A Syphilis Diagnosis and Treatment Primer

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DISCLOSURES

• Research Support
  • Hologic, Nabriva, SpeeDx
• Advisory Board
  • Nabriva

WARNING: There will be graphic images in this talk.
Outline

• Review Syphilis Natural History and Clinical Signs
• Review of syphilis diagnostics
• Review of staging and clinical management
• Cases & Clinical Pearls
Syphilis: Natural History

Exposure

10-90 days

Primary Syphilis: chancre

4-10 weeks after chancre disappears

Secondary Syphilis

24%

Latent Syphilis

Early (<1 year)

Late (>1 year)

1-50 years

Late Complications
Images of Primary Syphilis
Images of Secondary Syphilis
Available Syphilis Diagnostics by Stage

• Primary
  • Clinical diagnosis
  • Darkfield microscopy
  • Serologies (non-treponemal and treponemal)
    • Tests can be falsely negative

• Secondary
  • Clinical diagnosis
  • Darkfield for wet lesions (e.g. condyloma lata)
  • Serologies

• Latent
  • Screening test using serologies

• Neuro (not discussed today)
## Table 1. Sensitivity and Specificity of Serologic Tests for Syphilis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity during stage of infection, % (range)</th>
<th>Specificity, % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary</td>
<td>Secondary</td>
</tr>
<tr>
<td>Nontreponemal tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDRL [14]</td>
<td>78 (74-87)</td>
<td>100</td>
</tr>
<tr>
<td>TRUST [14]</td>
<td>85 (77-96)</td>
<td>100</td>
</tr>
<tr>
<td>RPR [14]</td>
<td>86 (77-99)</td>
<td>100</td>
</tr>
<tr>
<td>Early treponemal tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHA-TP [15]</td>
<td>76 (69-90)</td>
<td>100</td>
</tr>
<tr>
<td>TPPA [16]</td>
<td>88 (86-100)</td>
<td>100</td>
</tr>
<tr>
<td>TPHA [17]</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>FTA-ABS [14]</td>
<td>84 (70-100)</td>
<td>100</td>
</tr>
<tr>
<td>Enzyme immunoassays</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG-ELISA [18]</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>IgM-EIA [19]</td>
<td>93</td>
<td>85</td>
</tr>
<tr>
<td>ICE [20]</td>
<td>77</td>
<td>100</td>
</tr>
<tr>
<td>Immunochemiluminescence assays</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLIA [21]</td>
<td>98</td>
<td>100</td>
</tr>
</tbody>
</table>

**NOTE**: CLIA, chemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption assay; ICE, immune-capture EIA; MHA-TP, microhemagglutination assay for *Treponema pallidum*; NA, not available; TPHA, *T. pallidum* hemagglutination assay; TPPA, *T. pallidum* particle agglutination; TRUST, toluidine red unheated serum test.

False Negatives
- Relatively Common in Primary
- False positives possible but not common

Sena, A et al CID 2010
## Table 1: Sensitivity and Specificity of Treponemal Immunoassays for Diagnosis of Syphilis in Clinically Characterized Specimens (Published Data)

<table>
<thead>
<tr>
<th>Assay</th>
<th>Stage</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ADVIA Contour</td>
<td>Primary</td>
<td>62/65 (94.5%)</td>
<td>389/403 (96.5%)</td>
<td>Park [12]</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>88/99 (100%)</td>
<td>96.2-100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early Latent</td>
<td>41/41 (100%)</td>
<td>90.7-100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late Latent</td>
<td>64/68 (94.1%)</td>
<td>81.9-99.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>255/282 (89.5%)</td>
<td>94.6-98.9%</td>
<td></td>
</tr>
<tr>
<td>Architect Syphilis</td>
<td>Overall</td>
<td>97.2-100%</td>
<td>94.5-100%</td>
<td></td>
</tr>
<tr>
<td>Bioplex 2200 Syphilis IgG</td>
<td>Primary</td>
<td>62/65 (94.5%)</td>
<td>390/403 (96.9%)</td>
<td>Park [13]</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>88/99 (100%)</td>
<td>96.2-100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early Latent</td>
<td>41/41 (100%)</td>
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<tr>
<td></td>
<td>Overall</td>
<td>255/282 (89.5%)</td>
<td>94.6-98.9%</td>
<td></td>
</tr>
<tr>
<td>Captia Syphilis-C Assay</td>
<td>Primary</td>
<td>92.2-100%</td>
<td>97.3-100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early Latent</td>
<td>91.7-100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late Latent</td>
<td>94.7-100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elecsy Syphilis</td>
<td>Overall</td>
<td>57/67 (85.3%)</td>
<td>91.9-99.3%</td>
<td></td>
</tr>
<tr>
<td>LIASON</td>
<td>Primary</td>
<td>96.4-100%</td>
<td>94.5-100%</td>
<td>Marangoni [31], Park [13], Wellinghausen [26]</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early Latent</td>
<td>96.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late Latent</td>
<td>97.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>94.5-100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trep-Sure</td>
<td>Primary</td>
<td>52/55 (94.5%)</td>
<td>333/403 (82.9%)</td>
<td>Park [13], Gratzner [35]</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>99/98 (100%)</td>
<td>96.2-100%</td>
<td></td>
</tr>
<tr>
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<td>Early Latent</td>
<td>41/41 (100%)</td>
<td>90.7-100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late Latent</td>
<td>67/80 (83.5%)</td>
<td>92.1-99.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>296/292 (85.5%)</td>
<td>91.9-99.6%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

Note: Most studies are small sample size and used bank sera NOT clinical samples.
The Rapid Plasma Reagin Test (RPR)
Screen with Non-trep test
- Inexpensive,
- Relatively nonspecific
- But, highly sensitive
- Quantitative result

Confirm with a Trep test
- More expensive
- Highly specific
- Non-quantitative
- Positive for life
Treponemal Test (EIA/CIA or TP-PA) +/- duplicate

Quantitative Non-trep Test (RPR)

2nd Trep test

DISEASE old vs. new

DISEASE old vs. hx tx vs. early

History of syphilis? Last RPR titer? Ever tested?

- Do not use EIA in patients with a history of syphilis and in newborns
- False negatives occur in early disease. If high clinical suspicion, repeat tests.
## Syphilis Staging & Treatment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>2.4 million units Benzathine PCN IM x 1</td>
</tr>
<tr>
<td>Secondary</td>
<td>2.4 million units Benzathine PCN IM q week for 3 weeks</td>
</tr>
<tr>
<td>Early Latent* (Early nonprimary nonsecondary)</td>
<td>PCN Allergy- Doxy 100mg bid x 14 days</td>
</tr>
<tr>
<td>Late Latent or unknown duration</td>
<td>PCN Allergy- Doxy 100mg bid x 28 days</td>
</tr>
</tbody>
</table>
Jarisch-Herxheimer reaction

- Acute febrile reaction after initiation of antibiotics for the treatment of spirochete infections.
- Death of these bacteria → endotoxins and lipoproteins
- Fever, malaise, nausea, vomiting, chills, exacerbation of rash
- Especially in secondary
- Within 24 hours, resolves in 24 hours
- The intensity of the reaction indicates the severity of inflammation.
- Self-limiting. Supportive care
Cases
21 yo MSM who has never tested for HIV or STDs. Presents to the local STD clinic for STD testing since he has recently had 4 new cis-male sex partners. He has no symptoms at the day of testing. Traditional algorithm syphilis testing returns as RPR + (titer 1:32) and TPPA+.

**How would you stage and treat this patient?**

A. Primary syphilis, doxycycline 100mg PO BID x 14 days
B. Secondary syphilis, 3 injections of Bicillin 2.4 mu spaced weekly
C. Early latent, one injection of Bicillin 2.4 million units
D. Late Latent, 3 injections of Bicillin 2.4 mu spaced weekly
What else do you need to do?

A. Screen for complicated syphilis
B. Recommend PrEP
C. Encourage him to tell his sex partners to get epi treated, and also report to local public health
D. All of the above
<table>
<thead>
<tr>
<th>Question or Task</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) What stage of syphilis does the patient have?</td>
<td>Helps determine treatment plan.</td>
</tr>
<tr>
<td>2) Does the patient have complicated syphilis?</td>
<td>Determines whether additional work-up or alternate therapy is needed</td>
</tr>
<tr>
<td>3) Test for other STIs (including HIV), &amp; pregnancy.</td>
<td>Define need for additional therapy and appropriate follow-up</td>
</tr>
</tbody>
</table>
| 4) Define HIV treatment and/or prevention plan | -If HIV+ ensure patient on ARVs and suppressed  
-If HIV negative Recommend PrEP |
| 5) Define follow-up plan | Follow titers to ensure >2 titer (4-fold) decline over 6-12 months |
| 6) Report to health department. | Helps get partners treated and thus, decreased community transmission, and optimizes care. |
Case #2 --

- 28 yo cis-woman presents to ER with multiple new vulvar lesions. She thinks she got herpes from her new partner. Has had 4 cis-male partners in the past year. Lesions have been present for about a week. They are tender but not very painful. She also has had a sore throat and felt run down.

What is your next step in management?

A. HSV PCR lesion and send her home with acyclovir
B. HSV PCR lesion, send syphilis serologic testing; await results
C. Send her to Gyn for cryotherapy for warts and a PAP smear
D. HSV PCR lesion; send quantitative RPR, TPPA, GC/CT, HIV and treat with BIC x 1
E. Something else
Case #3 -

- 36 yo MSM on PrEP for the past 2 years. Very adherent to TDF/FTC and his regular testing schedule q3 months. Has a history of secondary syphilis 3 years ago. At that time his RPR was 1:256. For the past two years in your PrEP clinic his RPR has alternated between 1:4 and 1:8. Today his RPR is 1:32.

Is this a new infection? If so, what stage and how would you treat?

A. No. Does not need staging or treatment
B. Yes. Primary. Treat with BIC x 1
C. Yes. Secondary. Treat with BIC x 1
D. Yes, but we don’t have enough data to stage. Treat with BIC x 1
E. Yes. Late latent. Treat with BIC x 3
Interpreting RPR Titer Changes

Example 1:

- 2-fold Increase
- 1:1 → 1:32

Example 2:

- 4-fold Increase
- 1:1 → 1:64

Example 3:

- 8-fold Increase
- 1:1 → 1:128

Courtesy of David Spach
Interpreting Serologies

Clinical History/Physical Exam

Trep test
Non-trep Test
Local Epi
Case #4 --

• 48 yo MSM with HIV, well controlled on descovy + dolutegravir. Presents to PCP with generalized body rash. RPR on day of penicillin treatment is a 1:64. Three months later his RPR is 1:32. He missed his six month follow up appointment, but at 9 months his RPR is 1:32.

Is this an adequate serologic response?
A. Yes
B. No
C. Maybe, it’s too early to tell.
Syphilis Follow-up

Get quant RPR on day of treatment!

Serological Follow-up:
3, 6, 9 and 12 months

Treatment failure:
1) Sustained 2 titer (4-fold) increase in RPR

2) High titer (≥1:32) syphilis that does not decline 2 titers (4-fold) over 6-12 months (1º or 2º syphilis) or 12-24 months (latent syphilis) – soft indication
Example 1

2-fold Decrease

Example 2

4-fold Decrease

Example 3

8-fold Decrease
At 12 months his RPR is still 1:32.

What do you do next?

A. Retreat with BIC x 3
B. LP for CSF evaluation
C. Treat with doxycycline 100 mg PO BID x 28 days
D. Keep monitoring RPR until 24 months have past.
E. Something else
Who needs an LP?
CDC Criteria – 2021 STD Treatment Guidelines

• Neurologic, ophthalmic or otologic signs or symptoms
• Evidence of active tertiary disease – (aortitis, gumma, iritis)
• Consider if suspected treatment failure
  • **Sustained** 2 titer (4-fold) increase in VDRL/RPR & no reinfection
  • High titer (RPR≥1:32) syphilis that does not decline 2 titers (4-fold) over 6-12 months (1º or 2º syphilis) or 12-24 months (latent syphilis)
    • But 10-20% of 1º/2º won’t have 4-fold decline <12 months
Case #5 --

• 32 yo pregnant woman who attends her first prenatal visit. Her OB screens her using the traditional algorithm in the first trimester and gets a negative result. Her state has recently recommended universal third trimester screening. At 28 weeks, her OB screens her again with the reverse sequence algorithm. Now she is EIA+ / RPR neg /TPPA+. She has never tested for syphilis before.

• Would you treat her? If so, what would you treat her with?
  A) No.
  B) Yes. Bicillin 2.4 million units IM x 3
  C) Yes. Bicillin 2.4 million units IM x1
Syphilis Serology – Traditional Approach

**Screen** with Non-trep test
- Inexpensive,
- Relatively nonspecific
- But, highly sensitive
- Quantitative result

**Confirm** with a Trep test
- More expensive
- Highly specific
- Non-quantitative
- Positive for life

---

**Diagram Description**

1. **Non-treponemal testing** (RPR, VDRL)
   - Reactive
   - Non-reactive

2. **Treponemal testing** (FTA-ABS, TPPA, EIA)
   - Reactive
   - Non-reactive

   - **Syphilis infection:** Current untreated OR Previously treated infection
   - **False positive non-treponemal result:** Syphilis infection unlikely

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**Additional Notes**

- No serologic evidence of syphilis
- No further action needed in most cases
  - (Does not rule out incubating or early primary infection)
Reverse Sequence Syphilis Screening

Treponemal Test (EIA/CIA or TP-PA) +/- duplicate

- POS
  - Quantitative Non-trep Test (RPR)
    - POS: DISEASE old vs. new
    - NEG: 2nd Trep test
      - POS: DISEASE old vs hx treated vs very early
      - NEG: NO disease or False Negative*
        - NEG: False Pos Trep Test vs. False Neg

- NEG
  - NO disease or False Negative*
    - NEG: False Pos Trep Test vs. False Neg

Do not use EIA in patients with a history of syphilis and in newborns
False negatives occur in early disease. If high clinical suspicion, repeat tests.
Syphilis Diagnostic and Treatment Pearls

• No syphilis test is perfect, especially by itself.
  • Use non-trep and trep tests together with your history, physical exam findings and clinical judgement.

• Better to over-treat than under-treat.

• Don’t delay treatment of symptomatic syphilis awaiting serologic results

• Draw quantitative RPR on day of treatment

• Syphilis is complicated!
Resources

National STD Curriculum
Funded by a grant from the Centers for Disease Control and Prevention

https://www.std.uw.edu/

The Diagnosis, Management and Prevention of Syphilis
An Update and Review

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Contact Info:
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Syphilis serology

- TP specific IgG
- FTA - Abs
- TPHA
- RPR (Untreated cases)
- RPR (treated cases)

Primary syphilis: 10 to 90 days
Secondary syphilis: 6 weeks to 6 months
Latent syphilis: No signs and symptoms
Tertiary syphilis: 10 to 30 years