less muscle dissection [5–7] and less pronounced capsule formation [5,8]. A possible drawback is an increased risk for complications, such as infection, skin necrosis, loss of implant and seroma formation [9,10] and a non-negligible cost [11].

Reports have stated that the majority of plastic surgeons in the USA are now using a biological ADM in implant based breast reconstruction [4]. Nonetheless, no patient has had ADM *in situ* for more than 16 years, few more than 5 years, and we therefore know little about the long-term effects of ADM.

The aim of this systematic review was to examine differences in recurrence of cancer, impact on oncological treatment, health related quality of life, complications and aesthetic outcome between matrix and no matrix in immediate breast reconstruction. The report is based on a Health Technology Assessment (HTA) report [12].

Material and methods

Data sources and search strategies

During May 2016 systematic searches were performed in PubMed, Embase, the Cochrane Library, the CRD database and the websites of the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) and the Norwegian Knowledge Centre for the Health Services. Reference lists of relevant articles were also scrutinised for additional references. Searches were conducted using controlled vocabulary and title abstract words, using variations of *strattice OR veritas OR alloderm OR tigr OR surgisis OR permacol OR dermamatrix OR neoform OR*

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Human acellular dermis increases surgical site infection and overall complication profile when compared with submuscular breast reconstruction: An updated meta-analysis incorporating new products☆

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KEYWORDS
Tissue Engineering;
ADM;
Acellular Dermal Matrix;
Breast Reconstruction

Abstract *Background:* Human acellular dermal matrix (HADM) is an increasingly used adjunct to breast reconstruction. Previous meta-analyses demonstrate increased risks of complications, but these studies largely represent one product. The purpose of this study is to stratify outcomes on the basis of a meta-analysis of complications incorporating all new studies after 2012 and their associated new human-based products.
Methods: A query of the MEDLINE database for articles on HADM and breast reconstruction from January 2012 to October 2015 yielded 172 citations. Two levels of screening identified 47 relevant studies. Thirteen studies were used in comparative meta-analysis.
Results: Complication rates were higher in HADM patients: total complications, 17.7% versus 6.1%; seroma, 8.3% versus 5.4%; infection, 7.2% versus 5.9%; and flap necrosis, 14.7% versus 7.1%. Meta-analysis revealed a statistically significant increased risk of total complications in

☆Disclosures: Justin M. Sacks MD MBA is a consultant/speaker for LifeCell Inc.

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ORIGINAL ARTICLE – RECONSTRUCTIVE ONCOLOGY

Updated Evidence of Acellular Dermal Matrix Use for Implant-Based Breast Reconstruction: A Meta-analysis

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ABSTRACT

Background. Although the use of acellular dermal matrix (ADM) has increased exponentially, debates regarding its safety are still ongoing. There have been several meta-analyses; however, potential learning curve effects of using ADM might affect their outcomes. The present meta-analysis reappraised the potential benefits and risks of ADM on the outcome of implant-based breast reconstruction using recent publications.

Methods. Electronic databases were searched to identify relevant studies comparing the outcome of ADM use with traditional submuscular technique, which were published from 2011 to 2014. The relative risks of postoperative complications and mean difference of expander dynamics between the two groups were computed.

Results. A total of 23 studies representing 6199 cases were analyzed. There was one randomized controlled study and three prospective cohort studies. The use of ADM significantly elevated the risks of infection, seroma, and mastectomy flap necrosis, but did not affect the risks of implant loss, unplanned reoperation, and total complications. The risks of capsular contracture and implant malposition were significantly reduced by the application of ADM. The ADM allows for significantly greater intraoperative expansion and reduced frequency of injection to complete expansion.

Conclusions. According to this meta-analysis, the increasing risks for serious complication and overall morbidity related to ADM use might not be remarkable, while its benefits for preventing late complications and improving expander dynamics might be appreciable. Although future well-controlled studies would be required, the implant-based breast reconstruction using ADM may be reliable and advantageous.

Since acellular dermal matrix (ADM) was first introduced for the implant-based breast reconstruction in 2005, its application has gained rapid acceptance.[1] Its popularity has arisen from some putative benefits of ADM over traditional submuscular technique, including improved lower pole expansion, ease of defining inframammary fold, improved expander dynamics such as greater intraoperative expansion, decreased postoperative pain, and eventually improved cosmesis.[2–8]

However, there still remains a concern that the use of ADM may increase the risks of postoperative complications, which make surgeons hesitate to apply for it more widely.[9–11] Several studies have investigated the association between ADM use and the development of complications; however disparate results have been obtained.[9–15] To resolve this dispute, efforts for conducting a meta-analysis using previously published studies that compared the outcome of ADM use with that of submuscular technique have been made. To our knowledge, four systematic reviews have been published so far, three of which included meta-analysis.[16–19] Those showed similar outcomes that ADM use significantly increased the risks of infection, seroma, and even reconstruction failure compared with no use. However, the strength of their studies might be limited by potential learning curve effects, considering those reviews dealt with the studies that had been published up until 2010 or early 2011, which was conducted in relatively early experimental period of ADM.[9,13,20,21] Since the reviews have been published, ADM has been more popularly used with refinement of surgical technique for its application, and lots of 2-arm studies comparing the outcome of ADM group with

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Systematic review

Systematic review and critical appraisal of the impact of acellular dermal matrix use on the outcomes of implant-based breast reconstruction

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Background: **Acellular dermal matrix (ADM) may improve outcomes in implant-based breast reconstruction (IBBR). The aim of this study was critically to appraise and evaluate the current evidence for ADM-assisted IBBR.**

Methods: **Comprehensive electronic searches identified complete papers published in English between January 2000 and August 2013, reporting any outcome of ADM-assisted IBBR. All systematic reviews, randomized clinical trials (RCTs) and non-randomized studies (NRSs) with more than 20 ADM recipients were included. Studies were critically appraised using AMSTAR for systematic reviews, the Cochrane risk-of-bias tool for RCTs and its adaptation for NRSs. Characteristics and results of identified studies were summarized.**

Results: **A total of 69 papers (8 systematic reviews, 1 RCT, 40 comparative studies and 20 case series) were identified, all of which were considered at high risk of bias, mostly due to patient selection and selective outcome reporting. The median ADM group sample size was 51.0 (i.q.r. 33.0–127.0). Most studies were single-centre (54), and they were often single-surgeon (16). ADM was most commonly used for immediate (40) two-stage IBBR (36) using human ADM (47), with few studies evaluating ADM-assisted single-stage procedures (10). All reported clinical outcomes (for example implant loss) and more than half of the papers (33) assessed process outcomes, but few evaluated cosmesis (16) or patient-reported outcomes (10). Heterogeneity between study design and, especially, outcome measurement precluded meaningful data synthesis.**

Conclusion: **Current evidence for the value of ADMs in IBBR is limited. Use in practice should therefore be considered experimental, and evaluation within registries or well designed and conducted studies, ideally RCTs, is recommended to prevent widespread adoption of a potentially inferior intervention.**

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Introduction

Breast cancer affects over 50 000 women each year in the UK[1], of whom approximately 40 per cent[2] will require a mastectomy. The loss of a breast may impact profoundly on a woman's quality of life[3], and immediate breast reconstruction, reconstructive surgery performed at the same time as mastectomy, is offered routinely to all women unless contraindicated by co-morbidities or the need for adjuvant therapy, to improve outcomes[4]. Approximately one in five women requiring a mastectomy currently elects to undergo immediate breast reconstruction[5].

Implant-based breast reconstruction (IBBR) is the most commonly performed reconstructive procedure in the UK, accounting for almost 40 per cent of all immediate reconstructions performed after mastectomy for breast cancer[5,6]. Traditional subpectoral IBBR is usually performed as a two-stage procedure[7,8]. This is necessary because the subpectoral pocket created at the time of mastectomy is too small to accommodate a definitive implant and

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The cost effectiveness of acellular dermal matrix in expander–implant immediate breast reconstruction

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KEYWORDS
Acellular dermal matrix;
Cost effectiveness analysis

Summary *Background:* Expander–implant breast reconstruction is often supplemented with acellular dermal matrix (ADM). The use of acellular dermal matrix has allowed for faster, less painful expansions and improved aesthetics, but with increased cost. Our goal was to provide the first cost utility analysis of using acellular dermal matrix in two-stage, expander–implant immediate breast reconstruction following mastectomy.
Methods: A comprehensive literature review was conducted to identify complication rates for two-stage, expander–implant immediate breast reconstruction with and without acellular dermal matrix. The probabilities of the most common complications were combined with Medicare Current Procedural Terminology reimbursement codes and expert utility estimates to fit into a decision model. The decision model evaluated the cost effectiveness of acellular dermal matrix relative to reconstructions without it. Retail costs for ADM were derived from the LifeCell 2012 company catalogue for Alloderm.
Results: The overall complication rates were 30% and 34.5% with and without ADM. The decision model revealed a baseline cost increase of $361.96 when acellular dermal matrix is used. The increase in Quality-Adjusted Life Years (QALYs) is 1.37 in the population with acellular dermal matrix. This yields a cost effective incremental cost-utility ratio (ICUR) of $264.20/QALY. Univariate sensitivity analysis confirmed that using acellular dermal matrix is cost effective even when using retail costs for unilateral and bilateral reconstructions.

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Acellular Dermal Matrix for Reoperative Breast Augmentation

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Summary: Revisionary breast surgery in previously augmented patients is complex, with many variables that have to be considered. Obtaining durable repairs is challenging because these patients often present with thinned breast tissue, inadequate local tissue, and/or scarred breast envelope from multiple procedures. Capsular contracture, ptosis, tissue atrophy, and wrinkling/rippling are some of the most frequent reasons for reoperation. Conventional repair techniques generally involve a combination of capsule modification (capsular flaps), site change, mastopexy, and implant exchange. Recently, acellular dermal matrices have been introduced into revision surgery to reinforce soft tissue, reinforce the implant pocket, and potentially mitigate capsular contracture. Clinical outcomes of acellular dermal matrix–assisted revision surgery are reviewed from the published literature to evaluate the efficacy and safety of acellular dermal matrices for this indication. (*Plast. Reconstr. Surg.* 134: 932, 2014.)

Breast augmentation has been the most frequently performed cosmetic surgical procedure in the United States since 2006.[1] Approximately 290,000 breast augmentations were performed by members of the American Society of Plastic Surgeons in 2012. A percentage of these patients will undergo a reoperation in the near future. Reoperation is, in fact, a significant concern associated with breast augmentation. Data from rigorously followed patients from core clinical studies of implant manufacturers (Allergan, Mentor, and Sientra) indicate that 12 percent to 30 percent of patients undergo revision procedures within 6 years of their primary procedures, and among those with previous revision procedures (revision augmentation patients), 20 percent to 40 percent undergo further revisionary procedures (Table 1).[2–4] The primary reasons for revision are capsular contracture, implant malposition, ptosis, and hematoma/seroma. Other, less frequent reasons include asymmetry and wrinkling/rippling (Table 2). The higher rate of reoperation in revision augmentation patients underscores the difficulty in obtaining reliable repairs in these patients and the need for novel techniques. In the last 5 years, acellular dermal matrices have been introduced into reoperative breast augmentation procedures as a novel means to reinforce repairs. In this article, we review the published literature to date to evaluate the efficacy and safety of these matrices in reoperative breast surgery.

From the Department of Plastic Surgery, Loma Linda University Medical Center.
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RATIONALE AND INDICATIONS FOR USING ACELLULAR DERMAL MATRIX

Acellular dermal matrices are predominantly being used for four principal revisionary procedures: implant malposition, capsular contracture, ptosis, and implant wrinkling/rippling. Conventional repair techniques generally involve a combination of procedures, including capsule modification, site change (from subglandular to submuscular or from submuscular to neopectoral), mastopexy, and implant exchange. Matrices are used in conjunction with these conventional techniques. The rationale for their use for each of the indications is briefly described below. For a detailed description of revision techniques, we refer readers to our previously published articles on this topic.[5–7]

Implant Malposition

Implant malposition, manifesting as inferior, lateral, or medial (symmastia) malposition, is primarily related to pocket overdissection and

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OPEN

Implant Based Breast Reconstruction With Acellular Dermal Matrix

Safety Data From an Open-label, Multicenter, Randomized, Controlled Trial in the Setting of Breast Cancer Treatment

Fredrik Lohmander, MD,† Jakob Lagergren, MD, PhD,†‡ Pankaj G. Roy, MD, PhD,§ Hemming Johansson, MSc,¶ Yvonne Brandberg, PhD,¶ Catharina Eriksen, MD, PhD,|| and Jan Frisell, MD, PhD†*

Objective: To evaluate clinical outcomes of using acellular dermal matrix (ADM) with implant based breast reconstructions (IBBRs) in a randomized controlled trial.

Summary Background Data: The use of ADMs in IBBRs is widespread, but link between ADM and complications remain a controversial topic. In view of reports concerning harm, we present 6-months safety data of ADM-assisted IBBR in the setting of breast cancer treatment.

Methods: An open-label, randomized, controlled trial recruiting patients from 4 centers in Sweden and 1 in UK. Eligible were women with breast cancer planned for mastectomy with immediate IBBR. Participants were randomly allocated to IBBR with or without ADM (Strattice, Branchburg, NJ), with stratification by center in blocks of 6. Main primary endpoint was number of unplanned reoperations at 24 months, and safety expressed as the incidence of adverse events with a 6-month follow-up time for all participants. Analysis were done per protocol using Fisher exact test for complications and reoperations.

Results: From start of enrolment on April 24, 2014, to close of trial on May 10, 2017, 135 women were enrolled, of whom 64 with ADM and 65 without ADM were included in the final analysis. Four patients (6%) in each group had reconstructive failure with implant loss, but IBBR with ADM exhibited a trend of more overall complications and reoperations (difference 0·16, 95% CI, −0·01 to 0·32, $P = 0·070$), and with higher risk of wound healing problems ($P = 0·013$).

Conclusions: With 6-months follow-up for all participants, immediate IBBR with ADM carried a risk of implant loss equal to conventional IBBR without ADM, but was associated with more adverse outcomes requiring surgical intervention. Further investigation of risk factors and patient selection in a long-term follow-up is warranted.

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Despite the increasing availability of breast conserving surgery, removal of the breast is performed in up to 40% to 50% of breast cancer patients.[1] In recent years, there has been an increase in demand for breast reconstruction, and a significant rise in immediate breast reconstructions (IBR) has been observed.[2] IBR, performed at the time of mastectomy rather than as a delayed procedure, has the advantage of preserving the native skin envelope intact, creating a natural looking breast with reduced scarring in comparison with a delayed reconstruction. There is convincing data about psychological benefits for women with IBR.[3] Furthermore, the Swedish guidelines for care and treatment of breast cancer patients states that women should be informed about the option of breast reconstruction at the time of cancer surgery to facilitate informed decision-making.[4]

Although techniques for various autologous reconstructions have become more refined and efficient, implant based breast reconstruction (IBBR) remains the most commonly used method, especially in the immediate setting. In the United States, a relative decline in use of autologous flaps compared with implants has been noted.[5] A similar trend has also been seen in the United Kingdom.[6] Increasing rates of bilateral mastectomies for unilateral cancers, likely explained by patient-driven decisions, as well as economic inducements, are probable contributing reasons.[7] Other likely factors are increased uptake of skin- and nipple-sparing techniques for immediate IBBR, together with technological advances in the implant industry along with refinement of surgical techniques.[7] The shift from subcutaneous implant placement to complete muscle coverage in the 1990s was motivated by high complication rates, and a high frequency of capsular contracture.[8,9] The submuscular implant placement reduced wound-healing problems, skin necrosis, and reduced capsular contracture rates. However, the aesthetic outcome decreased, and created functional problems such as pain and muscle spasms resulting in impairment and impacting physical activity.[8,10]

Acellular dermal matrix (ADM) was introduced as a tool for utilizing the benefits of the subcutaneous implant placement by augmenting the subpectoral pocket, thereby accommodating a larger fixed-volume implant and potentially facilitating single-stage reconstructions.[11] Benefits of using ADM, such as decreasing or eliminating the need for tissue expanders, improved aesthetic outcome, fewer expansions, decreased incidence of capsular contracture, and reduced costs, were reported from several retrospective cohort studies and single surgeon experiences.[12,13] However, robust evidence supporting these advantages is lacking.[14] Furthermore, data from a systematic review and a recent randomized controlled trial (RCT) from the Netherlands have raised concerns regarding higher

Two-stage implant-based breast reconstruction compared with immediate one-stage implant-based breast reconstruction augmented with an acellular dermal matrix: an open-label, phase 4, multicentre, randomised, controlled trial

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Summary

Background **The evidence justifying the use of acellular dermal matrices (ADMs) in implant-based breast reconstruction (IBBR) is limited. We did a prospective randomised trial to compare the safety of IBBR with an ADM immediately after mastectomy with that of two-stage IBBR.**

Methods **We did an open-label, randomised, controlled trial in eight hospitals in the Netherlands. Eligible women were older than 18 years with breast carcinoma or a gene mutation linked with breast cancer who intended to undergo skin-sparing mastectomy and immediate IBBR. Randomisation was done electronically, stratified per centre and in blocks of ten to achieve roughly balanced groups. Women were assigned to undergo one-stage IBBR with ADM (Strattice, LifeCell, Branchburg, NJ, USA) or two-stage IBBR. The primary endpoint was quality of life and safety was assessed by the occurrence of adverse outcomes. Analyses were done per protocol with logistic regression and generalised estimating equations. This study is registered at Nederlands Trial Register, number NTR5446.**

Findings **142 women were enrolled between April 14, 2013, and May 29, 2015, of whom 59 (91 breasts) in the one-stage IBBR with ADM group and 62 (92 breasts) in the two-stage IBBR group were included in analyses. One-stage IBBR with ADM was associated with significantly higher risk per breast of surgical complications (crude odds ratio 3·81, 95% CI 2·67–5·43, p<0·001), reoperation (3·38, 2·10–5·45, p<0·001), and removal of implant, ADM, or both (8·80, 8·24–9·40, p<0·001) than two-stage IBBR. Severe (grade 3) adverse events occurred in 26 (29%) of 91 breasts in the one-stage IBBR with ADM group and in five (5%) of 92 in the two-stage IBBR group. The frequency of mild to moderate adverse events was similar in the two groups.**

Interpretation **Immediate one-stage IBBR with ADM was associated with adverse events and should be considered very carefully. Understanding of selection of patients, risk factors, and surgical and postsurgical procedures needs to be improved.**

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See Comment page 166

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Introduction

Breast cancer is the most common malignant disease in women, with an incidence of 1·8 million cases worldwide per year.[1] Survival has increased in high-income countries, meaning long-term clinical care to improve the quality of life of women who survive breast cancer has become ever more important. Mastectomy is indicated in most women with breast cancer, and the loss of a breast can intensely affect a woman's quality of life. In high-income countries, breast reconstructive surgery has become an important part of breast cancer treatment.[2,3] Additionally, increasing numbers of women with genetic predisposition for breast cancer are choosing prophylactic mastectomy followed by immediate reconstruction.[4] In many countries, immediate breast reconstruction, performed during the same session as mastectomy, is routinely offered to women without contraindications.

Several surgical techniques are available for breast reconstruction, and these fall into two main categories: implant-based breast reconstruction (IBBR) and reconstruction with autologous tissue.[5] IBBR accounts for most breast reconstruction procedures, and may be achieved in one stage (direct-to-implant reconstruction) or two stages (temporary implantation of a tissue expander followed by definite implant reconstruction). Many surgeons prefer two-stage IBBR despite the need for an additional operation, multiple visits for tissue expansion, the associated burden on the patient (time and number of procedures), and health-care costs. Generally, the subpectoral pocket left after mastectomy is assumed to be too small to accommodate an implant, which can lead to poor coverage of the lower part of the prosthesis.[6] The use of acellular dermal matrices (ADMs) to augment the subpectoral pocket and allow immediate implantation of a larger-volume implant or tissue expander has

The Role of Acellular Dermal Matrices in Capsular Contracture: A Review of the Evidence

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Summary: Despite advances in breast implant surgery, capsular contracture remains a challenging sequela of reconstructive and cosmetic breast implant surgery. Although there are established modalities for treatment, most recently, acellular dermal matrix products have been suggested to have a role in preventing or diminishing the pathologic process of capsular contracture. In this article, the author presents a review of the literature to highlight the level of evidence on the role of acellular dermal matrices in the treatment of capsular contracture. (*Plast. Reconstr. Surg.* 130 (Suppl. 2): 118S, 2012.)

Despite advances in breast implant surgery, capsular contracture remains a challenging sequela of reconstructive and cosmetic breast implant surgery. Although there are established modalities for treatment, most recently it has been suggested that acellular dermal matrices have a role in preventing or diminishing the pathologic process of capsular contracture. This article represents a review of the literature to highlight the level of evidence on the role of acellular dermal matrices in the treatment of capsular contracture.

The pathologic process of capsular contracture manifests from excessive peri-implant fibrosis or capsular formation beyond the normal state. Histologic analysis of silicone breast implant capsules reveal a relatively avascular layer of scar tissue or bundles of collagen and the presence of macrophages, inflammatory cells, synovial metaplasia, and granulomas.[1,2]

Clinically, capsular contracture can manifest as pain, hardening of the breast, and aesthetic distortion of the reconstructed breast. Although most would consider the degree of capsule thickness to be commensurate with the severity of capsular contracture, this has never been definitively proven.[3] The rate and risk of capsular contracture remain controversial. Some studies have shown this risk to range between 10 percent and 30 percent in up to a 5-year period.[4,5] In a large 25-year retrospective study of more than 1500 women, Handel and colleagues confirmed that the age of the implants correlated with the risk of capsular contracture, underscoring the progressive nature of pathologic capsular formation.[6] Regardless of the exact timing and risk of capsular contracture, it remains one of the top indications of reoperation in the breast implant patient.

The exact cause for capsular contracture has yet to be determined. Several theories on the pathomechanism and origin of capsular contracture associated with breast implants have been put forward. These theories underpin the pivotal role of an inflammatory reaction, which leads to induction of fibrosis and shrinking of the implant capsule and results in capsular contracture. A nonspecific inflammatory process directed against silicone and periprosthetic bacterial contamination is considered to be the primary pathogenic mechanism leading to excessive local inflammation.[7,8]

To thwart formation of the breast implant capsule, researchers have looked to the cellular mechanisms involved in wound healing and fibrosis. Analyses of targeted inhibitory treatments to affect capsule formation have included a study on angiotensin-converting enzyme inhibitors[9] and a study on 2-mercaptoethane sulfonate in a rabbit model.[10] The leukotriene inhibitor zafirlukast and

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The Use of AlloDerm in Postmastectomy Alloplastic Breast Reconstruction: Part I. A Systematic Review

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Background: Postmastectomy alloplastic breast reconstruction is a common procedure that continues to evolve. Increasingly, AlloDerm is being used in both direct-to-implant and two-stage breast reconstruction. The objective of this systematic review was to summarize the outcomes from studies describing this use of AlloDerm, and to compare outcomes to those from studies reviewing non-AlloDerm alloplastic reconstruction.
Methods: A computerized search was performed across multiple databases. Studies involving patients undergoing alloplastic breast reconstruction with AlloDerm were included. A systematic review was performed to include randomized controlled trials, comparative observational studies, noncomparative observational studies, and case series.
Results: A systematic review of the literature revealed 14 studies that satisfied inclusion criteria. Both acute and long-term complication rates were obtained. No objective validated outcomes were reported. Ninety-three percent of included studies were level IV evidence. Complication rates were as follows: infection, 0 to 11 percent; hematoma, 0 to 6.7 percent; seroma, 0 to 9 percent; partial flap necrosis, 0 to 25 percent; implant exposure with removal, 0 to 14 percent; implant exposure with salvage, 0 to 4 percent; capsular contracture, 0 to 8 percent; and rippling, 0 to 6 percent. No study included a cost analysis.
Conclusions: Complications using AlloDerm are comparable to those of non-AlloDerm alloplastic reconstructions. AlloDerm appears to confer a low rate of capsular contracture. A formal analysis is required to determine AlloDerm's cost effectiveness in use for direct-to-implant reconstructions. In addition, a randomized controlled trial comparing AlloDerm use to conventional two-stage reconstruction is currently absent from the literature. (*Plast. Reconstr. Surg.* 127: 2232, 2011.)

Breast cancer is the most common cancer in women, with a lifetime risk of one in eight.[1] There are many options for postmastectomy breast reconstruction. Approximately one-half to two-thirds of women who choose to proceed will undergo alloplastic reconstruction.[2] There were 79,000 breast reconstructions performed in the United States in 2008, of which 51,000 were two-stage tissue-expander/implant reconstructions and 5000 were single-stage (direct-to-implant) reconstructions.[3]

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AlloDerm (LifeCell Corp., Branchburg, N.J.) is an immunologically inert dermal matrix derived from cadaveric human skin that has gained widespread acceptance for use in breast reconstruction,[4,5] abdominal hernia repair,[6–9] pelvic reconstruction,[10,11] and head and neck contouring and reconstruction.[12–18] It is processed and sterilized to remove cells and antigenic components,[4] reducing the possibility of graft rejection.[19,20] The remaining dermal matrix is composed of collagen, elastin, hyaluronic acid, fibronectin, proteoglycans, and vascular channels.[4] After rehydration, the AlloDerm matrix is implanted in contact with viable tissue, acting as a biological scaffold for tissue remodeling as it becomes repop-

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AMERICAN SOCIETY OF PLASTIC SURGEONS®

Evidence-Based Clinical Practice Guideline: Breast Reconstruction with Expanders and Implants

INTRODUCTION

The American Cancer Society estimates that nearly 230,000 American women were diagnosed with invasive breast cancer in 2011.[1] Many of these individuals will require mastectomy and total reconstruction of the breast. The diagnosis and subsequent process can create significant confusion and distress for the affected persons and their families and, consequently, surgical treatment and reconstructive procedures are of utmost importance in the breast cancer care continuum. In 2011, the American Society of Plastic Surgeons® (ASPS) reported an increase in the rate of breast reconstructions, citing nearly 100,000 procedures, of which the majority employed expanders/implants.[2] The 3% increase in reconstructions over the course of just one year highlights the significance of maintaining patient safety and optimizing surgical outcomes.

Rationale and Goals

These guidelines were developed from a comprehensive review of the scientific literature and reflect the consensus of the Post-Mastectomy Expander/Implant Breast Reconstruction Guideline Work Group of the American Society of Plastic Surgeons.

Scope

These guidelines specifically address the risk factors, treatment, anticipated outcomes, and follow-up of patients undergoing breast reconstruction with expanders/implants for the treatment of cancerous defects. Graded practice recommendations can be found in Appendix A.

Intended Users

This guideline is intended to be used by the multidisciplinary team that provides care for patients with breast cancer through the use of breast cancer treatment, mastectomy and breast reconstruction. Healthcare practitioners should evaluate each case individually and treat patient preference as a key role in decision making. This guideline is also intended to serve as a resource for healthcare practitioners and developers of clinical practice guidelines and recommendations.

Disclaimer

Evidence-based guidelines are strategies for patient management, developed to assist physicians in clinical decision making. This guideline was developed through a comprehensive review of the scientific literature and consideration of relevant clinical experience, and describes a range of generally acceptable approaches to diagnosis, management, or prevention of specific diseases or conditions. This guideline attempts to define principles of practice that should generally meet the needs of most patients in most circumstances.

However, this guideline should not be construed as a rule, nor should it be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the appropriate results. It is anticipated that it will be necessary to approach some patients' needs in different ways. The ultimate judgment regarding the care of a particular patient must be made by the physician in light of all the circumstances presented by the patient, the available diagnostic and treatment options, and available resources.

This guideline is not intended to define or serve as the standard of medical care. Standards of medical care are determined on the basis of all the facts or circumstances involved in an individual case and are subject to change as scientific knowledge and technology advance and as practice patterns evolve. This guideline reflects the state of current knowledge at the time of publication. Given the inevitable changes in the state of scientific information and technology, this guideline will be reviewed, updated and revised periodically.

Funding Source

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Conflict of Interest

All contributors and preparers of the guideline, including ASPS staff and consultants, disclosed all relevant conflicts of interest via an on-line disclosure reporting database. In accordance with the Institute of Medicine's recommendations for guideline development, members with a conflict of interest represented less than half of the Breast Reconstruction Guideline Work Group.[3]

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METHODOLOGY

Work Group Selection Process

ASPS Members were invited to apply to the Work Group via society email and fax communication. All applicants were also required to submit an online conflict of interest disclosure form for membership consideration. Members of the Health Policy Committee reviewed and selected work group members to ensure a diverse representation of United States regions, practice type (large multispecialty group practice, small group practice, solo practice, and academic practice), and clinical, research, and evidence-based medicine experiences and expertise. Three stakeholder organizations, including the American Society of Breast Surgeons, American College of Radiology, and American Society of Clinical Oncology, were also invited to participate in the guideline development process by nominating one member from their respective organizations to serve on the work group.

Clinical Question Development

Work Group Members utilized the Nominal Group Technique to reach consensus on the clinical questions to be addressed in the evidence-based guideline. The Nominal Group Technique is ideal for face-to-face meetings and is designed to encourage equal participation in Work Group discussions and project contributions. The Work Group completed five rounds of the consensus process. Before the Introductory Meeting, all Work Group Members submitted ninety-seven potential clinical questions, which were compiled and dispersed at the Introductory Meeting for consideration and discussion.

The clinical questions were ranked according to the following criteria to assess for potential impact: 1) relevance to guideline scope; 2) addresses a gap in care; 3) can be developed into an actionable recommendation; 4) can be developed into an implementable recommendation; 5) is controversial or of significant interest; 6) is important to public health. The Work Group agreed on the following clinical questions to address in this evidence-based guideline, including:

1. In patients undergoing surgical treatment for breast cancer, what is the optimal time to discuss breast reconstruction options?
2. In patients undergoing mastectomy for the treatment of breast cancer, what is the optimal time for implant-based reconstruction (i.e., immediate versus delayed) when radiation treatment is not required?
3. In patients undergoing mastectomy for the treatment of breast cancer, what is the optimal time for implant-based reconstruction (i.e., immediate versus delayed) when radiation treatment is required?
4. In patients undergoing breast reconstruction following mastectomy, what are the risk factors when undergoing immediate implant-based reconstruction?
5. In patients requiring radiation therapy and undergoing immediate breast reconstruction after mastectomy, when is the optimal time for radiation therapy?
6. In patients undergoing implant-based reconstruction after mastectomy, what is the optimal duration of antibiotic prophylaxis for prevention of postoperative infections?
7. In patients undergoing mastectomy and implant-based breast reconstruction, what are the outcomes associated with utilizing acellular dermal matrix during reconstruction?
8. In patients undergoing mastectomy and implant-based breast reconstruction, what are the screening recommendations to monitor for cancer recurrence?
9. In patients undergoing breast reconstruction following mastectomy, what are the oncologic outcomes associated with undergoing immediate implant-based reconstruction?

The systematic review process yielded relevant evidence for six questions. The questions on radiation therapy were combined based on available evidence. Additionally, three clinical questions were addressed through supplemental research and cumulative work group clinical expertise.

Literature Search and Admission of Evidence

Published studies were sought by using electronic and manual search strategies. The primary search, executed from December 2011 to February 2012, was conducted in PubMed with the following keywords, MEDLINE Medical Subject Headings (indicated as [MeSH]), publication types (indicated as [ptyp]), Boolean operators, and limits:

1. (Mammaplasty[MeSH] AND reconstruction) OR "breast reconstruction"
2. Case reports[ptyp] OR Editorial[ptyp] OR Comment[ptyp] OR Letter[ptyp] OR News[ptyp] OR Newspaper article[ptyp] OR In Vitro[ptyp] OR Legal Cases[ptyp] OR Legislation[ptyp]
3. #1 NOT #2; Limits: English, Humans

Recent studies that may not have been indexed (e.g. publisher-supplied and pre-MEDLINE citations) were sought using a keyword search strategy similar to item 1 above, without MeSH terms or limits on publication type, up through the search cut-off date of December 31, 2011. Supplemental electronic searches were performed in the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Cochrane Library. In addition, a manual review of reference lists from the previous two years and studies accepted per the conditions designated for the literature search, supplemented the electronic searches.

Study selection for each clinical question was accomplished through two levels of study screening. Level I screening was performed by a single reviewer and involved a review of the titles and abstracts downloaded from the literature search noted above. At Level II screening, the full article was obtained, and the study was reviewed for fit with inclusion and exclusion criteria as outlined in Appendix B. The reason for exclusion (e.g. no outcomes of interest) was noted for all articles reviewed at Level II that were ultimately found ineligible for inclusion in the guideline. Work Group Members reviewed the list of excluded articles and the reasons for exclusion to determine whether articles should be excluded or reconsidered for inclusion.

Articles were selected for inclusion if they were relevant to clinical questions about risk factors, treatment options, and postoperative complications and if they were deemed high or moderate quality per the critical appraisal process, which is described below. The literature search identified a total of 2,749 articles that were subject to Level I screening, for a total of 295 remaining articles. After Level II screening and critical appraisal, the results were narrowed to 178 articles, of which ultimately 62 studies were deemed relevant and of high to moderate quality. These studies were used to develop practice recommendations. Additional references were included if considered necessary for discussion; however, these references were not critically appraised and are clearly documented in the guideline text. Details of literature search terms and search results are provided in Appendix B.

Critical Appraisal of the Literature

The ASPS evidence-based process includes a rigorous critical appraisal process. Each study is appraised by at least two reviewers. If a discrepancy exists between the reviewers, the literature is appraised by a third reviewer, and the level of evidence is determined by consensus. Studies are appraised and assigned levels of evidence according to the ASPS Evidence Rating Scales for therapy, risk, and diagnosis, which can be can be found in Appendix C. Checklists appropriate for the clinical question (therapy, prognosis/risk, or diagnosis) and study design (randomized controlled trial, cohort/comparative, case-control, etc) are employed. The checklists used by ASPS are similar to commonly used appraisal tools, (e.g., checklists developed by the Critical Appraisal Skills Programme (CASP) and the Centre for Evidence Based Medicine (CEBM)). Evidence ratings are not assigned to studies with inadequately described methods and/or worrisome biases.

Development of Clinical Practice Recommendations

Recommendations were developed through a consensus process. After a thorough review of the evidence, Guideline Work Group Members jointly drafted statements for each recommendation during conference call meetings and online discussions. After each meeting, members had an opportunity to individually comment and revise the draft recommendations via an email discussion. Guideline Work Group Members participated in several rounds of revisions until unanimous consensus was achieved on each recommendation statement. Each recommendation in this guideline is accompanied by a grade indicating the strength of supporting evidence, taking into account the overall level of evidence and the judgment of the guideline developers. Grading is determined as follows:

Grade	Descriptor	Qualifying Evidence	Implications for Practice
A	Strong Recommendation	Level I evidence or consistent findings from multiple studies of levels II, III, or IV	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
B	Recommendation	Levels II, III, or IV evidence and findings are generally consistent	Generally, clinicians should follow a recommendation but should remain alert to new information and sensitive to patient preferences.
C	Option	Levels II, III, or IV evidence, but findings are inconsistent	Clinicians should be flexible in their decision-making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.
D	Option	Level V: Little or no systematic empirical evidence	Clinicians should consider all options in their decision-making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

Peer Reviewer Process

The American Society for Therapeutic Radiology and Oncology (ASTRO) and The National Accreditation Program for Breast Centers (NAPBC) were invited to peer review this guideline. In addition, a total of 30 physicians and surgeons were invited to peer review the guideline. Peer review was also performed by volunteers from the ASPS Healthy Policy, Patient Safety, Coding and Payment Policy, and Quality and Performance Measurement Committees. Peer reviewers were given two weeks to review this guideline using an abbreviated version of the Appraisal of Guidelines Research & Evaluation Instrument developed by the AGREE Collaboration.

Guideline Approval Process

After the peer review process, the guideline draft was reviewed and modified by the Post-Mastectomy Expander/Implant Breast Reconstruction Guideline Work Group to address peer review comments. The final guideline was approved by the ASPS Executive Committee during its March 2013 meeting.

Plan for Updating Guideline

In accordance with the National Guideline Clearinghouse's inclusion criteria, this guideline will be updated within five years to reflect changes in scientific evidence, practice parameters, and treatment options.

BACKGROUND

Definitions

- Immediate breast reconstruction is defined as: A breast reconstruction procedure performed at the time of the mastectomy.
- Delayed breast reconstruction is defined as: A breast reconstruction procedure performed any time after the mastectomy.
- Acellular dermal matrix is defined as: A dermal graft used primarily to provide support and/or additional soft tissue coverage with expander/implant breast reconstruction.

Diagnostic Criteria

The patient usually presents to the plastic surgeon's office with a history of prior diagnosis and/or treatment for breast cancer. Patients who have had breast cancer may have had only a biopsy of the mass, a lumpectomy, or a simple mastectomy (alone or with axillary lymph node sampling or removal). Any of these surgical treatments may have been supplemented with radiation treatment to the breast and/or regional lymph nodes. Other cancer related treatments may include a modified radical mastectomy, chemotherapy and/or radiation, which may have an effect on the reconstructive site.

Physical Examination

Physical examination of the breast defect should include documentation of the size and configuration of the missing tissue. The presence of scarring and radiation changes and the condition of the pectoralis major muscle, nipple areola complex, and the contralateral breast should also be noted.

RECOMMENDATIONS

Considerations for Surgical Planning

Patient Education

The systematic literature search process did not retrieve any studies meeting inclusion criteria. Consequently, other widely accepted sources contributed to the creation of an expert clinical opinion for best practice.

While existing federal law through the 1998 Women's Health and Cancer Rights Act mandates insurance coverage for reconstructive surgery, there are limited additional mandated provisions that ensure women have the necessary information to be able to make an informed decision about their reconstructive options. In 2005, the American College of Surgeons created the National Accreditation Program for Breast Centers (NAPBC), which is a consortium of national and professional organizations that have developed standards for breast cancer care. Section 2.18 of the Standards for accreditation specifies that all appropriate patients undergoing mastectomy be offered a preoperative referral to a board certified reconstructive/plastic surgeon.[4] Despite this standard being applied at many breast centers throughout North America, disparities in access to reconstructive surgery remain.[5-8] Key national studies conducted at the University of Michigan and Dana Farber Cancer Institute have analyzed why many women did not receive reconstruction. They found that the two main limiting factors were the patient's ability to understand their options and breast surgeons' failures to refer their patients to a reconstructive surgeon.[7, 9] In response, New York enacted a law known as the Information and Access to Breast Reconstruction Surgery Act, that went one step further to ensure that patients were made aware of their options and coverage for breast reconstruction. This law mandates that hospitals providing mastectomy or lumpectomy surgery must provide the patient written information on breast reconstruction prior to obtaining consent for oncologic surgery. The law also details the minimum amount of information that must be provided including: a description of the various reconstructive options and the advantages and disadvantages of each, information assuring the coverage by both public and private insurance plans, instructions on how a patient may access reconstructive care including the potential transfer of care to a facility that provides reconstructive care and any other information as may be required by the commissioner.[10] Following suit, New Mexico and California also enacted similar patient-communication measures. Additionally, in 2012, a bipartisan effort led to the introduction of the Breast Cancer Education Act in the US House of Representatives. The bill would require the Department of Health and Human Services to plan and implement an education campaign to inform mastectomy patients of breast reconstruction availability and coverage, and of prostheses and other replacement options.[11] In the ideal situation, the patient would meet with both the oncology and reconstructive surgeon at the same time. Realistically, given time constraints and scheduling conflicts of both parties, as long as the above requirements are met, the patient will be able to make an informed decision.

Recommendation: Patients undergoing mastectomy should be offered a preoperative referral to a plastic surgeon. The adoption of this approach by practicing surgeons would benefit breast cancer patients nationwide and would result in enhanced patient education of reconstructive options.
Recommendation Grade: D

Immediate versus Delayed Reconstruction
The decision to start reconstruction at the time of the mastectomy should consider the psychosocial benefits to the patient of expediting the reconstructive process balanced by the potential increased surgical risk of starting reconstruction prior to the completion of adjuvant therapy. Beginning the reconstructive process at the time of the mastectomy has the advantage of preserving the skin envelope and shape, as well as maintaining the inframammary fold definition. Immediate reconstructions have the potential to help patients more quickly recover from the psychological impact of the breast amputation and can result in a smaller burden on patients' work or home life as fewer operations are required to reconstruct their breasts.

Commonly, the decision for immediate versus delayed reconstruction hinges on whether post-mastectomy radiation is indicated. Although studies comparing immediate versus delayed reconstruction and radiation therapy versus no radiation therapy have been published, randomized control trial data is not available. In one case series, logistic regression analysis identified timing of reconstruction to be an independent risk factor for postoperative complications, with a higher complication rate among those with immediate procedures.[12] Likewise, a retrospective cohort study found that patients who received immediate breast reconstruction were twice as likely to experience a postoperative complication compared with those who received delayed breast reconstruction (odds ratio 2.06 [95% CI 1.21-3.52]; p=0.008). In addition, patients who received immediate breast reconstruction were 5.2 times more likely to have a Baker Grade II, III, or IV capsular contracture compared to patients who received delayed breast reconstruction ($p<0.001$). It is important to note that ten percent of the total sample size received radiation therapy either before or after breast reconstruction in this study.[13]

In contrast, a case series identified delayed reconstruction as a statistically significant independent predictor of infection ($p<0.05$). When analyzed in the multivariate regression model, however, delayed reconstruction did not retain statistical significance.[14] Several other studies found no statistically significant associations between the timing of reconstruction and total complications, reconstruction failure, and infection.[15-17]

The timing, and in particular, the staging process of implant-based reconstruction is rapidly evolving. The increased acceptance of nipple-sparing mastectomy has created an opportunity for patients to receive immediate, one-stage implant reconstruction. These procedures may result in greater patient satisfaction due to the obvious benefits of fewer surgical procedures. However, high-level comparative studies are currently unavailable to assess clinical or patient-reported outcomes among patients undergoing these types of expedited reconstructive operations.
Recommendation: Evidence is varied and conflicting on the association between postoperative complications and the timing of post-mastectomy expander/implant breast reconstruction and is often confounded by the use of radiation. The inconsistent research findings and a lack of definitive evidence should alert physicians to evaluate each case individually.
Level II, III, IV Evidence
Recommendation Grade: C

Risk Factors for Post-Operative Complications with Expander/Implants
Smoking
The current evidence indicates that smoking increases the risk of postoperative complications in patients undergoing immediate expander/implant breast reconstruction. Among nine studies, six univariate and six multivariate analyses found nicotine use to be significantly correlated with increased postoperative complications. One study did not find nicotine use to be associated with postoperative infections,[14] and two studies did not find nicotine to be associated with overall complication rates.[16, 18] However, all nine studies suggested that smoking has a profoundly negative impact on expander/implant postoperative outcomes.

Complications associated with nicotine use ranged from wound complications to implant loss. Overall complication rates were found to be 2.2 to 3.07 times higher among smokers than non-smokers.[19-21] Smokers were 2.9 times more likely than nonsmokers to develop wound necrosis ($p=0.003$)[22] and 5.9 times more likely to experience reconstruction failure ($p=0.001$).[23] One retrospective case series indicated that smokers were at a 3 times higher risk of implant loss compared to nonsmokers (odds ratio 3.02 [95% CI 1.61-5.57]; $p=0.001$),[24] but the same study noted that nicotine use was not found to be significantly associated with overall complications that included seroma, hematoma, skin problems and infection. However, it is important to note that the number of smokers in this study is unknown; thus the power of the study to address these associations is unclear.
Recommendation: Smoking is associated with an increased risk of complications and an increased risk of reconstructive failure in patients undergoing post-mastectomy expander/implant breast reconstruction. Patients should be informed of the increased risks and advised on smoking cessation as means to decrease surgical complications. Additionally, it should be recognized that the decision to proceed with surgery may preclude timely smoking cessation.
Level II, III, IV Evidence
Recommendation Grade: A

Obesity

Evidence indicates that obesity increases the risk of postoperative complications in patients undergoing post-mastectomy expander/implant breast reconstruction. The global obesity definition – body mass index (BMI) greater than 30 – was used for these analyses. The majority of the eight studies addressing the association between BMI and postoperative expander/implant complications concluded that obesity was significantly associated with postoperative complications.[20-22, 25-27]

The incidence of wound infections and expander/implant failures were directly correlated to increasing BMI. Wound infections among patients with first stage expander/implant reconstructions were 3.3 times higher among patients with a BMI of 25-30 ($p=0.002$) and 18.5 times higher among those with a BMI greater than 30 when compared to patients with a BMI of less than 25 ($p<0.001$). The risk of implant loss was 3 times higher for those with a BMI of 25-30 (odds ratio 3.1 [95% CI 1.0-9.3]; $p=0.043$) and almost 6 times higher for those with a BMI greater than 30 when compared to those with BMI less than 25 (odds ratio 5.9 [95% CI 1.2-29.5]; $p=0.032$).[22] Several studies found a statistically significant link between obesity and an increased risk of overall reported complications including mastectomy skin flap necrosis, fat necrosis, wound dehiscence, infection, seroma, hematoma, and implant extrusion.[20-21, 25-27] Obese patients were almost twice as likely as patients of a normal weight to develop an expander/implant complication (odds ratio 1.8 [95% CI 1.1-3.0]; $p=0.02$).[21]

One retrospective case series did not find a significant association between BMI and overall complications, which included seroma, hematoma, skin problems and infection.[24] However, it is unknown how many patients were in the obese category and whether the study was adequately powered to address this association. Additionally, one retrospective case series did not find a significant association between BMI and infection, [14] but it is important to note that a large sample size would be required to adequately evaluate this association.

Recommendation: A BMI of 25 or greater is associated with an increased risk of postoperative complications and reconstructive failure among patients undergoing post-mastectomy expander/implant breast reconstruction. These risks are even higher among patients with a BMI greater than 30. Obese patients should be informed of their increased surgical risks with expander/implant reconstructions and advised on practical weight loss solutions. Additionally, it should be recognized that the decision to proceed with surgery may preclude timely weight management.

Level III, IV Evidence

Recommendation Grade: A

Breast Size

Evidence suggests that patients with a preoperative breast cup size of C or larger may be at an increased risk for postoperative complication with immediate expander/implant breast reconstructions compared to those with a preoperative breast cup size of A or B. In a retrospective case series, large preoperative breast size was significantly associated with higher infection rates in both the univariate and multivariate analyses. In the univariate analysis, 28% of patients with a preoperative breast cup sizes of D and DD had an infection compared to13% of those with a breast cup sizes of A, B, and C ($p<0.001$). In the multivariate analysis, preoperative breast cup size larger than C remained a statistically significant risk factor for infection; patients with a breast cup size of D or DD were nearly 3 times more likely than patients with smaller breasts to experience an infection (odds ratio 2.89 [95% CI 1.59-5.26]; $p<0.001$).[14] A retrospective comparative study observed a greater rate of skin necrosis in breasts larger than 600 grams (> C cup) compared with breasts smaller than 600 grams (A or B cup) (19% vs. 1.8%, respectively; $p<0.01$).[28] Similar results were also reported in a multivariate analysis, which indicated for every 100-cc increase in final implant volume, the risk of developing a complication increases by 1.32 times ($p<0.001$).[27] One retrospective case series, however, found the exact opposite. The association between breast size and incidence of implant failure in an univariate statistical analysis demonstrated that patients with preoperative cup sizes of A and B were more likely to experience implant failure than patients with cup sizes of C and D (35.9% vs. 16.7%, respectively; $p=0.009$). However, a multivariate analysis could not be conducted due to small sample size; therefore, it is unclear if this association would have remained significant when controlling for the effects of other confounding factors.[23]

Recommendation: Preoperative breast size, specifically C or larger, may be associated with an increased risk of complication and an increased risk of reconstructive failure in patients undergoing post-mastectomy expander/implant breast reconstruction. However, much of the currently available evidence does not control for BMI, which is associated with both preoperative breast size and complication rates. Given the limited evidence and contradictory literature, physicians should be aware of this potential complicating factor.

Level III, IV Evidence

Recommendation Grade: D

Diabetes

Evidence suggests that among patients with expander/implant breast reconstructions, diabetes is not a significant risk factor for postoperative complications, including implant failure, pulmonary embolism, seroma, necrosis, wound dehiscence, mastectomy flap necrosis, infection, and capsular contracture[14,16,18,21] or reconstructive failure, defined as the premature removal of expander or implant.[16, 21] Among the five studies that analyzed the impact of diabetes on surgical outcomes, one retrospective comparative study suggested that diabetes negatively impacted postoperative outcomes. In a univariate analysis, diabetes was shown to be a significant independent risk factor for development of total complications. Patients with diabetes had a higher rate of complications than patients without diabetes (56.7% vs. 30.8%, respectively; $p<0.004$). However, diabetes was not a statistically significant risk factor when controlling for other variables in a multivariate logistic regression model.[26]

Recommendation: There is no evidence to indicate that diabetes is a significant independent risk factor for the development of either postoperative complications or reconstructive failure in patients undergoing post-mastectomy expander/implant breast reconstruction. However, this information should not deter surgeons from continuing to practice glycemic control in the peri-operative period for breast cancer patients.

Level II, III, IV Evidence
Recommendation Grade: B

Radiation Therapy

Overview

Research has found that radiation therapy is an independent risk factor for postoperative complications in patients undergoing immediate expander/implant breast reconstruction. Complications associated with radiation therapy include infection, wound dehiscence, necrosis, seroma, hematoma, capsular contracture, extrusion, implant loss and reconstruction failure.[12, 17-18, 26, 29, 30-32] A retrospective cohort study found that 40.7% of patients who received radiation therapy experienced a postoperative complication compared with only 16.7% of patients who received no radiation therapy ($p<0.01$).[18] Using multivariate logistic regression analysis, other studies revealed similar disparities in total complication rates depending on radiation status when controlling for comorbidities and other confounding factors. The risk of total complications increased by 3.3 times[12] and 4.99 times[26] in patients who received radiation therapy compared with patients who did not receive radiation therapy ($p<0.05$). The use of postoperative radiation therapy significantly increased the risk of most implant associated complications among patients with immediate expander/implant reconstructions.[31] Compared with patients who received no adjuvant radiation therapy, those who received postoperative radiation therapy had higher rates of infection (3.8% vs. 20.5%, respectively), Baker Grade III and IV capsular contracture (2.7% vs. 15.4%, respectively), and implant loss (9.4% vs. 41%, respectively) (all $p<0.05$).[31]

Level III, IV Evidence
Recommendation Grade: B

Previous Radiation

Retrospective studies suggest an increased risk of postoperative complications among patients who receive radiation therapy prior to expander/implant breast reconstruction.[14, 33] Complication rates reported in two studies that evaluated expander/implant patients with and without radiation prior to reconstruction were 25% vs. 13.9%, respectively ($p<0.01$),[14] and 30% vs. 14%, respectively ($p=0.007$).[33] Furthermore, a multivariate analysis that controlled for confounding factors found that expander/implant patients were 2.55 times as likely to have an infection as patients without radiation ($p=0.002$).[14] Results also suggest that previous radiation therapy may increase the risk of capsular contracture. Among the 20 patients who received whole-beam external radiation therapy, 40% experienced a Baker Grade III/IV capsular contracture compared with only 6.9% of patients not receiving radiation therapy ($p=0.03$).[34] A retrospective study comparing major and minor complication rates between patients with and without radiation therapy found that complications were more frequent in the radiation group, but the difference did not achieve statistical significance.[35] Other retrospective case series findings suggest that pre-reconstruction radiation therapy did not have a significant impact on overall complications, infection rates, and necrosis.[36]

Level III, IV Evidence
Recommendation Grade: C

Radiation Therapy to Expander

Surgical outcomes were evaluated among three studies of patients who did and did not receive radiation during the expansion process. Two out of the three studies suggest that radiation therapy leads to higher rates of postoperative complications, including infection, mastectomy flap necrosis, seroma, hematoma, implant exposure, and explantation, although these differences did not reach statistical significance.[37-38] The third study found that 51% of patients who received radiation to expanders experienced a complication compared with only 14% of patients who did not receive radiation ($p=0.005$).[39] Radiation therapy could not be placed into the multivariate logistic regression model for further statistical analysis, however, due to small sample size. Furthermore, the optimal time between radiation to the expander and exchange of expander for a permanent implant is a clinically relevant question but one without supporting data to guide clinical decision-making.

Level III, IV Evidence
Recommendation Grade: B

Radiation Therapy to Implant

In nine studies, postoperative outcomes of patients who received radiation therapy following implant exchange were compared with patients who did not receive radiation therapy. Several of these studies found postoperative radiation therapy to be a significant risk factor for the development of capsular contracture ($p<0.05$).[34, 40-42] A prospective cohort study, which controlled for confounding factors in multivariate logistic regression analysis, demonstrated that postoperative radiation therapy was associated with a six-fold increase in risk of complications compared with no radiation therapy (odds ratio 6.4 [95% CI 1.6-25.0]) Patients who received postoperative radiation therapy were also 5.1 times more likely than patients who received no radiation therapy to experience reconstructive failure ($p=0.02$).[16] Additionally, a five year follow-up retrospective cohort study found that implant patients with radiation had a 61% total complication rate compared to only 21% among patients without radiation ($p=0.003$).[44] Other studies also found an association between radiation to implant and higher postoperative complications rates; however, these differences were not statistically significant.[21, 33, 43]

Level II, III, IV Evidence
Recommendation Grade: B

Optimal Timing of Radiation and Reconstruction

Evidence to support a recommendation on the appropriate timing of radiation therapy to a patient undergoing expander/implant breast reconstruction is limited. In a retrospective cohort study, no significant differences were found in the incidence of major or minor complications between patients who received external beam radiation therapy to the expander compared with those who received radiation therapy to the implant.[45] Likewise another retrospective cohort study found no significant differences in complication rates by timing of radiation.[18] A small subgroup analysis of patients who received radiation therapy during the expansion process versus after implant exchange found that patients who received radiation therapy to expanders had numerically higher rates of capsular contracture; however, the difference was not statistically significant.[42] A prospective cohort study evaluated the impact of radiation therapy to expanders versus implants to determine the outcome of implant failure and capsular contracture. The rate of implant reconstruction failure was 40% among patients who received radiation therapy to expanders and 6.4% among those who received radiation therapy to implants ($p<0.0001$). The rate of Baker Grade IV capsular contracture was significantly higher in patients who received radiation therapy during the expansion process compared with patients who received radiation therapy to the implant or no radiation therapy at all (13.3% vs. 10.1% vs. 0%, respectively; $p<0.001$).[46] An additional clinically important question is the impact of reconstruction on the delivery of radiation. Currently, there is no evidence that reconstruction delays the administration of radiation. The optimal time for radiation is within eight weeks of the mastectomy. Patients who receive radiation later than eight weeks post-mastectomy have higher five-year local recurrence rates. [47]

Level II, III Evidence
Recommendation Grade: C

Overall Recommendation: The optimal timing of radiation is within eight weeks of the mastectomy. Radiation is associated with an increased risk of complications and reconstructive failure among patients undergoing post-mastectomy expander/implant breast reconstruction. Patients should be counseled in regards to these increased risks.

Level II, III, IV Evidence
Recommendation Grade: B

Chemotherapy

Most of the evidence regarding the impact of chemotherapy on complications with post-mastectomy expander/implant breast reconstructions does not address outcomes based on the timing of the chemotherapy. A retrospective case series found similar infection rates between patients who received chemotherapy before or after implant exchange compared to those without chemotherapy.[17] Another case series did not find a significant association between chemotherapy and implant failures.[23] However, a prospective cohort study found higher infection rates among patients who received chemotherapy after mastectomy but before breast reconstruction compared to those without chemotherapy (44% vs 25%, respectively; $p=0.05$). It should be noted that one-third of patients included in this study received an autologous breast reconstruction and two-thirds underwent an expander/implant technique. No information was provided on the infection rate among those with autologous procedures and chemotherapy; therefore, it is unclear if this subgroup of patients experienced a higher or lower rate of infections compared to patients who received expander/implant reconstructions and chemotherapy.[48]

Small studies suggest that chemotherapy before breast reconstruction may not be a significant risk factor for the development of surgical complications.[36, 48-49] Complications evaluated in these statistical assessments included implant explantation, seroma, necrosis, infection, and hematoma. A study that separated neoadjuvant from adjuvant therapy among mastectomy patients with immediate expander/implant reconstruction showed no difference in rates of implant loss based on timing of chemotherapy or due to chemotherapy.[48] Also, neoadjuvant chemotherapy was not recognized as a significant risk factor for total complications in patients undergoing mastectomy and immediate expander/implant breast reconstructions.[49] Additionally, a case series found no significant relationship between neoadjuvant chemotherapy and early complications or prosthesis removal,[36] and another case series had similar findings although patients receiving either neoadjuvant or adjuvant therapy were not stratified by chemotherapy timing.[21]

The impact of reconstruction on the delivery of chemotherapy is an important question with potential impact on disease-free survival. A 12 week or greater delay in starting chemotherapy after mastectomy adversely impacts disease-free and overall survival.[50] Among patients treated at a National Comprehensive Cancer Network (NCCN) facility, 98% of breast cancer patients regardless of surgical treatment received chemotherapy within 12 weeks of definitive surgery. [51]

Recommendation: Preoperative chemotherapy does not appear to be a significant risk factor for either postoperative complications or implant failure in patients undergoing post-mastectomy expander/implants breast reconstruction.

Level II, III, IV Evidence
Recommendation Grade: C

Hormonal Therapy:

Evidence is limited regarding the impact of adjuvant hormonal therapy on breast reconstruction outcomes. When looking specifically at capsular contracture, a retrospective case series found that the use of hormonal therapy was not a significant risk factor for capsular contracture, and multivariate analysis confirmed these findings.[23] A prospective cohort study that looked at a broader definition of implant reconstruction failure was able to demonstrate a significantly higher rate of implant reconstruction failure in patients who received tamoxifen compared with patients who did not receive this therapy

(28% vs. 5%, respectively; p=0.01). On multivariate analysis, when controlling for the effect of radiation therapy and other confounding factors, the use of tamoxifen was found to be a statistically significant risk factor for the development of reconstructive failure (odds ratio 6.4; p=0.03).[16] However, the analysis did not include clinically relevant factors such as age and incidence of hormonally sensitive disease.

Recommendation: Hormonal therapy may increase the risk of postoperative complications and reconstruction failure in patients undergoing post-mastectomy expander/implant breast reconstruction. However, inconsistent research findings and a lack of definitive evidence should alert physicians to evaluate each case individually.

Level II, IV Evidence

Recommendation Grade: D

Collagen Vascular Disease

Although the authors were interested in collagen vascular disease and associated outcomes, the systematic literature search process did not retrieve any studies meeting inclusion criteria.

Previous Breast Surgery

Although a history of previous breast surgery is not uncommon and despite the authors' interest in the relationship between previous breast surgery and reconstructive complications and/or failure, the systematic literature search process did not retrieve any studies meeting inclusion criteria.

Treatment

Antibiotic Prophylaxis

The systematic literature search process did not retrieve any studies meeting inclusion criteria. Consequently, other widely accepted sources contributed to the creation of an expert clinical opinion for best practice.

The Surgical Care Improvement Project (SCIP), which began in 2005, is a national effort to substantially reduce surgical morbidity and mortality and may be the best, most well-researched guideline available. It is a national partnership coordinated through a steering committee of 10 national organizations with technical expertise panels from more than 20 other organizations.[52] The SCIP guidelines for antibiotics are three-fold. The purpose of these measures is to establish therapeutic antibiotic serum and tissue levels at the time of incision while minimizing risks to the patient and population. The guidelines state that 1) the antibiotics must be administered within one hour prior to incision, although two hours is acceptable for medications with longer infusion times such as fluoroquinolones and vancomycin; 2) the antibiotics must be appropriately selected for the surgical site; 3) the antibiotics should be discontinued within 24-hours of the end of the surgical procedure.[53] For breast cancer reconstruction cases, a first or second-generation cephalosporin would meet these requirements.[54] When patients are allergic to beta-lactams, appropriate antibiotics include vancomycin, fluoroquinolones, or clindamycin.[55]

Preoperative antibiotic use, as defined by SCIP, is standard of care regardless of the type of breast reconstruction being performed. However, patients with implant-based breast reconstruction have a feature that distinguishes them from most other surgical patients: an external surgical drain in proximity to the implant that remains for an extended, and highly variable, period of time postoperatively. To date there is a paucity of data on the appropriate length of postoperative antibiotic use when surgical drains are used in the setting of implants.

Recommendation: Patients undergoing post-mastectomy expander/implant breast reconstruction should receive a preoperative dose of an appropriate IV antibiotic initiated sixty minutes or less from the time of incision (within two hours for antibiotics with longer infusion times). Unless a drain is present, antibiotics should be discontinued within 24-hours of the completion of the procedure. If a drain is present, the role of antibiotics is less clear and should be left to physician preference. Of note, documenting a drain in proximity to the implant as a reason for continuation of IV antibiotics beyond the 24-hour postoperative period or switching to postoperative antibiotics within 24-hours of procedure completion is compliant with current SCIP guidelines. Presently, there is limited evidence on post-operative antibiotic prophylaxis. Overall, surgeons should adhere to their specific state and hospital guidelines on antibiotic administration.

Recommendation Grade: D

Acellular Dermal Matrix (ADM)

Current evidence suggests that the use of acellular dermal matrix (ADM), although increasingly common in post-mastectomy expander/implant breast reconstruction, can result in increased risk of complications in the presence of certain risk factors. In a retrospective review of immediate two-stage breast reconstructions that compared complication rates between an ADM cohort and two non-ADM cohorts (concurrent and consecutive), patients who received ADM had increased complications, particularly seroma (7.2% vs. 1.6%, respectively) and reconstructive failure, most commonly due to infection, (5.9% vs. 1.9%, respectively). Multivariate analysis showed these complications to be further exacerbated in the presence of risk factors such as smoking (p=0.054), older age (p=0.041), higher BMI (p=0.023), and axillary dissection (p=0.002).[25] Additionally, in a retrospective comparative study, it was found that the use of ADM in immediate two-stage implant-based reconstructions was associated with a significant increase in major complications compared to those without ADM (15.3% vs. 5.4%, respectively; respectively). These complications included infection requiring antibiotics (8.6% vs. 2.7%, respectively; p = 0.001), flap necrosis requiring excision (6.7% vs. 2.7%, respectively; p = 0.015), and explantation of the tissue expander (7.7% vs. 2.7%, respectively; p = 0.004).[56] In a retrospective review of immediate prosthesis-based reconstruction with and without ADM, the overall surgical complication rate was significantly higher in the ADM group (19.5 vs. 12.3, respectively; p<0.001). This was most relevant to overall wound infection, which was statistically significant in the univariate analysis (p=0.031) but not significant in the multivariate

analysis (p=0.097). The use of ADM did not significantly increase the incidence of minor wound infection, mastectomy flap necrosis, seroma, and hematoma. When overall surgical complications were examined in a univariate analysis, the use of ADM, smoking, higher BMI, higher initial volume, and larger implant size were statistically associated with a significantly higher rate of overall surgical complications; these remained statistically significant in the multivariate analysis. The authors hypothesized that the increased incidence of surgical complications in the ADM cohort may be attributable to other significant risk factors.[20] Results from a retrospective review of immediate two-stage reconstructions with and without ADM indicated that the ADM cohort had a significantly higher rate of infection (p=0.022), reoperation (p=0.11), expander explantation (p=0.020), and overall complications (p=0.007). However, when reconstructed breasts were stratified by size, ADM use was not associated with higher complication rates in patients with breasts weighing less than 600g; whereas, ADM use was significantly associated with higher infection rates in breasts larger than 600g. These results suggest that high BMI and high breast volume in conjunction with ADM use are factors that could increase the risk of postsurgical complications.[28]

Six additional retrospective studies suggest that use of ADM is not associated with increased complication rates. The only exception was in a systematic review of nine studies that found a significantly higher rate of seroma in the ADM compared to the non-ADM group (p=0.03). Otherwise, both ADM and non-ADM cohorts had similar rates of infection leading to expander/implant explantation (p=0.18), incidence of cellulitis or wound infection not requiring surgical intervention (p=0.09), incidence of reported hematoma (p=0.11), and incidence of partial mastectomy flap necrosis (p=0.08).[57] Likewise, a previous study by the same authors found no significant difference in total complication rates between ADM and non-ADM cohorts (p=0.79).[58] A retrospective cohort study found similar complications rates between an ADM cohort (immediate single-stage reconstruction) and non-ADM (immediate two-stage reconstruction) cohort (14.8% vs. 19.6%, respectively; p=0.18). Initially, the non-ADM cohort was perceived to be more susceptible to complications than the ADM cohort, but this was attributed to the presence of irradiation, which when controlled for, resulted in similar complication rates between both groups. Irradiation and inexperience with surgical technique were the only two variables that appeared to be significantly associated with the incidence of a complication.[33] A retrospective cohort study further supported the use of ADM. Compared with patients without ADM, those with ADM reconstructions had fewer overall complications, such as seroma/hematoma, infection and wound complications; ADM use was also associated with lower rates of capsular contracture (odds ratio 0.16 [95% CI 0.73-0.38]; p<0.001) and fewer overall complications (odds ratio 0.61 [95% CI 0.38-0.97]; p=0.038).[59] Another retrospective review also found no significant difference in complications between the ADM and non-ADM cohorts.[60]

Recommendation: Evidence on acellular dermal matrix (ADM) in post-mastectomy expander/implant breast reconstruction is varied and conflicting. Surgeons should evaluate each clinical case individually and objectively determine the use of ADM.
Level III Evidence
Recommendation Grade: C

Outcomes

Monitoring for Cancer Recurrence

The systematic literature search process did not retrieve any studies meeting inclusion criteria. Consequently, other widely accepted sources contributed to the creation of an expert clinical opinion for best practice.

Current guidelines for detecting local recurrence of post-mastectomy breast cancer, with or without breast reconstruction, recommend clinical examination alone. The American Society of Clinical Oncology (ASCO) advises clinical exam every 3-6 months in years 1-3, every 6-12 months in years 4-5, and then annually.[61] The National Comprehensive Cancer Network (NCCN) recommends clinical exam every 4-6 months for 5 years, and then annually.[62] There is no data to support screening for local recurrence following implant or tissue-based breast reconstruction by any imaging method, including mammography, ultrasound, or MRI. Additionally, a review of the evidence for surveillance mammography following breast reconstructions illustrates wide variation in the reporting of stage at diagnosis, use of radiotherapy, systemic treatment, length of follow-up, mammography regimen, and concurrent clinical findings. Although not consistently reported, it appears that most local recurrences found by mammography were also apparent on clinical exam.[63]
Recommendation: Clinical examination is sufficient to detect local cancer recurrence in patients undergoing post-mastectomy expander/implant breast reconstruction. Imagining studies are not required as part of routine surveillance. On the basis of clinical suspicion, imaging studies can be used for clinical indications on a case by case basis. Diagnostic imaging is indicated if there is any clinical concern for recurrence.
Recommendation Grade: D

Effect of Implant-Based Reconstruction on Oncologic Outcomes

Evidence indicates that local control and survival are related for breast cancer. An overview of randomized trials found that the 10 year risk of local recurrence with and without post-mastectomy radiotherapy was 3.1% and 8%, respectively, for node-negative breast cancer, and 7.5 vs. 27.6%, respectively for node-positive disease. This reduction in risk of local recurrence was associated with a statistically significant 5-7% improvement in survival at 15 years, a benefit that was apparent only when the absolute reduction in local recurrence was more than 10%.[64] The aim of post-mastectomy radiation therapy is to minimize local recurrence in those patients at greatest risk, typically patients with T3 tumors and/or greater than 3 positive axillary nodes but

possibly also including patients with smaller tumors and/or fewer positive nodes. A randomized trial comparing the results of mastectomy with breast reconstruction versus mastectomy without breast reconstruction is not feasible, but evidence from retrospective studies shows that expander/implant breast reconstruction does not increase the risk of cancer recurrence or mortality. A retrospective analysis from the SEER registry provided comparison of 46,177 patients treated by mastectomy alone versus 3,620 patients treated by mastectomy and implant reconstruction versus 4,863 treated by mastectomy and tissue-based reconstruction. About 20% of patients in each cohort received post-mastectomy radiation therapy, and at a median follow-up of five years, breast cancer specific mortality was lower in the reconstructed patients. These differences persisted on a multivariate analysis incorporating stage of disease.[65] Similar results were cited in another study also using SEER data and reporting on 52,249 patients.[66] A matched cohort study comparison of 300 controls to 300 expander/implant patients observed no differences in local or regional recurrence, and higher rates of distant metastases (27% vs. 20%, respectively) and of breast cancer mortality (23% vs. 17%, respectively) in the control group.[67] In a comparison of 580 patients with delayed implant reconstruction to 1,158 matched controls, better disease free survival at 10 years (hazard ratio 0.78) and overall survival at 20 years (hazard ratio 0.90) was observed in the reconstructed patients; however, the study concluded that these differences were due to socioeconomic and health factors and not to the performance of breast reconstruction.[68] In a matched cohort study of 309 women who had mastectomy with immediate tissue expander/implant reconstruction compared to 309 women who had mastectomy alone, similar rates of locoregional recurrence (6.8% vs. 8.1%, respectively) and of time to locoregional recurrence (2.3 yrs vs. 1.9 yrs, respectively) were found, suggesting that reconstruction neither increased the risk nor delayed the diagnosis of locoregional recurrence.[69] In a comparison of 494 patients who had mastectomy with reconstruction to 427 who had mastectomy alone, similar rates of locoregional recurrence (2.2% vs. 4%, respectively) and time to locoregional recurrence (1.6 yrs vs. 1.6 yrs, respectively) were observed at a median follow-up of 4.5 years, and a lower rate of local and/or distant recurrence in the reconstructed patients (5.9% vs. 11.5%, respectively) was observed. All locoregional recurrences in the reconstructed patients were detected on clinical exam.[70]

Recommendation: Post-mastectomy expander/implant breast reconstruction does not adversely affect oncologic outcomes. The need for post-mastectomy radiation therapy is often, but not always, apparent prior to surgery; accordingly, decisions regarding the sequencing of post-mastectomy breast reconstruction and radiation therapy are best made by a multidisciplinary team including the oncologic surgeon, plastic surgeon, medical oncologist and radiation oncologist.

Level III Evidence

Recommendation Grade: B

Complications Associated with Expander/Implant Breast Reconstruction

Complications, although not limited to, most commonly include the following: infection, hematoma, seroma, wound dehiscence, skin flap necrosis, expander/implant loss, malposition, expander/implant deflation, capsular contracture, hypertrophic or keloid scaring, and venous thromboembolism disease.

Conclusions

Currently in the US, expander/implant reconstruction is the most commonly performed technique for post-mastectomy breast reconstruction.[71] This guideline is designed to promote evidence-based clinical decision-making and to improve the quality of care for breast cancer patients. As a professional society, ASPS aims to ensure that patients are well-informed of all available reconstructive options, including the types of procedures and timing options for post-mastectomy breast reconstruction.

Diagnosis Codes	ICD-9-CM *Scheduled to expire September 30, 2014*	ICD-10-CM *Scheduled to be effective October 1, 2014. This list of codes is not all-inclusive*
• Malignant neoplasm of female breast	174.0-174.9	C50.01-
• Malignant neoplasm of male breast	175.0-175.9	C50.02-
• Secondary malignant neoplasm of other specified sites; breast	198.81	C79.81
• Carcinoma in situ of breast	233.0	D05.90-
• Capsular contracture of breast implant	611.83	N64.89-
• Unspecified abnormal mammogram	93.80	R92.8-
• Acquired absence of breast	V45.7	Z90.10-
• Encounter for breast reconstruction following mastectomy	V51.	Z42.1
• Personal history of malignant neoplasm of breast	V10.3	Z85.3
• Family history of malignant neoplasm of breast	V16.	Z80.3
• Genetic susceptibility to malignant neoplasm of breast	V84.01	Z15.01

Procedure Codes (CPT Codes)	
• Immediate insertion of breast prosthesis following mastopexy, mastectomy or in reconstruction	19340
• Delayed insertion of breast prosthesis following mastopexy, mastectomy or in reconstruction	9342
• Breast reconstruction, immediate or delayed, with tissue expander, including subsequent expansion	19357
• Breast reconstruction with latissimus dorsi flap, without prosthetic implant	19361
• Replacement of tissue expander with permanent prosthesis	11970
• Removal of tissue expander(s) without insertion of prosthesis	11971
• Removal of intact mammary implant	19328
• Removal of intact mammary material	19330
• Nipple/areolar reconstruction	19350
• Open periprosthetic capsulotomy, breast	19370
• Periprosthetic capsulectomy, breast	19371
• Revision of reconstructed breast	19380
• Implantation of biologic implant (e.g., acellular dermal matrix) for soft tissue reinforcement (e.g., breast, trunk) (List separately in addition to code for primary procedure)	15777
• Tissue grafts, other (eg, paratenon, fat, dermis)	20926

HCPS Codes (Please check payer's policies).	
• Implantable breast prosthesis, silicone or equal	L8600
• Prosthesis, breast (implantable) (Saline Implant)	C1789

Appendix A. Summary of Graded Recommendations, Benefits and Harms

Clinical Questions and Recommendations	Supporting Evidence *(References and Level of Evidence)*	GRADE
PATIENT EDUCATION **Clinical Question** In patients undergoing surgical treatment for breast cancer, what is the optimal time to discuss breast reconstruction options? **Recommendation** Although federal law mandates insurance coverage for reconstructive surgery, there are limited mandates that ensure women have the necessary information to make informed decisions about available reconstructive options. Since 2009, New York, New Mexico, and California have enacted laws that address the concerns about patient communication measures. Additionally, in 2012, a bill was introduced in the US House of Representatives that would require the Department of Health and Human Services to plan and implement an education campaign to inform mastectomy patients of breast reconstruction availability, coverage, and relevant options. Overall, patients undergoing post-mastectomy expander/implant breast reconstruction should be given a preoperative referral to a plastic surgeon who can educate the patient about reconstructive options. • **Benefits:** Timely patient education can improve patient satisfaction with the surgical decision-making process and satisfaction with the surgical outcome, without delaying cancer treatment. • **Harms:** Potential delay in cancer care if coordination of care is not expedited.	Literature was not critically appraised for this clinical question	**D**
IMMEDIATE VS. DELAYED RECONSTRUCTION **Clinical Questions** • In patients undergoing mastectomy for the treatment of breast cancer, what is the optimal time for implant-based reconstruction (i.e., immediate versus delayed) when radiation treatment is not required? • In patients undergoing mastectomy for the treatment of breast cancer, what is the optimal time for implant-based reconstruction (i.e., immediate versus delayed) when radiation treatment is required? **Recommendation** Evidence is varied and conflicting on the association between timing of post-mastectomy expander/implant breast reconstruction and postoperative complications. Additionally, postoperative outcomes are often affected by radiation therapy. Consequently, physicians should evaluate each patient case individually and give priority to patient preference. • **Benefits:** Immediate breast reconstruction may benefit patients' self-esteem and body image by patients not having to live with a mastectomy defect. Immediate reconstruction also limits surgical recovery time. Delayed reconstruction is helpful to those patients who need more time to process their cancer diagnosis and treatment plan or to patients who have preventable surgical risk factors such as nicotine use or obesity. • **Harms:** Immediate reconstruction may have added risks for post-operative complications if the patient has a risk factor that can be avoided, such as use of nicotine products. Delayed reconstruction may cause added psychosocial stress among those who are distressed by the mastectomy defect.	12 (R:IV); 13 (T:III); 14 (R:IV); 15 (T:IV); 16 (T:II); 17 (T:IV)	**C**

Clinical Questions and Recommendations	Supporting Evidence *(References and Level of Evidence)*	GRADE
RISK FACTORS **Clinical Questions** In patients undergoing breast reconstruction following mastectomy, what are the risk factors when undergoing immediate implant-based reconstruction?		
Smoking **Recommendation** Evidence indicates that smoking is associated with an overall increased risk of complications and reconstructive failure in patients undergoing post-mastectomy expander/implant breast reconstruction. Patients should be informed of complications associated with smoking. • **Benefits:** There is no benefit to smoking and patients should be counseled on smoking cessation. • **Harms:** Complications associated with nicotine use range from wound complications to implant loss, and smokers are at a 3 to 6 times greater risk of experiencing a postoperative complication compared to non-smokers.	14 (R:IV); 16 (T:II); 18 (T:III); 19 (R:II); 20 (T:III); 21 (T:IV); 22 (T:IV); 23 (T:IV); 24 (T:IV)	**A**
Obesity **Recommendation** Evidence indicates that obesity, defined as body mass index (BMI) greater than 30, increases the risk of postoperative complications in patients undergoing post-mastectomy expander/implant breast reconstruction. Obese patients should be informed of increased surgical risk with expander/implant reconstructions. • **Benefits:** There is no benefit to obesity, and patients should be counseled on practical weight loss solutions. • **Harms:** Wound infections and expander/implant failures are directly correlated with obesity. This correlation is evident in overweight patients (BMI greater than 25) but is amplified in patients who are obese (BMI greater than 30). Additional complications may include seroma, skin flap necrosis, fat necrosis, hematoma, seroma, wound dehiscence, and infection.	14 (R:IV); 20 (T:III); 21 (T:IV); 22 (T:IV); 24 (T:IV); 25 (T:III); 26 (R:III); 27 (T:III)	**A**
Breast Size **Recommendation** Evidence suggests the breast size, specifically breast cup size C or larger, may be associated with an increased risk of reconstructive failure in patients undergoing post-mastectomy expander/implant breast reconstruction. However, the current evidence does not control for BMI, which is directly associated with both breast size and complication rates. Therefore, physicians should remain flexible with regards to breast size and give priority to patient preference. • **Benefits:** Macromastia may allow for more expander fill volume at the time of surgery or larger implants with direct-to-implant procedures. • **Harms:** Some evidence suggests that macromastia is associated with higher post-surgical complication rates.	14 (R:IV); 23 (T:IV); 27 (T:III); 28 (T:III);	**D**
Diabetes **Recommendation** Evidence indicates that diabetes is not a significant independent risk factor for development of postoperative complications and/or reconstruction failure in patients undergoing post-mastectomy expander/implant breast reconstruction. However, for diabetic patients, physicians should aim to practice glycemic control during the peri-operative period. • **Benefits:** Diabetic patients do not require additional preventative measures for expander/implant reconstruction. • **Harms:** Hyperglycemia can be associated with impaired wound healing and infections.	18 (T:III); 14 (R:IV); 16 (T:II); 21 (T:IV); 26 (R:III)	**B**

Clinical Questions and Recommendations	Supporting Evidence *(References and Level of Evidence)*	GRADE
Radiation Therapy ***Overview*** **Recommendation** Evidence indicates that patients undergoing post-mastectomy expander/implant breast reconstruction and receiving radiation therapy experience more postoperative complications than patients who do not require radiation therapy. • **Benefits:** Radiation therapy has been proven to improve local control and overall survival among appropriately selected breast cancer patients. • **Harms:** Complications associated with reconstruction and radiation therapy include infection, wound dehiscence, necrosis, seroma, hematoma, capsular contracture, extrusion, implant loss, and reconstruction failure.	12 (R:IV); 17 (T:IV); 18 (T:III); 26 (R:III); 29 (T:III); 30 (T:III); 31 (T:III); 32 (T:III)	**B**
Previous Radiation **Recommendation** Evidence suggests that post-mastectomy expander/implant breast reconstruction patients are at an increased risk of experiencing postoperative complications if they receive radiation therapy prior to reconstruction. However, these results are inconsistent across the literature and better quality evidence is required. • **Benefits:** Radiation therapy has been proven to improve local control and overall survival among appropriately selected breast cancer patients. • **Harms:** Complications may include infection and capsular contracture.	14(R:IV); 33 (T:III); 34 (T:IV); 35 (T:III); 36 (T:IV)	**C**
Radiation Therapy to Expander **Clinical Question** In patients undergoing mastectomy and radiation for the treatment of breast cancer, does radiation to the expander affect surgical outcomes? **Recommendation** Evidence suggests that in patients undergoing post-mastectomy expander/implant breast reconstruction, radiation therapy to the expander leads to higher rates of postoperative complications. • **Benefits:** Radiation therapy has been proven to improve local control and overall survival among appropriately selected breast cancer patients. • **Harms:** Postoperative complications include infection, skin flap necrosis, seroma, hematoma, implant exposure, and explantation.	37 (T:III); 38 (T:IV); 39 (T:III)	**B**
Radiation Therapy to Implant **Clinical Question** In patients undergoing mastectomy and radiation for the treatment of breast cancer, does radiation to the implant affect surgical outcomes? **Recommendation** Evidence suggests that in patients undergoing post-mastectomy expander/implant breast reconstruction, radiation therapy to the implant leads to higher rates of postoperative complications. • **Benefits:** Radiation therapy has been proven to improve local control and overall survival among appropriately selected breast cancer patients. • **Harms:** Complications include capsular contracture and reconstructive failure.	16 (T:II); 21 (T:IV); 33 (T:III); 34 (T:IV); 40 (T:II); 41 (T:III); 42 (T:III); 44 (T:III); 43 (T:III)	**B**

Clinical Questions and Recommendations	Supporting Evidence *(References and Level of Evidence)*	GRADE
Optimal Timing of Radiation and Reconstruction **Clinical Question** In patients requiring radiation therapy and undergoing immediate breast reconstruction after mastectomy, when is the optimal time for radiation therapy? **Recommendation** Evidence is limited to support optimal timing of radiation therapy for patients undergoing post-mastectomy implant/expander breast reconstruction. However, it is indicated that optimal time for radiation is within eight weeks of the mastectomy • **Benefits:** Radiation therapy has been proven to improve local control and overall survival among appropriately selected breast cancer patients. Decisions about appropriate time for radiation take priority over reconstruction. • **Harms:** Overall disease-free survival may be compromised if radiation is not provided at the optimal time. Decisions about reconstruction should be optimized in order to reduce the chance for a post-surgical complication that could delay radiation therapy.	18 (T:III); 42 (T:III); 45 (T:III); 46 (T:II); 47 (NR)	**C**
Radiation Therapy **Overall Recommendation** Evidence indicates that radiation therapy, regardless of when it is administered, is associated with an increased risk of complications and/or reconstructive failure in patients undergoing post-mastectomy expander/implant breast reconstruction. Patients should be counseled regarding associated complications. • **Benefits:** Radiation therapy has been proven to improve local control and overall survival among appropriately selected breast cancer patients. • **Harms:** Evidence suggests that radiation is a risk factor for reconstructive surgery, both in regards to complications and aesthetic outcomes.	All literature that was appraised for the above commentary on radiation therapy was considered for this overall recommendation	**B**
Chemotherapy **Recommendation** Evidence suggests that chemotherapy does not appear to be a significant risk factor for patients undergoing post-mastectomy expander/implant breast reconstruction. Mostly, the currently available literature does not address postoperative outcomes based on the timing of chemotherapy. • **Benefits:** Chemotherapy can decrease mortality rates in appropriately selected breast cancer patients. • **Harms:** Currently, there is no persuasive evidence to suggest that chemotherapy impacts reconstruction outcomes.	17 (T:IV); 21 (T:IV); 23 (T:IV); 36 (T:IV); 48 (T:II); 49 (T:III); 50 (NR); 51 (NR)	**C**
Hormonal Therapy **Recommendation** Evidence is inconclusive regarding the impact of hormonal therapy on postoperative outcomes for patients undergoing post-mastectomy expander/implant reconstruction. There is a possibility that hormonal therapy may increase risk, however, physicians should evaluate each patient case individually and give priority to patient preference • **Benefits:** Hormonal therapy can decrease mortality rates in appropriately selected breast cancer patients. • **Harms:** Currently, there is no persuasive evidence to suggest that hormonal therapy impacts reconstruction outcomes.	16 (T:II); 23 (T:IV)	**D**

Clinical Questions and Recommendations	Supporting Evidence *(References and Level of Evidence)*	GRADE
ANTIBIOTIC PROPHYLAXIS **Clinical Question** In patients undergoing implant-based reconstruction after mastectomy, what is the optimal duration of antibiotic prophylaxis for prevention of postoperative infections? **Recommendation** SCIP protocol dictates that patients undergoing post-mastectomy expander/implant breast reconstruction should receive preoperative antibiotics in accordance with published guidelines. Documentation of drains in proximity to an implant provides sufficient reason for continuation of intravenous antibiotics beyond the currently advised 24 hour postoperative period. Overall, surgeons should adhere to their specific state and hospital guidelines on antibiotic administration. • **Benefits:** Appropriate antibiotic prophylaxis will decrease the risk of postoperative infections without significantly increasing drug resistant organisms. • **Harms:** Inappropriate antibiotic prophylaxis may not adequately protect patients against postoperative infections and can increase the incidence of drug resistant organisms.	Literature was not critically appraised for this clinical question	**D**
ACELLULAR DERMAL MATRIX **Clinical Question** In patients undergoing mastectomy and implant-based breast reconstruction, what are the outcomes associated with utilizing Acellular Dermal Matrix during reconstruction? **Recommendation** Evidence regarding the use of acellular dermal matrix (ADM) in patients undergoing post-mastectomy expander/implant reconstruction is varied and conflicting. Although, the currently available evidence indicates a trend toward increased complications with ADM use, it should be noted that the evidence does not control for selection biases. • **Benefits:** ADM is currently used to increase soft tissue coverage, support the implant pocket, improve contour and reduce pain with expansion. However, evidence to support these improved surgical outcomes are limited. • **Harms:** Some evidence suggests that use of ADM is associated with increased postoperative complications, specifically related to infection and seroma.	20(T:III); 25 (T:III); 56 (NR); 57 (T:III); 58 (T:III); 59 (T:III); 60 (T:III)	**C**
MONITORING FOR CANCER RECURRENCE **Clinical Question** In patients undergoing mastectomy and implant-based breast reconstruction, what are the screening recommendations to monitor for cancer recurrence? **Recommendation** Per clinical expertise, examination is sufficient to detect local recurrence in patients who have undergone post-mastectomy expander/implant breast reconstructions. Diagnostic imaging is indicated if there is any clinical concern for recurrence. • **Benefits:** Breast exams are a highly reliable way to detect a cancer recurrence post-mastectomy. • **Harms:** There is no evidence to suggest that reconstruction interferes with the detection of a cancer recurrence.	Literature was not critically appraised for this clinical question	**D**
IMPLANT-BASED RECONSTRUCTION AND ONCOLOGIC OUTCOMES **Clinical Question** In patients undergoing breast reconstruction following mastectomy, what are the oncologic outcomes associated with undergoing immediate implant-based reconstruction? **Recommendation** Evidence indicates that post-mastectomy expander/implant breast reconstruction does not adversely affect oncologic outcomes. Administration of radiation therapy varies per patient and so, decisions regarding sequencing of treatment should be made by a multidisciplinary team. • **Benefits:** Breast reconstruction confers significant quality of life and psychosocial benefits among those that desire to undergo the procedures. • **Harms:** No evidence to suggest that breast reconstruction negatively impacts cancer surveillance or increases recurrence rates.	64 (NR); 65 (T:III); 66 (NR); 67 (T:III); 68 (T:III); 69 (T:III); 70 (T:III)	**B**

Appendix B. Literature Search Process

Literature Search Goal

A literature search was conducted to identify published evidence relevant to several clinical topics in breast reconstruction procedures using tissue expanders and/or implants. Clinical topics to be addressed in an evidence-based guideline were chosen by an expert panel (ASPS Breast Reconstruction Guideline Work Group), and the search and initial screening was performed under a prospective work plan in order to minimize bias.

Literature Search Process

Database(s) Searched

PubMed (including MEDLINE and pre-MEDLINE citations)

Search Terms:
(Mammaplasty[MeSH] AND reconstruction) OR "breast reconstruction"
Limits: English only; Humans; January 1, 2001 to December 31, 2011; NOT publication types case reports, editorial, comment, letter, news, newspaper article, in vitro, legal cases, or legislation

CINAHL (Cumulative Index to Nursing and Allied Health Literature)

Search Terms:
"Breast reconstruction" OR (mammaplasty AND reconstruction)
Limits: English only; January 1, 2001 to December 31, 2011; non-MEDLINE citations

The Cochrane Library

Search Terms:
"Breast reconstruction"
Limits: Cochrane Database of Systematic Reviews (protocols of pending reviews omitted)

Manual reference checks

Search terms: N/A. Bibliographies from accepted studies and recent reviews were reviewed by hand for potentially relevant citations, and compared to the overall yield from the electronic searches.

Study Screening

Inclusion Criteria

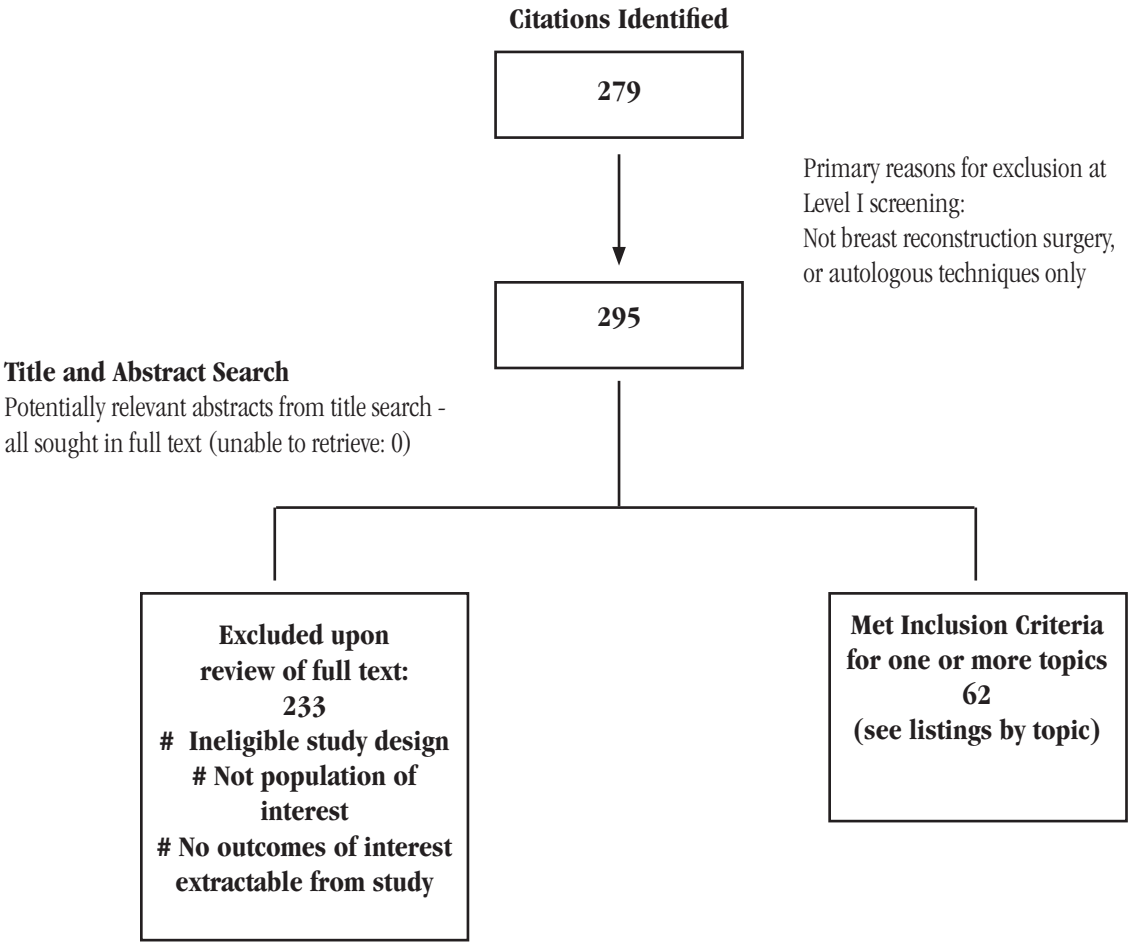
Studies published in English from 2001-2011, reporting outcomes of interest for at least 10 women undergoing breast reconstruction using tissue expanders and/or implants. Reconstruction procedures performed after mastectomy for breast cancer, precancerous conditions (e.g. DCIS), or prophylactically (e.g. BRCA carriers, contralateral mastectomy) were eligible. Studies with a mixed population of autologous and implant-based reconstruction were eligible if at least one outcome was separately available for the subgroup of patients with implant-based reconstruction. Outcomes of interest varied by clinical question, but in general, included safety (rates of complication), risk as stratified by patient characteristics, aesthetic outcomes, and patient satisfaction. Single-arm studies were eligible but are a lower tier of evidence than comparative studies; if sufficient higher-tier evidence is available, these studies may not be summarized.

Exclusion Criteria

Languages other than English; Meeting abstracts; Narrative reviews or commentary; Studies with fewer than 10 patients; Studies of autologous techniques only; Breast augmentation with implant (not reconstruction); No outcomes of interest; mixed populations with no separable data.

Primary Search
Databases:

- PubMed (2,731)
- CINAHL (13 non-duplicates)
- Cochrane (0 non-duplicates*)
- Bibliography search (5 non-duplicates)



Appendix C
ASPS Evidence Rating Scales

AMERICAN SOCIETY OF PLASTIC SURGEONS®

Evidence Rating Scale for Therapeutic Studies

Level of Evidence	Qualifying Studies
I	High-quality, multi-centered or single-centered, randomized controlled trial with adequate power; or systematic review of these studies
II	Lesser-quality, randomized controlled trial; prospective cohort or comparative study; or systematic review of these studies
III	Retrospective cohort or comparative study; case-control study; or systematic review of these studies
IV	Case series with pre/post test; or only post test
V	Expert opinion developed via consensus process; case report or clinical example; or evidence based on physiology, bench research or "first principles"

Evidence Rating Scale for Diagnostic Studies

Level of Evidence	Qualifying Studies
I	High-quality, multi-centered or single-centered, cohort study validating a diagnostic test (with "gold" standard as reference) in a series of consecutive patients; or a systematic review of these studies
II	Exploratory cohort study developing diagnostic criteria (with "gold" standard as reference) in a series of consecutive patient; or a systematic review of these studies
III	Diagnostic study in nonconsecutive patients (without consistently applied "gold" standard as reference); or a systematic review of these studies
IV	Case-control study; or any of the above diagnostic studies in the absence of a universally accepted "gold" standard
V	Expert opinion developed via consensus process; case report or clinical example; or evidence based on physiology, bench research or "first principles"

Evidence Rating Scale for Prognostic/Risk Studies

Level of Evidence	Qualifying Studies
I	High-quality, multi-centered or single-centered, prospective cohort or comparative study with adequate power; or a systematic review of these studies
II	Lesser-quality prospective cohort or comparative study; retrospective cohort or comparative study; untreated controls from a randomized controlled trial; or a systematic review of these studies
III	Case-control study; or systematic review of these studies
IV	Case series with pre/post test; or only post test
V	Expert opinion developed via consensus process; case report or clinical example; or evidence based on physiology, bench research or "first principles"

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Acellular dermal matrix (ADM) assisted breast reconstruction procedures: Joint guidelines from the Association of Breast Surgery and the British Association of Plastic, Reconstructive and Aesthetic Surgeons

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Abstract

Tissue expansion with delayed insertion of a definitive prosthesis is the most common form of immediate breast reconstruction performed in the United Kingdom. However, achieving total muscle coverage of the implant and natural ptosis is a key technical challenge. The use of acellular dermal matrices (ADM) to supplement the pectoralis major muscle at the lower and lateral aspects of the breast has been widely adopted in the UK, potentially allowing for a single stage procedure. There is however little published data on the clinical and quality criteria for its use, and no long term follow-up.

The guidelines have been jointly produced by the Association of Breast Surgery and the British Association of Plastic, Reconstructive and Aesthetic Surgeons and their aims are: to inform those wishing to undertake ADM assisted breast reconstruction and, to identify clinical standards and quality indicators for audit purposes.

The guidelines are based on expert opinion of a multi-disciplinary working group, who are experienced in the technique, and a review of the published data.

Keywords: Acellular dermal matrix; Breast cancer; Reconstruction; Guidelines; Breast implant; Expander

Introduction

This document has been produced with the joint involvement of the Association of Breast Surgery and the British Association of Plastic, Reconstructive and Aesthetic Surgeons. Recommendations were derived after a review of published data regarding the use of acellular dermal matrix in breast reconstruction. Each recommendation is assigned a "level of evidence" (I–V) adapted from the designations set by the Centre for Evidence Based Medicine and others (discussed in detail in Appendix A). This document supplements a previous publication "Oncoplastic breast surgery: A guide to good practice" which gives an in depth practical guide on all types of breast reconstruction.[1]

The aims of this document are to:

i) describe clinical criteria, quality criteria and audit for acellular dermal matrices (ADMs) in breast reconstruction procedures for those units introducing this new technique
ii) inform those developing and commissioning services of the identified clinical standards and quality indicators associated with the procedure

The source materials for the document are published articles in peer review journals. Randomised trial data for breast reconstruction using ADM does not exist. Other

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Section 8.0

Coverage Guidances

Health Evidence Review Commission (HERC)

Coverage Guidance: Temporary Percutaneous Mechanical Circulatory Support with Impella Devices

DRAFT for 8/8/2019 VbBS/HERC meeting materials

HERC Coverage Guidance

Temporary percutaneous mechanical circulatory support with Impella devices is not recommended for coverage in elective high-risk percutaneous coronary intervention (PCI) for patients with stable coronary artery disease (*weak recommendation*).

Temporary percutaneous mechanical circulatory support with Impella devices during PCI is recommended for coverage (*weak recommendation*) only for patients with acute myocardial infarction when all of the following conditions are met:

- Non-ST-elevation myocardial infarction (NSTEMI) without cardiogenic shock
- A heart team discussion determines that the patient needs revascularization with coronary artery bypass graft (CABG) or PCI
- Two cardiothoracic surgeons are consulted and agree that the patient is inoperable (i.e., surgeons are not willing to perform CABG, but agree that revascularization is indicated)
- Patient has complex left main or last remaining conduit disease
- Ejection fraction less than 30%

Temporary percutaneous mechanical circulatory support with Impella devices is recommended for coverage (*weak recommendation*) only for patients with cardiogenic shock who might be candidates for left ventricular assist device (LVAD) (destination therapy) or transplant (bridge to transplant), AND an advanced heart failure and transplant cardiologist agrees that Impella should be used as a bridge to a decision for LVAD or a transplant. Appropriate effort should be made to consult with a heart failure and transplant cardiologist, but coverage is recommended in circumstances where consultation cannot reasonably be obtained without endangering the patient's life and the treating physician believes the patient meets the criteria above.

Note: Definitions for strength of recommendation are in Appendix A. GRADE Table Element Description.

Rationales for each recommendation appear below in the GRADE table.

Table of Contents

Coverage Guidance: Temporary Percutaneous Mechanical Circulatory Support with Impella Devices 1

Rationale for development of coverage guidances and multisector intervention reports 3

GRADE Table 5

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for elective high-risk percutaneous coronary intervention? 5

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for cardiogenic shock? 8

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage to support PCI for acute myocardial infarction without cardiogenic shock? 11

Background 13

Indications 13

Technology Description 13

Evidence Review 14

Evidence Summary 15

Policy Landscape 23

Payer Coverage Policies 23

Recommendations from Others 24

Quality Measures 24

References 25

Evidence Sources 25

Other Citations 26

Appendix A. GRADE Table Element Descriptions 28

Appendix B. GRADE Evidence Profile 30

Appendix C. Methods 32

Scope Statement 32

Search Strategy 33

Appendix D. Applicable Codes 34

Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patients' experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

HERC uses the following principles in selecting topics for its reports to guide public and private payers:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on diagnostic and clinical interventions, evidence is evaluated using an adaptation of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness could depend on the environment in which the intervention is implemented.

GRADE Table

HERC develops recommendations by using the concepts of the GRADE system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and assesses each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. Assessments of confidence are from the published systematic reviews and meta-analyses, where available and judged to be reliable.

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from the Center for Evidence-based Policy. Unless otherwise noted, statements regarding resource allocation, values and preferences, and other considerations are the assessments of HERC, as informed by the evidence reviewed, public testimony, and subcommittee discussion.

Recommendations for coverage are based on the balance of benefit and harms, resource allocation, values and preferences, and other considerations. See Appendix A for more details about the factors that constitute the GRADE table.

GRADE Table

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for elective high-risk percutaneous coronary intervention?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
All-cause mortality *(Critical outcome)*	No significant difference in all-cause mortality 7.6% for Impella vs. 5.9% for intra-aortic balloon pump (IABP) at 30 days p = 0.47 12.1% for Impella vs. 8.7% for IABP at 90 days p = 0.244 ●●○○ *(Low confidence, based on 1 RCT, n = 448)*	Impella is extremely expensive and may cost as much as 20 times more than an IABP.	Patients would strongly prefer interventions that improve their outcomes (with regard to death or major adverse cardiac events [MACE]) and have fewer harms. The mechanism by which this is achieved (i.e., IABP or Impella) is unlikely to be important to patients. There is likely to be low	

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for elective high-risk percutaneous coronary intervention?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Major adverse cardiovascular events *(Critical outcome)*	No significant difference in composite outcome of major adverse events (including repeat revascularization): 35.1% for Impella vs. 40.1% for IABP at 30 days p = 0.227 40.6% for Impella vs. 49.3% for IABP at 90 days p = 0.066 ●●○○ *(Low confidence, based on 1 RCT, n = 448)*		variability in these values and preferences.	
Successful bridge to recovery *(Important outcome)*	Not applicable			
Successful bridge to transplant *(Important outcome)*	Not applicable			

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for elective high-risk percutaneous coronary intervention?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Harms *(Important outcome)*	No significant difference in major bleeding complications between Impella and IABP ●○○○ *(Very low confidence, based on 1 observational study, n = 75)* No significant difference in vascular complications between Impella and IABP ●○○○ *(Very low confidence, based on 1 observational study, n = 75)*			

Balance of benefits and harms: We have low confidence that there is no difference between Impella and IABP in terms of all cause-mortality and MACE and very low confidence of no difference in complications between major bleeding and vascular complications. The balance suggests no net benefit and no net harms based on limited evidence.

Rationale: We make a recommendation against coverage for elective high-risk PCI in stable coronary artery disease because there appears to be no benefit for Impella over IABP and no difference in complications. Impella is much more expensive than the comparator, and patient values and preferences would not lean toward either direction. It is a weak recommendation because of the low confidence in the estimate of effect.

Recommendation: Temporary percutaneous mechanical circulatory support with Impella devices is not recommended for coverage for patients receiving elective high-risk PCI (*weak recommendation*).

Temporary percutaneous mechanical circulatory support with Impella devices during PCI is recommended for coverage for patients with acute NSTEMI without cardiogenic shock (*weak recommendation*) when all of the following conditions are met:

- A heart team discussion determines that the patient needs revascularization with CABG or PCI.
- Two cardiothoracic surgeons are consulted and agree that the patient is inoperable (i.e., surgeons are not willing to perform CABG, but agree that revascularization is indicated).
- Patient has complex left main or last remaining conduit disease
- Ejection fraction less than 30%

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for cardiogenic shock?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
All-cause mortality *(Critical outcome)*	No significant difference in all-cause mortality 40.8% for Impella vs. 41.3% for IABP at 30 days RR 0.99 (95% CI 0.62 to 1.58, p = 0.95) 46.9% for Impella vs. 41.3% for IABP at 6 months RR 1.15 (95% CI 0.74 to 1.48, p = 0.53) ●●○○ *(Low confidence, based on 3 RCTs, n = 95)*	Impella is extremely expensive and may be as much as 20 times more than an IABP.	Patients would strongly prefer interventions that improve their outcomes (with regard to death or MACE) and have fewer harms. The mechanism by which this is achieved (i.e., IABP or Impella) is unlikely to be important to patients. There is likely to be low variability in these values and preferences.	There was insufficient evidence to include in the GRADE table for non-ischemic cardiogenic shock. There were no studies found examining patients bridging to LVAD or transplant.
Major adverse cardiovascular events *(Critical outcome)*	No significant difference in major adverse cardiovascular events 26% for Impella vs. 33% for IABP at 4 months p = 0.74 37% for Impella vs. 47% for IABP at 12 months p = 0.72 ●○○○ *(Very low confidence, based on 1 RCT, n = 21)*			
Successful bridge to recovery *(Important outcome)*	Insufficient data			

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for cardiogenic shock?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Successful bridge to transplant *(Important outcome)*	Insufficient data			
Harms *(Important outcome)*	Range of reported vascular complications Impella: 3% to 25% IABP: 0% to 6.4% ●○○○ *(Very low confidence, based on 4 studies, n = 222)* Range of reported bleeding complications Impella: 8% to 38.4% IABP: 0% to 32.2% ●○○○ *(Very low confidence, based on 5 studies, n = 272)*			

Balance of benefits and harms: We have low confidence that there is no difference between Impella and IABP in terms of all-cause mortality, and very low confidence that there is no difference in MACE. We have very low confidence that significant harms (such as bleeding, stroke, and vascular events) are greater with Impella compared to IABP. The evidence reviewed suggests that the balance is neutral to negative for Impella in ischemic cardiogenic shock. Insufficient evidence was found for non-ischemic cardiogenic shock to make an assessment of the balance of benefits and harms.

Rationale: We recommend against Impella for ischemic cardiogenic shock because of a lack of proven benefit, possibility of greater significant harms, and significant increase in resource allocation compared to IABP. No studies were found for non-ischemic cardiogenic shock, and so the recommendation applies to all types of cardiogenic shock.

Patients who are candidates for LVAD or bridging to a transplant are an unstudied population, but it might be appropriate to consider Impella on an individual basis, based on expert opinion.

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage for cardiogenic shock?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Recommendation: Temporary percutaneous mechanical circulatory support with Impella devices is recommended for coverage (*weak recommendation*) only for patients with cardiogenic shock who might be candidates for left ventricular assist device (LVAD) (destination therapy) or transplant (bridge to transplant), AND an advanced heart failure and transplant cardiologist agrees that Impella should be used as a bridge to a decision for LVAD or a transplant. Appropriate effort should be made to consult with a heart failure and transplant cardiologist, but coverage is recommended in circumstances where consultation cannot reasonably be obtained without endangering the patient's life and the treating physician believes the patient meets the criteria above.				

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage to support PCI for acute myocardial infarction without cardiogenic shock?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
All-cause mortality *(Critical outcome)*	Insufficient data	Impella is extremely expensive and may be as much as 20 times more than an IABP.	Patients with acute myocardial infarction would likely strongly prefer an intervention thought to result in survival benefit. If Impella were thought to be necessary to allow revascularization for high-risk patients, their preferences would likely be in favor of Impella.	An RCT of these populations is feasible, however, given widespread use of Impella in current practice, might not be performed.
Major adverse cardiovascular events *(Critical outcome)*	Insufficient data			
Successful bridge to recovery *(Important outcome)*	Insufficient data			
Successful bridge to transplant *(Important outcome)*	Insufficient data			
Harms *(Important outcome)*	Insufficient data			

Balance of benefits and harms: There is insufficient evidence to evaluate the balance of benefits and harms. Expert opinion indicates that protected PCI might provide a significant survival benefit in patients with NSTEMI who are not eligible for CABG.

Should temporary percutaneous mechanical circulatory support (i.e., Impella) be recommended for coverage to support PCI for acute myocardial infarction without cardiogenic shock?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Rationale: Patients with NSTEMI and low ejection fraction are an unstudied population for whom expert opinion indicates that protected PCI might provide a significant survival benefit and PCI might not otherwise be done without Impella devices. Although resource allocation and the lack of evidence would argue against coverage, values and preferences and expert opinion suggest in this carefully selected population a true survival benefit may exist. The coverage recommendation is weak because of the lack of evidence. There was no evidence in patients with NSTEMI without shock, but this population is very likely to be revascularized regardless of their risk. Given that the availability of Impella is unlikely to change whether or not a patient is going to be revascularized, and given the lack of evidence and the high cost, a recommendation is not made for coverage.				
Recommendation: Temporary percutaneous mechanical circulatory support with Impella devices during PCI is recommended for coverage (*weak recommendation*) only for patients with acute myocardial infarction when all of the following conditions are met: • NSTEMI without cardiogenic shock • A heart team discussion determines that the patient needs revascularization with CABG or PCI • Two cardiothoracic surgeons are consulted and agree that the patient is inoperable (i.e., surgeons are not willing to perform CABG, but agree that revascularization is indicated) • Patient has complex left main or last remaining conduit disease • Ejection fraction less than 30%				

Note: GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Background

Temporary mechanical circulatory support may be needed in patients with cardiogenic shock or who are undergoing elective high-risk coronary interventions. The intra-aortic balloon pump (IABP) has been the most frequently used ventricular assist device since its introduction in the 1960s because of the ease of insertion and use (Ait Ichou, 2017). For some patients in severe cardiogenic shock with a systolic aortic pressure that cannot be improved to more than 60 mmHg by vasopressors, the IABP might not provide sufficient circulatory support (Ait Ichou, 2017). Temporary percutaneous mechanical circulatory support devices, such as Impella, offer greater augmentation of cardiac output and left ventricular unloading. It has been hypothesized that these hemodynamic advantages would result in improved clinical outcomes. Other circulatory support devices (not in scope for this Coverage Guidance) require open surgery or septal puncture, and could be appropriate for longer-term use.

Indications

Temporary percutaneous mechanical circulatory support devices are indicated for patients in cardiogenic shock and those undergoing elective high-risk percutaneous coronary interventions (PCI).

Technology Description

Impella is a device for mechanical circulatory support that has a small pump at one end of a thin, flexible tube and is implanted through an artery in the leg. The other end of the tube is connected to a control system outside the body that controls the pump rate (Health Quality Ontario, 2017). Impella works by increasing the maximal blood flow by unloading blood from the left ventricle into the ascending aorta, resulting in improved coronary perfusion pressure and end-organ perfusion. In addition to increasing cardiac output, it also decreases myocardial oxygen consumption and pulmonary capillary wedge pressure, potentially reducing the size of a myocardial infarction and accelerating its recovery (Ait Ichou, 2017).

Impella has four models: 2.5, CP (or 3.5), RP, and 5.0/LD (Abiomed, 2018). The most frequently used devices, Impella 2.5 and 5.0, are capable of increasing cardiac output by up to 2.5 and 5.0 L/min, respectively (Ait Ichou, 2017). Most Impella devices can be placed percutaneously through the femoral artery (or the femoral vein for Impella RP), but the Impella 5.0 typically requires an arterial cut-down procedure, and the Impella LD is placed during open chest procedures (Ait Ichou, 2017).

In 2015, the U.S. Food and Drug Administration (FDA) granted premarket approval to Impella 2.5 (FDA, 2015). This approval order stated that Impella was indicated for temporary (< 6 hours) ventricular support during high-risk PCI performed in elective or urgent, hemodynamically stable patients with severe coronary artery disease and depressed left ventricular ejection fraction (LVEF) (FDA, 2015). A 2016 supplemental order from the FDA approved Impella for patients experiencing ongoing cardiogenic shock immediately (< 48 hours) after acute myocardial infarction or open-heart surgery for the Impella Ventricular Support Systems (FDA, 2016). A February 2018 supplemental order expanded the indications to include patients with ongoing cardiogenic shock in the setting of cardiomyopathy, including peripartum cardiomyopathy or myocarditis (FDA, 2018).

Evidence Review

Our search identified two systematic reviews and one briefly reported meta-analysis for inclusion. Because of the small number of comparative studies of Impella and because of the incomplete overlap of included studies (see Table 1) in the reviews, the individual comparative studies included in those reviews are summarized in Tables 2-4. The characteristics of the individual comparative studies are summarized in Table 2 and their relevant outcomes are summarized in Tables 3 and 4.

The Health Quality Ontario review (2017) is a high-quality systematic review and health technology assessment of the benefits and harms of Impella for high-risk PCI or cardiogenic shock. For the high-risk PCI group, the authors identified one randomized controlled trial (RCT) (O'Neill et al., 2012), two comparative observational studies (Boudoulas et al., 2012; Schwartz et al., 2011), and eight non-comparative observational studies. The authors assessed the risk of bias in the RCT to be moderate because of insufficient statistical power, concern for selection bias, and early termination of the trial due to futility. The comparative observational studies were limited by selection bias, insufficient adjustment for confounding, and high rates of loss to follow-up.

For the cardiogenic shock group, the authors identified one small RCT (Seyfarth et al., 2011), one comparative observational study (Manzo-Silberman et al., 2013), and six non-comparative observational studies. The RCT was assessed to be at high risk of bias due to small sample size and the risk of model misclassification, as well as imbalance in baseline characteristics. The comparative observational study was judged to be at moderate risk of bias because of selection bias (including an imbalance in baseline LVEF between cohorts) and potential treatment bias due to a high degree of physician discretion in managing the patients. The relevant results from the included comparative studies are summarized in Tables 3 and 4 below. Applying a GRADE methodology, the authors of the review concluded that there was:

- No difference in 30-day mortality or MACE between Impella 2.5 and IABP for high-risk PCI (low strength of evidence)
- No difference in bleeding or vascular complications between Impella 2.5 and IABP for high-risk PCI (very low strength evidence)
- No difference in 30-day mortality or MACE between Impella 2.5 and IABP for cardiogenic shock (low strength of evidence)
- Significantly higher rate of hemolysis with Impella 2.5 compared to IABP for cardiogenic shock (low strength of evidence)
- No difference in vascular complications between Impella 2.5 and IABP for cardiogenic shock (low strength of evidence)

The review by Ait Ichou et al. (2017) is a fair-quality systematic review of the effectiveness and safety of Impella devices in patients undergoing high-risk PCI. The review is mainly limited by incomplete reporting of risk of bias assessments. The authors identified four RCTs (Seyfarth et al., 2008; O'Neill et al., 2012; Ouweneel et al., 2017b; Ouweneel et al., 2016), two comparative observational studies (Boudoulas et al., 2012; Schwartz et al., 2011), and 14 non-comparative observational studies, for a total of 1,287 patients. The authors judged three of the RCTs to be at low risk of bias and one (Ouweneel et al., 2016) to be at high risk of bias due to early termination and changes to inclusion criteria during recruitment. The two comparative observational studies were considered to be at high risk of bias

because of their design and the likelihood of confounding by indication. All of the non-comparative observational studies were regarded as having serious or critical risk of bias. The relevant results from the included comparative studies are summarized in Tables 3 and 4 below.

Overall, the authors concluded that there were no differences in all-cause mortality between Impella and IABP, but noted a possible reduction in major adverse events at 90 days in a per-protocol analysis of the PROTECTII trial (O'Neill et al., 2012). They observed high levels of clinical heterogeneity in the studies and that most studies were inadequately powered to detect differences in clinical events. Finally, the authors asserted the need for larger RCTs to better clarify the clinical effectiveness and safety of Impella, and noted that one such trial (DANSHOCK, NCT01633502) is currently underway.

The review by Ouweneel et al. (2017a) is a briefly reported meta-analysis that combines the results of the three small RCTs of Impella compared to IABP in patients with cardiogenic shock (Seyfarth et al., 2008; O'Neill et al., 2012; Ouweneel et al., 2017b; Ouweneel et al., 2016). The total population of these studies was 95 patients. In the meta-analysis (it is not stated whether a fixed or random effects model was used), there was no difference in all-cause mortality at 30 days (RR 0.99, 95% CI 0.62 to 1.58) or at six months (RR 1.15, 95% CI 0.74 to 1.48). There was also no difference in LVEF of survivors between the two groups at two to six months.

Our search did not identify any additional RCTs published after the most recent systematic review (Ait Ichou et al., 2017). Additionally, the search did not identify any systematic reviews or RCTs examining the use of Impella in the setting of acute non-ischemic cardiogenic shock.

Evidence Summary

On the basis of a relatively small number of comparative studies, the use of Impella devices to support elective high-risk PCI or in the setting of ischemic cardiogenic shock did not improve clinical outcomes compared to IABP. In some studies of patients with ischemic cardiogenic shock, Impella appears to increase the risk of bleeding and vascular complications compared to IABP, although a wide range of adverse effect rates are reported in the comparative studies. There were no systematic reviews or RCTs of Impella in the setting of non-ischemic cardiogenic shock.

Table 1. Studies Included in Systematic Reviews

	Seyfarth 2008 (Risk of bias assessment)	O'Neill 2012 (Risk of bias assessment)	Ouweneel 2017b (Risk of bias assessment)	Ouweneel 2016 (Risk of bias assessment)	Schwartz 2011 (Risk of bias assessment)	Manzo-Silberman 2013 (Risk of bias assessment)	Boudoulas 2012 (Risk of bias assessment)
Ait Ichou 2017	X (Low)	X (Low)	X (Low)	X (High)	X (Serious)		X (Serious)
Ouweneel 2017a	X (Not rated)		X (Not rated)	X (Not rated)			
Health Quality Ontario 2017	X (High)	X (Moderate)			X (Moderate)	X (Moderate)	X (Moderate)

Table 2. Characteristics of Individual Comparative Studies

	Study type Setting	Population	Intervention (N) Comparator (N)
Seyfarth 2008	Randomized controlled trial 2 centers in Germany	Adults with acute myocardial infarction < 48 hours and cardiogenic shock	Impella 2.5 (13) IABP (13)
Schwartz 2011	Retrospective cohort Single center	Adults undergoing high-risk PCI supported with Impella, IABP, or TandemHeart between 2008 and 2010	Impella 2.5 (13) TandemHeart (32) IABP (5)
Boudoulas 2012	Retrospective cohort Single center	All patients with ACS undergoing high-risk PCI supported with Impella 2.5 or IABP between 2008 and 2010	Impella 2.5 (12) IABP (62)

	Study type Setting	Population	Intervention (N) Comparator (N)
O'Neill 2012	Randomized controlled trial 112 centers in the US, Canada, and Germany	Adults undergoing high-risk elective PCI (defined as unprotected left main or last patent vessel with LVEF < 35% or 3 vessel disease with LVEF < 30%)	Impella 2.5 (225) IABP (223)
Manzo-Silberman 2013	Retrospective cohort Single center	Adult survivors of out-of-hospital cardiac arrest and post-resuscitation shock supported with Impella or IABP after coronary angiography between 2007 and 2010	Impella 2.5 (35) IABP (43)
Ouweneel 2017b	Randomized controlled trial	Adults with STEMI and severe cardiogenic shock (SBP < 90 mmHg for more than 30 minutes or need for inotropes or vasopressors to maintain SBP > 90 mmHg), and requiring mechanical ventilation	Impella CP (24) IABP (24)
Ouweneel 2016	Randomized controlled trial 5 centers	Adults with anterior STEMI and cardiogenic pre-shock (defined as HR > 100 and/or SBP < 100 mmHg with clinical signs of shock)	Impella 2.5 (11) IABP (9)

Table 3. Outcomes from RCTs

	All-cause mortality, 30 days	All-cause mortality, 90-360 days	MACE, 30 days	MACE, 90-360 days	Adverse events
Seyfarth 2008 n = 26	46% Impella 46% IABP	NR	NR	NR	1 case of acute limb ischemia following Impella removal RBC transfusion requirement (mean) 2.6 units Impella

	All-cause mortality, 30 days	All-cause mortality, 90-360 days	MACE, 30 days	MACE, 90-360 days	Adverse events
					1.2 units IABP
O'Neill 2012 n = 448	7.6% Impella 5.9% IABP	12.1% Impella 8.7% IABP (at 90 days)	35.1% Impella 40.1% IABP (outcome defined as major adverse events)	40.6% Impella 49.3% IABP (outcome defined as major adverse events at 90 days)	NR
Ouweneel 2017b n = 48	46% Impella 50% IABP	50% Impella 50% IABP	NR	NR	Stroke 4.2% Impella 4.2% IABP Major vascular event 4.2% Impella 0% IABP Bleeding 33.3% Impella 8.3% IABP
Ouweneel 2016 n = 21	NR	26% Impella 11% IABP (at 4 months)	NR	26% Impella 33% IABP (at 4 months)	Severe vascular events 25% Impella 0% IABP

	All-cause mortality, 30 days	All-cause mortality, 90-360 days	MACE, 30 days	MACE, 90-360 days	Adverse events
				37% Impella 47% IABP (at 12 months)	Need for renal replacement therapy 18% Impella 0% IABP Ventricular arrhythmias 8% Impella 11% IABP Stroke 8% Impella 0% IABP Severe bleeding 8% Impella 0% IABP Hemolysis 8% Impella 0% IABP

Table 4. Outcomes of Comparative Observational Studies

	All-cause mortality, 30 days	All-cause mortality, 90-360 days	MACE, 30 days	MACE, 90-360 days	Adverse events
Schwartz 2011 n = 50	15% Impella 13% TandemHeart 0% IABP	NR	15% Impella 19% TandemHeart 40% IABP	NR	Limb ischemia 0% Impella 6% TandemHeart 0% IABP Major bleeding 31% Impella 13% TandemHeart 20% IABP
Boudoulas 2012 n = 75	In-hospital mortality 0% Impella 20.9% IABP	15.3% Impella 25.8% IABP	NR	NR	Vascular complications 15.3% Impella 6.4% IABP Leg ischemia 15.3% Impella 3.2% IABP Mesenteric ischemia 0% Impella 1.6% IABP

	All-cause mortality, 30 days	All-cause mortality, 90-360 days	MACE, 30 days	MACE, 90-360 days	Adverse events
					Aortic rupture 0% Impella 1.6% IABP Bleeding 38.4% Impella 32.2% IABP CVA 0% Impella 3.2% IABP Bacteremia 0% Impella 4.7% IABP
Manzo-Silberman 2013 n = 78	Survival at day 3 34% Impella 67% IABP Survival with CPC score 1 at 28 days	NR	NR	NR	Hemolytic anemia 6% Impella 0% IABP Sustained ventricular arrhythmias

	All-cause mortality, 30 days	All-cause mortality, 90-360 days	MACE, 30 days	MACE, 90-360 days	Adverse events
	23% Impella 29.5% IABP				17% Impella 24% IABP Bleeding requiring transfusion 26% Impella 9% IABP Vascular complications 3% Impella 2% IABP

Policy Landscape

Payer Coverage Policies

Medicaid

The Washington State Medicaid Program billing guide (7/1/2018) provides coverage for FDA-approved percutaneous left ventricular assist devices for these indications:

- Providing short-term circulatory support in cardiogenic shock
- As an adjunct to PCI in the following high-risk patients:
  - Clients undergoing unprotected left main or last-remaining-conduit PCI with ejection fraction less than 35%
  - Clients with three vessel disease and diastolic ejection fraction less than 30%

Medicare

No Medicare National Coverage Determination (NCD) or Local Coverage Determinations were found for percutaneous mechanical circulatory support. The NCD on ventricular assist devices provides coverage only for ventricular assist devices that are surgically attached to one or both intact ventricles.

Private Payers

The Aetna policy on ventricular assist devices (last review 3/22/18) provides coverage for Impella for these indications:

- Providing short-term circulatory support in cardiogenic shock
- As an adjunct to PCI in the following high-risk patients:
  - Persons undergoing unprotected left main or last-remaining-conduit PCI with ejection fraction less than 35%
  - Persons with three vessel disease end diastolic ejection fraction less than 30%.

The Cigna policy on ventricular assist devices and percutaneous cardiac support systems (effective 2/15/18) provides the following coverage:

- Impella RP System for up to 14 days in a child or adult with a BSA ≥ 1.5m^2 for the treatment of acute right heart failure or decompensation following left ventricular assist device implantation, myocardial infarction, heart transplant, or open-heart surgery
- Impella Recover LP 2.5 Percutaneous Cardiac Support System, Impella 5.0 Catheters, or Impella 2.5 Plus for the treatment of cardiogenic shock for up to six hours

Moda's list of procedures and services requiring prior authorization (updated 7/1/2018) includes left ventricular assist devices.

The Regence policy on ventricular assist devices and total artificial hearts (effective 2/1/2018) states that this policy does not address the use of percutaneous ventricular assist devices, which may be considered medically necessary.

Recommendations from Others

Three guidelines were identified that include recommendations on temporary percutaneous mechanical circulatory support:

- Guideline for the Management of ST-Elevation Myocardial Infarction published in 2013 by the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) Task Force on Practice Guidelines (O'Gara et al., 2013)
- Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care published by the Society for Cardiovascular Angiography and Interventions, American College of Cardiology Foundation, Heart Failure Society of America, and Society for Thoracic Surgery (Rihal et al., 2015)
- The 2013 International Society for Heart and Lung Transplantation Guidelines for Mechanical Circulatory Support (Feldman et al., 2013)

The ACCF/AHA guideline includes a recommendation that alternative left ventricular assist devices for circulatory support may be considered in patients with refractory cardiogenic shock (O'Gara et al., 2013). The guideline from the Society for Cardiovascular Angiography and Interventions states that percutaneous mechanical circulatory support may be considered in carefully selected patients with severe hemodynamically unstable cardiovascular presentations. Suggested indications for percutaneous mechanical circulatory support include complications of acute myocardial infarction, severe heart failure in the setting of non-ischemic cardiomyopathy, acute cardiac allograft failure, post-transplant right ventricle failure, refractory arrhythmias, high-risk ablation of ventricular tachycardia, and high-risk PCI (Rihal et al., 2015).

The following recommendation from the International Society for Heart and Lung Transplantation guidelines is based on level of evidence C, or consensus agreement: "The use of temporary mechanical support should be strongly considered in patients with multiorgan failure, sepsis, or on mechanical ventilation to allow successful optimization of clinical status and neurologic assessment prior to placement of a long-term [mechanical circulatory support device]*"* (Feldman et al., 2013, p. 165)

Quality Measures

No quality measures were identified when searching the National Quality Measures Clearinghouse for percutaneous mechanical circulatory support or Impella.

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Appendix A. GRADE Table Element Descriptions

Element	Description
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors., but further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, and values and preferences, but further research or additional information could lead to a different conclusion.

Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

Appendix B. GRADE Evidence Profile

Quality Assessment (Confidence in Estimate of Effect) for Elective High-Risk PCI							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
All-cause mortality							
1	RCT	Moderate	Not serious	Not serious	Serious		Low ●●○○
Major adverse events							
1	RCT	Moderate	Not serious	Not serious	Serious		Low ●●○○
Bridge to recovery							
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bridge to transplant							
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Harms							
1	Observational	Moderate	Not serious	Not serious	Not serious		Very low ●○○○

Quality Assessment (Confidence in Estimate of Effect) for Ischemic Cardiogenic Shock							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
All-cause mortality							
3	RCTs	Moderate to high	Not serious	Not serious	Serious		Low ●●○○
Major adverse events							
1	RCT	High	N/A	Not serious	Very serious		Very low ●○○○
Bridge to recovery							
0	N/A	N/A	N/A	N/A	N/A	N/A	Insufficient data
Bridge to transplant							
0	N/A	N/A	N/A	N/A	N/A	N/A	Insufficient data
Harms							
4	Mix of RCTs and observational	Moderate to high	Serious	Not serious	Very serious		Very low ●○○○

Appendix C. Methods

Scope Statement

Populations

Adults with cardiogenic shock or refractory heart failure (from right heart failure, left heart failure, or biventricular failure) and adults undergoing high-risk percutaneous coronary interventions (PCI)

Population scoping notes: None

Interventions

Temporary percutaneous mechanical circulatory support devices (Impella)

Intervention exclusions: Devices not marketed in the U.S., TandemHeart, extracorporeal membrane oxygenation (ECMO).

Comparators

Usual care, inotropes, other forms of active circulatory support (i.e., intra-aortic balloon pumps or more permanent left ventricular assist devices), extracorporeal membrane oxygenation (ECMO)

Outcomes

Critical: Mortality, major adverse cardiovascular events

Important: Successful bridge to transplantation or bridge to recovery, length of hospitalization, harms

Considered but not selected for the GRADE table: None

Key Questions

KQ1: What is the comparative effectiveness of temporary percutaneous mechanical circulatory support in the management of adults with heart failure or cardiogenic shock, or undergoing high-risk PCI?

KQ2: Does the comparative effectiveness of temporary percutaneous mechanical circulatory support vary by:

a. Indication for left ventricular support
b. Patient characteristics
c. Left ventricular function
d. Right ventricular function
e. Comorbid conditions
f. Device flow rate
g. Timing and duration of Impella placement

KQ3: What are the harms of temporary percutaneous mechanical circulatory support?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2013.

The following core sources were searched:

Agency for Healthcare Research and Quality (AHRQ)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Online Library)
Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

A MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search terms Impella, ventricular support system, and axial flow pumps. The search was limited to publications in English published since 2013. In addition, a MEDLINE® search was conducted for randomized controlled trials published after 2013.

Searches for clinical practice guidelines were limited to those published since 2013. A search for relevant clinical practice guidelines was also conducted using MEDLINE® and the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Centers for Disease Control and Prevention (CDC), Community Preventive Services
National Guidelines Clearinghouse
National Institute for Health and Care Excellence (NICE)
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, randomized controlled trials, or clinical practice guidelines.

Appendix D. Applicable Codes

CODES	DESCRIPTION
CPT Codes	
33990	Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; arterial access only
33991	Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; both arterial and venous access, with transseptal puncture
33992	Removal of percutaneous ventricular assist device at separate and distinct session from insertion
33993	Repositioning of percutaneous ventricular assist device with imaging guidance at separate and distinct session from insertion

Note: Inclusion on this list does not guarantee coverage.

Temporary Percutaneous Mechanical Circulatory Support with Impella Devices

Question: Should the draft Coverage Guidance on Temporary Percutaneous Mechanical Circulatory Support with Impella Devices be adopted as previously recommended by EbGS or modified?

Question source: HERC, EbGS

Issue summary:

At the January 17, 2019 HERC meeting there was discussion of the draft coverage guidance approved by the Evidence-based Guidelines Subcommittee. HERC decided to table the decision for approving the draft coverage guidance based on compelling discussion with a number of interventional cardiologists and other stakeholders. HERC recommended revisiting the Coverage Guidance with more investigation into the implementation considerations and specific subpopulations who may be affected by the coverage guidance. Some of the concerns that were raised included:

1. Need for clarity about which patient circumstances would be affected by which coverage decisions
2. Clinical implementation concerns: With patients in cardiogenic shock, there may not be time to determine 1) if a patient is a candidate for LVAD or transplant and 2) connect with an Advanced Heart Failure and Cardiac Transplantation cardiologist (there are reportedly only 3 of these in Oregon)
3. The evidence does not support the utility of the Impella 2.5 device. Should coverage vary depending on type of devices?
4. Is there evidence that PCI improves angina symptoms in high-risk patients?

Following this HERC discussion, this topic was re-addressed at the April 2019 EbGS meeting. EbGS discussion focused on addressing the primary concerns above raised by HERC. Staff also identified some interim data that was published about harms of these devices.

Concern 1: Clarity about which patient circumstances would be affected by which coverage decisions

Population	Evidence	EbGS Draft Coverage Recommendation	Impact on patients
Elective high-risk PCI for chronic stable angina	No difference in effectiveness compared to IABP for mortality and Major Adverse Cardiovascular Events (MACE). No evidence on angina in this subpopulation, and a	Temporary percutaneous mechanical circulatory support with Impella devices is not recommended for coverage in elective high-risk percutaneous coronary intervention (PCI) for patients with stable coronary	May not get high-risk PCI. Options would be PCI without Impella, CABG or optimized medical therapy.

	benefit is controversial in a normal risk population.	artery disease (*weak recommendation*).	
NSTEMI without cardiogenic shock	No evidence	Impella is recommended for coverage (*weak recommendation*) only for patients with acute myocardial infarction when all of the following conditions are met: • Non-ST-elevation myocardial infarction (NSTEMI) without cardiogenic shock • A heart team discussion determines that the patient needs revascularization with CABG or PCI • Two cardiothoracic surgeons are consulted and agree that the patient is inoperable (i.e., surgeons are not willing to perform CABG, but agree that revascularization is indicated) • Patient has complex left main or last remaining conduit disease • Ejection fraction less than 30%	CABG, high-risk PCI without Impella, or optimized medical therapy
Cardiogenic shock, ischemic	Ineffective. Higher risk of harms.	Only if bridge to LVAD or transplant	Very ill patients. Options would be IABP, ECMO, pressors
Cardiogenic shock, nonischemic	No evidence	Only if bridge to LVAD or transplant	Very ill patients. Options would be IABP, ECMO, pressors
Bridge to LVAD or transplant	None. None likely to come.	Recommended for coverage (*weak recommendation*) only for patients with cardiogenic shock who might be candidates for left	Very sick patients who may need to be transferred out of state.

		ventricular assist device (LVAD) (destination therapy) or transplant (bridge to transplant), AND an advanced heart failure and transplant cardiologist agrees that Impella should be used as a bridge to a decision for LVAD or a transplant.	

Concern 2: Timeliness of determination of candidacy for LVAD and transplant and availability of Advanced Heart Failure and Cardiac Transplantation Cardiologists in Oregon

There are reportedly only 3 Advanced Heart Failure and Cardiac Transplantation cardiologists in Oregon. However, two major health systems are actively developing cardiac transplant programs and it is possible these numbers will increase. In current practice, a phone conversation could be had with these specialists before deciding whether to place an Impella for many patients. However, EbGS discussed that sometimes a phone consultation would not be able to take place because of the acuity of the decision. EbGS members thought it was important to allow coverage in this scenario if the cardiologist believed that the patient would likely meet criteria and the urgency was very high. They also discussed that cardiologists would generally be able to quickly ascertain if the patient was clearly not a candidate for LVAD or transplant. EbGS therefore proposed adding the following language:

> Appropriate effort should be made to consult with a heart failure and transplant cardiologist, but coverage is recommended in circumstances where consultation cannot reasonably be obtained without endangering the patient's life and the treating physician believes the patient meets the criteria above.

Concern 3: Evidence regarding specific devices.

Given the evidence does not support the utility of the Impella 2.5 device, a question was raised about potentially having differential coverage recommendations of the different devices. EbGS discussed a recommendation for noncoverage of a device with proven lack of benefit (i.e. Impella 2.5), and a simultaneous positive coverage recommendation for devices with no evidence of benefit and thought this was not appropriate. The idea that unstudied devices could get a "free pass" seemed inappropriate. Therefore, EbGS recommended making no statements about which specific devices were recommended for coverage or noncoverage.

Concern 4: Is there evidence that PCI improves angina symptoms in high-risk patients?

Additional evidence considered (Dr. Obley reviewed, see separate document)

Conclusions: We did not identify any trials comparing high-risk PCI to medical management for relief of angina in patients with stable ischemic heart disease. The benefit of non-high-risk PCI over medical management for stable angina remains a subject of continued debate, and most studies comparing PCI to medical management are likely to be confounded by a well-established placebo effect on anginal symptoms.

Additional interim publications about harms

Additional publications that are relevant (published after search dates of the draft coverage guidance and would have not met inclusion criteria), for new information about harms:

Schrage, 2019

- Retrospective cohort study of IABP-SHOCK II patients in European tertiary care centers
- 237 patients matched to 237 patients from the IABG-SHOCK II trial
- Results:
    - No difference in 30-day all-cause mortality (48.5% versus 46.4%, *P*=0.64).
    - Severe or life-threatening bleeding (8.5% versus 3.0%, *P*<0.01) and peripheral vascular complications (9.8% versus 3.8%, *P*=0.01) occurred significantly more often in the Impella group.

FDA letter, February 4, 2019

- Letter of concern regarding Impella RP interim post-approval study (PAS)
- Higher mortality rate than previously observed in the pre-market clinical studies
- The primary endpoint is survival to 30 days post device explant or hospital discharge (whichever is longer), or to the start of next longer-term therapy
- Primary survival endpoint achieved in:
    - Pre-market studies: 44 out of 60 patients (73.3 percent) met the survival endpoint
    - Post-approval study: Only 4 out of the 23 enrolled PAS patients (17.4 percent) met the primary survival endpoint
- 16 of the 23 patients would not have met the pre-market study criteria. Specifically, before getting the Impella RP system implanted, patients in the PAS were more likely than the pre-market clinical study patients to have been in cardiogenic shock for longer than 48 hours, experienced an in-hospital cardiac arrest, been treated with an intra-aortic balloon pump, or suffered a pre-implant hypoxic or ischemic neurologic event.

EbGS discussion about these included recognizing that the FDA letter illustrates that the Impella RP system is being used much more broadly than the indications and criteria in the pre-market studies with remarkably poorer outcomes.

HERC Staff Recommendations

1. **Modify the draft Coverage Guidance box language as recommended by the Evidence-based Guidelines Subcommittee**

DRAFT HERC Coverage Guidance

Temporary percutaneous mechanical circulatory support with Impella devices is not recommended for coverage in elective high-risk percutaneous coronary intervention (PCI) for patients with stable coronary artery disease (weak recommendation).

Temporary percutaneous mechanical circulatory support with Impella devices during PCI is recommended for coverage (weak recommendation) only for patients with acute myocardial infarction when all of the following conditions are met:

- Non-ST-elevation myocardial infarction (NSTEMI) without cardiogenic shock
- A heart team discussion determines that the patient needs revascularization with CABG or PCI
- Two cardiothoracic surgeons are consulted and agree that the patient is inoperable (i.e., surgeons are not willing to perform CABG, but agree that revascularization is indicated)
- Patient has complex left main or last remaining conduit disease
- Ejection fraction less than 30%

Temporary percutaneous mechanical circulatory support with Impella devices is recommended for coverage (weak recommendation) only for patients with cardiogenic shock who might be candidates for left ventricular assist device (LVAD) (destination therapy) or transplant (bridge to transplant), AND an advanced heart failure and transplant cardiologist agrees that Impella should be used as a bridge to a decision for LVAD or a transplant. Appropriate effort should be made to consult with a heart failure and transplant cardiologist, but coverage is recommended in circumstances where consultation cannot reasonably be obtained without endangering the patient's life and the treating physician believes the patient meets the criteria above.

CG - Impella Devices

Question: How should the Coverage Guidance *Temporary Percutaneous Mechanical Circulatory Support With Impella Devices* be applied to the Prioritized List?

Question source: EbGS

Current Prioritized List Status:

CODES	DESCRIPTION		
CPT Codes		**Current Placement**	**Code History**
33990	Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; arterial access only	82 MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS 98 HEART FAILURE 264 CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL HEART DISEASE	Added in 2013 as part of CPT 2012 code review without discussion
33991	Insertion of ventricular assist device, percutaneous including radiological supervision and interpretation; both arterial and venous access, with transseptal puncture	82,98,264	Same
33992	Removal of percutaneous ventricular assist device at separate and distinct session from insertion	82,98,264	Same
33993	Repositioning of percutaneous ventricular assist device with imaging guidance at separate and distinct session from insertion	82,98,264	Same

Illustrative ICD-10 codes

Code	Code Description	Line Placement
R57.0	Cardiogenic shock	69 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION
T81.11XA	Postprocedural cardiogenic shock, initial encounter	69
T81.11XD	Postprocedural cardiogenic shock, subsequent encounter	69
I20.0	Unstable angina	69
I20.1	Angina pectoris with documented spasm	189 CHRONIC ISCHEMIC HEART DISEASE
I20.8	Other forms of angina pectoris	189
I20.9	Angina pectoris, unspecified	189

I25.110	Atherosclerotic heart disease of native coronary artery with unstable angina pectoris	69 264 CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL HEART DISEASE/TRANSPLANT
I25.11X	Atherosclerotic heart disease of native coronary artery with angina pectoris…	189
I21.XX	ST elevation (STEMI) myocardial infarction	69
I21.4	Non-ST elevation (NSTEMI) myocardial infarction	69
I22.2	Subsequent non-ST elevation (NSTEMI) myocardial infarction	69

Recommendations:

1) Add 33990, 33991, 33992, and 33993 to Line 69 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION
    a. 33991 was out of scope, but confirmed with the expert that this is only for Tandem Heart and is no longer likely to be in use.
2) Remove 33990 and 33991 from Lines 82,98,264
3) Do NOT add 33990 to Line 189 CHRONIC ISCHEMIC HEART DISEASE as this would be for elective high-risk percutaneous coronary intervention (PCI) for patients with stable coronary artery disease
4) Create a new guideline note

GUIDELINE NOTE XXX , TEMPORARY PERCUTANEOUS MECHANICAL CIRCULATORY SUPPORT WITH IMPELLA DEVICES

Line 69

Temporary percutaneous mechanical circulatory support with Impella devices is included on Line 69 only in the two following circumstances:

1) During percutaneous coronary intervention (PCI) in patients with acute myocardial infarction when all of the following conditions are met:
    - NSTEMI without cardiogenic shock
    - A heart team discussion determines the patient needs revascularization with coronary artery bypass graft (CABG) or PCI
    - Two cardiothoracic surgeons are consulted and agree the patient is inoperable (i.e., are not willing to perform CABG but agree revascularization is indicated)
    - Patient has complex left main or last remaining conduit disease
    - Ejection fraction (EF) < 30%

2) In patients with cardiogenic shock in patients who may be candidates for Left Ventricular Assist Device (LVAD) (destination therapy) or transplant (bridge to transplant), AND an advanced heart failure and transplant cardiologist agrees that Impella should be used as a bridge to decision for LVAD or transplant. Appropriate effort should be made to consult with a heart failure and transplant cardiologist, but coverage is recommended in circumstances where consultation cannot reasonably be obtained without endangering the patient's life and the treating physician believes the patient meets the criteria above.

Temporary percutaneous mechanical circulatory support with Impella devices is not included on this or any other line for elective high-risk PCI for patients with stable coronary artery disease.

High-risk PCI Evidence Summary

Subcommittee Question: What is the evidence that high-risk PCI for stable ischemic heart disease results in relief of angina or improves quality of life?

Response:

The strongest line of evidence that PCI improves anginal symptoms and/or quality of life comes from the COURAGE trial. As reported by Weintraub and colleagues in 2008[1], PCI with optimal medical management led to greater improvements in angina relief (as measured by freedom from angina and the Seattle Angina Questionnaire [SAC]) compared to optimal medication therapy alone. The incremental benefit of PCI was mainly apparent through 24 to 36 months of follow-up; beyond 36 months PCI did not confer an apparent symptomatic benefit over medical management. Some critics of COURAGE contend that the absence of more durable symptomatic relief may have resulted from the near-exclusive use of bare metal stents (which are more prone to in-stent restenosis). In any case, the population included in the COURAGE trial does not reflect the population that was considered for high-risk PCI in the PROTECT II study. Specifically, patients with LVEF <30% (or <35% with 3 vessel disease) and patients with unprotected left main disease were excluded from COURAGE, as were patients with coronary arteries deemed unsuitable or hazardous for PCI.

Other randomized trials of PCI compared to medical management for stable coronary disease have been conducted and were summarized in a systematic review by Stergiopolous and colleagues in 2014[2]. In the meta-analysis, the authors found that PCI did not reduce angina during follow-up compared with medical management (OR 0.90, 95% CI 0.57 to 1.44, I^2=72%). The major outlying trial with respect to angina relief was the FAME 2 study[3] which used fractional flow reserve to establish the presence of a physiologically significant stenosis prior to randomization and which found a significant improvement in the PCI group, albeit at a follow-up interval of just over 6 months. Like the COURAGE trial, all of the trials included in this systematic review and meta-analysis excluded patients who would generally be regarded as constituting a high-risk PCI group.

Most of the evidence establishing the symptomatic benefit of PCI over medical management is complicated by the existence of a significant placebo effect. This placebo effect has been well characterized in drug trials (for example, in the ERICA trial[4] patients treated with ranolazine experienced an improvement of 22.5 points on the SAQ angina frequency score compared with an improvement of 18.5 points in the placebo group). Mitigating the placebo effect in trials of procedures or devices requires sham controls and few such studies have been conducted. Indeed, the sham-controlled ORBITA study[5] has raised the question of whether PCI affords any symptomatic benefit over high-intensity medical management. It should be noted that the population studied in ORBITA would not meet the definition of high-risk PCI. Similarly, a procedure known as transmyocardial laser revascularization was largely abandoned after the sham controlled DIRECT trial[6] found no benefit for angina relief. Parenthetically, the DIRECT trial offers additional evidence of a substantial placebo effect on angina symptoms, and the magnitude of that placebo effect may be greater for procedural placebos than for drug placebos.

Conclusions:

We did not identify any trials comparing high-risk PCI to medical management for relief of angina in patients with stable ischemic heart disease. The benefit of non-high-risk PCI over medical management

for stable angina remains a subject of continued debate, and most studies comparing PCI to medical management are likely to be confounded by a well-established placebo effect on anginal symptoms.

1. Weintraub WS, Spertus JA, Kolm P, et al. Effect of PCI on Quality of Life in Patients with Stable Coronary Disease. *New England Journal of Medicine.* 2008;359(7):677-687. doi: 10.1056/NEJMoa072771.
2. Stergiopoulos K, Boden WE, Hartigan P, et al. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. *JAMA Intern Med.* 2014;174(2):232-240. doi: 10.1001/jamainternmed.2013.12855.
3. De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease. *New England Journal of Medicine.* 2012;367(11):991-1001. doi: 10.1056/NEJMoa1205361.
4. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol.* 2006;48(3):566-575. doi: 10.1016/j.jacc.2006.05.044.
5. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet.* 2018;391(10115):31-40. doi: 10.1016/s0140-6736(17)32714-9.
6. Leon MB, Kornowski R, Downey WE, et al. A blinded, randomized, placebo-controlled trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease. *J Am Coll Cardiol.* 2005;46(10):1812-1819. doi: 10.1016/j.jacc.2005.06.079.

Circulation

ORIGINAL RESEARCH ARTICLE

Impella Support for Acute Myocardial Infarction Complicated by Cardiogenic Shock

Matched-Pair IABP-SHOCK II Trial 30-Day Mortality Analysis

Editorial, see p 1259

Benedikt Schrage, MD
et al

BACKGROUND: Percutaneous mechanical circulatory support devices are increasingly used in acute myocardial infarction complicated by cardiogenic shock (AMI-CS), despite limited evidence for their effectiveness. The aim of this study was to evaluate outcomes associated with use of the Impella device compared with intra-aortic balloon pump (IABP) and medical treatment in patients with AMI-CS.

METHODS: Data of patients with AMI-CS treated with the Impella device at European tertiary care hospitals were collected retrospectively. All patients underwent early revascularization and received optimal medical treatment. Using IABP-SHOCK II (Intraaortic Balloon Pump in Cardiogenic Shock II) trial inclusion and exclusion criteria, 372 patients were identified and included in this analysis. These patients were matched to 600 patients from the IABP-SHOCK II trial. The following baseline criteria were used as matching parameters: age, sex, mechanical ventilation, ejection fraction, prior cardiopulmonary resuscitation, and lactate. Primary end point was 30-day all-cause mortality.

RESULTS: In total, 237 patients treated with an Impella could be matched to 237 patients from the IABP-SHOCK II trial. Baseline parameters were similarly distributed after matching. There was no significant difference in 30-day all-cause mortality (48.5% versus 46.4%, P=0.64). Severe or life-threatening bleeding (8.5% versus 3.0%, P<0.01) and peripheral vascular complications (9.8% versus 3.8%, P=0.01) occurred significantly more often in the Impella group. Limiting the analysis to IABP-treated patients as a control group did not change the results.

CONCLUSIONS: In this retrospective analysis of patients with AMI-CS, the use of an Impella device was not associated with lower 30-day mortality compared with matched patients from the IABP-SHOCK II trial treated with an IABP or medical therapy. To further evaluate this, a large randomized trial is warranted to determine the effect of the Impella device on outcome in patients with AMI-CS.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT03313687.

The full author list is available on page 1257.

Key Words: cardiopulmonary resuscitation ■ Impella ■ intraaortic balloon pumping ■ myocardial infarction ■ shock, cardiogenic

Sources of Funding, see page 1257

https://www.ahajournals.org/journal/circ

Increased Rate of Mortality in Patients Receiving Abiomed Impella RP System - Letter to Health Care Providers

February 4, 2019

Dear Cardiologists, Cardiothoracic Surgeons and Transplant Surgeons,

The FDA is evaluating recent interim post-approval study (PAS) results which suggest a higher mortality rate for patients treated with the Abiomed Impella RP System than the rate previously observed in the premarket clinical studies. The Impella RP System is a temporary right heart pump system intended to help patients maintain stable heart function without open chest surgery. The FDA wants to ensure you are aware of the mortality rate that has been observed in the ongoing PAS.

Although the FDA is concerned about the high mortality rate from the interim PAS results, we believe that when the device is used for the currently approved indication in appropriately selected patients, the benefits of the Impella RP system continue to outweigh the risks. Our current analysis of these results and recommendations for health care providers who may use the Impella RP System follow below.

BACKGROUND

The FDA approved the **Impella RP System (https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm581165.htm)** on September 20, 2017. The device is implanted centrally via peripheral access to help patients who require temporary emergency support of right ventricular function. Use of the device, which may be up to 14 days, requires patients to stay in the hospital.

In the **premarket clinical studies (https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170011B.pdf)**, where strict inclusion and exclusion criteria were followed, a total of 44 out of 60 patients (73.3 percent) survived to 30 days post device explant or hospital discharge (whichever was longer), or to the start of next longer term therapy, including heart transplant or implantation of a surgical right ventricular assist device (RVAD).

The FDA mandated the firm, Abiomed, to conduct a PAS as a condition of approval for the Impella RP System. The **Impella RP PAS (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=615919&c_id=4556)** will follow 60 newly treated patients for one year through the firm's cVAD registry. The primary endpoint is survival to 30 days post device explant or hospital discharge (whichever is longer), or to the start of next longer term therapy. Interim

results from the most recent PAS report, which reflect device use in a broader patient population, indicate that only 4 out of the 23 enrolled PAS patients (17.4 percent) met the primary survival endpoint.

The FDA required additional analyses from Abiomed, and data submitted by the firm in January 2019 suggest that the high mortality rate observed in the PAS may be primarily related to differences in pre-implant characteristics of the PAS patients compared to the patients in the premarket clinical studies. Sixteen (16) of the 23 patients enrolled in the PAS would not have met the enrollment criteria for the premarket clinical studies. Specifically, before getting the Impella RP system implanted, patients in the PAS were more likely than the premarket clinical study patients to have been in cardiogenic shock for longer than 48 hours, experienced an in-hospital cardiac arrest, been treated with an intra-aortic balloon pump, or suffered a pre-implant hypoxic or ischemic neurologic event.

It is important to note that the Impella RP PAS and FDA's evaluation into this issue are ongoing. We do not know the root cause for the high mortality rate, and the results are not adjusted for potential confounders.

RECOMMENDATIONS

The FDA has the following recommendations for health care providers:

- Be aware that FDA approval of the Impella RP System was based on the results of premarket clinical studies that included patients who had been in cardiogenic shock for less than 48 hours prior to device implant. Additionally, none of the patients in the premarket clinical studies experienced an in-hospital cardiac arrest, or were treated with an intra-aortic balloon pump, or suffered a hypoxic or ischemic neurologic event, prior to Impella RP being implanted. Although these clinical events may not preclude a clinical decision to use the device, physicians should be aware that the occurrence of one or more of these events prior to Impella RP implantation may decrease expected survival rate.
- Carefully consider these interim survival results from the ongoing PAS when making treatment decisions and discuss the risks and benefits of the Impella RP System with patients and their caregivers. Additionally, be aware that there are currently no other device interventions that have been approved by the FDA under the premarket application (PMA) process for the patient population demonstrating a higher mortality rate in the PAS and as such, other interventions pose risks, as well, that should be considered and discussed with patients and their caregivers.
- Report any adverse events or suspected adverse events experienced with the Impella RP System:
  - Voluntary reports can be submitted through **MedWatch, the (http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)FDA Safety Information and Adverse Event Reporting program (http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)**.
  - Device manufacturers and user facilities must comply with the applicable **Medical Device Reporting (MDR) regulations (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm2005737.htm)**.
  - Health care personnel employed by facilities that are subject to the **FDA's user facility reporting requirements (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuid-**

ance/PostmarketRequirements/ReportingAdverseEvents/default.htm) should follow the reporting procedures established by their facilities.

Prompt reporting of adverse events can help the FDA identify and better understand the risks associated with medical devices.

FDA ACTIONS

The FDA will continue to review data from the ongoing PAS, and other available data sources as they become available. The FDA will work with Abiomed to ensure the product labeling addresses the PAS interim results. We will continue to keep the public informed if new or additional information becomes available.

CONTACT US

If you have questions about this communication, please contact the Division of Industry and Consumer Education (DICE) at **DICE@FDA.HHS.GOV (mailto:DICE@FDA.HHS.GOV)**, 800-638-2041 or 301-796-7100.

Sincerely,
/s/
William Maisel, MD, MPH
CDRH Chief Medical Officer
Center for Devices and Radiological Health
U.S. Food and Drug Administration

More in Letters to Health Care Providers (/MedicalDevices/Safety/LetterstoHealthCareProviders/default.htm)

MINUTES

Evidence-based Guidelines Subcommittee

Clackamas Community College
Wilsonville Training Center, Rooms 210
29353 SW Town Center Loop E
Wilsonville, Oregon 97070
April 4, 2019
2:00-5:00pm

Members Present: Devan Kansagara, MD, Chair; Eric Stecker, MD, MPH, Vice-Chair; Alison Little, MD, MPH; Angela Senders, ND; Lynnea Lindsey, PhD; Leslie Sutton.

Members Absent: none

Staff Present: Darren Coffman (by phone); Cat Livingston, MD, MPH; Jason Gingerich.

Also Attending: Adam Obley, MD, Val King MD, MPH, Moira Ray MD and Craig Mosbaek (OHSU Center for Evidence-based Policy); Stacey Bunk, Amir Medjamia, Jenn Weddell (Abiomed); Erik Schulwolf (Foley Hoag/Abiomed); Alice Taylor, CNM, Duncan Neilson (Legacy Health); Mohamed Abdiasis (Oregon Health Authority Office of Equity and Inclusion); Kim (Renae) Wentz (Oregon Health Authority Health Systems Division); Silke Akerson, Celeste Kersey (Oregon Midwifery Council); Missy Cheyney, PhD (Oregon State University, by phone).

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1. Call to Order

Devan Kansagara called the meeting of the Evidence-based Guidelines Subcommittee (EbGS) to order at 2:00 pm.

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2. Minutes Review

Minutes from the 2/7/2019 meeting were reviewed and approved as submitted, 6-0.

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3. Staff Report

Livingston reported Coffman is out sick, and Crispin Davies, the appointed expert for the Impella topic, is not able to attend, though he may call in. She reported the State Health Improvement Plan (SHIP) is looking at five categories: institutional bias, adversity, trauma and toxic stress, economic drivers of health, access to equitable preventive health care and behavioral health. This is different from prior SHIPs, which were related to more standard public health goals such as immunization and access to preventive services. The groups are meeting to develop the strategies and metrics. She encouraged EbGS members to get involved if they are interested and asked whether there are topics EbGS should take on in light of the SHIP.

Gingerich added Adler will be joining the subcommittee for the out-of-hospital birth topic. After that review, he may (or may not) return to the HTAS subcommittee.

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4. Temporary Percutaneous Mechanical Circulatory Support with Impella Devices

Kansagara reported on the deliberations of the Health Evidence Review Commission (HERC) members related to this topic. It was a lot for HERC to absorb, and concerns were raised about access to advanced heart failure and transplant cardiologists, as there are only a few in the state. The task is to revisit the Impella discussion in light of the previous review and expert testimony. The report would then return to a future VbBS and HERC meeting.

Livingston said there were three issues. The first was regarding the consultation mentioned by Kansagara. Staff has researched this, and these consultations can generally happen by phone, so it is not unreasonable. The subcommittee discussed the issue; Stecker said there may well be times when it's not possible to reach such a cardiologist by phone immediately. He said there's a fairly narrow group of VAD or transplant candidates experiencing cardiogenic shock, but if every cardiogenic shock patient would require a call to a transplant cardiologist, it would burden the transplant centers. There are, however, many patients who the average treating cardiologist would appropriately identify as not being candidates.

The second issue was a lack of clarity about which patients would be affected by the policy. Livingston created a table listing various patient groups and providing an assessment of the evidence. Livingston reviewed the additional table provided in the meeting materials, and Obley reviewed the information showing the lack of evidence to say whether there is a benefit of PCI for angina symptoms in high-risk patients.

Livingston said there are two pieces of observational evidence that have come out recently that focus on harms. The first had 237 patients with acute myocardial infarction and cardiogenic shock who received Impella compared to 237 who did not. It found no difference in 30-day mortality but much higher rates of life-threatening bleeding and peripheral vascular complications in the Impella group. We shouldn't look at this for effectiveness, but rather for harms. Obley said within the Impella group, 156 were treated with Impella CP (a newer, higher-volume model), and 74 with Impella 2.5. Subroup analysis showed no difference in mortality. Kansagara said the registry study, which showed a higher rate of bleeding, showed this result despite a larger portion of patients in the balloon pump group (which would increase a patient's risk of bleeding). The incremental risk of bleeding was on top of that imbalance in groups. This study doesn't include the high-risk PCI group.

The second piece of evidence was an FDA letter of concern about the Impella RP based on a much higher mortality rate than observed in pre-market studies. For the postmarket study, most of the patients would not have met the entry criteria for the pre-market studies. People are using this device (a right-sided device) for a broader range of patients than the device was approved for.

The third issue is that we have evidence that Impella 2.5 does not work, so there was a question about requiring the use of newer models. Livingston said it doesn't make sense to make recommendations

about different models; if the only device that has been studied is ineffective, it doesn't give the other devices a free pass.

Obley said since Davies is not present he would do his best to present Davies' perspective. He would say that there may be clinical scenarios where the Impella 2.5 is preferred, despite lower volume, due to smaller vascular access for a patient.

Senders said she understands there isn't any evidence to support the 3.5 device, but there isn't any evidence to support noncoverage either. She expressed concern based on how many people appeared at HERC. Lindsey said we are caught between when we know things might work for people and what we can look at in terms of evidence. We can revisit the topic if more evidence comes in, but we can't move ahead without evidence. Livingston said all the evidence we have does not support efficacy; typically, that would support a noncoverage recommendation. For the newer models, there is no randomized trial evidence at all; typically, devices without support of randomized trials are treated by the HERC, or by any insurer, as experimental.

Kansagara said the concern about precedent is important as there are iterations of devices in any field. If we get into recommendations around iterations of device, that leaves us open to covering any new iteration of a device. He agrees with a lot of the sticking points from a patient perspective, but the charge of the subcommittee is to recommend coverage for the population as a whole where there are limited resources. Use of these devices is increasing rapidly, so the amount of money is significant. Stecker said we would happily change these recommendations in light of a positive randomized controlled trial. Kansagara said the carveouts where there is no evidence is to protect against harm for the most vulnerable groups of patients.

Kansagara invited public comment.

Two representatives from Abiomed testified. Stacey Bunk, global director of healthcare economics for Abiomed spoke first. All the physicians who wanted to come are currently with patients, so one of them, Dr. Jason Wollmuth, asked her to read a statement.

Wolmath is a cardiologist at Providence. He urged continued coverage for Impella for patients requiring high-risk PCI and patients with cardiogenic shock. He cited the FDA indication and the Protect II trial, noting that the 90-day data in Protect II showed a significant reduction in adverse events. He said patients who were previously turned away from surgery either received medication or an unsupported PCI. These high-risk PCIs were often poorly-performed or incomplete procedures as they would try to get in and out with the minimum amount of work. This led to poor long-term outcomes. With Impella they can take more time and completely revascularize the patients. He has been practicing since 2002 and doing PCI since 2005. He has seen three dramatic advances in his career—drug-eluting stents, hybrid algorithm to treat chronically occluded arteries and the development of Impella.

Bunk also read a portion of a letter from Abiomed, which had been supplied to the subcommittee prior to the meeting. The letter covered the following points:

1. Recommended revisions to the Draft Guidance based on clinical evidence and Impella use in practice;
2. Impella's clinical use in a small, critically ill patient population;
3. Impella's FDA-approved indication for high risk PCI and cardiogenic shock;

4. Medicare and Medicaid coverage policies consistent with our recommended coverage criteria;
5. Clarification that payment for Impella is not made on a pass-through basis; and
6. Clarification on the FDA post-approval study for Impella RP.

Next Erik Schulwolf, an attorney at Foley Hoag LLP, spoke. He was representing Abiomed and highlighted the less restrictive coverage policies of other payers, including Medicare. He noted Abiomed recommended separating the cardiogenic shock recommendation from the bridge to transplant/LVAD recommendation, to remove consultation requirements for cardiogenic shock and myocardial infarction, and remove the 30% ejection fraction requirement for MI and recommend Impella for coverage of high-risk PCI for hemodynamically stable patients with severe coronary artery disease. These changes align with major payers, including Aetna, Moda and Cigna as well as Medicare. He said OHP would be the first payer in Europe or the U.S. to not make a positive coverage recommendation for Impella after a public hearing process, for a small but severely ill population of patients. The current recommendation would make Oregon Medicaid patients an outlier, receiving inferior coverage to other patients in Oregon and to patients in Washington.

Kansagara clarified one point about the Protect II trial; there was not a difference in 90-day outcomes. Rather, there was a trend towards reduced need for revascularization. That outcome was the major driver for the composite outcome at 90 days.

Senders suggested language be added to clarify that a consultation with an advanced heart failure and transplant cardiologist can be made by phone. There was also concern about the ability to reach such an expert in a timely fashion when the patient was rapidly deteriorating. Stecker agreed that delay could be problematic in many scenarios. He also said a retrospective review might result in the need to remove the Impella after insertion for a patient who is not a candidate for transplant or LVAD, which would actively facilitate the patient's death. After discussion, the subcommittee agreed to change the language to allow for situations where it's not possible to contact an appropriate cardiologist by the time a decision is needed. Little and others said the language may be more useful for retrospective review than for prospective review.

Stecker addressed the testimony about this policy being an outlier. We need to decide whether we want to be the first on the map. We need to be conscious of creating a second standard for Oregon Medicaid patients. Wentz said in hearings, judges recognize that Oregon's Prioritized List is absolutely unique. Stecker agreed, but said this is a rapidly moving train and we are approaching consensus without evidence among clinicians that this is an essential lifesaving treatment. We need to be cognizant of where that line is and if it is crossed, the topic would need to be readdressed. It is, however, a conundrum as we are the Evidence-based Guidelines Subcommittee. Kansagara said in the course of his year on the subcommittee he has come to appreciate the uniqueness of Oregon. He said the equity question can be argued the other way, as a policy like this can preserve equity for other treatments. Kansagara agreed the topic can be revisited as new evidence arises.

A motion was made to refer the draft coverage guidance back to VbBS and HERC, as amended. **Motion approved 5-0 (Adler abstained).**

DRAFT HERC Coverage Guidance

Temporary percutaneous mechanical circulatory support with Impella devices is not recommended for coverage in elective high-risk percutaneous coronary intervention (PCI) for patients with stable coronary artery disease (weak recommendation).

Temporary percutaneous mechanical circulatory support with Impella devices during PCI is recommended for coverage (weak recommendation) only for patients with acute myocardial infarction when all of the following conditions are met:

- Non-ST-elevation myocardial infarction (NSTEMI) without cardiogenic shock
- A heart team discussion determines that the patient needs revascularization with CABG or PCI
- Two cardiothoracic surgeons are consulted and agree that the patient is inoperable (i.e., surgeons are not willing to perform CABG, but agree that revascularization is indicated)
- Patient has complex left main or last remaining conduit disease
- Ejection fraction less than 30%

Temporary percutaneous mechanical circulatory support with Impella devices is recommended for coverage (weak recommendation) only for patients with cardiogenic shock who might be candidates for left ventricular assist device (LVAD) (destination therapy) or transplant (bridge to transplant), AND an advanced heart failure and transplant cardiologist agree~~s~~ that Impella should be used as a bridge to a decision for LVAD or a transplant. Appropriate effort should be made to consult with a heart failure and transplant cardiologist, but coverage is recommended in circumstances where consultation cannot reasonably be obtained without endangering the patient's life and the treating physician believes the patient meets the criteria above.

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5. Community Health Workers for Patients with Chronic Disease

Obley reviewed the public comment disposition. He also referenced a letter sent after the public comment deadline, praising the utility of the report. Mohamed Abdiasis, from OHA's Office of Equity and Inclusion spoke briefly in support of the report's relevance in the context of Oregon's CCO 2.0 procurement. After brief discussion, the subcommittee voted to refer the draft report to the Value-based Benefits Subcommittee and HERC. **Motion approved 6-0.**

DRAFT MULTISECTOR INTERVENTIONS

To improve beneficial outcomes in patients with chronic conditions, the preponderance of evidence supports that community health workers (CHWs) serving as a part of an integrated care team appear to improve outcomes in:

- Children with asthma with preventable emergency department visits
- Adults with uncontrolled diabetes or uncontrolled hypertension

This evidence includes an emphasis on minority and low-income populations.

Characteristics of effective interventions include:

- Higher intensity interventions including longer duration
- Targeting populations with more severe chronic disease at baseline

Limited or insufficient evidence is available on the use of CHWs to improve outcomes for the following:

- HIV
- Serious mental illness
- Congestive heart failure

6. Planned Out-of-Hospital Birth

Livingston reminded the subcommittee of the introduction to this topic given at the previous meeting. No decisions will be made today, as the guidelines portion of the review is not complete. She said the discussion of the evidence review at today's meeting may be curtailed somewhat to ensure time for discussion of values and preferences and other issues around the topic.

Gingerich introduced Taylor, Cheyney and Neilson, who serve as ad hoc experts. He read the following statement regarding Taylor's qualifications and conflicts of interest, since she was appointed since the February meeting:

Alice Taylor, CNM, NP MPH *is a certified nurse midwife, recently retired. She previously practiced at Bright Eyes Midwifery and Wild Rivers Women's Health LLC in Gold Beach, Oregon. She also served on the medical staff of Curry General Hospital with independent privileges for normal vaginal birth and normal newborn care from November, 1978 to January, 2019. Since 2016, she has served as a Vice President for the American Association of Birth Centers; responsibilities include serving as the education chair and service on the Board.*

Ray reviewed the partial draft report that captured the evidence. Kansagara asked for a general sense of the typical methodological issues that would qualify these studies as poor. Ray said the issues were around the definitions of the groups as well as the lack of adjustments in some studies. In poor studies the groups were not contemporaneous or were subject to different protocols or were otherwise not comparable.

Adler asked about the cesearean group; he confirmed that the patients in the out-of-hospital group were low-risk patients, but in the hospital it is a mix of all patients. Ray said studies frame it differently, but the study he refers to is all comers in the hospital and there are adjusted risk differences to compensate for that. Ray said the hospital rate might still be a little high, but the out-of-hospital rate is likely true, and the hospital c-section rate is significantly higher.

In discussion of neonatal mortality, Wentz asked whether the Snowden study had a relative risk. Ray said it only has adjusted odds ratios. The issue is they did three different adjustment procedures, so it's adjusted differently than some of the other risk differences.

For neonatal morbidity, Sutton asked whether availability of NICU might be one of the reasons why the numbers are higher. Ray said they do not get into geography or availability of providers, though some studies get into length of stay.

In the noncomparative studies, Kansagara asked about the risk factors. Ray clarified that the noncomparative studies are all large registries for out-of-hospital settings, and while risk factors may be associated with certain outcomes, these kinds of studies cannot show causation. The same risk factors also exist for women in the hospital; we cannot say whether the risk increases more than in the hospital setting.

In discussion of the Grunebaum study about maternal risk factor subgroups, Kansagara asked whether the risk differences were significant. Ray said they are not performing subgroup analyses but rather reporting subgroup findings. The studies don't look for interaction. Some of the confidence intervals overlap. The relative risks in this study appear high because the comparator group is a very low-risk group (midwife-attended hospital births). Wentz asked whether hospital midwives would be allowed to do higher-risk patients than out-of-hospital attendants. Ray said they actually have a narrower scope compared to out-of-hospital. Taylor agreed.

Kansagara asked about the absolute numbers. Ray said there were 90,000 or so planned out-of-hospital births versus 1 million planned hospital births. When you break it into subpopulations, what are the event rates within subpopulations. Ray said you are looking at neonatal deaths, which are incredibly rare, and a single death may appear in multiple high-risk groups. King added that that number of neonatal deaths in intended home birth was 113 compared to 97,000 intended home births. The statistical analysis in the study is relatively unsophisticated because of the rare events. They didn't attempt a regression.

Ray said in the British Birthplace study, for the composite outcome, 4.2% of women had the outcome, but for nulliparous women, it's 9.3%. In freestanding birth centers the rate goes down all, and less for nulliparous women. Overall there was no difference between home and hospital births in this study, but the odds of the composite outcome did increase in the home setting for nulliparous women. In the U.S.-based Grunebaum study, they tried combining risk factors. This study found that nulliparous women over 35 and nulliparous over 41 weeks had the highest standardized mortality ratio. This study excluded women with several high-risk condition such as breech. However, it included all kinds of providers delivering out-of-hospital, including family members and friends.

Another issue with some of the U.S. based data is that it's based on birth certificates. The newer data identifies planned home birth, but if there is a transfer to the hospital, any associated bad outcomes

may get allocated to the hospital birth group. The studies don't try to address residual confounding by race, gestational diabetes, etc.

Ray said the new evidence affirms higher risk for groups identified in the previous coverage guidance. One study also finds higher risk for nulliparous women, women over 35 and women at 41 weeks or greater of pregnancy, though it has significant limitations.

Adler asked Ray to consider the effect of electronic fetal monitoring versus auscultation as a determinate of difference in cesarean section rate. Ray said she can't adjust for that. He said it may partially explain the difference.

Kansagara invited public comment. Silke Akerson of the Oregon Midwifery Council testified. She said it is frustrating to hear discussion of data which includes unattended out-of-hospital births. It would be like reviewing data around setting bones, where the data includes bones set by untrained family members. Family members aren't attendants but account for some of the deaths. She would like this fact acknowledged. This is the case in the Oregon biorecords data as well as the Snowden study. They account for 5 deaths in 6 years in the Oregon data. This is also the case in the Grunebaum studies (Editor's note: One of the Grunebaums studies is limited to births with attendants who have licensure). She would love to be able to know whether there is a variable harm to newborns, but it's hard to come to a conclusion based on faulty evidence.

Akerson said there was some self-identified quality problems in the 2012-2013 data in Oregon. In 2015-2017, since the quality program was started, the perinatal mortality rate for attended out-of-hospital birth (including community midwives) is 0.72 per thousand, very different from what is being presented.

Even though there aren't the studies that meet HERC requirements about breastfeeding, the MANA stats study shows a 98% breastfeeding rate at 6 weeks.

Finally, there is some misunderstanding of misattribution bias, that places other than Oregon aren't tracking births that are planned out-of-hospital but ended in a transfer to hospital. She's heard it said that this makes the mortality rate look lower than it actually is for planned out-of-hospital births. However, her understanding is that misattribution bias actually works in reverse; the majority of deaths in the Oregon dataset actually occur before transfer. What we are missing is a large denominator of births that transferred in non-emergent situations. There are a high number of transfers that are low-risk transfers. We're missing the high number of people who transfer for an epidural.

Akerson expressed empathy for the subcommittee trying to draw conclusions from such poor data. But it is frustrating to see that the data that is reviewed includes bad outcomes from unattended births.

Kansagara said that we haven't made any conclusions yet. The review team has appropriately identified a lot of the insufficiencies in the evidence base. It may be worth adding the issue about unattended births to the weaknesses in the evidence base.

Neilson said we also need to understand the systems issues. The hospital support for planned out-of-hospital birth varies within Oregon and in other settings. Dr. Cheyney has demonstrated a significant risk difference based on whether hospitals accept transfers. Using only U.S. data gives us part of the picture, but the non-U.S. data shows a much broader range of systems support. The Netherlands, for instance, has a highly integrated system. This is a major factor that doesn't come through in the evidence. Taylor

agreed, we have systems issue in our country. Women are cared for in such a way that they are more comfortable in the hospital; they understand that they will be cared for and respected and that the people that care for them will be respected in the hospital. She has enjoyed 40 years of integrated practice, and it worked similar to the UK, Canada and the Netherlands. She used similar criteria and consulted with hospital-based providers. She also had hospital privileges. Without an integrated system, there is a cutoff.

Livingston asked the subcommittee to discuss the other GRADE domains. For values and preferences, Lindsey said for many people choosing a birth place is part of the cultural norm. For others it's seeing birth as a natural phenomenon. Sometimes people prefer a birth center for similar reasons. There may be ethnic cultural factors as well, such as having an attendant who speaks your language. Livingston agreed, and the difficulty is how to weigh increase of neonatal harms versus the improved maternal outcomes and strong values and preferences. Sutton said in her work they look at risk in terms of dignity of risk. Sometimes it's not our job to do anything but inform people of their risk and accept that people are most successful when they live a way that they are choosing and have the supports that help them do what they want to in their life. She said she views it as a dignity of risk conversation with informed choice, where providers give the information to the women and families and allow them to choose. Kansagara said that way of phrasing it is helpful, but one of the challenges is that the numbers are based on very low confidence evidence. In terms of informing people of what the risk is, he hasn't even heard data that would help inform people. He asked the experts how they handle this.

Taylor said if she is doing a postdates discussion, she will start by saying women have gone overdue from the beginning of time. We shouldn't start with thinking this is the most normal thing. At some point in the discussion she has to say the word "stillbirth" so they understand that risk. It is a conversation that takes some time. She said there is also a cutoff in her birth center for how far postdate you can be; every risk factor requires an artful and evidence-based discussion.

Stecker asked Taylor if she is talking about maternal or fetal risk. Taylor said she addresses both types of risks at all stages of pregnancy and delivery. Stecker said individual autonomy is more complex when there are risks to both the baby and mother. Taylor said this does need to be addressed, and it is a delicate conversation where families typically value the interests of an infant more than they value those of a fetus. Stecker said the moment the fetus becomes an infant the parent's autonomy becomes constrainted. Taylor said this comes up in Group B strep prophylaxis. She talks about why screening is recommended for Group B strep and that antibiotics are recommended. The recommendations came about with some conflict between ACOG and AAP. You can't have the discussion with parents anticipating out-of-hospital birth without reviewing the history. In this case, it's about the child. If they make a decision not to accept antibiotics, they are going to have to hear about how a perfectly normal, healthy baby can deteriorate very quickly over a really short period of time. A community birth provider might describe the signs of a healthy newborn and say that the baby can go from good tone, lusty cry and pink color to be on death's door in 3 hours. Just because you have an appointment tomorrow, you can't wait to make that phone call.

Kansagara said he feels uncomfortable with the subcommittee trying to figure out values and preferences based on this discussion. He asked staff to look for literature on values and preferences. King said there is an enormous amount of literature on this. Kansagara asked staff to get a summary on this from Dr. Cheyney.

Lindsey and Stecker said it may be helpful to include a discussion of accepted bioethical principles. Kansagara agreed. Kansagara said we need to be clear that we don't know the absolute risk, that it's the dignity of accepting the uncertainty of risk. Finally, he asked the subcommittee to be mindful of steering in directions that are far afield of our usefulness. He said he believes systems improvements are important and where the opportunity for improvement lies but he doesn't know how much the subcommittee can inform this. He said the guidelines reviewed at the next meeting should inform the discussion.

Gingerich drew the subcommittee to the conclusion that there is evidence of benefit to the mother and some evidence in U.S. studies of neonatal harms. He said Livingston would need to write a statement on behalf of the subcommittee. He asked the subcommittee how the evidence should be weighed in a decision versus other factors as happened with the earlier Impella discussion. Kansagara said very low-quality evidence is a synonym for insufficient evidence. We could talk about the boundaries of the evidence, for example. It's not wrong to highlight uncertainty and the potential for increased risk.

Wentz said she has four years and three months of experience with OHP doing PA on out-of-hospital births. Three years and three months used the HERC guidelines. The Medicaid population is not the same as the statewide population. They have many disadvantages in terms of social determinants of health level. She is not advocating including Medicaid coverage itself a risk factor. However, looking at the outcomes, they are not as good as we would expect and not as good as statewide. We've had some transfers that happened because people became homeless or experienced domestic violence or relapsed into substance use disorder. Transfer for pain has not been significant in our population. In a 2.5-year population out of 70 patients who transferred, only 4 transferred for pain. The rest were urgent and for medical reasons. This adds more uncertainty, but we need to keep this in mind.

Kansagara said we don't have a methodology for this, but it underscores the utility of case reviews. That won't fall to this group to figure out, but there are opportunities for improving care based on this sort of analysis.

Little said the previous report was based on guidelines, and the subcommittee was to look at changes based on those guidelines, not looking at higher risk overall. Are we looking at the previously-identified high-risk subgroups and looking for changes in guideline recommendations? Livingston said yes. Gingerich agreed but reminded the subcommittee that HERC requested this review based on concerns about the Grunebaum and Snowden studies. If EbGS assesses that those are concerning, staff need to know that. Otherwise staff can continue to the guideline review. Livingston said it was the newer Grunebaum studies that changed things. King said the decision was based on the headline, not a deep dive, and asked EbGS to do the deep dive.

Sutton asked how much information we have about the deaths in Oregon for out-of-hospital births. Do we have more details about those? If those births had occurred in the hospital would those deaths have happened? The 2014 public health report included such a detailed review, but the newer report doesn't include that information. King said that the Center contacted Public Health about additional analysis. One of the criticisms we have heard is that the numbers presented include unattended births, but they didn't feel they could do an additional analysis.

7. Adjournment

The meeting was adjourned at 5:15 pm. The next meeting is scheduled for June 6, 2019 from 2:00-5:00 pm at Clackamas Community College, Wilsonville Training Center, Rooms 111-112, 29353 SW Town Center Loop E, Wilsonville, Oregon 97070.