Reverse Sequence Syphilis Screening

An Overview by CDC
Learning objectives

- Describe the evaluation and management of persons with a reactive treponemal enzyme immunoassay (EIA+) result
- Identify three possible explanations for discordant test results (i.e., EIA+ and RPR-) with reverse sequence screening
- Discuss the management of a person who has a discordant test result (i.e., EIA+ and RPR-) that is nonreactive by confirmatory treponemal testing with a *Treponema pallidum* particle agglutination (TP-PA) test
- Compare the performance of the reverse sequence algorithm in populations with high and low prevalence of infection
Target Audience

- Clinicians who provide screening, diagnosis, and clinical care for persons at risk for or infected with syphilis
- Other health care professionals, such as laboratorians, epidemiologists and public health program staff, whose work involves syphilis screening or management of persons at risk for or infected with syphilis
Presenters

Karen Hoover, MD, MPH
Medical Epidemiologist
Division of STD Prevention
Centers for Disease Control and Prevention

Ina Park, MD, MS
Chief
Medical and Scientific Affairs Unit
STD Control Branch
California Department of Public Health
Webinar Overview

- Syphilis screening with serologic tests
- Enzyme immunoassays (EIA) and chemiluminescence immunoassays (CIA) increasingly used as syphilis screening tests
  - Large proportion of EIA+/RPR- results
  - Confusion about patient management
- Performance and clinical data for the use of reverse sequence screening
  - MMWR February 11, 2011 / 60(05);133-137
  - JID 2011 (under review)
- CDC recommendations for the use of EIA/CIA to screen for syphilis
- Research needs to provide an evidence basis for future guidelines
Diagnosis of syphilis

- *Treponema pallidum* cannot be cultured
- Ideally, early syphilis would be diagnosed using direct detection methods
  - Darkfield microscopy
  - Polymerase chain reaction (PCR)
  - Direct fluorescent antibody test for *T. pallidum* (DFA-TP)
- Direct detection methods are not widely available
- Direct detection methods can miss cases
  - Fail to detect up to 30% of primary cases
- Most persons present without symptoms or signs of syphilis
  - Healed early lesions
  - Inapparent lesions
  - Latent infection
- Syphilis is usually diagnosed with serologic tests
Sero logic diagnosis of syphilis

- Serologic diagnosis always requires detection of two types of antibodies
  - Nontreponemal antibodies
    - Antibodies directed against lipoidal antigens
      - Damaged host cells
      - Possibly from treponemes
  - Treponemal antibodies
    - Antibodies directed against \textit{T. pallidum} proteins
Serologic diagnosis of syphilis

- **Nontreponemal tests**
  - Rapid plasma reagin (RPR) test
  - Venereal Disease Research Laboratory (VDRL) test
  - Toluidine red unheated serum test (TRUST)

- **Treponemal tests**
  - Fluorescent treponemal antibody absorbed (FTA-ABS) test
  - Treponema pallidum article agglutination (TP-PA) test
  - Enzyme immunoassays (EIAs)
    - Trep-Chek
    - Trep-Sure
  - Chemiluminescence immunoassays (CIAs)
    - LIAISON
    - Architect
  - Microbead immunoassays (MBIA)
    - BioPlex 2200 Syphilis IgM and IgG
Serologic reactivity in syphilis patients

![Graph showing serologic reactivity over time and stages of syphilis](image-url)
Syphilis serologic screening algorithms

Traditional

- Quantitative RPR
  - RPR+
    - TP-PA or other trep. test
      - TP-PA+ Syphilis (past or present)
      - TP-PA- Syphilis unlikely
  - RPR-

Reverse sequence

- EIA or CIA
  - EIA/CIA+
  - EIA/CIA-
    - Quantitative RPR
      - RPR+
        - TP-PA or other trep. test
          - TP-PA+ Syphilis (past or present)
          - TP-PA- Syphilis unlikely
      - RPR-
        - TP-PA
          - TP-PA+ Syphilis (past or present)
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Which algorithm?

- **Traditional algorithm**
  - Detects active infection
  - High rate of biologic false positives
    - Confirmation with treponemal test
      - Use of both tests results in a high positive predictive value
  - Can miss early primary and treated infection

- **Reverse sequence algorithm**
  - Detects early primary and treated infection that might be missed with traditional screening
  - Nontreponemal test needed to detect active infection
  - Ideally, EIAs and CIAs should have perfect specificity
    - EIAs and CIAs are nonspecific
    - High rate of false positive results
    - Varies by risk of population
EIA/CIA AS SYPHILIS SCREENING TESTS
Syphilis Screening Paradigm

**Non-treponemal tests** (RPR, VDRL)
- NON-SPECIFIC ANTIBODY AGAINST LIPOIDAL ANTIGENS
- QUANTITATIVE
- REACTIVITY DECLINES WITH TIME

**Treponemal tests** (TP-PA, FTA-Abs)
- SPECIFIC ANTIBODY AGAINST T pallidum
- QUALITATIVE
- REACTIVITY PERSISTS OVER LIFETIME

reflex to
Traditional Use of Treponemal Tests

- Confirming reactive non-treponemal tests
- Screening the blood supply
Syphilis Screening Paradigm

EMERGING / NEW…

Treponemal tests (EIA, CIA, MBIA)
- SPECIFIC ANTIBODY TO *T. pallidum*
- QUALITATIVE
- REACTIVITY PERSISTS OVER LIFETIME

reflex to

Non-treponemal tests (RPR, VDRL)
- NON-SPECIFIC ANTIBODY AGAINST LIPOIDAL ANTIGENS
- QUANTITATIVE
- REACTIVITY DECLINES WITH TIME
**Treponemal Immunoassay: A timeline**

- **1980s**: EIA is FDA cleared for use as confirmatory test & in blood bank screening

- **2000**: UK Public Health Laboratory Guidelines: EIA “appropriate alternative” to VDRL/RPR + TPHA

- **2008**: EU Guidelines: EIA/TPPA recommended for screening, VDRL and RPR *no longer recommended*

- **2009**: CDC-APHL Report: Presents algorithm for screening with Trep EIA
Why switch to EIA/CIA?

- Automated (high throughput)
- Low cost in high volume settings
- Less lab occupational hazard (pipetting)
- No false negatives due to prozone reaction
- Objective results
- Some EIA/CIAs detect IgM antibodies; potentially useful for diagnosis of early syphilis
Why switch to EIA/CIA?

180 tests per hour, no manual pipetting
Syphilis Tests by Test Type, 1996-2009

Number of VDRLs and EIA/CIA Tests

- VDRL
- RPR
- EIA/CIA

California Department of Public Health, STD Control Branch, 2009
Challenges and limitations of the EIA/CIA

- Cannot distinguish between active disease and old disease (treated/untreated)
- Studies to compare test performance with other serologic tests are lacking
- Studies evaluating performance of EIA/CIA to detect IgM antibodies in early syphilis are lacking
- Confusion re: management of patients with discrepant serology (e.g., positive EIA/CIA and a negative RPR)
PERFORMANCE AND CLINICAL DATA FOR THE USE OF THESE TESTS
Discordant Results from Reverse Sequence Syphilis Screening
Five Laboratories, United States, 2006–2010
Methods

- Analyzed data from five laboratories that used reverse sequence screening during 2006-2010
  - 140,176 sera screened with a treponemal EIA/CIA
  - Data from sera with equivocal EIA/CIA test results were not included as reactive tests

- EIA tests
  - Trep-Chek
  - Trep-Sure

- CIA test
  - LIAISON

- Reflex nontreponemal test
  - RPR

- Confirmatory treponemal tests
  - TP-PA
  - FTA-ABS
Methods

- Three sites served patient populations with low prevalence for syphilis
  - Large managed-care organizations

- Two sites served patient populations with high prevalence
  - MSM
  - HIV-infected patients

- Calculated
  - Reactive EIA/CIAs among all sera (i.e., EIA+)
  - Discordant sera among reactive EIA/CIAs (i.e., EIA+/RPR-)
  - Nonreactive confirmatory TP-PA or FTA-ABS tests among discordant sera (i.e., EIA+/RPR-/TP-PA-)
Results of reverse sequence syphilis screening — five laboratories, United States, 2006 – 2010

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Reasons for discordant test results (i.e., EIA/CIA+ / RPR-)

- **False-positive EIA/CIA**
  - EIAs and CIAs are very sensitive
  - But have lower specificity

- **Treated syphilis**
  - Treponemal antibodies are detected by sensitive EIAs and CIAs
  - Seroreversion of nontreponemal antibodies

- **Early primary syphilis**
  - Treponemal antibody titer rises before nontreponemal antibody titer
Conclusions

- EIA/CIA have high sensitivity but lower specificity
- All reactive EIA/CIA must be reflexly tested with a quantitative RPR
  - Confirm reactive EIA/CIA
  - Detect active infection
- Although test performance varies by prevalence of syphilis in the population, all discordant specimens (EIA+/RPR-) must be confirmed with a confirmatory treponemal test
- Confirmatory treponemal test must have at least equivalent sensitivity and higher specificity compared to the screening treponemal test
  - TP-PA recommended
  - FTA-ABS not recommended
Screening for syphilis with the treponemal immunoassay:

*Analysis of discordant serology results and implications for clinical management*
Methods

- Cross sectional analysis of individuals tested with Diasorin LIAISON chemiluminescence immunoassay (CIA) at Kaiser Permanente Northern California Regional Laboratory from Aug-Oct 2007

- Data abstracted from electronic medical records (laboratory and clinical) using standardized protocol

- HIV-status, sexual orientation, pregnancy status, prior syphilis history and CIA index values were compared for all CIA-positive, RPR-negative patients according to TP-PA status.
CIA Testing Results

- N=21,623 specimens
- CIA+ = 2%
- CIA+ / RPR− = 1.3%

CIA

+ 2%
  n=439

− 98%

RPR

+ 34%
  n=151

− 66%
  n=288

Managed like prior RPR screening algorithm

TPPA

+ 72%
  n=184

− 28%
  n=71

* 33 duplicate or infant tests
<table>
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<th>Demographics</th>
<th>CIA+/RPR-TPPA+ (N=184)</th>
<th>CIA+/RPR-TPPA- (N=71)</th>
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<tbody>
<tr>
<td>Mean age (SD)*</td>
<td>50 (14)</td>
<td>42 (16)</td>
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<tr>
<td>Males*</td>
<td>149 (81%)</td>
<td>33 (47%)</td>
</tr>
<tr>
<td>MSM*</td>
<td>60 (33%)</td>
<td>7 (10%)</td>
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<tr>
<td>Heterosexual</td>
<td>15 (8%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Females</td>
<td>35 (19%)</td>
<td>38 (53%)</td>
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<tr>
<td>Pregnant</td>
<td>12 (34%)</td>
<td>16 (42%)</td>
</tr>
<tr>
<td>HIV-positive*</td>
<td>86 (47%)</td>
<td>14 (20%)</td>
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<tr>
<td>Prior syphilis*</td>
<td>105 (57%)</td>
<td>6 (9%)</td>
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*P= <0.0001
Management based on initial serology and syphilis history

CIA+ / RPR- / TP-PA+
N=184

Prior treated syphilis
N=105 (57%)
• 10 (9%) received repeat treatment
• 95 (91%) no antibiotic treatment

No prior syphilis
N=79 (43%)
• 51 (65%) received treatment
• 28 (35%) no antibiotic treatment
Management based on initial serology and syphilis history

CIA+ / RPR- / TP-PA-
N=71

Prior treated syphilis
N=6 (8%)
• 2 (33%) received repeat treatment
• 4 (66%) no antibiotic treatment

No prior syphilis
N=65 (92%)
• 7 (11%) received treatment
• 58 (89%) no antibiotic treatment
Repeat Serology Testing Results

CIA+ / RPR- / TP-PA+  
N=184

Repeat Serology  
N=78

Initially treated n=31 (64%)
- 0 seroreverted to CIA-
- 27 (87%) remained CIA+/RPR-/TPPA+
- 4 (13%) seroconverted to CIA+/RPR+

Not treated initially n=47 (36%)
- 0 seroreverted to CIA-
- 41 (87%) remained CIA+/RPR-/TPPA+
- 6 (13%) seroconverted to CIA+/RPR+
Repeat Serology Testing Results

CIA+/ RPR- / TP-PA- 
N=71

Repeat Serology 
N=31

Initially treated N=6 (19%)
• 0 seroreverted to CIA-
• 6 (100%) remained CIA+/RPR-/TPPA-
• 0 seroconverted to CIA+/RPR+

Not treated initially N=25 (81%)
7 (28%) seroreverted to CIA-
17 (68%) remained CIA+/RPR-/TPPA-
1 (4%) seroconverted to CIA+/RPR+
High EIA/CIA index values may predict TP-PA positivity (n=255)

N=79 individuals with CIA index value >12.0; 100% of were TP-PA positive

Park IU et al. unpublished data
Kaiser Study Conclusions

- Among CIA+/RPR- patients, reflex testing with a second treponemal test is useful in low prevalence settings to guide treatment decisions.

- Conflicting treponemal results (CIA+/TP-PA-) and isolated CIA+ results with low index values may represent false positives. Repeat testing should be considered.

- Among CIA+/RPR- patients at high risk, repeat testing should be performed to rule out early syphilis.
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CDC RECOMMENDATIONS FOR THE USE OF EIA/CIA
Recommended algorithm for reverse sequence syphilis screening

- **EIA or CIA**

- **EIA/CIA+**
  - **Quantitative RPR**
    - **RPR+**
      - **Syphilis (past or present)**
    - **RPR-**

- **EIA/CIA-**

- **TP-PA**

  - **TP-PA+**
    - **Syphilis (past or present)**
  - **TP-PA-**
    - **Syphilis unlikely**
Recommended algorithm for reverse sequence syphilis screening

- **EIA or CIA**
  - **EIA/CIA+**
    - **Quantitative RPR**
      - **RPR+**
        - Syphilis (past or present)
      - **RPR-**
        - **TP-PA**
          - **TP-PA+**
            - Syphilis (past or present)
          - **TP-PA-**
            - Syphilis unlikely
  - **EIA/CIA-**

If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units IM x 1
Recommended algorithm for reverse sequence syphilis screening

1. **EIA or CIA**
   - **EIA/CIA+**
   - **EIA/CIA-**
     - **Quantitative RPR**
       - **RPR+**
         - **Syphilis (past or present)**
       - **RPR-**
         - **TP-PA**
           - **TP-PA+**
             - **Syphilis (past or present)**
           - **TP-PA-**
             - **Syphilis unlikely**

If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units IM x 1.

Evaluate clinically, determine if treated for syphilis in the past, assess risk of infection, and administer therapy according to CDC’s STD Treatment Guidelines if not previously treated.
Recommended algorithm for reverse sequence syphilis screening

EIA or CIA

If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units IM x 1

EIA/CIA+

EIA/CIA-

Quantitative RPR

Evaluate clinically, determine if treated for syphilis in the past, assess risk of infection, and administer therapy according to CDC’s STD Treatment Guidelines if not previously treated

RPR+

Syphilis (past or present)

RPR-

TP-PA

Evaluate clinically, determine if treated for syphilis in the past, assess risk of infection, and administer therapy according to CDC’s STD Treatment Guidelines if not previously treated

TP-PA+

Syphilis (past or present)

TP-PA-

Syphilis unlikely
If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units IM x 1.

Evaluate clinically, determine if treated for syphilis in the past, assess risk of infection, and administer therapy according to CDC's STD Treatment Guidelines if not previously treated.

If at risk for syphilis, repeat RPR in several weeks.
RESEARCH NEEDS TO PROVIDE AN EVIDENCE BASIS FOR FUTURE GUIDELINES
Research needs

- Compare head-to-head the performance of EIAs, CIAs, TP-PA, FTA-ABS test, and microbead immunoassay
  - Well-defined patient populations whose clinical history and syphilis risk are known
    - HIV-infected persons
    - Pregnant women

- Characterize discordant sera with nonreactive confirmatory treponemal tests by immunoblotting
  - Define reactivities with *T. pallidum* antigens

- Study utility of immunoglobulin M treponemal testing
  - Diagnosis of early primary syphilis
  - Evaluation of infection in asymptomatic, seropositive, untreated persons
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Clinician Resources

- 2010 STD Treatment Guidelines
  - www.cdc.gov/std/treatment/2010

- Condoms and STDs: Fact Sheet for Public Health Personnel
  - www.cdc.gov/condomeffectiveness/latex.htm

- Expedited Partner Therapy
  - www.cdc.gov/std/ept

- Get Yourself Tested
  - www.itsyoursexlife.com/gyt
Educational and Training Resources

National Network of STD/HIV Prevention Training Centers
www.nnptc.org

CDC Division of STD Prevention
www.cdc.gov/std/training
stdtraining@cdc.gov or 404.639.8360