Syphilis Testing Guidelines

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Boldly Going Where No One Has Gone Before
Objectives

- Describe the changes in syphilis diagnostics including a preliminary new serologic algorithm
- Discuss how these guidelines will impact practices in public health and clinical laboratories

*Please, Spock, do me a favor ... 'n' don't say it's `fascinating’... No... but it is... interesting...*
Syphilis Consultants

**CDC (U.S. and Canada)**
- Ron Ballard
- David Cox
- Moreshed Muhammad
  - BC CDC, Canada

**Public Health**
- Susan Blank, NYC PH
- Gail Bolan, CA PH
- Anthony Muyombwe, MI PHL
- Susie Zanto, MT PHL

**Clinical / Research**
- Sheila Lukehart, UW
- Christina Marra, UW
- Justin Radolf, UCHC
- Ken Bromberg, SUNY
- Edward (Ned) Hook, UAB
Syphilis

Infection → Primary Chancre → Secondary Rash → Latent Asymptomatic → Tertiary

Early Syphilis: 1 – 2 years

Late Syphilis: Many years to a lifetime

Incubation period: 9 – 90 days

Primary Chancre

Secondary Rash

Latent Asymptomatic

Tertiary

Many years to a lifetime

Begnin gumatous
Cardio-vascular syphilis
Neurosyphilis

~ 18 months
Syphilis Workgroups

- Direct Detection of *T. pallidum* (Tp)
- Congenital Syphilis
- Neurosyphilis
- Adult Serology
Direct Detection

- Key Questions addressed
  - How can the quality of Dark Field microscopy be ensured?
  - Should serologic testing be used to confirm Dark Field?
  - What is the role of immunostaining in the U.S.?
  - What is the role of PCR for the diagnosis of primary and secondary syphilis in the U.S.?
Direct Detection Recommendations

- The use of DF microscopy should be maintained and expanded in high prevalence sites, but QA is essential.
- Serologic testing should always be used in conjunction with Direct Detection.
- Immunostaining for identification of primary syphilis lesions has high sensitivity and specificity.
Direct Detection Recommendations (2)

- PCR can be a very useful test in lesions of Primary Syphilis
  - Usefulness in secondary syphilis is unclear
  - Not sensitive enough for identification of Tp in blood, serum, plasma or CSF
- PCR for amniotic fluid equivalent to RIT
- A mechanism for Proficiency Testing (MPEP?) should be established
Direct Detection Needs

- A FDA approved rapid POC immunostaining test for detection of Tp in lesions
- A FDA approved Tp PCR test
  - In absence of FDA approval, develop and validate “home brew” assays
Direct Detection Research Needs

- Evaluation of PCR for detection of Tp in secondary lesions
- Investigation of the persistence of Tp in tissues and fluids after treatment
- Evaluation of the quality and specificity of commercially available Tp antisera
Congenital Syphilis

Key Questions addressed

- What criteria should be used for the serological diagnosis of congenital syphilis?
- What is the value of testing for specific IgM antibodies to detect congenital syphilis?
Congenital Syphilis Recommendations

- IgM should be used in concert with Tp detection—immunostaining, PCR, DF
- A reactive IgM test is useful, but a non-reactive IgM test does not rule out congenital syphilis
- A four-fold or greater ratio of neonatal to maternal titers is rarely useful
- Treatment decisions should not be based on laboratory results
Congenital Syphilis Research Needs

- A standardized immunoblot or line-probe assay to detect syphilis IgM
- Development of monoclonal antibodies for formalin fixed tissues
- Development of assays for examining umbilical vein brushings
Neurosyphilis

Key Questions addressed

- What criteria should be used for the serologic diagnosis of neurosyphilis?
- What tests should be used for testing CSF specimens for syphilis?
- What are the indications for performing lumbar puncture in syphilis patients?
Neurosyphilis Recommendations

- Neurosyphilis cannot be diagnosed serologically.
- Serum RPR > 1:32 can predict which asymptomatic individuals are most likely to have CSF findings consistent with neurosyphilis.
- The use of VDRL in evaluating CSF may still be worthwhile.
  - WBC cutoffs, TP-PA of 1:320, CXCL13 show promise.
- Protein levels and TPHA titer index are not useful tests for evaluating CSF.
Indications for Lumbar Puncture

To prevent risk of neurorelapse in asx HIV + Σ individuals, early dx/rx of NeuroΣ is critical

Early CNS abnormalities are not predictive of serious sequelae in HIV + persons

There are no data to resolve this issue
Neurosyphilis Research Needs

- Further evaluation of optimal diagnostic test combinations for CSF examination
  - Establish cutoffs, testing algorithms
- Longitudinal data on prognostic relevance of CSF VDRL reactive tests in early syphilis infection in HIV infected individuals
Capt. Kirk: *Spock, give me an update on the dark area ahead.*
Spock: *No analysis due to insufficient information.*
Capt. Kirk: *Insufficient information is not sufficient, Mr Spock! You're the science officer. You’re supposed to have sufficient data all the time!*
Adult Serology

- **Key Questions addressed**
  - What serologic tests should be used for screening and diagnosis and in which order (non-treponemal vs treponemal)?
  - What factors need to be considered in test selection?
  - What is the implication of using treponemal tests for screening?
  - Are there differences in the performance of treponemal tests?
    - Are all syphilis EIAs created equally and perform equally?
  - How should the performance of serologic tests be measured?
Adult Serology

Key Questions addressed

- Is there value in performing a quantitative treponemal test?
- What is the value of testing for IgM to detect early syphilis?
- What tests can be recommended for patient management and possible reinfection?
- Is there a relationship between non-treponemal antibody titers and activity/stage of disease?
- What is the role of POC tests in the U.S.?
- Which diseases are responsible for biological false positives?
Selection of Tests for Adult Serology

Considerations

- Prevalence of disease in population
- Performance characteristics of test
- Purpose of the test (screening, confirmation, disease management)
- Subjectivity of the test/experience of the technologist
- Need for capital equipment
- Automation needs
- Technical requirements
- Cost
Adult Serology Recommendations

- The selection of specific tests for screening depends on the setting, the population and the individual patient – multiple algorithms may be necessary
  - One using a non-treponemal test as initial screen
  - One using a treponemal test as initial screen
  - One based on the level of risk of infection in various settings?
- A combination of treponemal and non-treponemal tests must be used; a single treponemal test cannot be relied upon for syphilis diagnosis
Implications of Treponemal Screening

**PROS**
- High Sensitivity
- High Specificity
- Automation
- Interface with LIS
- Objective endpoint

**CONS**
- Cannot distinguish between active and previously treated disease
- Potential for over diagnosis and over treatment
- Requires more resources for EPI/DIS investigations
Testing Algorithm Using EIA or CIA as Initial Test

A1
Syphilis EIA or CIA

A1+
A1+ A2+
Consistent with Syphilis (past or current infection)

A1+ A2-
A1+ A2- A3+
Possible Syphilis infection; Requires further historical and clinical evaluation

A1+ A2- A3-
A1+ A2- A3-
Unconfirmed EIA; Unlikely to be Syphilis; If patient is at risk for syphilis, re-test in 1 month

A2
Quantitative Nontreponemal (i.e. RPR)

A1-
A1-
Negative for Syphilis antibodies

A3
Treponemal Test that uses a different antigen or platform from A1 (i.e. TPPA, FTA)

* Laboratory should report the results of all three assays (if applicable) within 7 days
Adult Serology Recommendations

- Most EIAs perform equally well for screening purposes
  - Those detecting both IgM and IgG appear more sensitive in early disease
  - Insufficient data for CIA assays at this time

- There is variability in the performance of different treponemal tests
  - Due to antigens, conjugates and methods
  - The overall agreement between treponemal tests is usually >95%, even in 1° disease
    - FTA appears to seroconvert earliest
    - TP-PA appears to be the most sensitive
Adult Serology Recommendations

- There is no apparent advantage to performing quantitative treponemal tests.
- There is insufficient data to definitively recommend IgM tests at this time.
  - May have a role in resolving a reactive treponemal screening test with a non-reactive non-treponemal test.
- The serologic response following successful treatment of syphilis infection remains unclear.
POC tests cannot be recommended for use in the U.S. at this time

- Existing POC tests have low PPV in detecting active disease in low prevalence settings
- May be a role in areas where prevalence is high and where immediate treatment is the overriding concern due to a likely lack of follow up care
Adult Serology Recommendations

- Most biological false positive reactions (both non-treponemal and treponemal) are seen in the sera of healthy individuals.
- Data generally does not support that pregnant women have a higher rate of BFPs.
- High rates in elderly may point to periodontal disease as a cause of BFPs.
Adult Serology Research Needs

- EIAs or other treponemal assays that are based on antigens different from the current three used (47, 17, and 15 kDA antigens)
- A gold standard – possibly a Western blot or pseudo-blot assay
- Better POC tests
- Additional data about the persistence of IgM and the usefulness of IgM serology tests
Adult Serology Research Needs

- A serum bank of well characterized sera differentiated by clinical stage – including co-infected HIV sera
- Comprehensive study to compare treponemal and non-treponemal assays currently FDA-approved in the U.S.
- Studies to determine cause of BFPs
- Studies designed to determine how soon after exposure a person can be screened, or time frame for rescreening if initial test is negative
Adult Serology Program Needs

- An approach for automatic reflex (and reimbursement) of positive screens for subsequent testing according to the recommended algorithm
- Alter reporting requirements to ensure that laboratories report to the health department and clinician all tests performed in evaluating the specimen for syphilis
Adult Serology Training Needs

- Education of clinicians as to what constitutes a “high risk” patient and to communicate this to the laboratory in order to ensure appropriate test utilization
Syphilis Testing Guidelines

- Guidelines from CDC targeted for early 2010
- Meeting proceedings are being published to aid clinical and public health laboratories in planning their syphilis testing strategies

"... a dream that became a reality and spread throughout the stars"

Captain Kirk (Whom Gods Destroy)