CONGENITAL SYphilis

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EPIDEMIOLOGY

- Worldwide:
  - Latin America, Africa, Europe

- United States:
  - Racial and ethnic minorities: Blacks
  - South (48%); urban areas
  - Young, unmarried women: lower SEC
  - Congenital cases: inadequate prenatal care
  - Increase in adults since 2001—increase in congenital cases up to 2008, decrease since (322 cases in 2012)
Congenital Syphilis—Reported Cases Among Infants by Year of Birth and Rates of Primary and Secondary Syphilis Among Women, United States, 2004—2013

* CS=congenital syphilis; P&S=primary and secondary syphilis.
SURVEILLANCE CASE DEFINITION: CONGENITAL SYPHILIS

- **Confirmed case**: identification of *T. pallidum*
- **Presumptive case**: 
  - Infant whose mother had untreated or inadequately treated syphilis at delivery
  - Reactive treponemal test and abnormal physical exam, long bone x-rays, reactive CSF VDRL, elevated CSF cell count or protein, or reactive IgM test
- **Syphilitic stillbirth**: fetal death at >20 wk gestation or BW >500 g and mother with untreated or inadequately treated syphilis

- 14,627 cases of CS (78% decline): 942 deaths, 760 stillbirths
- Case fatality rate: 6.4% (stable)
- 87% of deaths: untreated, inadequately treated, or undocumented treatment during pregnancy
- Less prenatal care: ↑ risk of death
- 52% of deaths occurred by 30 wks of gestation

CONGENITAL SYphilis

◆ Early manifestations:
  – Due to hematogenous spread of organism and resultant inflammatory response in various organs and tissues
  – Extramedullary hematopoiesis
  – Immune-mediated

◆ Late manifestations:
  – Scarring or stigmata from early disease
  – Reaction to persistent inflammation
  – Noninfectious
PROBLEMS IN THE DIAGNOSIS OF CONGENITAL SYPHILIS

- Inability to detect or culture *T. pallidum* in neonatal clinical specimens
- Difficulty in interpretation of serologic tests due to transplacentally acquired maternal IgG
- Difficulty in identification of infants with CNS invasion by *T. pallidum*
DIAGNOSTIC STRATEGIES FOR CONGENITAL SYPHILIS

- IgM immunoblot:
- Polymerase chain reaction (PCR)
- Rabbit infectivity test (RIT):
DIAGNOSTIC STRATEGIES FOR CONGENITAL SYPHILIS

- Vertical transmission
- “Asymptomatic” newborn
- Central nervous system invasion
- Evidence-based rationale for the management of infants born to mothers with reactive serologic tests for syphilis (CDC, AAP)
CONGENITAL SYPHILIS: VERTICAL TRANSMISSION

- **In utero:**
  - Transplacental route following maternal spirochetemia

- **Intrapartum:**
  - Contact with genital lesion
CONGENITAL SYPHILIS: INTRAUTERINE TRANSMISSION

- Isolation of the organism from umbilical cord blood and amniotic fluid
- The isolation of *T. pallidum* from as many as 74% of amniotic fluid specimens obtained from women with early syphilis also suggests that the organism is capable of traversing the fetal membranes, gain access to the amniotic fluid and result in fetal infection.
CONGENITAL SYPHILIS: INTRAUTERINE TRANSMISSION

- Clinical disease *in utero* and at birth
- Detection of specific IgM antibody to *T. pallidum* in fetal serum obtained by amniocentesis and in neonatal serum obtained at birth
CONGENITAL SYPHILIS: VERTICAL TRANSMISSION

- Increases as stage of pregnancy advances but can occur at any time in gestation
- Related to stage of maternal syphilis

<table>
<thead>
<tr>
<th>No. of Mothers</th>
<th>1°</th>
<th>2°</th>
<th>Early Latent</th>
<th>Late Latent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>26</td>
<td>53</td>
<td>145</td>
<td>27</td>
</tr>
<tr>
<td>Congenital Syphilis</td>
<td>1 (4)</td>
<td>14 (26)</td>
<td>31 (21)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>6 (23)</td>
<td>32 (60)</td>
<td>52 (36)</td>
<td>2 (7)</td>
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</table>
SYPHILIS: SEROLOGIC TESTS

◆ **Nontreponemal tests**: RPR / VDRL
  
  – **Antigen**: lecithin, cholesterol and cardiolipin (diphosphatidylglycerol); detects an antibody against cardiolipin that is present in sera of patients with syphilis
  
  – **Quantitative tests**: Useful to assess adequacy of treatment and to detect reinfection
SYPHILIS: SEROLOGIC TESTS

- RPR: more sensitive than VDRL; preferred for screening of pregnant women
- Perform the same nontreponemal test on the infant that was performed on the mother
- Diagnosis of congenital syphilis is supported by infant’s RPR / VDRL $\geq 4x$ maternal RPR/VDRL
SYPHILIS: SEROLOGIC TESTS

◆ Treponemal tests:
  - Detect antibody (IgG) to *T. pallidum*
  - Confirm reactive nontreponemal test result
    - FTA-ABS (lyophilized *T. pallidum*)
    - TP-PA: hemagglutination test (lysate of *T. pallidum*)
    - Enzyme / chemiluminescence immunoassays (EIA / CIA)
SYPHILIS: SEROLOGIC TESTS

- Treponemal tests:
  - Non-quantitative tests
  - Remain reactive indefinitely
  - Not useful for distinguishing active infection from past infection or assessing adequacy of treatment
  - Not useful in evaluation of newborn
RPR/VDRL ON INFANT: SERUM OR UMBILICAL CORD BLOOD (UCB)?

- AAP: serum; UCB: false ⊕ (5-10%) and false-neg (5-20%) results can occur
- CDC: serum; UCB: contamination with maternal blood may yield a false ⊕ result
- UCB: Easy to obtain; readily available
  - Avoid contamination
  - DON’T use for screening!
Evaluation and Treatment of Infants During the First Month of Life
SCENARIO 1:
PROVEN OR HIGHLY PROBABLE
SYPHILIS
PROVEN OR HIGHLY PROBABLE SYphilis

- Infant physical exam abnormal
- Serum VDRL/RPR $\geq 4x$ maternal titer
- Positive darkfield or fluorescent antibody test of body fluid(s) or tissue
Histopathology: necrotizing funisitis, villous enlargement, acute villitis

Increased detection of congenital syphilis from 67% to 89% in live-born infants, and 91% to 97% in stillborns (Obstet Gynecol 2002:100:126)
PROVEN OR HIGHLY PROBABLE SYPHILIS: EVALUATION

- Lumbar puncture, CBC / platelet count
- Bone X-rays:
  - CDC: as clinically indicated
  - AAP: unless the diagnosis has been otherwise established
- Other tests (eye exam, LFTs, HUS, ABR, CXR) as clinically indicated
PROVEN OR HIGHLY PROBABLE SYPHILIS: BONE X-RAYS

- Periostitis
- Osteochondritis
- Frequently abnormal: 65% (Houston/Dallas)
- Abnormal findings do not change therapy
Lumbar puncture:
- Why? To establish a baseline for follow-up
- Why not?
CENTRAL NERVOUS SYSTEM INFECTION IN CONGENITAL SYPHILIS

76 INFANTS, CSF RIT: 17 POS, 59 NEG

◆ Sensitivity; Specificity:
  
  Reactive CSF VDRL: 53%; 90%
  
  CSF Pleocytosis: 38%; 88%
  
  Elevated CSF Protein: 56%; 78%

Michelow et al. NEJM, 2002
CENTRAL NERVOUS SYSTEM INFECTION IN CONGENITAL SYPHILIS

- 22% (17/76): positive CSF RIT
- 41% of those with abnormal clinical, laboratory, or radiographic evaluation
- 60% of those with abnormal PE
- 100%, +serum IgM; 94%, +blood PCR; 65%, +CSF PCR
- 3 infants: +CSF RIT, normal CSF indices (2 abn evaluation, 1 pos IgM)

Michelow et al. NEJM, 2002
### CONGENITAL SYPHILIS: SYMPTOMATIC INFANTS

<table>
<thead>
<tr>
<th></th>
<th>SERUM/BLOOD (n=46)</th>
<th>CSF (n=39)</th>
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<tbody>
<tr>
<td><strong>POS IgM</strong></td>
<td>98%</td>
<td>41%</td>
</tr>
<tr>
<td><strong>POS RIT</strong></td>
<td>57% (20/35)</td>
<td>47% (16/34)</td>
</tr>
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CONGENITAL SYPHILIS: TREATMENT

- Infant VDRL/RPR ≥ 4x Maternal VDRL/RPR OR Physical Exam is ABNORMAL OR TP body fluid:
  - Aqueous PCN G 50,000 U/kg IV q 8-12 hr x 10 d, or
  - Procaine PCN G 50,000 U/kg IM q day x 10 d
CONGENITAL SYPHILIS: TREATMENT

- Penicillin dosed missed > 1 day, restart course
- Alternative therapy: NONE
  - Ampicillin: no data, penicillin should be used, and if not, close serologic follow-up required
SCENARIO 2
CONGENITAL SYPHILIS: ASYMPTOMATIC INFANTS BORN TO MOTHERS WITH UNTREATED SYPHILIS

<table>
<thead>
<tr>
<th>Test</th>
<th>Serum/Blood (n=86)</th>
<th>CSF (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POS IgM</td>
<td>16%</td>
<td>3% (2/62)</td>
</tr>
<tr>
<td>POS RIT</td>
<td>7%</td>
<td>2% (1/62)</td>
</tr>
</tbody>
</table>
### MATERNAL TREATMENT

**4 WKS BEFORE DELIVERY:**

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Infants:</strong></td>
<td>23*</td>
<td>21*</td>
</tr>
<tr>
<td><strong>⊕ IgM</strong></td>
<td>30%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>⊕ RIT</strong></td>
<td>5%</td>
<td>0/19</td>
</tr>
</tbody>
</table>

*1 Mother HIV-Ab ⊕

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* 4 weeks before delivery
CONGENITAL SYPHILIS: EVALUATION AND TREATMENT

 Infant physical exam normal AND VDRL/RPR <4x maternal titer:

– Maternal Rx:
  • None, inadequate, unknown
  • Erythromycin, azithromycin, non-penicillin drug
  • ≤ 4 wks before delivery

– Mother re-infected (RPR ↑ 4x)
CONGENITAL SYPHILIS: “Asymptomatic” INFANT

- Physical exam normal; VDRL/RPR reactive and <4x maternal titer (cont):
  - Evaluation: CBC, platelets, LP, bone X-rays
  - Treatment: options
    - Penicillin G (aqueous/procaine) x 10d: evaluation optional; evaluation abnormal, not done or incomplete
    - Benzathine PCN G 50,000 u/kg IM: normal CBC, platelet, lumbar puncture, bone X-rays and follow-up certain
CONGENITAL SYPHILIS: “Asymptomatic” INFANT

Evaluation and Treatment:

- Full evaluation (LP, bone x-rays, CBC, platelets) MUST be performed and be completely normal if benzathine PCN used.

- Complete evaluation unnecessary if aqueous PCN G/procaine PCN x 10 d, but tests may be performed to document CSF abnormalities or support a diagnosis of syphilis.
BENZATHINE PENICILLIN G: WHY NOT?

- 3 treatment failures (3 infants):
  - 2 mothers with untreated syphilis (EL; UNK) and 1 mother with 2° syphilis treated 1 month before delivery
  - None fully evaluated (no bone x-rays; 1 no evaluation); developed signs of congenital syphilis at 4, 9 and 14 wks of age
- CSF penicillin concentrations are low after benzathine penicillin treatment
CONGENITAL SYPHILIS: “Asymptomatic” INFANT

- Physical Exam NORMAL and serum VDRL/RPR nonreactive (cont):
  - Evaluation: none (no CBC, x-rays, LP)
  - Treatment:
    - Benzathine PCN G 50,000 u/kg IM
“Asymptomatic” Infant: Physical Exam Normal and RPR/VDRL NR

- 154 infants (1984-2002) at PMH, Dallas:
  - 39 wk, 3110 g (mean), 17% HIV-exposed
  - NL CSF (54), bone x-rays (74), H&H (72), platelets (65); blood/CSF RIT neg (19)
  - 5 infants:
    - Positive serum IgM: 3/65
    - Positive serum PCR: 2/54
    - Mothers: untreated (4) or rx < 4 wks (1)

Wozniak et al, PAS 2015
SCENARIO 3
CONGENITAL SYPHILIS

- Infant physical exam normal AND VDRL/RPR <4x maternal titer:
  - Maternal Rx:
    - During pregnancy, appropriate for stage of infection, > 4 wks before delivery
  - No evidence of reinfection or relapse
CONGENITAL SYPHILIS: “ASYMPTOMATIC” INFANT

- No evaluation

- Treatment:
  - Benzathine penicillin G IM x 1
  - “some experts” would not treat but provide close serologic follow-up
    - AAP: follow-up preferably monthly, until RPR NR
SCENARIO 4
CONGENITAL SYPHILIS: “ASYMPTOMATIC” INFANT

- Infant physical exam normal AND VDRL /RPR <4x maternal titer:
  - Maternal Rx: Before pregnancy, no evidence of re-infection or relapse
  - Infant: No evaluation, follow-up only
    - Benzathine PCN IM x1 if F/U uncertain
Evaluation and Treatment of Older Infants and Children
EVALUATION

- CSF analysis
- CBC / platelet count
- Other tests (long bone radiographs, chest radiograph, eye exam, LFTs, abdominal ultrasound, ABR, neuroimaging) as clinically indicated
TREATMENT

- Aqueous PCN G 50,000 U/kg IV q4-6 hr x 10 d
- “Some specialists” suggest giving a single dose of benzathine penicillin G 50,000 U/kg IM after the 10-day course
- If child has no clinical manifestations of disease, the CSF exam is normal, and the CSF VDRL test result is negative, some specialists would treat with up to 3 weekly doses of benzathine penicillin G 50,0000 U/kg IM
Special Considerations

- **Penicillin allergy**: desensitize, data insufficient to recommend other agents, but if nonpenicillin agent used, close serologic and CSF follow-up

- **HIV infection**: infants born to mothers coinfected with HIV do not require different evaluation, therapy, or follow-up for syphilis

- **Penicillin shortage**: penicillin G, procaine penicillin, benzathine penicillin, ceftriaxone

www.cdc.gov.nchstp/dstd/penicillinG.htm/
CONGENITAL SYPHILIS: PREVENTION

- Ensure adequate universal prenatal care
- Serologic screening (RPR) at 1st prenatal visit; repeat at 28-32 wks, delivery in high-risk areas
- Screening with treponemal test?
“REVERSE SEQUENCE” SCREENING
MMWR, 2/2011

- 5 laboratories in USA
- 140,176 sera screened with treponemal EIA/CIA
- 3.4% (4834) had reactive test result
- 57% (2743/4834): RPR nonreactive
- 32% (866/2743) NR by TP-PA or FTA-ABS – initial EIA/CIA false-positive?
- Discordant results (NR TP-PA/FTA-ABS) were almost 3x more frequent in low vs high prevalence populations (41% vs. 14%)
“REVERSE SEQUENCE” SCREENING: CDC RECOMMENDATIONS

- EIA or CIA POSITIVE
  - RPR NEGATIVE
  - RPR POSITIVE: Syphilis
  - TP-PA
    - POSITIVE: Syphilis (past or present)
    - NEGATIVE: Syphilis unlikely

MMWR, 2/2011
CONGENITAL SYPHILIS: FOLLOW-UP

- Serologic testing (RPR) q 2-3 months until nonreactive. Persistent, stable titer beyond 1 yr: retreat?
- Treponemal test: Reactive beyond 18 months indicates congenital infection
- Initial CSF abnormal: Repeat at 6 months and if abnormal, retreat
CONGENITAL SYPHILIS: PREVENTION

- Do not discharge infant without maternal serologic status documented at least once during pregnancy
- Report all cases to Health Dept. for contact tracing and identification of core populations and environments
Nationwide Children’s Hospital
Center for Perinatal Research