Health Evidence Review Commission (HERC)

Coverage Guidance: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

DRAFT for HERC meeting 5/19/2022

HERC Coverage Guidance

Tonsillectomy, adenoidectomy, adenotonsillectomy, and prophylactic antibiotic therapy are not recommended for coverage to treat pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS) (*weak recommendation*).

Up to 3 monthly immunomodulatory courses of intravenous immunoglobulin (IVIG) therapy or therapeutic plasma exchange are recommended for coverage to treat PANDAS and PANS (*weak recommendation*) when both of the following are met:

A) A clinically appropriate trial of two or more less-intensive treatments (for example, appropriate limited course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, short-course antibiotic therapy) was either not effective, not tolerated, or did not result in sustained improvement in symptoms (as measured by a lack of clinically meaningful improvement on a validated instrument directed at the patient's primary symptom complex). These trials may be done concurrently, AND

B) A consultation with and recommendation from a pediatric subspecialist (for example, pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist, pediatric infectious disease specialist) as well as the recommendation of the patient's primary care provider (for example, family physician, pediatrician, pediatric nurse practitioner, naturopath). The subspecialist consultation may be a teleconsultation. For adolescents, an adult subspecialist consult may replace a pediatric subspecialist consult.

A reevaluation at 3 months by both the primary care provider and pediatric expert is required for continued therapy of IVIG or plasma exchange. This evaluation must include clinical testing with a validated instrument, which must be performed pretreatment and posttreatment to demonstrate clinically meaningful improvement.

Note: Other treatments (corticosteroids, SSRIs, NSAIDs, short-course antibiotics, and behavioral therapies) were included in an initial version of this report. These therapies were determined to be beyond the scope of a HERC coverage guidance, as these therapies are commonly used for many indications and are not typically subject to utilization control. Only treatments subject to coverage criteria were retained for the final version of this report.

Note. Definitions for strength of recommendation are in Appendix A, GRADE Table Element Descriptions. Rationales for each recommendation appear below in the GRADE tables.

Oregon Health Authority

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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 Tables

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. The level of confidence in the estimate is determined by HERC based on the assessment of 2 independent reviewers from the Center for Evidence-based Policy.

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 Tables

Should prophylactic antibiotics be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	In a single RCT (N = 37) comparing penicillin to placebo for 4 months, there was no significant difference in neuropsychiatric symptoms between children when they received penicillin or placebo. The cross-over design meant that each participant was in both the intervention and control group for the analysis. In a second RCT comparing prophylactic azithromycin (N = 17) to placebo (N = 14) for 4 weeks, the azithromycin group had a significantly greater reduction OCD severity, but no significant difference in number of obsessions and compulsions. Significantly more children were classified as responding at a clinically significant level in the azithromycin group (7/17) than in the placebo group (1/14). In a third RCT that tested prophylactic antibiotic therapy for 1 year, significantly more (5/11) children who received penicillin demonstrated significant reduction in symptoms compared to (1/12) children who received azithromycin. Compared to the year before baseline, children in both groups had fewer exacerbations during the trial year. ●○○○ *(very low confidence, based on 3 RCTs, n = 91)*	Antibiotics are inexpensive and readily available. Treatment of complications of long-term or frequent antibiotic use would add cost.	Some parents would want any treatment that might help their child's symptoms. However, other parents would have concerns about the risks and side effects of long-term or frequent antibiotic use.	Long-term or frequent antibiotic use is associated with a range of negative consequences, including but not limited to *C. difficile* infection, gut flora disruption, diarrhea, and increased antibiotic resistance leading to reduced ability to treat other infections with antibiotics. Most health plan cover short-term antibiotics without prior authorization criteria but may scrutinize or not cover long-term prescriptions.
Hospitalizations *(Critical outcome)*	No evidence identified.			

Should prophylactic antibiotics be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Harms *(Important outcome)*	The few harms that were reported included heart rate irregularity (9/12) for children who received azithromycin, and loose stool (no statistics reported). ●○○○ *(very low confidence, based on 1 RCTs, n = 23)*			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			

Balance of benefits and harms: We have very low confidence that prophylactic antibiotic use is helpful in PANDAS/PANS, given the small sample sizes in the included studies. There are concerning known harms of frequent or long-term antibiotic use.
Rationale: Prophylactic antibiotic therapy is not recommended for coverage for PANDAS/PANS because of insufficient comparative evidence that prophylactic antibiotic use leads to any measurable benefit for these conditions. The known risks of prophylactic or long-term antibiotic use outweigh potential benefits in these conditions. The recommendation is weak because of the very low quality of the evidence.
Recommendation: Prophylactic antibiotic therapy is not recommended for coverage for PANDAS/PANS (*weak recommendation*).

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.
Abbreviations. OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; RCT: randomized controlled trial.

Should tonsillectomy and/or adenoidectomy be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	No difference in neuropsychiatric symptoms between surgery and non-surgery groups among children diagnosed with PANDAS. ●●○○ *(low confidence, based on 2 comparative cohort studies, n = 232)*	Tonsillectomy and adenoidectomy are invasive procedures requiring general anesthesia and specialty surgical care.	Parents would not value an invasive surgery with risks as well as the risks of general anesthesia for a procedure that has no evidence of benefits.	Tonsillectomy and/or adenoidectomy frequently have coverage limitations, such as multiple streptococcal infections in one year. This procedure has historically been overused.
Hospitalizations *(Critical outcome)*	No evidence identified.			
Harms *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			

Balance of benefits and harms: We have low confidence that that there is no benefit from tonsillectomy and/or adenoidectomy for PANDAS/PANS, and this procedure has known harms.
Rationale: Tonsillectomy and/or adenoidectomy are not recommended for coverage for treatment of PANDAS/PANS because these procedures have known harms and because evidence shows that these procedures do not improve the outcomes in this condition. The recommendation is weak because of the low quality of the evidence.
Recommendation: Tonsillectomy and/or adenoidectomy are not recommended for coverage (*weak recommendation*) for treatment of PANDAS/PANS.

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Abbreviations. PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome.

Should IVIG be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	<u>Compared to Saline Placebo</u> Among children meeting the criteria for PANDAS and OCD in an RCT, 7/18 had a significant decrease in symptoms 6 weeks after receiving 2 consecutive days of IVIG infusions, and 4/17 children in the placebo group had a significant decrease in symptoms. When comparing the IVIG group and placebo group, there were no statistically significant differences. During an open-label phase of this same trial, 17/24 children meeting the criteria for PANDAS and OCD had a significant decrease in symptoms 12 to 18 weeks after receiving 2 consecutive days of IVIG infusions on 1 or 2 occasions. Another RCT compared children who received IVIG (N = 9) to children who received saline placebo (N = 10) 1 month after treatment reported that the IVIG group improved significantly more on most measures compared to the placebo group. One year after treatment, the improvements in the IVIG group were maintained, but the placebo group was not followed to determine whether the IVIG group's symptoms remained significantly better than the placebo group's symptoms. <u>Compared to plasma exchange</u> No significant difference 1 month or 1 year after treatment between children receiving IVIG (N = 9) or plasma exchange (N = 10); both groups had	IVIG is expensive and requires the cost of an infusion center, nursing care, and possible hospitalization. Treatment for side effects of IVIG would add cost. IVIG is a scarce resource and shortages have been reported in the past.	Parents would value any treatment that would improve their child's symptoms. However, many parents would value avoiding a treatment with known side effects that has little evidence of effectiveness.	IVIG is a blood product with the inherent risks that accompany accepting any form of blood product. IVIG therapy has a significant rate of mild side effects including fever, body aches, nausea, rash, and fatigue. Severe side effects include thrombosis, renal dysfunction, and acute renal failure, and life-threatening allergic reaction. IVIG can interfere with vaccine effectiveness for vaccines given

Should IVIG be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
	significant improvement in symptoms compared to baseline at both 1-month and 1-year follow-ups ●○○○ *(very low confidence, based on 2 RCTs, N = 54)*			within several months of IVIG. Several products on the market are FDA-approved for people under the age of 19.
Hospitalizations *(Critical outcome)*	No evidence identified.			
Harms *(Important outcome)*	1/33 children who received IVIG infusions had an allergic reaction to the IVIG infusion that resolved without complication. 31/33 children reported mild or moderate adverse events such as nausea, vomiting, headache, fever, joint pain, tiredness, stomach pain, or decreased appetite. ●○○○ *(very low confidence, based on 2 RCTs, N = 64)*			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			
Function or quality of life for patient *(Important outcome)*	No evidence identified.			

Balance of benefits and harms: There were mixed results from 2 very small trials regarding the clinical effectiveness of IVIG. Outside of PANDAS, no evidence met inclusion criteria for PANS. IVIG has a significant rate of known harms.
Rationale: Expert opinion and lower-quality observational data indicate there may be benefit for some patients with these conditions, but recommended treatment protocols and criteria for treatment vary widely. Due to the severe impact of symptoms associated with PANDAS/PANS on child health, growth and development, and the lack of known effective treatments, coverage of IVIG is recommended when recommended by the patient's PCP and a pediatric subspecialist and after less-intensive therapies were not effective, were not tolerated or did not result in sustained improvement in symptoms. The recommendation is weak because of the very low quality of the evidence.

Should IVIG be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Recommendation: Up to 3 monthly immunomodulatory courses of intravenous immunoglobulin (IVIG) therapy are recommended for coverage to treat PANDAS and PANS (*weak recommendation*) when both of the following are met: a) A clinically appropriate trial of two or more less-intensive treatments (for example, appropriate limited course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, short-course antibiotic therapy) was either not effective, not tolerated, or did not result in sustained improvement in symptoms (as measured by a lack of clinically meaningful improvement on a validated instrument directed at the patient's primary symptom complex). These trials may be done concurrently, AND b) A consultation with and recommendation from a pediatric subspecialist (for example, pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist, pediatric infectious disease specialist) as well as the recommendation of the patient's primary care provider (for example, family physician, pediatrician, pediatric nurse practitioner, naturopath). The subspecialist consultation may be a teleconsultation. For adolescents, an adult subspecialist consult may replace a pediatric subspecialist consult. A reevaluation at 3 months by both the primary care provider and pediatric expert is required for continued therapy of IVIG. This evaluation must include clinical testing with a validated instrument, which must be performed pretreatment and posttreatment to demonstrate clinically meaningful improvement.				

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.
Abbreviations. IVIG: intravenous immunoglobulin; OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; RCT: randomized controlled trial.

Should therapeutic plasma exchange be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in psychiatric symptom scores *(Critical outcome)*	<u>Compared to saline placebo</u> In the same RCT that is described in the IVIG table, the plasma exchange group (N = 10) was compared to the same placebo group (N = 10) 1 month after treatment. The plasma exchange group improved significantly more on most measures compared to the placebo group. One year after treatment, the improvements in the plasma exchange were maintained, but the placebo group was not followed to determine whether the plasma exchange group's symptoms remained significantly better than the placebo group's symptoms. <u>Compared to intravenous immunoglobulin</u> No significant difference 1 month or 1 year after treatment between children receiving IVIG (N = 9) or plasma exchange (N = 10); both groups had significant improvement in symptoms compared to baseline at both 1-month and 1-year follow-ups ●○○○ *(very low confidence, based on 1 RCT, N = 29)*	Plasma exchange is an expensive therapy which requires a monitored infusion in a clinical setting. Children in the studies included in this review required multiple treatment sessions.	Parents would value any treatment that would improve their child's symptoms. However, many parents would value avoiding a treatment with known side effects that has little evidence of effectiveness.	High rates of patients undergoing plasma exchange report side effects, including fever, chills, and muscle cramps. Known complications of plasma exchange include circuit clotting, low or high blood pressure, nausea, vomiting, itchy skin, hives, low calcium levels in the blood, venous access malfunction, infections, thrombosis, and anaphylactic shock.
Hospitalizations *(Critical outcome)*	No evidence found.			
Harms *(Important outcome)*	All children who received plasma exchange (10/10) experienced mild side effects such as nausea, vomiting, anxiety, or fever. ●○○○ *(very low confidence, based on 1 RCT, N = 29)*			

Should therapeutic plasma exchange be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Function or quality of life for patient *(Important outcome)*	No evidence found.			
Function or quality of life for patient *(Important outcome)*	No evidence found.			

Balance of benefits and harms: The comparative evidence that plasma exchange is effective for treating PANDAS is very limited and shows no clear benefit. The harms of this treatment are generally mild but serious complications can occur.
Rationale: Expert opinion and lower-quality observational data indicate there may be benefit for some patients with these conditions, but recommended treatment protocols and criteria for treatment vary widely. Due to the severe impact of symptoms associated with PANDAS/PANS on child health, growth and development, and the lack of known effective treatments, coverage of plasma exchange is recommended when recommended by the patient's PCP and a pediatric subspecialist and after less-intensive therapies were not effective, were not tolerated or did not result in sustained improvement in symptoms.

Should therapeutic plasma exchange be recommended for coverage for PANDAS/PANS?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Recommendation: Up to 3 monthly immunomodulatory courses of therapeutic plasma exchange are recommended for coverage to treat PANDAS and PANS (*weak recommendation*) when both of the following are met: a) A clinically appropriate trial of two or more less-intensive treatments (for example, appropriate limited course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, short-course antibiotic therapy) was either not effective, not tolerated, or did not result in sustained improvement in symptoms (as measured by a lack of clinically meaningful improvement on a validated instrument directed at the patient's primary symptom complex). These trials may be done concurrently, AND b) A consultation with and recommendation from a pediatric subspecialist (for example, pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist, pediatric infectious disease specialist) as well as the recommendation of the patient's primary care provider (for example, family physician, pediatrician, pediatric nurse practitioner, naturopath). The subspecialist consultation may be a teleconsultation. For adolescents, an adult subspecialist consult may replace a pediatric subspecialist consult. A reevaluation at 3 months by both the primary care provider and pediatric expert is required for continued therapy of plasma exchange. This evaluation must include clinical testing with a validated instrument, which must be performed pretreatment and posttreatment to demonstrate clinically meaningful improvement.				

Note. GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.
Abbreviations. IVIG: intravenous immunoglobulin; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; RCT: randomized controlled trial.

Background

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS are conditions associated with a sudden onset of changes or regression in behaviors and experiences prior to puberty in multiple domains, such as motor, neurological, psychiatric, and biological systems.[1-3] Care providers and researchers from multiple disciplines (including microbiology, neurology, neuroimmunology, immunology, child psychiatry, infectious diseases, rheumatology, and pediatrics) have contributed to publications seeking to define these conditions.[3] These conditions have an abrupt onset of symptoms and may include exacerbations, sudden worsening of symptoms in short bursts, in a sawtooth-like pattern.[1-3]

In PANDAS, the triggering mechanism for these changes is hypothesized to be a beta-hemolytic streptococcal infection within 6 months of symptom onset, and is characterized by sudden onset of obsessive-compulsive disorder (OCD), along with verbal or motor tics.[2,4] This hypothesized disease pathway aligns with large epidemiological cohort studies of children in Europe[5] and Asia[6] that observed an 18% to 22% increased risk of any neuropsychiatric disorders in children who had streptococcal infections as compared with children without streptococcal infections, including a higher risk for obsessive-compulsive and tic disorders.[5,6] However, some researchers suggest that tying the diagnosis to streptococcus infection to the exclusion of other etiologies has limited the exploration of other disease pathways that could inform diagnosis and treatment of symptoms.[7,8]The prevalence of PANDAS is not known, but some studies suggest that males are more likely than females to be diagnosed with PANDAS.[9]

PANS is characterized by sudden onset of OCD, with or without severe eating restrictions, and 2 or more other symptoms in neurological, behavioral, or cognitive domains.[3] PANDAS can be considered a subset of PANS. These symptoms could result from multiple disease pathways or other disorders, including but not limited to streptococcus, varicella, or bacterial pneumonia infections.[3,10] The prevalence of PANS is not known.

Two other conditions with similar symptoms are pediatric infection-triggered autoimmune neuropsychiatric disorders (PITAND) and childhood acute neuropsychiatric syndromes (CANS).[10,11]

The natural histories of PANDAS and PANS are still being studied, but early signals suggest that 60% to 80% of pediatric patients have a significant reduction in symptoms over time, similar to childhood-onset OCD.[12] The American Academy of Child and Adolescent Psychiatry published a practice parameter for assessing and treating childhood-onset OCD; they noted some clinical experts believe a small subset of children that have been diagnosed with OCD or Tourette disorder might have clinical exacerbations linked to streptococcal infection.[13] The authors report that more males than females are diagnosed with pediatric OCD, typically diagnosed between the ages of 7 and 12 years; earlier onset is associated with comorbid psychiatric diagnoses (e.g., mood disorders, attention deficit disorder, anxiety disorders, phobias).[13]

There is some discussion about whether PANDAS and PANS is related to pediatric autoimmune encephalitis, which is also characterized by abrupt onset of similar abnormal behavioral symptoms and disruptions in multiple biological systems (e.g., gastrointestinal, nervous).[1,14-16] Autoimmune encephalitis in children is characterized by a sudden onset of symptoms including seizures, irritability, aggression, and abnormal movements, and could be associated with an acute infection or presence of a tumor.[1,14,17]

The prevalence of pediatric autoimmune encephalitis is not known, but a population study of adults and children suggested the incidence rate of autoimmune encephalitis was 0.8 per 100,000, and that males had more than twice the prevalence of females.[18] Autoimmune encephalitis is a life-threatening condition usually treated in a hospital setting.[1,15] Because of the differences in diagnostic criteria and disease process between autoimmune encephalitis and PANDAS/PANS, the scope of this report excludes autoimmune encephalitis.

Diagnostic Criteria and Tests

Table 1 presents diagnostic criteria and tests by condition and includes information from publications summarized in the Evidence Review and Clinical Practice Guidelines sections of this coverage guidance.[3,11,14-17,19-32]

Table 1. Proposed Diagnostic Criteria, Tests and Processes

Proposed Diagnostic Criteria	Proposed Diagnostic Tests and Processes
PANDAS[2]	
Presence of OCD, symptoms similar to attention deficit hyperactive disorder, or tics	In patients with OCD, complete blood count, erythrocyte sedimentation rate, C-reactive protein, metabolic panel, urine analysis, pharyngeal swab and anti-streptococcal antibodies. Positive results from the pharyngeal swab and anti-streptococcal antibodies indicate exposure to the streptococcal infection do not differentiate between the state of carrier and acute infection. For children with neurological and psychiatric symptoms, physical or neurological examination require the analysis of the cerebrospinal fluid and neuroimaging exams.
Onset of symptoms occurs between the ages of 3 and 12 (or prior to puberty)	
Symptoms had sudden onset, or existing symptoms worsened for a short period	
Confirmed culture or antibodies related to a streptococcal infection temporally associated with onset of symptoms	
Neurological anomalies such as hyperactivity, choreiform motor movements, bedwetting, anxiety, emotional lability, developmental regression or mood changes	
Rule out Sydenham's chorea, Tourette syndrome, OCD, central nervous system vasculitis, autoimmune encephalitis, and neuropsychiatric lupus	Differential diagnosis.
PANS[3,22]	
Sudden onset of OCD or eating restrictions, and at least 2 of the following:	Complete medical and psychiatric history, physical examination, laboratory testing of blood and possibly cerebrospinal fluid, and selected paraclinical evaluations, such as magnetic resonance imaging, electrocardiogram/ echocardiography, electroencephalography, and polysomnography.
• Anxiety (particularly separation anxiety)	
• Emotional lability or depression	
• Irritability, aggression, and/or severely oppositional behaviors	
• Deterioration in school performance (related to attention-deficit/hyperactivity disorder-like behaviors, memory deficits, and cognitive changes)	
• Sensory or motor abnormalities	

Proposed Diagnostic Criteria	Proposed Diagnostic Tests and Processes
• Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency	
Rule out Sydenham chorea, autoimmune encephalitis, neuropsychiatric lupus, central nervous system vasculitis, and other conditions that better account for the symptoms	Differential diagnosis.

Abbreviations. OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome.

We identified 4 publications that specifically presented or summarized evidence for diagnostic criteria and tests related to PANDAS or PANS.[4,9,33,34] Nielsen and colleagues performed a systematic review and meta-analysis of studies on the association between streptococcal infections and exacerbations of neuropsychiatric symptoms.[34] The authors concluded that although children diagnosed with PANDAS had more neuropsychiatric exacerbations than children with streptococcal infections without a follow-up diagnosis of PANDAS, these exacerbation were not significantly temporally associated with streptococcal infections.[34]

Baj and colleagues reviewed published literature in search of distinguishing features of patients diagnosed with PANDAS and concluded that despite more than 20 years of research into this condition, it remains challenging to differentiate PANDAS from OCD or tic disorders.[9] Their observations of characteristics that appear to be different for children diagnosed with PANDAS include[9]:

- some alterations of cortico-basal ganglia circuitry, due to the effect of antibodies produced in response to the condition on various neuronal proteins, including tubulin, lysoganglioside, and dopamine receptors;
- deposits of antibodies which are also accumulated in the striatal interneurons;
- significantly enlarged volumes of corpus striatum, caudate, putamen, globus pallidus, and basal ganglia; and
- significant alterations to the gut microbiota.

Gamucci and colleagues described the clinical, neuropsychological, and biological characterization of PANDAS and PANS, and recommended 4 categories of tools to add in the diagnostic process.[4] Proposed neuropsychological tests to assess motor and vocal tics, obsession and compulsion[4]:

- Children's Yale–Brown Obsessive Compulsive Scale for presence and severity of motor and vocal tics; and
- Yale Global Tic Severity Scale for presence and severity of child's obsession and compulsion.

Proposed neuropsychological tests to assess anxiety[4]:

- Multidimensional Anxiety Scale for Children (MASC) for the presence and types of child's anxiety symptoms for ages 8 to 19 years.

Proposed neuropsychological tests to assess short-term memory and attention[4]:

- Digit Span subtest Wechsler Intelligence Scale for Children for verbal short-term memory for ages 6 to 16 years;

- Coding subtest Wechsler Intelligence Scale for Children for visual-motor dexterity and nonverbal short-term memory for ages 6 to 16 years; and
- Symbol Search subtest Wechsler Intelligence Scale for Children for accuracy, attention and concentration for ages 6 to 16 years.

Proposed neuropsychological tests to assess processing speed[4]:

- Processing Speed Index Wechsler Intelligence Scale for Children (WISC III-IV) for speed of cognitive processes and response output on visual-motor tasks for ages 6 to 16 years

In addition to the scales proposed by Gamucci and colleagues above, Leibold and colleagues validated a Global Impairment Score scale to measure impairment in children and adolescents as part of the diagnostic process for PANS.[33] This scale was designed to be answered by a child's caregiver, and is scored on a scale of 0 to 100.[33]

For additional measures proposed in guidelines, please refer to the Clinical Practice Guidelines section of this coverage guidance.

Treatments

Table 2 presents treatments by condition and includes information about treatments from the publications summarized in the evidence review and clinical practice guidelines sections of this coverage guidance.[3,11,14-17,19-32] Not all treatments in Table 2 have been evaluated in studies with prospective comparative designs; the evidence review portion of this coverage guidance will synthesize findings from comparative studies related to treatments and outcomes.

Table 2. Treatments Proposed for PANDAS and PANS

Treatments	PANDAS	PANS
Antibiotics		
Amoxicillin	X	X
Aripiprazole		X
Azithromycin	X	
Penicillin	X	
Surgical Interventions		
Tonsillectomy	X	
Adenoidectomy	X	
Intravenous Immunoglobulin and Plasma Exchange		
Intravenous immunoglobulin	X	X
Plasma exchange	X	X
SSRIs		
Fluoxetine	X	
NSAIDs		
Naproxen sodium	X	
Antipsychotics		
Pimozide	X	
Risperidone		X
Corticosteroids		
Dexamethasone		X

Treatments	PANDAS	PANS
Prednisone	X	
Behavioral Interventions		
Cognitive behavioral therapy	X	

Abbreviations. NSAID: nonsteroidal anti-inflammatory drug; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; SSRI: selective serotonin reuptake inhibitor.

Evidence Review

We identified 2 systematic reviews, 5 RCTs with 6 publications, and 2 comparative cohort studies that reported interventions for children diagnosed with PANDAS or PANS.[11,24-32] Table 3 summarizes key characteristics of each included study. Given the varied study designs, treatments, and outcomes collected, neither of the systematic reviews included a meta-analysis section.

Sigra and colleagues included in their systematic review any report of any treatments for children with PANDAS, PANS, CANS, or PITAND published in English that also reported outcomes; this expansive inclusion criteria resulted in 5 RCTs, 7 observational survey study, and 65 case reports.[24] We rated this systematic review itself as having a low risk of bias, although it is important to note that the review authors concluded that there is not enough rigorous research about treatments for children with PANDAS, PANS, CANS, or PITAND, and the existing studies themselves have a high risk of bias. Sigra and colleagues concluded there was insufficient evidence to clearly recommend specific treatments for children with these diagnoses, but that psychiatric behavioral interventions, immunomodulatory therapies, and antibiotics likely have roles in the treatment of these disorders and should be more systematically investigated.[24]

In addition to summarizing comparative evidence regarding antibiotics, tonsillectomy, IVIG, and therapeutic plasma exchange, Sigra and colleagues sumarized noncomparative evidence for behavioral therapy, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs). The first draft of this coverage guidance included the latter interventions, although it was not possible to make a clear determination of effectiveness or harms of these interventions due to the lack of comparative evidence.

Farhood and colleagues included in their systematic review 13 studies testing treatments for PANDAS that also reported outcomes related to change in symptoms, and excluded case reports; 3 included studies were RCTs, and 10 had retrospective designs.[27] We rated this review as having a high risk of bias. This review included studies of adenotonsillectomy, antibiotic therapy, intravenous immunoglobulin (IVIG) therapy, and cognitive behavioral therapy.[27] The authors suggested that immunoglobulin therapy might be effective for certain populations, and that psychotherapy and antibiotic therapies were likely low-risk interventions.[27] However, the authors concluded that the study designs left results open to question due to inability to account for confounding factors, such as co-occurring treatments, and were unable to strongly recommend any specific course of treatment.[27] All of the studies included in Farhood and colleagues' systematic review were also included in Sigra and colleagues' systematic review. Given the later search and publication dates and the lower risk of bias for Sigra and colleagues' review, we restrict our summary of review findings to the Sigra review in the following sections.

The RCTs all had fewer than 40 participating children, so the number of children in each treatment and placebo group was also small during comparative stages of the trials. These RCTs compared antibiotics to placebo and had moderate to high risk of bias,[25,30,31] or compared IVIG to placebo or plasma exchange and had low to high risk of bias.[26,32] At the end of the trial phase, the investigators of 3 of the RCTs offered the active treatment under consideration to the children who had been in the group receiving a placebo, which makes the long-term follow-up of participants in these trials an open-label observation follow-up (range, 4 weeks to 57 months).[11,25,26,31]

The number of children included in the 2 comparative cohort studies was larger (more than 100), and both studies focused on surgical interventions for symptom relief for children diagnosed with PANDAS.[28,31] We rated both studies as having a high risk of bias, primarily due to an inability to account for confounding factors.

The following sections organize findings from these studies by type of intervention. First, we summarize relevant RCTs and comparative cohort studies, and then we compare those findings with conclusions from the systematic reviews that included results from noncomparative study designs such as case reports.

Table 3. Characteristics of Included Studies

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
Systematic Reviews				
Sigra et al., 2018[24] 5 RCTs, 7 observational survey studies, and 65 case reports Not applicable	Studies in which patients with PANDAS, PANS, CANS, or PITAND were given treatment, that presented outcome data, and were written in English	No exclusion criteria explicitly listed	Cognitive behavior therapy, antibiotics, tonsillectomy, corticosteroids, therapeutic plasma exchange, IVIG, rituximab, nonsteroidal anti-inflammatory drugs	Low
Farhood et al., 2016[27] 3 RCTs and 10 retrospective designs Not applicable	Studies testing treatments for PANDAS and reported outcomes, and were written in English or Spanish	Review articles, single case reports, and studies of natural history or diagnostic strategies	Tonsillectomy, adenoidectomy, antibiotics, IVIG, cognitive behavioral therapy, or SSRIs	High
RCTs				
Murphy et al., 2017[25] N = 31 2 and 4 weeks	Children with an acute onset or acute relapse within 6 months of evaluation (abrupt, dramatic overnight onset) of moderate or worse OCD symptoms and presence of a sudden and severe co-occurrence of at least 2 neuropsychiatric symptoms.	Children with a gradual onset or duration of OCD symptoms of more than 6 months; who were receiving extended-course antibiotics (i.e., not a typical treatment course of antibiotics for an infection, or prophylactic antibiotics) and/or other immune therapy for PANS; with a primary diagnosis of tics; who were receiving exposure-based cognitive behavioral therapy; who had a history of nonresponse to a prior antibiotic trial; or who had a diagnosis of moderate to severe autism spectrum disorder,	Azithromycin and probiotics versus placebo with probiotics for 4 weeks; after this all participants were offered azithromycin	Moderate

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
		intellectual disability, and/or chronic neurological disease.		
Williams et al., 2016[26] Leon et al., 2018[11] N = 35 3 and 6 months during the trial, and a 57-month observational follow-up	Children who were 4 to 13 years of age in first episode of PANDAS symptoms and documentation that symptoms first appeared within 6 to 8 weeks of streptococcal infection or exposure; who had a sudden onset or exacerbation of OCD (reaching peak severity and impairment within 24 to 48 hours); and had at least 3 neuropsychiatric symptoms (which meets criteria for PANS).	Children with a history of Sydenham chorea or acute rheumatic fever; who had symptoms consistent with autism spectrum disorder or schizophrenia; who had severe physical, behavioral, or psychiatric symptoms that would prevent study participation; or prior corticosteroid or immunomodulatory therapy for PANDAS	IVIG versus placebo for 6 weeks; participants in the placebo group were then given the opportunity to receive IVIG; 31 participants received at least 1 dose of IVIG over the course of the study	Low risk for original trial, and high risk for long-term follow-up
Snider et al., 2005[30] N = 23 12 months	Children with a tic disorder and/or OCD; who had a history of a sudden onset of symptoms or an episodic course with abrupt symptom exacerbations interspersed with periods of partial or complete remission; who had onset of neuropsychiatric symptoms prior to puberty; and who had documentation of a temporal association between a preceding streptococcal infection and the onset or exacerbation of neuropsychiatric symptoms.	No specific exclusion criteria listed.	Azithromycin versus penicillin for 12 months	High

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
Garvey et al., 1999[31] N = 37 4 months	Children between 4 and 15 years of age with a tic disorder and/or OCD; who had history of a sudden onset of symptoms or an episodic course with abrupt symptom exacerbations interspersed with periods of partial or complete remission (a sawtooth, rather than a waxing and waning course); who had an onset of symptoms prior to puberty; and evidence of a temporal association between a preceding streptococcal infection and the onset or exacerbation of neuropsychiatric symptoms.	Children who had tics or OCD of such a severity that hospitalization was considered; who required treatment for severe, active comorbid major psychiatric disorders; who had with autism, pervasive developmental delay, or "mental retardation"[a]; or who had neurologic diagnoses other than tics and Tourette syndrome, serious concurrent or chronic medical disorders, and a personal history of penicillin allergy.	Penicillin versus placebo for 4 months; cross-over design meant that all participants received penicillin during the 8 months of the study	High
Perlmutter et al., 1999[32] N = 29 1 month and 12 months	Children ages 5 to 14 years with a tic disorder and/or OCD; onset of neuropsychiatric signs and symptoms before puberty; a history of sudden onset of signs and symptoms, or an episodic course characterized by abrupt exacerbations and periods of partial or complete remission; evidence of, and association between, streptococcal infection and onset or exacerbation of signs and symptoms; and current exacerbation severe	Children with a history of Sydenham's chorea or rheumatic fever, autism, schizophrenia or other psychotic disorder, a neurological disorder other than a tic disorder, an autoimmune disorder, or other medical illness. Immunoglobulin concentrations were measured, and children were excluded from the study if they had IgA deficiency (a contraindication to IVIG administration).	Plasma exchange, IVIG, or placebo for 2 weeks	High

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
	enough to cause significant distress and interfere with the child's social functioning in at least 2 spheres (home, school, social relations).			
Comparative Cohort Studies				
Pavone et al., 2014[28] N = 120 Every 2 months for 2 years	Children with a tic disorder and/or OCD; who had infection-related symptom flare-ups, history of dramatic onset of either OCD or tics, new onset anxiety, sensory or motor abnormalities, behavioral regression, deterioration in school performance, emotional lability, or urinary symptoms (all these neuropsychiatric phenomena were in temporal association to streptococcal pharyngeal tonsillitis). The surgical group (n = 56) were referred to surgery based on a clinical history of recurrent inflammation in addition to the symptoms above.	No specific exclusion criteria listed	Surgery versus no surgery; surgery group had 25 tonsillectomies and 31 adenotonsillectomies	High
Murphy et al., 2013[29] N = 112 Not reported	Children with a tic disorder and/or OCD; and with infection-related symptom flare-ups, history of dramatic onset of either OCD or tics, new onset anxiety, sensory or motor	Children with a psychotic disorder, significant medical illness, or non-tic neurologic disorder	Surgery versus no surgery; surgery group had 4 tonsillectomies, 10 adenoidectomies, and 22 had both procedures	High

First Author, Year Number Follow-up(s)	Inclusion Criteria	Exclusion Criteria	Intervention	Risk of Bias
	abnormalities, behavioral regression, deterioration in school performance, emotional lability, or urinary symptoms. Participants on stable doses of psychotropic medication for their condition were not excluded. The surgical group comprised children who had a tonsillectomy and/or adenoidectomy procedure, and were matched to nonsurgery participants on age and sex.			

Note. This language was taken directly from the study; the coverage guidance authors recognize this language is no longer acceptable.
Abbreviations. CANS: childhood acute neuropsychiatric syndromes; IgA: immunoglobulin A; IVIG: intravenous immunoglobulin; OCD: obsessive-compulsive disorder; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute-onset neuropsychiatric syndrome; PITAND: pediatric infection-triggered autoimmune neuropsychiatric disorders; RCT: randomized controlled trial; SSRI: selective serotonin reuptake inhibitor.

Antibiotics

We identified 3 RCTs that tested antibiotics as a primary intervention for children diagnosed with PANDAS or PANS.[25,30,31] As a reminder, children meeting the criteria for PANDAS also meet the criteria for PANS. Conclusions from both systematic reviews agreed with author conclusions of these 3 RCTs: there is some evidence that antibiotic prophylaxis might reduce exacerbations of neuropsychiatric symptoms for children diagnosed with PANDAS.[24,27]

Azithromycin

Murphy and colleagues conducted a double-blind RCT with 31 participants randomized to receive azithromycin prophylaxis (N = 17) for 4 weeks or to receive a placebo (N = 14) for 4 weeks; participants in the placebo group were then given the option to begin taking azithromycin, which launched the open-label observational portion of the study.[25] Both groups also received twice daily probiotics.[25] We rated the outcomes from the trial portion of this study as having a moderate risk of bias; no outcomes were reported for the open-label portion.

When comparing scores on the OCD Clinical Global Impressions Severity scale (which has a scale of 1 to 7), participants who received azithromycin reported statistically significantly greater reductions in symptom frequency 4 weeks after baseline (azithromycin group mean, 4.06; azithromycin group standard deviation [SD], 0.23; placebo group mean, 4.93; placebo group SD, 0.25; effect size, 0.11; $P = .003$).[25] The effect size for the difference in symptoms between the azithromycin and placebo groups suggests that there was only a very small difference between the 2 groups, and that the difference was not likely to be clinically significant. No significant difference was found between the group on the Children's Yale-Brown Obsessive-Compulsive Scale, and no difference between groups for the severity of symptoms.[25]

Investigators also assessed whether participants responded to their assigned therapy, using a 30% or greater reduction in symptoms to judge whether a participant responded. In the azithromycin group, 52.9% (9 of 17) were categorized as responders, and 21.4% (3 of 14) were categorized as responders in the placebo group.[25]

The authors reported that among participants with greater tic severity scores at baseline (measured as 1 standard deviation greater than average number of tics), participants in the azithromycin group were significantly more likely to have at least a 30% reduction in tic symptoms during the 4-week trial than control group participants (no statistics reported; $P < .05$).[25] If there is a treatment benefit to azithromycin, this suggests that it might have greater benefit for children with more severe tics.

Penicillin

Garvey and colleagues conducted a double-blind, balanced crossover study with 37 participants randomized to receive either penicillin prophylaxis or a placebo for 4 months.[31] After the first 4 months passed, the treatment assignment was reversed for 4 months; therefore, participants were followed for 8 months.[31] There was no wash out period between the reversal of treatment assignment.[31] We rated this study as having a high risk of bias. No statistically significant difference was reported between treatment groups for exacerbations of neuropsychiatric symptoms, with 38 exacerbations during the placebo phase and 35 exacerbations during the penicillin phase.[31] There were no clinically meaningful differences in depression or anxiety symptoms between the treatment phases.[31] Of the 27 parents who

provided global ratings of their child's behaviors, 22 reported an improvement of behavior during the penicillin phase; 18 of these parents correctly identified this as the active treatment phase when rating their child's behavior.[31] There were no statistically significant differences in neuropsychiatric symptoms between the penicillin and placebo phases, as measured by the Children's Yale-Brown Obsessive Compulsive Scale (P = .16) or the Yale Global Tic Severity Scale (P = .28).[31]

Azithromycin Versus Penicillin

Snider and colleagues conducted a double-blind RCT with 23 participants randomized to receive either azithromycin or penicillin prophylaxis for 12 months.[30] We rated this study as having a high risk of bias. The authors reported that both antibiotic therapies reduced the number of streptococcal infections during the study year compared to the year prior to the study (mean reduction of about 2 infections per year), with no significant difference between the 2 groups (mean for both groups, 0.1; SD for both groups, 0.3; P > .05).[30] Parent and child reports at baseline and the end of the study were reviewed and rated by the study authors to determine the presence and frequency of exacerbations of neuropsychiatric symptoms.[30] Both groups reported decreased neuropsychiatric exacerbations, but the participants who received penicillin reported significantly fewer exacerbations of neuropsychiatric symptoms (penicillin group mean, 0.5; penicillin group SD, 0.5; azithromycin group mean, 0.9; azithromycin group SD, 0.5; P < .01).[30]

Tonsillectomies and Adenoidectomies

We identified 2 comparative cohort studies that examined the association of tonsillectomies and adenoidectomies with change in symptoms for children diagnosed with PANDAS, and both compared children with PANDAS who had either or both of these surgeries (N = 88) to children with PANDAS who had received neither surgery (N = 140).[28,29] Both studies specifically named PANDAS as the diagnosis of focus.[28,29] We rated both of these studies as having a high risk of bias. Both systematic reviews agreed with the conclusions of the authors from these 2 studies that tonsillectomy and adenoidectomy do not appear to reduce neuropsychiatric symptom severity or exacerbations.[24,27] We did not identify any studies that tested the surgical interventions of tonsillectomies and adenoidectomies for the broader diagnosis of PANS.

In a prospective comparative cohort study including 120 participants, Pavone and colleagues reported that there was no significant difference in symptom remission rates between the surgery and nonsurgery groups (relative risk [RR], 1.39; 95% confidence interval [CI], 0.75 to 2.55; P = 0.29).[28] The authors also reported no significant difference in days to first symptom relapse (surgery group mean, 45.1; surgery group SD, 17.8; nonsurgery group mean, 39.3; nonsurgery group SD, 14.2; P = .09).[28]

Murphy and colleagues conducted a prospective comparative cohort study including 112 children who met the criteria for an OCD or tic diagnosis, and were divided into a group meeting the criteria for PANDAS and a group that did not meet criteria for PANDAS, according to a temporal relationship with a streptococcal infection.[29] The authors reported no significant difference in OCD or tic severity between the surgery and nonsurgery groups among children with or without a PANDAS diagnosis, as measured by the Children's Yale-Brown Obsessive Compulsive Scale (surgery group mean, 17.9; surgery group SD, 9.9; nonsurgery group mean, 18.7; nonsurgery group SD, 10.5; P = .71) or the Yale Global Tic Severity Scale (surgery group mean, 33.4; surgery group SD, 23.5; nonsurgery group mean, 33.6; nonsurgery group SD, 21.6; P = .97).[29] The authors also reported that there was no relationship between surgery status and

age of onset of OCD or tic symptoms (surgery group mean, 5.9 years; surgery group SD, 2.1 years; nonsurgery group mean, 6.5 years; nonsurgery group SD, 2.7 years; P = .32).[29] There was no statistically significant relationship between surgery status and duration of symptoms (surgery group mean, 2.5 years; surgery group SD, 2.1 years; nonsurgery group mean, 3.3 years; nonsurgery group SD, 2.5 years; *P* = .09).[29]

Both comparative cohort studies concluded that the surgical interventions had no effect on severity of symptoms or symptom progression.[28,29]

IVIG

We identified a single RCT that tested IVIG versus placebo,[11,26] and a single RCT that tested IVIG versus a placebo or plasma exchange.[32] Both RCTs enrolled children who met the diagnostic criteria for PANDAS and OCD.[26,32]

IVIG Versus Saline Placebo

Williams and colleagues randomized 35 children to receive IVIG or an intravenous saline placebo for 2 consecutive days at trial start.[26] All children were prescribed prophylactic antibiotics for the duration of the 6 months of this study, and penicillin was reported as the most commonly prescribed antibiotic (no number reported).[11] The investigators then offered the opportunity to children who had received the placebo to enter an open-label phase in which they received IVIG along with the children in the intervention group who were judged to be nonresponders to the treatment 6 weeks after the first infusion.[26] The investigators defined responding to treatment before the trial began as a 30% or greater decrease in symptoms as measured by the Children's Yale Brown Obsessive Compulsive Scale, or by a "much" or "very much" improved rating on the Clinical Global Impressions Improvement scale.[26] We rated the first phase of this trial as having a low risk of bias, and the 6- to 12-week open-label phase and the 24-week follow-up with any associated outcomes as having a high risk of bias.

At the conclusion of the 6-week blinded trial phase, there were no significant differences between the intervention and control groups for neuropsychiatric symptoms, as measured by changed in scores between baseline and 6-week follow-up on the Clinical Global Impressions Improvement scale and the Children's Yale Brown Obsessive Compulsive Scale.[26]

- Seven of the participants in the intervention group (38.9%; intervention group N = 18) were classified as responders to the treatment, meaning that they either demonstrated a 30% or greater decrease in symptoms as measured by the Children's Yale Brown Obsessive Compulsive Scale, or by a "much" or "very much" improved rating on the Clinical Global Impressions Improvement scale.[26] In the placebo group, 4 children were classified as having a significant decrease in symptoms (23.5%; placebo group N = 17).[26]
- There was not a significant difference in the number of children in each group who had a significant improvement in symptoms (*P* = .40).[26] The authors also reported that was no significant difference in the average change in symptoms between the intervention group and placebo group, as measured by the Clinical Global Impressions Improvement scale (*P* = .12) or the Children's Yale-Brown Obsessive Compulsive Scale (*P* = .44).[26]

During the nonblinded, open-label phase, 24 participants received IVIG.[26] This included 10 of 18 participants who were originally randomized to the intervention group and who were classified as

nonresponders at the end of the 6-week blinded phase; these participants therefore received doses of IVIG on 2 consecutive days twice: at baseline and 6 weeks after baseline.[26] Of the participants in the open-label phase, 17 (70.8%) were classified as responding to the treatment by 24 weeks.[26] However, there was no comparator group for this phase of the study and the authors did not report follow up at 24 weeks for the group of initial responders in the blinded phase of the RCT.

Leon and colleagues conducted additional follow-up interviews by telephone for all 35 original study participants for up to 5 years.[11] The authors reported that after the trial, 6 participants had tonsillectomy, 11 participants were diagnosed with new psychiatric conditions (i.e., attention-deficit/hyperactivity disorder, depression, anxiety, phobia, or chronic tic disorder), and 24 (68.6%) had experienced an exacerbation of symptoms.[11] Those exacerbations were treated with a variety of approaches, including additional IVIG, antibiotics, psychiatric medications, and cognitive behavioral therapy; treatments were often combined and used at the same time.[11]

IVIG Versus Plasma Exchange or Saline Placebo

Perlmutter and colleagues randomized 29 children who met the diagnostic criteria for PANDAS or OCD to receive IVIG, plasma exchange, or a saline placebo.[32] The authors compared symptoms at baseline to the same symptoms measured 1 month after treatment.[32] Participants in the plasma exchange group (N = 10) received 5 or 6 exchange transfusions, which required 85 to 121 minutes per transfusion.[32] Participants in the IVIG group (N = 9) received infusions during 2 days at the start of the trial; participants in the control group received a saline placebo (N = 10).[32] On average, participants in both the plasma exchange group and IVIG group reported significant reduction in symptoms from baseline to 1 month and between baseline and the 1-year follow-up, as measured by obsessive-compulsive symptoms, psychosocial functioning (i.e., anxiety, depression, and emotional lability), and global functioning.[32]

The authors reported comparisons of the change in symptoms for the 2 intervention groups to the change in symptoms for the saline placebo group between baseline and 1-month follow-up.[32] In comparison with the changes in scores in the saline placebo group (N = 10) 1 month after treatment, the IVIG group's (N = 9)[32]:

- scores for obsessions and compulsions decreased (45% vs. 3%; $P < .05$);
- scores for tics did not decrease significantly (19% vs. 12%; $P > .05$);
- sum of obsessions, compulsions, and tics decreased (45% vs. 6%; $P < .05$);
- scores for global impairment improved (26% vs. 1%; $P < .05$);
- scores for psychosocial functioning did not significantly improve (20% vs. 0%; $P > .05$); and
- scores for global severity improved significantly (26% vs. 1%; $P < .05$).

One year after treatment, all 9 participants who received IVIG were successfully followed and readministered the measures described above; 7 of 9 were judged to be "much" or "very much" improved in a global assessment of symptoms by their parents.[32] There were no comparisons made between the control group and the intravenous exchange group 1 year after baseline.[32]

The authors noted that there was not a statistically significant difference between the IVIG and plasma exchange groups for improvement in any symptoms at 1 month or 1 year after treatment.[32] They reported that scores for both active intervention groups remained significantly improved from baseline for obsessions and compulsions, psychosocial functioning, and global severity.[32] However, the

participants who received IVIG did not show a statistically significant improvement in tics at 1 year after baseline when compared to their own scores. [32]

Plasma Exchange

We identified a single RCT that tested plasma exchange versus placebo or IVIG for children who met the criteria for PANDAS and OCD; this study conducted by Perlmutter and colleagues is also described in the section that describes studies of IVIG.[32] We rated this study as having a high risk of bias. In comparison with the placebo group (N = 10) 1 month after treatment, the plasma exchange group's (N = 10)[32]:

- scores for obsessions and compulsions decreased (58% vs. 3%; *P* < .05);
- scores for tics decreased (49% vs. 12%; *P* <.05);
- sum of obsessions, compulsions, and tics decreased (54% vs. 6%; *P* < .05);
- scores for global impairment improved (36% vs. 1%; *P* < .05);
- scores for psychosocial functioning did not significantly improve (30% vs. 3%; *P* > .05); and
- scores for global severity improved (26% vs. 1%; *P* < .05).

One year after baseline, 8 of 10 participants who received plasma exchange were successfully followed and readministered the measures described above; 7 of 8 were judged to be "much" or "very much" improved in a global assessment of symptoms by their parents.[32] There were no comparisons made between the control group and the intravenous exchange group 1 year after treatment.[32]

The authors noted that there was not a statistically significant difference between the IVIG and plasma exchange groups for improvement in any symptoms at 1 month or 1 year after treatment.[32] They reported that scores for both active intervention groups remained significantly improved from baseline for obsessions and compulsions, psychosocial functioning, and global severity.[32] In addition to those measures, the participants who received plasama exchange also remained signifcantly improved on the measure of tics when compared to their scores at baseline.[32]

Harms

Sigra and colleagues' systematic review of any treatment for PANDAS, PANS, CANS or PITAND reported that adverse events reported in included studies were typically mild to moderate in nature, including nausea, vomiting, headache and stomachache.[24]

Antibiotics

Murphy and colleagues reported that some participants who received prophylactic azithromycin had loose stools (no number reported), and 9 out of 12 children who received azithromycin had heart rate irregularities.[25]

Other known adverse events associated with long-term antibiotic therapy include skin rashes, gastrointestinal disturbance, increased risk of childhood-onset chronic conditions (e.g., asthma, obesity, attention deficit hyperactivity disorder), and contribute to antibiotic resistance.[35,36] Use of azithromycin may also result in changes in the electrical activity of the heart that can lead to fatal irregular heart rhythm.[37]

Tonsillectomy and Adenoidectomy

Although the included studies did not report harms, adverse events associated with tonsillectomy and adenoidectomy may include hemorrhage, complications from anesthesia, and infection.[38,39]

IVIG

Williams and colleagues reported that a single participant appeared to have an allergic reaction to the IVIG infusion, but that the reaction resolved without complication. The authors also reported that several participants noted minor discomforts during treatment, such as joint pain, headache, stomach pain, tiredness, and anxiety.[26] Perlmutter and colleagues reported that 6 of 9 children receiving immunoglobulin infusions reported experiencing 1 or more of the following: nausea, vomiting, mild to moderately severe headache, and low grade fever.[32] All of these symptoms were resolved with hydration therapy, paracetamol, or diphenhydramine.[32] No long-term adverse events were reported, and none of the studies mentioned intending to collect information about long-term adverse events.[11,26,32]

The FDA categorized IVIG as a biologic agent, and 8 of the 12 products listed are approved for use in children under 18 years of age (ASCENIV, Flebogamma, Gammagard Liquid, Gammagard S/D, Gammaplex, Gamunex-C, PANZYGA, and Privigen).[40] None of the approved indications include PANDAS or PANS for these products, and the age range for approved use vary by product.[40] The package inserts for IVIG products include black box warnings for thrombosis, renal dysfunction, and acute renal failure.[40]

Plasma Exchange

Perlmutter and colleagues reported that 7 of 10 children who received plasma exchange reported pallor, dizziness, and nausea during the first exchange transfusions; 2 of these children also experienced vomiting.[32] Three additional children reported feeling anxious during the exchange transfusions.[32]

Known complications of plasma exchange include circuit clotting, low or high blood pressure, nausea, vomiting, itchy skin, hives, low calcium levels in the blood, venous access malfunction, infections, thrombosis, anaphylactic shock, and high fever.[41-44]

Ongoing Studies

We identified 3 ongoing studies that might provide upcoming information about diagnosis and treatment of PANDAS or PANS.[45-47]

A single double-blinded RCT plans to enroll 44 children diagnosed with PANDAS to test the effectiveness of taking naproxen sodium twice daily for 8 weeks on the severity of OCD symptoms, as measured by the second edition of the Children's Yale-Brown Obsessive-Compulsive Scale.[46] Enrolled participants will be between 6 and 15 years of age with first OCD symptom onset within 18 months prior to trial start date, and have symptoms that significantly interfere with daily life.[46] The estimated primary completion date is October 2022.[46]

A single RCT plans to enroll 92 children from 6 to 17 years of age with a confirmed diagnosis of PANS or PANDAS, and will randomize participants to receive intravenous immunoglobulin therapy or a placebo; the participant, care provider, investigator, and outcomes assessor will all be blinded.[47] The estimated study start date is August 30, 2021, and the estimated primary completion date is March 2023.[47] The

primary outcome measure will be the Children's Yale-Brown Obsessive Compulsive Scale at 9 weeks after treatment, which will be measured as a secondary outcome at week 18 along with Clinical Global Impression assessment, the Parent Obsessive-Compulsive Impact Scale, the Child Obsessive-Compulsive Impact Scale, the Swanson, Nolan, And Pelham Scale - Version IV (SNAP-IV; measures symptoms and behaviors that could impact child's behaviors at school), and the Parent Tic Questionnaire.[47]

This study will exclude children whose symptoms had first onset more than 6 months before the trial start date, children with current relapse of symptoms whose first onset was more than 12 months before the trial start date; who have a contraindication for intravenous immunoglobulin; who have severely restricted food intake, whose body mass index is 40 or greater; who have symptoms of autism or schizophrenia, bipolar disorder, or other psychotic disorder; who have serious or unstable mental illness; who have been treated with corticosteroids or began cognitive behavioral therapy within the 8 weeks prior to randomization; who have a history of rheumatic fever; who have had prior immunomodulatory treatment; who had taken antibiotics or antivirals for an acute infection within 1 week of randomization; who have severe liver disease; who have known hepatitis B, hepatitis C, or HIV infection; pregnant or lactating women or women unwilling to comply with contraception protocol; or who participated in another interventional trial within 3 months of randomization or during the course of this study.[47]

A single observational matched cohort study plans to enroll 500 children diagnosed with PANS who have not yet received any treatment, whose symptoms began within 1 month of enrollment date, and who are 18 years of age or younger.[45] The investigators plan to match these children with healthy children without a PANS diagnosis to examine immunologic, neurologic, genomic, and behavioral differences between the two cohorts.[45] This study began in 2013 and has an estimated primary completion date of March 2028.[45] Outcome measures include the following, measured ever every 2 to 4 weeks for up to 12 years: Global Impairment Score, Children's Yale-Brown Obsessive Compulsive Scale, Columbia Impairment Score, Caregiver Burden Inventory, and neurological findings (e.g., irregular movements).[45]

Evidence Summary

The origins and progression of symptoms associated with PANDAS and PANS are still being studied and documented; there are few published studies that tested whether antibiotic therapy, surgical interventions, IVIG, or plasma exchange might improve symptoms in children diagnosed with these conditions. It is also difficult to know how long any improvements in symptoms last after children receive the treatments we reviewed in this coverage guidance, because they often receive multiple treatments (simultaneously or 1 after another). Additionally, it is hard to distinguish whether patterns of exacerbation and resolution of symptoms can be directly attributed to infections and treatments, or if there is an underlying pattern of increase of symptoms followed by a decrease of symptoms that would occur without these treatments. It is not clear how long any treatment benefit might be sustained before another exacerbation, or whether any treatment alone or in combination with other treatments can prevent or shorten the length of exacerbations.

- We have very low confidence that prophylactic antibiotic therapy reduces exacerbations of neuropsychiatric symptoms. Risks for long-term antibiotic use include skin rashes, gastrointestinal disturbance, increased risk of childhood-onset chronic conditions (e.g., asthma, obesity, attention deficit hyperactivity disorder), and contribute to antibiotic resistance.[35,36]

- We did not identify any evidence testing antibiotics in response to current psychiatric exacerbation.
- We have low confidence that surgical interventions such as tonsillectomy and adenoidectomy do not reduce neuropsychiatric symptom exacerbations. Harms of tonsillectomy and adenoidectomy may include hemorrhage, complications from anesthesia, and infection.[38,39]
- We have very low confidence that IVIG decreases neuropsychiatric symptoms. It is not clear how long any treatment benefit might be sustained. There is an ongoing trial of IVIG for children with PANS or PANDAS that might have published results in 2023 or 2024. The package inserts for IVIG products include serious warnings for thrombosis, renal dysfunction, and acute renal failure.[48]
- We have very low confidence that plasma exchange decreases neuropsychiatric symptoms. It is not clear how long any treatment benefit might be sustained. Known complications of plasma exchange transfusions include high fever, blood clots, infection, minor or severe allergic reactions, and high or low blood pressure.[41-44]

The very low and low confidence we have in the findings above means that findings from new comparative studies that test treatments for PANDAS or PANS could change the recommendations that we make for which treatments should be covered for children diagnosed with PANDAS or PANS.

Clinical Practice Guidelines

We identified 6 publications that included recent guidelines for the diagnosis and treatment of individuals with PANDAS or PANS.[3,19-23] We rated all the guidelines as having poor methodological quality.

PANS/PANDAS Clinical Research Consortium

The most recent clinical guidelines written and published in the US for treating PANS was written by members of the PANS/PANDAS Research Consortium at workgroup meetings partially sponsored by the National Institutes of Health.[3] The workgroups reviewed literature, reviewed more than 1,000 cases of children diagnosed with PANDAS/PANS, and then prepared summaries to be reviewed by review panels of clinical experts who either worked with children suspected of having PANDAS/PANS or were experts in child psychiatry, pediatrics, infectious diseases, microbiology, neurology, neuroimmunology, immunology, and rheumatology.[3] Not all experts agreed on all treatments proposed in the guidelines, so the guideline committee opted to describe multiple treatment options beyond the treatments that had the highest consensus.[3] The authors of the committee summary stated that they expect the guidelines to be altered over time in response to the initiation and completion of new controlled clinical trials testing the efficacy of treatments.[3]

As an overview, the guidelines recommend a 3-pronged approach to treating PANS[3,19,20,22]:

- "treating the symptoms with psychoactive medications, psychotherapies (particularly cognitive behavioral therapy), and supportive interventions;
- removing the source of the inflammation with antimicrobial interventions; and
- treating disturbances of the immune system with immunomodulatory and/or anti-inflammatory therapies" (pp. 562; Swedo et al., 2017).

The guidelines presented the following 6 principles for the identification and treatment of PANS:

1. Establish that PANS is the correct ‘‘diagnosis of exclusion’’ by completing a comprehensive diagnostic evaluation.[23]
2. Provide symptomatic relief with psychiatric medications and behavioral interventions, prioritizing treatment of symptoms causing the greatest distress and interference.[22]
3. Treat underlying infections and consider use of therapeutic or prophylactic antibiotics.[20]
4. Treat symptoms resulting from neuroinflammation or postinfectious autoimmunity with anti-inflammatory or immunomodulatory therapies, chosen on the basis of symptom severity and disease trajectory.[19]
5. Evaluate effectiveness of the treatment regimen at frequent intervals, making modifications as warranted by improvement or worsening of symptoms.[3]
6. Treatment can be tapered downward or stopped when symptoms resolve. However, treatment may be necessary again at some point in the future, given the relapsing–remitting nature of PANS symptoms.[3]

Clinical Guidance About PANS from Nordic Countries

The Nordic Pediatric Immunopsychiatry group published guidance for diagnosis and management of suspected PANS in 2021, and included pediatric neurologists, child psychologists, and child psychiatrists from Denmark, Norway, Sweden and Great Britain.[21] The authors intended this guidance to propose a standard set of diagnostic criteria for PANDAS and PANS, and to propose a standard process for diagnostic evaluation.[21]

The authors agreed to adopt the clinical criteria proposed by Chang and colleagues for PANS that was published in 2015[21,23]:

1. Abrupt, dramatic onset (culmination within 72 hours) of OCD or severely restricted food intake.
2. Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories (see reference for full description):
    - Anxiety,
    - Emotional liability and/or depression,
    - Irritability, aggression and/or severely oppositional behaviors,
    - Behavioral (developmental) regression,
    - Deterioration in school performance,
    - Sensory or motor abnormalities and
    - Somatic signs and symptoms, including sleep disturbances, enuresis or increased urinary frequency.
3. Symptoms are not better explained by a known medical disorder, such as Sydenham's chorea, systemic lupus erythematosus, Tourette disorder or others.

The authors agreed to adopt Swedo and colleagues’ diagnostic criteria for PANDAS that were published in 1998[21,49]:

1. Presence of Obsessive Compulsive Disorder and/or a tic disorder: The patient must meet lifetime diagnostic criteria (DSM- III- R or DSM- IV) for Obsessive Compulsive Disorder or a tic disorder.
2. Pediatric onset: Symptoms of the disorder first become evident between 3 years of age and the beginning of puberty.

3. Episodic course of symptom severity: Clinical course is characterized by the abrupt onset of symptoms or by dramatic symptom exacerbations. Symptoms usually decrease significantly between episodes and occasionally resolve completely between exacerbations.
4. Association with group A Beta- hemolytic streptococcus infection: Symptom exacerbations must be temporally related to group A Beta- hemolytic streptococcus infection, that is associated with positive throat culture and/or significantly elevated anti- group A Beta- hemolytic streptococcus antibody titers.
5. Association with neurological abnormalities: During symptom exacerbations, patients will have abnormal results on neurological examination. Motoric hyperactivity and adventitious movements (including choreiform movements or tics) are particularly common.

In addition to the criteria listed above, the authors further proposed a definition of severe symptoms and required that the child meet at least 1 major criteria and 1 minor criteria.[21] The major criteria included: total Children's Yale- Brown Obsessive Compulsive Scale (CY- BOCS) score ≥24; reduced intake of food or fluid, leading to less urine production (less than three urinations daily) or weight loss (more than 10%); and severe tics (Yale Global Tic Severity Scale (YGTSS) total tic severity score ≥40 but <50).[21] Minor criteria included being absent from school at least 50% of class days during 1 month, and inability to participate in leisure activities or loss of social contact.[21]

The authors then proposed a standard clinical work-up, which is described in Table 4.

Table 4. Nordic Pediatric Immunopsychiatry Group's Proposed Clinical Work-Up for PANS

Examination	Instrument or Analysis	Description
Psychiatric		
General	Achenbach System of Empirically Based Assessment (ASEBA),19 Mini international neuropsychiatric interview (M.I.N.I.- KID) or equivalent	General assessment of psychiatric conditions
	Child and Adolescent Trauma Screen (CATS)	Trauma screening
	Children's Global Assessment Scale (C- GAS)	Assessment of general functioning
	Clinical Global Impression- Severity Scale (CGI- S)	Clinician- rated severity of the patient's illness at time of assessment
	Pediatric Quality of Life Inventory (PedsQL)	Assessment of quality of life
	Optional: Work and Social Adjustment Scale (WSAS) 2	Measure of impaired functioning
	Optional: KIDSCREEN	Assessment of subjective health and well- being
Symptom-specific	Children's Yale- Brown Obsessive Compulsive Scale (CY- BOCS)	OCD inventory
	The Screen for Child Anxiety Related Disorders (SCARED)	Screening for child anxiety related disorders
	Yale Global Tic Severity Scale (YGTSS)	Tics inventory

Examination	Instrument or Analysis	Description
	Kiddie Schedule for Affective Disorders and Schizophrenia (Kiddie- SADS)	Interview screening for psychiatric diagnoses
	ADHD rating scale (ADHD- RS)	Questionnaire related to inattention, hyperactivity and impulsivity
	Behavior Rating Inventory of Executive Function (BRIEF)	Behavior Rating Inventory of Executive Function
Infectious		
General	Throat: bacterial culture	No description
	Blood: complete blood cell count with differential count, antistreptolysin- O and anti-deoxyribonuclease B antibodies	No description
Symptom-specific	Throat: Mycoplasma Polymerase Chain Reaction (PCR)	No description
	Nasopharynx: Aspirate PCR panel	Common viral airway infections such as influenza virus and enterovirus
	Urine analysis and culture	No description
Extended workup	Cerebrospinal fluid cell count, protein, glucose, lactate; Epstein- Barr-virus/cytomegalovirus/varicella zoster virus/ herpes simplex virus/Mycoplasma/ enterovirus/influenza virus immunoglobulin G and immunoglobulin M +Polymerase Chain Reaction (PCR); Borrelia burgdorferi immunoglobulin G and immunoglobulin M (paired with serum)	No description
Immunological		
General	Blood: erythrocyte sedimentation rate (ESR), antiphospholipid antibodies (anticardiolipin and beta2 glycoprotein 1 antibodies), antinuclear antibodies (antidsDNA, ANA IIF, anti- ENA screen: Anti- SSA, anti- SSA, anti- SSB, anti- Sm, anti-Scl–70, anti- Jo1, anti- Centromer B (- CENP- B) and anti- U1- RNP), immunoglobulins subclasses, tissue- transglutaminase IgA and deamined gliadinpeptide IgG (Celiac disease), neuronal antibodies, Myelin oligodendrocyte glycoprotein (MOG) antibodies, antithyroperoxidase (TPO), thyroid stimulating hormone (TSH) receptor antibodies, TSH, T3 and free T4, complement C3 and C4, angiotensin- converting enzyme (ACE), Vitamin- D, Vitamin B12, ferritin, cupper, ceruloplasmin, cytokines	No description

Examination	Instrument or Analysis	Description
Extended work-up	Cerebrospinal fluid Lumbar opening pressure, neuronal antibodies (standard panel), immunoglobulin G, index and electrophoresis for oligoclonal bands (paired with serum), and cytokines	No description
Toxicological		
Symptom-specific	Drug screening	No description
Metabolic		
Symptom-specific	Urine metabolic screening	No description
Radiological		
Extended work-up	Cerebral MRI including contrast: structural, diffusion and FLAIR sequences	No description
Neuropsychological		
Extended work-up	Standard or sleep electroencephalogram	No description

Note. This table is reproduced from Tables 3 and 4 on pages 4 and 5 of the Nordic Pediatric Immunopsychiatry group's published guidance for diagnosis and management of suspected PANS.[18,21] *Abbreviations. FLAIR: fluid attenuated inversion recovery; MRI: magnetic resonance imaging; OCD: obsessive-compulsive disorder; PANS: pediatric acute-onset neuropsychiatric syndrome.*

The authors recommended that verified or strongly suspected bacterial infections should be treated at the discretion of the provider for a maximum of 14 days; however, they do not recommend prophylactic antibiotic therapy.[21] They further recommended that any other treatment occur within ongoing clinical research or under the guidance of centers that specialize in the care of children with suspected PANS.[21] Such treatments for children with severe symptoms might begin with oral non-steroidal anti-inflammatory drugs, proceed to steroids if ineffective, and finally proceed to intravenous immunoglobulin.[21] The authors state that plasma exchange, and cytostatic and immunomodulatory drugs are only clinically indicated when a child has been diagnosed with autoimmune encephalitis.[21]

Policy Landscape

Payer Coverage Policies

We did not identify coverage policies for Washington State's Medicaid program or national or local coverage determinations for Medicare related to PANDAS or PANS.

We identified coverage policies related to PANDAS and PANS from 2 private payers (Aetna and Cigna), but we did not identify coverage policies related to PANDAS or PANS for BlueCross BlueShield or for Moda.

Private Payers

Aetna considers parenteral immunoglobulins, rituximab, and plasmapheresis to be investigational or experimental for PANDAS and autoimmune encephalitis.[50-52]

Cigna considers plasmapheresis, immune globulin, and rituximab to be investigational or experimental for PANDAS and PANS in policies last updated in 2021.[53-55] These coverage policies consider plasmapheresis to be medically necessary as a primary therapy for autoimmune encephalitis characterized by the presence of the n-methyl D-aspartate receptor antibody.[55]

Recommendations from Others

We did not identify policy statements or recommendations for PANDAS or PANS from the American Neurology Association, the American Academy of Pediatrics, the American Association of Immunologists, the Infectious Diseases Society of America, or the American Psychiatric Association.

PANDAS Physician Network

The PANDAS Physician Network maintains a website with tools such as flowcharts for diagnosing and treating PANS and PANDAS, and for classifying symptoms into mild, moderate, or severe cases.[56] The authors recommend that children with moderate or severe symptoms be treated by an experienced team of multidisciplinary providers or a PANS/PANDAS specialist.[56] To summarize the proposed elements of the treatment guidelines (please note that this list is simplified)[56]:

1. Start with 14 days of antibiotic therapy, and consider the appropriateness of prophylactic antibiotic therapy; lengthen therapy if infection is not resolved or symptoms persist.
2. Consider 5 to 7 days of non-steroidal anti-inflammatory drugs.
3. Ensure family access to cognitive behavioral therapy, and parenting management techniques.
4. Consider steroid course if no improvement from first 3 steps.
5. Escalate to intravenous immunoglobulin therapy if first 4 steps have not resolved symptoms.
6. If symptoms do not resolve, consider a second course of intravenous immunoglobulin or evaluate the need for plasma exchange, and prescribe prophylactic antibiotic therapy.

References

1. Garg D, Mohammad SS, Sharma S. Autoimmune encephalitis in children: an update. *Indian Pediatr.* 2020;57(7):662-670.
2. Dop D, Marcu IR, Padureanu R, Niculescu CE, Padureanu V. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (Review). *Experimental Ther.* 2021;21(1):94. doi: https://dx.doi.org/10.3892/etm.2020.9526.
3. Swedo SE, Frankovich J, Murphy TK. Overview of treatment of pediatric acute-onset neuropsychiatric syndrome. *J Child Adolesc Psychopharmacol.* 2017;27(7):562-565. doi: 10.1089/cap.2017.0042.
4. Gamucci A, Uccella S, Sciarretta L, et al. PANDAS and PANS: clinical, neuropsychological, and biological characterization of a monocentric series of patients and proposal for a diagnostic protocol. *J Child Adolesc Psychopharmacol.* 2019;29(4):305-312. doi: 10.1089/cap.2018.0087.
5. Orlovska S, Vestergaard CH, Bech BH, Nordentoft M, Vestergaard M, Benros ME. Association of Streptococcal Throat Infection With Mental Disorders: Testing Key Aspects of the PANDAS Hypothesis in a Nationwide Study. *JAMA psychiatry.* 2017;74(7):740-746. doi: https://dx.doi.org/10.1001/jamapsychiatry.2017.0995.
6. Wang HC, Lau CI, Lin CC, Chang A, Kao CH. Group A Streptococcal Infections Are Associated With Increased Risk of Pediatric Neuropsychiatric Disorders: A Taiwanese Population-Based Cohort Study. *J Clin Psychiatry.* 2016;77(7):e848-854. doi: 10.4088/JCP.14m09728.
7. Hyman SE. PANDAS: too narrow a view of the neuroimmune landscape. *Am J Psychiatry.* 2021;178(1):5-7. doi: https://dx.doi.org/10.1176/appi.ajp.2020.20111598.
8. Wald ER. A pediatric infectious disease perspective on pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection and pediatric acute-onset neuropsychiatric syndrome. *Pediatr Infect Dis J.* 2019;38(7):706-709. doi: 10.1097/INF.0000000000002295.
9. Baj J, Sitarz E, Forma A, Wroblewska K, Karakula-Juchnowicz H. Alterations in the nervous system and gut microbiota after beta-hemolytic streptococcus group a infection-characteristics and diagnostic criteria of pandas recognition. *International Journal of Molecular Sciences.* 2020;21(4):21. doi: https://dx.doi.org/10.3390/ijms21041476.
10. Zibordi F, Zorzi G, Carecchio M, Nardocci N. CANS: childhood acute neuropsychiatric syndromes. *Europ J Paediatr Neurol.* 2018;22(2):316-320. doi: https://dx.doi.org/10.1016/j.ejpn.2018.01.011.
11. Leon J, Hommer R, Grant P, et al. Longitudinal outcomes of children with pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS). *Eur Child Adolesc Psychiatry.* 2018;27(5):637-643. doi: 10.1007/s00787-017-1077-9.
12. Wilbur C, Bitnun A, Kronenberg S, et al. PANDAS/PANS in childhood: controversies and evidence. *Paediatr child health.* 2019;24(2):85-91. doi: https://dx.doi.org/10.1093/pch/pxy145.
13. Geller D, March JS, Walter J, et al. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry.* 2012;51(1):98-113. doi: 10.1016/j.jaac.2011.09.019.
14. Abboud H, Probasco JC, Irani S, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry.* 2021;92(7):757-768. doi: https://dx.doi.org/10.1136/jnnp-2020-325300.
15. Cellucci T, Van Mater H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm.* 2020;7(2). doi: 10.1212/NXI.0000000000000663.

16. Mooneyham GC, Ferrafiat V, Stolte E, Fuchs DC, Cohen D. Developing consensus in the assessment and treatment pathways for autoimmune encephalitis in child and adolescent psychiatry. *Front Psychiatry.* 2021;12:638901. doi: 10.3389/fpsyt.2021.638901.
17. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet neurol.* 2016;15(4):391-404. doi: https://dx.doi.org/10.1016/S1474-4422(15)00401-9.
18. Dubey D, Pittock S, Kelly C, et al. The incidence and prevalence of autoimmune encephalitis and a comparison to infectious encephalitis: a population-based study. *Neurology.* 2018;90.
19. Frankovich J, Swedo S, Murphy T, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part ii—use of immunomodulatory therapies. *J Child Adolesc Psychopharmacol.* 2017;27(7):574-593. doi: 10.1089/cap.2016.0148.
20. Cooperstock MS, Swedo SE, Pasternack MS, Murphy TK, for the PPC. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part iii—treatment and prevention of infections. *J Child Adolesc Psychopharmacol.* 2017;27(7):594-606. doi: 10.1089/cap.2016.0151.
21. Pfeiffer HCV, Wickstrom R, Skov L, et al. Clinical guidance for diagnosis and management of suspected Pediatric Acute-onset Neuropsychiatric Syndrome in the Nordic countries. *Acta Paediatr.* 2021;13:13. doi: 10.1111/apa.15875.
22. Thienemann M, Murphy T, Leckman J, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part i-psychiatric and behavioral interventions. *J Child Adolesc Psychopharmacol.* 2017;27(7):566-573. doi: 10.1089/cap.2016.0145.
23. Chang K, Frankovich J, Cooperstock M, et al. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. *J Child Adolesc Psychopharmacol.* 2015;25(1):3-13. doi: 10.1089/cap.2014.0084.
24. Sigra S, Hesselmark E, Bejerot S. Treatment of PANDAS and PANS: a systematic review. *Neurosci Biobehav Rev.* 2018;86:51-65. doi: 10.1016/j.neubiorev.2018.01.001.
25. Murphy TK, Brennan EM, Johnco C, et al. A double-blind randomized placebo-controlled pilot study of azithromycin in youth with acute-onset obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol.* 2017;27(7):640-651. doi: 10.1089/cap.2016.0190.
26. Williams KA, Swedo SE, Farmer CA, et al. Randomized, controlled trial of intravenous immunoglobulin for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *J Am Acad Child Adolesc Psychiatry.* 2016;55(10):860-867 e862. doi: 10.1016/j.jaac.2016.06.017.
27. Farhood Z, Ong AA, Discolo CM. PANDAS: a systematic review of treatment options. *Int J Pediatr Otorhinolaryngol.* 2016;89:149-153. doi: 10.1016/j.ijporl.2016.08.008.
28. Pavone P, Rapisarda V, Serra A, et al. Pediatric autoimmune neuropsychiatric disorder associated with group a streptococcal infection: the role of surgical treatment. *Int J Immunopathol Pharmacol.* 2014;27(3):371-378. doi: 10.1177/039463201402700307.
29. Murphy TK, Lewin AB, Parker-Athill EC, Storch EA, Mutch PJ. Tonsillectomies and adenoidectomies do not prevent the onset of pediatric autoimmune neuropsychiatric disorder associated with group A streptococcus. *Pediatr Infect Dis J.* 2013;32(8):834-838. doi: 10.1097/INF.0b013e31829062e2.
30. Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biol Psychiatry.* 2005;57(7):788-792. doi: 10.1016/j.biopsych.2004.12.035.
31. Garvey MA, Perlmutter SJ, Allen AJ, et al. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. *Biol Psychiatry.* 1999;45(12):1564-1571. doi: 10.1016/s0006-3223(99)00020-7.

32. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet.* 1999;354(9185):1153-1158. doi: 10.1016/S0140-6736(98)12297-3.
33. Leibold C, Thienemann M, Farhadian B, Willett T, Frankovich J. Psychometric properties of the pediatric acute-onset neuropsychiatric syndrome global impairment score in children and adolescents with pediatric acute-onset neuropsychiatric syndrome. *Journal of Child & Adolescent Psychopharmacology.* 2019;29(1):41-49. doi: https://dx.doi.org/10.1089/cap.2018.0029.
34. Nielsen MO, Kohler-Forsberg O, Hjorthoj C, Benros ME, Nordentoft M, Orlovska-Waast S. Streptococcal infections and exacerbations in PANDAS: a systematic review and meta-analysis. *Pediatr Infect Dis J.* 2019;38(2):189-194. doi: https://dx.doi.org/10.1097/INF.0000000000002218.
35. Ahmed H, Davies F, Francis N, Farewell D, Butler C, Paranjothy S. Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials. *BMJ Open.* 2017;7(5):e015233. doi: 10.1136/bmjopen-2016-015233.
36. Aversa Z, Atkinson EJ, Schafer MJ, et al. Association of infant antibiotic exposure with childhood health outcomes. *Mayo Clin Proc.* 2021;96(1):66-77. doi: 10.1016/j.mayocp.2020.07.019.
37. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med.* 2012;366(20):1881-1890. doi: 10.1056/NEJMoa1003833.
38. Erwin DZ, Heichel PD, Wright LB, et al. Post-tonsillectomy hemorrhage control with nebulized tranexamic acid: A retrospective cohort study. *Int J Pediatr Otorhinolaryngol.* 2021;147:110802. doi: 10.1016/j.ijporl.2021.110802.
39. Dhaduk N, Rodgers A, Govindan A, Kalyoussef E. Post-tonsillectomy bleeding: A national perspective. *Ann Otol Rhinol Laryngol.* 2021;130(8):941-947. doi: 10.1177/0003489420987438.
40. US Food and Drug Administration. Immune globulins. 2020; https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulins. Accessed August 16, 2021.
41. Sik G, Demirbuga A, Annayev A, Akcay A, Citak A, Ozturk G. Therapeutic plasma exchange in pediatric intensive care: Indications, results and complications. *Ther Apher Dial.* 2020;24(2):221-229. doi: 10.1111/1744-9987.13474.
42. Veerachit OLT, Siritho S, Prayoonwiwat N. Retrospective study of the adverse events of the treatment for an acute attack of neuromyelitis optica spectrum disorder. *Ther Apher Dial.* 2020;24(4):453-460. doi: 10.1111/1744-9987.13456.
43. Abe Y, Kusaoi M, Tada K, Yamaji K, Tamura N. Successful treatment of anti-MDA5 antibody-positive refractory interstitial lung disease with plasma exchange therapy. *Rheumatology (Oxford).* 2020;59(4):767-771. doi: 10.1093/rheumatology/kez357.
44. Lu J, Zhang L, Xia C, Tao Y. Complications of therapeutic plasma exchange: A retrospective study of 1201 procedures in 435 children. *Medicine (Baltimore).* 2019;98(50):e18308. doi: 10.1097/MD.0000000000018308.
45. Clinical Trials Registry. Neurobiologic, immunologic, and rheumatologic markers in youth with PANS. 2016; https://clinicaltrials.gov/ct2/show/NCT02889016. Accessed August 4, 2021.
46. Clinical Trials Registry. Trial of naproxen sodium for the treatment of OCD in children with PANDAS. 2020; https://www.clinicaltrials.gov/ct2/show/NCT04015596.
47. Clinical Trials Registry. Study to compare the effect of panzyga versus placebo in patients with pediatric acute-onset neuropsychiatric syndrome. 2021; https://clinicaltrials.gov/ct2/show/NCT04508530. Accessed August 16, 2021.
48. Octapharma. PANZYGA package insert. 2021; https://www.fda.gov/media/115397/download. Accessed August 16, 2021.

49. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry.* 1998;155(2):264-271.
50. Aetna. Medical clinical policy bulletins: parenteral immunoglobulins. 2021; https://www.aetna.com/cpb/medical/data/200_299/0206.html. Accessed July 21, 2021.
51. Aetna. Medical clinical policy bulletins: Rituximab. 2021; https://www.aetna.com/cpb/medical/data/300_399/0314.html. Accessed July 21, 2021.
52. Aetna. Medical clinical policy bulletins: plasmapheresis plasma exchange therapeutic apheresis. 2021; https://www.aetna.com/cpb/medical/data/200_299/0285.html. Accessed July 21, 2021.
53. Cigna. Drug and biologic coverage policy: immune globulin. 2021; https://static.cigna.com/assets/chcp/pdf/coveragePolicies/pharmacy/ph_5026_coveragepositioncriteria_Immune_Globulin_Intravenous_IGIV.pdf. Accessed July 21, 2021.
54. Cigna. Drug and biologic coverage policy: rituximab for non-oncology indications. 2021; https://static.cigna.com/assets/chcp/pdf/coveragePolicies/pharmacy/ph_5108_coveragepositioncriteria_rituximab_rituxan.pdf. Accessed July 21, 2021.
55. Cigna. Medical coverage policy: plasmapheresis. 2021; https://static.cigna.com/assets/chcp/pdf/coveragePolicies/medical/mm_0153_coveragepositioncriteria_plasmapheresis.pdf. Accessed July 21, 2021.
56. PANDAS Physician Network. Clinician resources for PANS/PANDAS. 2021; https://www.pandasppn.org/. Accessed August 16, 2021.

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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 Antibiotics							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
3	RCTs	Moderate to High	Not serious	Not serious	Serious	Small sample sizes, short follow-up	Very Low ●○○○
Hospitalizations							
Harms							
1	RCT	High	Unable to rate	Not serious	Serious	Small sample sizes, short follow-up	Very Low ●○○○
Function or Quality of Life for Patient							
0							
Function or Quality of Life for Parent							
0							

Abbreviation. RCT: randomized controlled trial.

Quality Assessment (Confidence in Estimate of Effect) for Tonsillectomy or Adenoidectomy							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
2	Comparative cohort	High	Not serious	Serious	Not serious	None	Low ●●○○
Hospitalizations							
0							
Harms							
0							
Function or Quality of Life for Patient							
0							
Function or Quality of Life for Parent							
0							

Quality Assessment (Confidence in Estimate of Effect) for IVIG							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
2	RCTs	High	Not serious	Not serious	Not Serious	Very small samples, incomplete reporting	Very low ●○○○
Hospitalizations							
Harms							
2	RCTs	High	Not serious	Not Serious	Not Serious	Very small samples, incomplete reporting	Very low ●○○○
Function or Quality of Life for Patient							
Function or Quality of Life for Parent							

Abbreviation. RCT: randomized controlled trial.

Quality Assessment (Confidence in Estimate of Effect) for Plasma Exchange							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Level of Confidence**
Change in Psychiatric Symptoms							
1	RCT	High	Not serious	Not serious	Not Serious	Very small sample, incomplete reporting	Very low ●○○○
Hospitalizations							
Harms							
1	RCT	High	Not serious	Not Serious	Not Serious	Very small sample, incomplete reporting	Very low ●○○○
Function or Quality of Life for Patient							
Function or Quality of Life for Parent							

Abbreviation. RCT: randomized controlled trial.

Appendix C. Methods

Scope Statement

Populations

Children diagnosed with:

- Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS),
- Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

Population scoping notes: Patients without either of the above conditions are excluded

Interventions

Therapeutic plasma exchange; intravenous immunoglobulin (IVIG); antibiotics; tonsillectomy and/or adenoidectomy

Intervention exclusions: Behavioral interventions, selective serotonin reuptake inhibitors, nonsteroidal inflammatory drugs

Comparators

Usual care or other interventions

Outcomes

Critical: Change in psychiatric symptom scores (e.g., Children's Yale-Brown Obsessive Compulsive Scale, Clinical Global Impressions-Improvement, Yale Global Tic Severity scale); Hospitalizations, including institutionalization or emergency visits

Important: Harms; standardized measures of function or quality of life for patients and caregivers

Considered but not selected for the GRADE table: None

Key Questions

KQ1: What is the effectiveness of treatments for PANDAS/PANS as compared to the named comparators?

KQ2: Does the comparative effectiveness of treatments for PANDAS/PANS differ by:

a. Patient characteristics
b. Condition characteristics
c. Intervention
d. Provider characteristics (e.g., Center of Excellence)

KQ3: What are the harms of interventions for PANDAS/PANS in children?

Contextual Questions

CQ1: What are the evidence-based criteria available for the diagnosis of PANDAS/PANS, and what are the diagnostic accuracy of available criteria or tests?

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 2015.

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

An Ovid MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search terms *paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection, pediatric acute-onset neuropsychiatric syndrome, pediatric infection triggered autoimmune neuropsychiatric disorder, childhood acute onset neuropsychiatric syndrome, paediatric acute-onset neuropsychiatric syndrome, autoimmune encephalitis*. The search was limited to publications in English published since 2012. In addition, a MEDLINE® search was conducted for randomized controlled trials and comparative cohort studies.

Searches for clinical practice guidelines were limited to those published since 2015. 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 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, comparative cohort studies, or clinical practice guidelines.

Appendix D. Applicable Codes

Coding note: PANS does not have ICD-10-CM index entries; PANDAS is indexed to D89.89.

CODES	DESCRIPTION
ICD-10-CM Codes	
D89.89	Other specified disorders involving the immune mechanism, not elsewhere classified
D89.9	Disorder involving the immune mechanism, unspecified
G04.81	Other encephalitis and encephalomyelitis
CPT Codes	
Behavioral therapy	
90832	Psychotherapy, 30 minutes with patient
90833	Psychotherapy, 30 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90834	Psychotherapy, 45 minutes with patient
90836	Psychotherapy, 45 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90837	Psychotherapy, 60 minutes with patient
90838	Psychotherapy, 60 minutes with patient when performed with an evaluation and management service (List separately in addition to the code for primary procedure)
90839	Psychotherapy for crisis; first 60 minutes
Intravenous immunoglobulin therapy	
90283	Immune globulin (IVIG), human, for intravenous use
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
99601	Home infusion/specialty drug administration, per visit (up to 2 hours)
Plasma exchange	
36514	Therapeutic apheresis; for plasma pheresis
Tonsillectomy and adenoidectomy	
42820	Tonsillectomy and adenoidectomy; younger than age 12
42821	Tonsillectomy and adenoidectomy; age 12 or over
42825	Tonsillectomy, primary or secondary, younger than age 12
42826	Tonsillectomy, primary or secondary, age 12 or over
42830	Adenoidectomy, primary; younger than age 12
42831	Adenoidectomy, primary; age 12 or over
42835	Adenoidectomy, secondary; younger than age 12
42836	Adenoidectomy, secondary; age 12 or over
HCPCS Level II Codes	
Intravenous immunoglobulin therapy	
J1459	Injection, immune globulin (privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1555	Injection, immune globulin (cuvitru), 100 mg
J1556	Injection, immune globulin (bivigam), 500 mg
J1557	Injection, immune globulin, (gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1558	Injection, immune globulin (xembify), 100 mg
J1559	Injection, immune globulin (hizentra), 100 mg
J1561	Injection, immune globulin, (gamunex-c/gammaked), non-lyophilized (e.g., liquid), 500 mg
J1562	Injection, immune globulin (vivaglobin), 100 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg

J1568	Injection, immune globulin, (octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (gammagard liquid), non-lyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (flebogamma/flebogamma dif), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg
S9338	Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
SSRIs, NSAIDs, and corticosteroids	
J1094	Injection, dexamethasone acetate, 1 mg
J1100	Injection, dexamethasone sodium phosphate, 1 mg
J0702	Injection, betamethasone acetate 3 mg and betamethasone sodium phosphate 3 mg
J1700	Injection, hydrocortisone acetate, up to 25 mg
J1710	Injection, hydrocortisone sodium phosphate, up to 50 mg
J1720	Injection, hydrocortisone sodium succinate, up to 100 mg
J2650	Injection, prednisolone acetate, up to 1 ml
J7510	Prednisolone oral, per 5 mg
J7512	Prednisone, immediate release or delayed release, oral, 1 mg
J8540	Dexamethasone, oral, 0.25 mg
J7624	Betamethasone, inhalation solution, compounded product, administered through DME, unit dose form, per mg
J1130	Injection, diclofenac sodium, 0.5 mg

Note. Inclusion on this list does not guarantee coverage.