Syphilis Testing, new and old, rapid and not so rapid

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The National Plan to Eliminate Syphilis from the United States

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SYPHILIS ELIMINATION
History in the Making
Rates of early syphilis by sex and year—Oregon, 2000–2013

*Preliminary data

Year

Men 19.6*
Overall
Women
Attribution:

Many slides adapted from...

You’ll leave knowing something about…

• “Treponemal” and “non-treponemal” tests for syphilis

• “Traditional” and “reverse syphilis” screening

• Rapid diagnostic tests for syphilis
Outline

• Syphilis
  • Causative agent
  • Key facts about syphilis
• Laboratory tests for diagnosis of syphilis
  • Non-treponemal tests
  • Treponemal tests
• Traditional algorithm for syphilis screening
• Reverse algorithm for syphilis screening
• Interpretation and follow-up
• New rapid diagnostic test for syphilis
Treponema pallidum

- Bacterium
  - “Spirochete”
  - Motile (“corkscrew”)
  - Can’t culture in lab
- Transmission
  - Sexual
  - Trans-placental
  - Percutaneous following contact with infectious lesions
  - Bloodborn
    - Extremely rare
- **Spirochaete**
  - **Spirochaetaceae**
    - **Treponema**
      - *pallidum* (syphilis, yaws), *carateum* (pinta), *denticola*
    - **Borrelia**
      - *burgdorferii/afzelii* (lyme), *hermsii/duttoni/parkeri* (tick-borne relapsing fever)
  - **Leptospiraceae**
    - **Leptospira**
      - *interrogans* (leptospiroisis)
  - **Spirillaceae**
    - **Spirillium**
      - *minus* (rat-bite fever)
Syphilis—a few key concepts

- Highly infectious
  - Infectious Dose ~57 organisms
  - Attack rate 1/3

- Incubation – 21 days (median)

- 3 clinical stages
  - Primary:
    - Painless sore (chancre) at inoculation site
  - Secondary:
    - Rash, fever, lymphadenopathy, malaise
  - Symptomatic Late/Tertiary:
    - Dementia, tabes dorsalis, cardiovascular disease
Lab Diagnosis—uncommon methods
Lab Diagnosis—common methods

- Serology (tests for antibodies produced upon syphilis infection)
  - Mainstay for syphilis testing
  - Two kinds
    - Non-treponemal
    - Treponemal
Non-treponemal serologic tests

- *T. pallidum* causes cells to release cardiolipin
- Reagin = antibody to cardiolipin
- Non-treponemal tests measure levels of reagin:
  - Rapid Plasma Reagin (RPR)
  - Venereal Disease Research Laboratory (VDRL)
  - Toluidine red unheated serum test (TRUST)
- RPR and VDRL are agglutination assays
- Reagent is carbon particles + cardiolipin
- No reagin present, no agglutination
Reagin present...agglutination of the charcoal
Non-Treponemal Test Advantages

- Rapid turnaround time – minutes
- Inexpensive
- No specialized instrumentation required
- Usually revert to negative following therapy
  - Can be used to monitor response to therapy
Non-Treponemal Test Limitations

- Results are subjective
  - Intra- and Inter-laboratory variability
- False positives (lower specificity)
  - lupus, pregnancy, viral hepatitis
- Might be negative (lower sensitivity) in very early syphilis and late syphilis even if never treated
- Low “throughput” = can’t be “batched”
Treponemal serologic tests

- Syphilis ⇒ Antibodies against *T. pallidum*
- Tests detect ‘treponeme specific’ antibodies
  - Fluorescent treponemal antibody absorption test (FTA-ABS)
  - Microhemagglutination assay (MHA)
  - *T. pallidum* particle agglutination (TP-PA)
  - Enzyme Immunoassay (EIA)
  - Immunochromatographic strips (ICS...point of care tests)
Treponemal Test Advantages

- Few false positives (high specificity)
- Fewer false negatives (more sensitive) especially during early and late syphilis
- Objective result interpretation
- Automation option
- High throughput = “batchable”
- High reproducibility/precision
Treponemal Test Limitations

- Remain positive for life
  - Cannot be used to monitor response to therapy
- Conventional (older) versions (e.g. FTA-ABS, TP-PA)
  - Subjective interpretation like non-treponemal tests
- Newer versions
  - Expensive instrumentation
  - Higher cost/test
Syphilis Screening Algorithms: Traditional versus ‘Reverse’
Traditional Algorithm

Non-treponemal test (e.g., RPR)

- Reactive
- Treponemal test (e.g., FTA)
  - Reactive
    - Syphilis
  - Non-reactive
    - Not syphilis

- Non-reactive
  - Not syphilis
Traditional algorithm pros and cons

• Pros
  • Familiar
  • One confirmation test, typically done reflexively, leads to clear result
  • Rapid, inexpensive
  • Recommended by CDC

• Cons
  • Manual
  • Subjective interpretation
  • False-positives
  • False negatives, especially late syphilis
Reverse Algorithm

Treponemal test (eg, EIA)

Reactive

Non-Treponemal test (eg, RPR)

Non-reactive

Not syphilis

Reactive

Syphilis

Non-reactive

Second Treponemal Test (eg., FTA)

Reactive

Probably syphilis

Non-reactive

Not syphilis
Reverse algorithm pros and cons

• **Pros**
  • Objective
  • Can be batched for high volume labs
  • Recommended by public health agencies in Europe and Canada
  • More sensitive and more specific...more cases of syphilis diagnosed and treated

• **Cons**
  • Unfamiliar
  • Cost
  • Complexity – often second confirmatory test needed, not yet typically done reflexively
  • Disfavored by CDC
Interpreting reverse algorithm

Case #1

- 37-year-old man with HIV
- 2-weeks of fatigue, fever and rash on palms and soles
- Previously resolved genital lesion
- Syphilis IgG by EIA: positive
- RPR: positive, titer of 1:64
Interpreting reverse algorithm

Case #1 Conclusion

• Untreated or recently treated syphilis
• Follow treatment guidelines
• No further testing needed on this sample
• For follow-up after treatment
  • RPR titers only, should fall 4-fold (2 dilutions, e.g. 1:64 to 1:16)
Interpreting reverse algorithm

Case #2

- 23-year-old female
- First-trimester pregnancy screening
- Previously healthy
- Syphilis IgG by EIA: positive
- RPR: negative
- Second treponemal test, FTA: negative
Interpreting reverse algorithm

Case #2 conclusion

- False positive EIA
- Not syphilis
- No further screening at this time
- Consider screening again at 28 weeks and delivery if syphilis prevalent in community
Interpreting reverse algorithm

Case #3

- 50-year-old Somalian immigrant
- Kidney transplant evaluation
- No known history of syphilis or treatment
- Syphilis IgG by EIA: positive
- RPR: negative
- FTA: positive
Interpreting reverse algorithm

Case #3 Conclusion

• Possible latent syphilis

• Evaluate and treat according to current guidelines

• Consider lumbar puncture if neurologic symptoms consistent with late neurosyphilis
Interpreting reverse algorithm

Case #4

- 30-year-old inmate
- Past history of treated syphilis (10 years prior)
- Syphilis IgG by EIA: positive
- RPR: negative
Interpreting reverse algorithm

Case #4 Conclusion
- Consistent with successfully treated syphilis
- No additional testing needed
Summary

• Syphilis usually diagnosed by serology
  • Non-treponemal (e.g., RPR, VDRL)
  • Treponemal (e.g., FTA, TP-PA, EIA, MFI)

• Traditional Algorithm
  • Non-treponemal test (RPR) first
  • Treponemal test to confirm

• Advantages
  • Recommended by CDC
  • Cost-effective
  • Suitable for most lower throughput labs

• Limitations
  • May miss very early or late/latent infection
Summary

- Reverse Algorithm
  - Treponemal test first
  - Confirm with RPR
  - If RPR negative, use different treponemal ‘tiebreaker’ test
- Advantages
  - High volume throughput
  - More sensitive, same specificity
- Limitations
  - Result interpretation can be challenging
  - ‘Tiebreaker’ test not yet reflexive in most labs
Rapid diagnostic tests for syphilis
DPP® Syphilis Screen and Confirm Assay (Chembio)

- Not FDA approved for US use
- Non-treponemal + treponemal test on same point-of-care device
- Immunochromatographic strip
- Accommodates serum, plasma, whole blood
- In confirmed cases, non-treponemal component is positive in 95% of low RPR titer and 98% of high RPR titer cases
- Specificity of treponemal component was poor (68%)—doesn’t do a great job of weeding out previously treated syphilis or late infections
Rapid diagnostic tests for syphilis

- Many in use worldwide, only one licensed in US
- Treponemal tests
- Immunochromatographic strip test (e.g. home pregnancy test)
- Point of care tests
- Not much US experience yet
Rapid diagnostic test sensitivity and specificity

• Performance likely comparable to existing treponemal tests

  – Median Sensitivity 86%
  – Median Specificity 99%

  – Evaluated 3 dual HIV, *T. pallidum rapid test*
  – *T. pallidum* sensitivity 93%–99%
  – *T. pallidum* specificity 97%–100%
Rapid diagnostic tests for syphilis

Advantages

• Cheap
• Can be combined with HIV and other ICS tests for STIs
• No instrumentation required
• Point of care...could be used in bars or clubs
• Can be used as single screening test if risk or cost of overtreatment judged to be < risk or cost of untreated syphilis (e.g. in pregnancy)

Disadvantages

• Might be misinterpreted by unsophisticated user
• Overdiagnosis or overtreatment if not confirmed
DEPARTMENT OF CORRECTION-CITY OF NEW YORK

DON'T WAIT

70% ARE DOOMED
IF TREATMENT OF SYPHILIS IS DELAYED FOR 3 YEARS AFTER THE DISEASE IS CONTRACTED

CONSULT A REPUTABLE PHYSICIAN
Clinical stages of syphilis infection

- Exposure
  - Primary Incubation (10-90 Days From Exposure)
    - Primary Syphilis (Chancre Formation)
      - Secondary Incubation (4-10 Weeks After Appearance of Chancre)
        - Recurrence 24%
        - Secondary Syphilis
          - Early Latent Syphilis (Asymptomatic) (1 Year or Less Postinfection)
          - Late Latent Syphilis (Asymptomatic) (More Than 1 Year Postinfection)
    - Central Nervous System Invasion
      - Early Neurosyphilis
        - Asymptomatic
        - Symptomatic 5%
          - Meningitis
          - Cranial Neuritis
          - Ocular Involvement
          - Meningovascular Disease
      - Infectious via Mother-to-Child Transmission
    - Infectious via Sexual or Mother-to-Child Transmission
      - Late Latent Syphilis (Asymptomatic) (More Than 1 Year Postinfection)

- Noninfectious
  - Cardiovascular Syphilis 10% (Onset 20-30 Years Postinfection)
  - Gummatous Disease 15% (Onset 1-46 Years Postinfection)

- Late Neurosyphilis
  - General Paresis 2%-6% (Onset 2-30 Years Postinfection)
  - Tabes Dorsalis 2%-9% (Onset 3-50 Years Postinfection)

+ congenital disease
<table>
<thead>
<tr>
<th>Population/laboratory</th>
<th>Screen test</th>
<th># Screened</th>
<th>Reactive EIA/CIA (%)</th>
<th>Non reactive RPR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>140,176</td>
<td>4834 (3.4%)</td>
<td>2,743 (56.7%)</td>
</tr>
<tr>
<td>Southern California</td>
<td>Trep-Chek</td>
<td>47,952</td>
<td>1,278 (2.7%)</td>
<td>765 (59.9%)</td>
</tr>
<tr>
<td>Northern California</td>
<td>Liaison</td>
<td>21,623</td>
<td>438 (2.0%)</td>
<td>287 (65.5%)</td>
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<tr>
<td>Southern California</td>
<td>Trep-Sure</td>
<td>57,827</td>
<td>1,268 (2.2%)</td>
<td>755 (59.5%)</td>
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<tr>
<td>New York City</td>
<td>Trep-Chek</td>
<td>7,607</td>
<td>1,165 (15.3%)</td>
<td>639 (54.8%)</td>
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<tr>
<td>Chicago</td>
<td>Trep-Sure</td>
<td>5,167</td>
<td>685 (13/3%)</td>
<td>297 (43.4%)</td>
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<tr>
<td></td>
<td>High Prevalence</td>
<td>Low Prevalence</td>
<td>RR</td>
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<tr>
<td>Prevalence</td>
<td>14.5%</td>
<td>2.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discordant Results</td>
<td>50.6%</td>
<td>60.6%</td>
<td>1.2</td>
<td></td>
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<tr>
<td>(EIA/CIA +, RPR non-reactive)</td>
<td></td>
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<tr>
<td>False positive</td>
<td>14.1%</td>
<td>40.8%</td>
<td>2.9</td>
<td></td>
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<tr>
<td>(EIA/CIA +, TPPA/FTA-)</td>
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