Congenital Syphilis, Management

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Learning Objectives

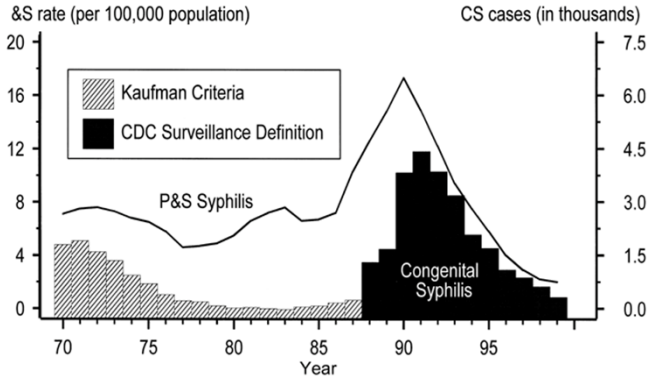
- Surveillance Case Definition
- Diagnostic Considerations
- Congenital Syphilis Scenarios, Treatment and Follow-up
- What would you do if….

Surveillance Definition

Surveillance Case Definitions

▪ Syphilitic stillbirth	Fetal death occurring after a 20 week gestation OR weighing more than 500g, in which the mother had untreated or inadequately treated syphilis at delivery
▪ Confirmed	Positive darkfield, fluorescent antibody or other specific stains showing *T. pallidum* in specimens from infant's skin, body fluids, umbilical cord, placenta, or autopsy material
▪ Probable	Mother was untreated or inadequately treated OR Infant has positive non-trep test AND one of the following: Evidence of CS on exam, long bone x-ray, or CSF

Surveillance vs. Clinical Case Definitions



Reported cases of congenital syphilis in infants younger than 1 year of age and rates of primary and secondary syphilis among women, United States, 1970 to 1999. (Courtesy of Emmett Swint and Kathy Dry, Division of STD Prevention, NCHSTP, CDC, Atlanta, GA.)

Diagnostic Considerations

Diagnosing Congenital Syphilis: Contexts

- Mortality – stillbirth
- Vertical transmission – prenatal diagnosis?
- Symptomatic newborn
- Asymptomatic newborn

* Includes primary, secondary, and early latent syphilis.

Rev. 7/2018

CS Mortality, 1999-2013

- **6383 cases of CS** – defined by surveillance
  - (decrease from 14,627 cases in 1992-1998; 56% decline)
- Neonatal mortality: 11.6/1000 live births
- 418 deaths, **342 (82%) stillbirths**
- Case fatality rate: 6.5% (stable)
- **89% of deaths: untreated (73%) or inadequately treated** during pregnancy
- **59%** of deaths occurred by **31 weeks** of gestation

Su et al. *Am J Obstet Gynecol* 2015

CS Mortality - a closer look

- Case-fatality rate*:
  - **Confirmed** congenital syphilis: 35% (67/191)
    - Stillbirths: **79% of deaths** (53/67)
    - Majority of stillbirths occurred **before 28 weeks'** gestation (74%)

- CDC surveillance case definition: 11%
  - **CDC surveillance case definition under-estimated mortality by >300%**

*Pablo Sanchez, 2018

Meta-analysis: Reduction of CS stillbirths with treatment

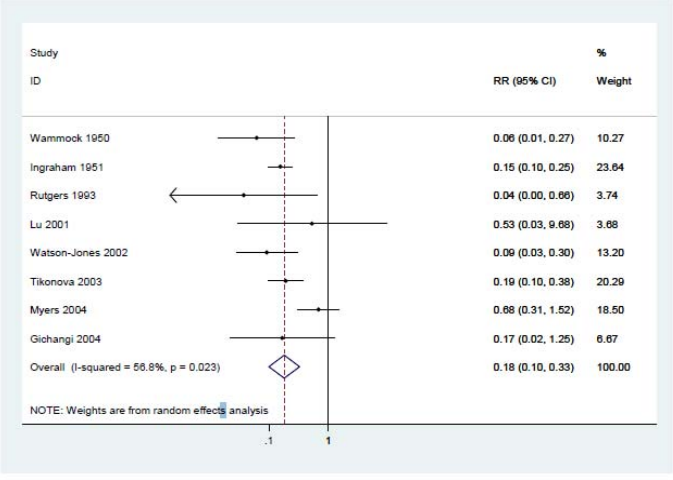


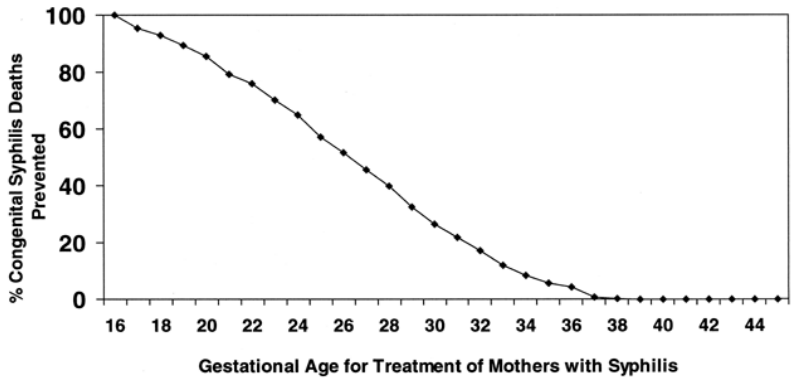
Figure 3 Meta analysis of 8 observational studies showing effect of penicillin on stillbirth in pregnant women with active syphilis.

Risk Reduction = 0.18
(95% CI 0.10, 0.33)

Blencowe, Hannah, et al. "Lives Saved Tool supplement detection and treatment of syphilis in pregnancy to reduce syphilis related stillbirths and neonatal mortality." *BMC public health* 11.3 (2011): S9.

Mathematical model: Early Rx = Fewer CS Infant Deaths

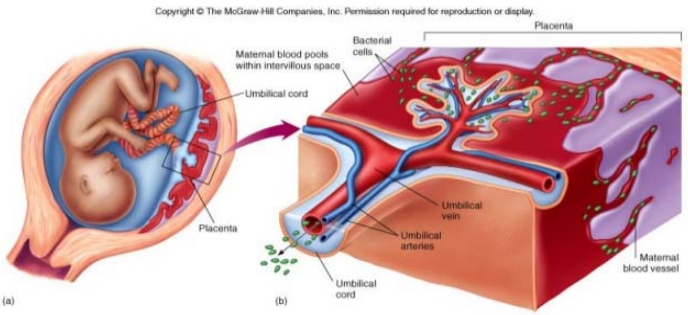
% CS deaths preventable by treating pregnant women with syphilis at a given gestational age.



(Gust DA, Levine WC, St. Louis, M, *et al*. Mortality associated with congenital syphilis in the United States, 1992-1998. Pediatrics, 2002; 109(5):E79-9.)

Vertical (Mother To Child) Transmission

- Earlier maternal **stage**
- High maternal disease **titers** (VDRL, RPR)
  - Nonspecific to T. pallidum
  - Associated with earlier stage



Prenatal Diagnosis? Not Routinely Done

- The isolation of *T. pallidum* from up to **74% of amniotic fluid specimens** from women with early syphilis
- Suggests organism can traverse fetal membranes, and result in fetal infection.

** Wendel et al. Obstet Gynecol. 1991;78:890*
Nathan et al. J Ultrasound Med 1993;2:97
Hollier et al. Obstet Gynecol. 2001;97:947

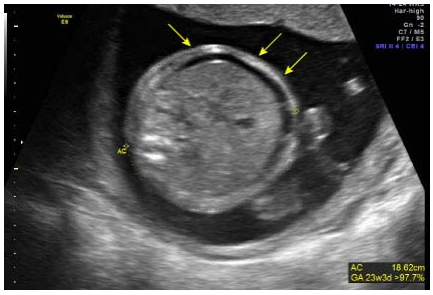
Sonography? Only if diagnosed after 20 weeks' gestation

*** Should not delay treatment in pregnancy**

Sonographic signs:

- hepatomegaly (70-80%)
- thickened placenta (25%)
- ascites (10%)
- Non-immune hydrops
- fetal anemia (25-30%)

Cases accompanied by these signs should be managed in consultation with obstetric specialists. No specific regimens.



Live born Infants: Diagnostic Tools

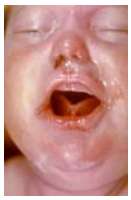
- Physical Exam
- Serology
- Histopathology
- CSF evaluation
- Long bone X-ray

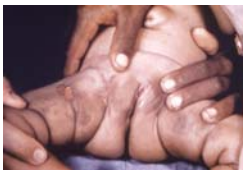
Live Born Infants: Physical Findings

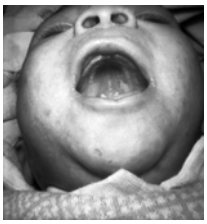
- **Early** manifestations (< 2years of age):
  - Due to **hematogenous spread** of organism and resultant **inflammatory response** in various organs and tissues
  - Immune-mediated
- **Late** manifestations (>2 years of age):
  - **Scarring or stigmata** from early disease
  - Reaction to **persistent inflammation**
  - Noninfectious

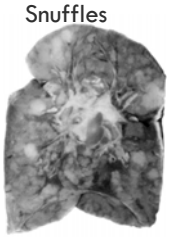
Physical Findings: Early (Birth – 8 weeks, but up to 2 years)

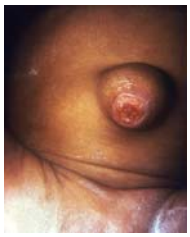
- **Hepatomegaly** (enlarged liver)
- **Splenomegaly** (enlarged spleen)
- **Snuffles** (copious nasal secretions – infectious!)
- **Mucocutaneous lesions** (infectious!)
- **Pneumonia Alba**
- **Osteochondritis**
- **Pseudoparalysis**
- **Edema**
- **Rash**
- **Hemolytic anemia or thrombocytopenia.**


Snuffles


Cutaneous lesion


Mucous patches

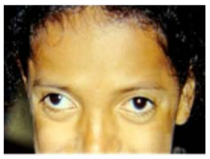

Pneumonia Alba

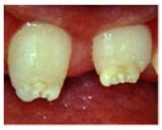

Umbilical lesion

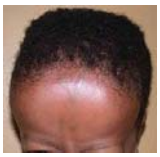
Courtesy CDC Public Health Image Library

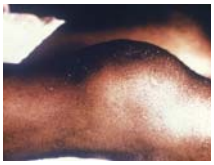
Physical Findings: Late (2 years +)

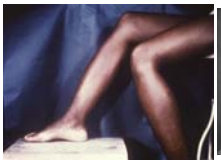
- **Interstitial keratitis** (5–20 years of age)
- **Eighth cranial nerve deafness** (10–40 years of age)
- **Hutchinson teeth** (peg-shaped, notched central incisors)
- **Mulberry molars**
- **Anterior bowing of the shins**
- **Frontal bossing**
- **Clutton joints** (symmetric, painless swelling of the knees)
- **Saddle nose**
- **Rhagades** (perioral fissures)

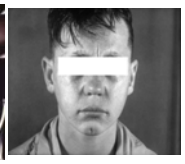

Interstitial keratitis


Hutchinson's teeth


Frontal bossing


Clutton's joints


"Saber shins"


Rhagades

Courtesy CDC Public Health Image Library

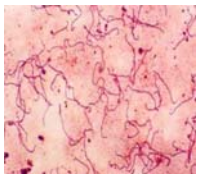
Citation: 1. L. Pessoa and V. Galvao, "Unusual presentation of more common disease/injury: clinical aspects of congenital syphilis with Hutchinson's triad," BMJ Case Reports, vol. 2011, pp. 1–3, 2011.

Laboratory criteria for diagnosis: T. pallidum

Demonstration of *Treponema pallidum* by one of the following:

- **Darkfield microscopy**
  - lesions, body fluids, or neonatal discharge

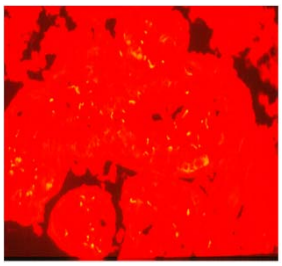
- **Polymerase chain reaction (PCR)** or other equivalent direct molecular methods
  - lesions, neonatal nasal discharge, placenta, umbilical cord, or autopsy material



- **Immunohistochemistry (IHC)**, or special stains
  - lesions, placenta, umbilical cord, or autopsy material.

https://www.cdc.gov/std/stats16/appendix-c.htm

Laboratory criteria for diagnosis: Placental pathology



- **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)

Courtesy of Pablo Sanchez, MD

Why are some infants asymptomatic, even if they are infected?

Some contributing factors:

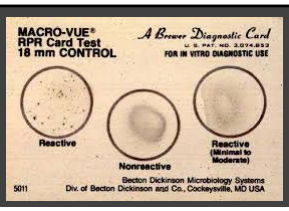
- Virulence of *T. pallidum* **may be modulated by maternal immune response,** and the conceptus' genetic background
- *T. Pallidum* **can vegetate until appropriate biological conditions promote virulence** and pathogenicity
  - Includes late gestation infections
- **SO: treatment is important even late in pregnancy and in the post-partum period when infants look normal.**

Victoria Wicher, Konrad Wicher; Pathogenesis of Maternal-Fetal Syphilis Revisited, *Clinical Infectious Diseases*, Volume 33, Issue 3, 1 August 2001, Pages 354–363.
Kim, Chong Jai, et al. "Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance." *American Journal of Obstetrics & Gynecology*213.4 (2015): S53-S69.
Salyers, A. A., and D. D. Whitt. "Virulence factors that promote colonization." *Bacterial pathogenesis a molecular approach, ASM Press, Washington DC* (1994): 16-29.

Limitations in diagnosing asymptomatic infants with CS:

- 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*

Serology: Nontreponemal Tests – RPR/VDRL



- **Antigen:** detects an antibody against cardiolipin, present in blood of patients with syphilis
- **Quantitative:** Useful to assess adequacy of treatment and to detect reinfection (fourfold difference, e.g. 1:8 vs. 1:32)
- **RPR more sensitive than VDRL;** preferred for screening of pregnant women
- Perform the **same test** on the infant that was performed on the mother

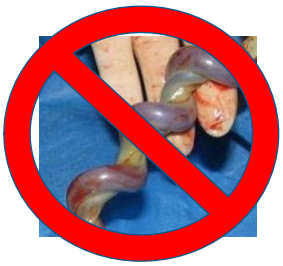
Fun fact: VDRL and RPR use beef heart extract

Serology: Treponemal Tests – TP-PA, FTA-ABS, EIA/CIA

- Detect antibody (IgG) to *T. pallidum*, Confirm reactive nontreponemal test result
  - TP-PA: hemagglutination test (lysate of *T. pallidum*)
  - FTA-ABS: (lyophilized *T. pallidum*)
  - EIA/CIA: Enzyme / chemi luminescence immunoassays
- Maternal TP-PA can stay positive in Infant serum for up to 15 months.
- **NOT NEEDED IN INFANT SCREENING**

Which specimen? Umbilical Cord or Serum?

- **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



*Grimprel et al. J Clin Microbiol 1991;29:1711

CSF Evaluation – *Symptomatic* Infants

	SERUM/BLOOD (n=46)	CSF (n=39)
+IgM*	98%	41%
+RIT**	57% (20/35)	47% (16/34)

IgM – Specific Trep test, not commercially available for infant screening. Used for research
RIT – Rabbit Infectivity Test

Courtesy of Pablo Sanchez, MD

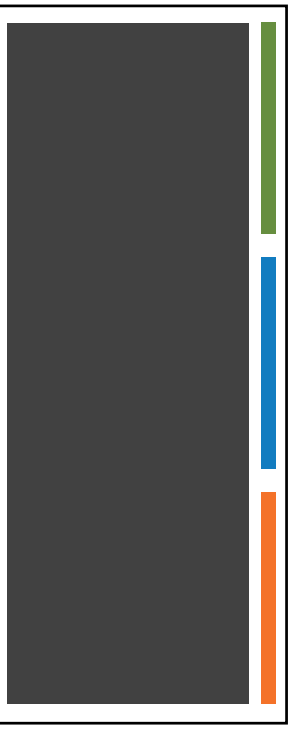
CSF evaluation

76 CS INFANTS, CSF RIT: 17 (22%) POS, 59 NEG

CSF Test	Sensitivity	Specificity
VDRL	53%	90%
Elevated WBC	38%	88%
Elevated Protein	56%	78%

Michelow et al. NEJM, 2002

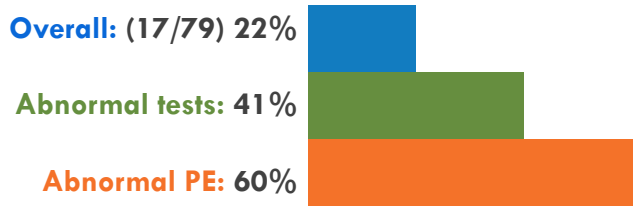
Courtesy of Pablo Sanchez, MD



CSF evaluation

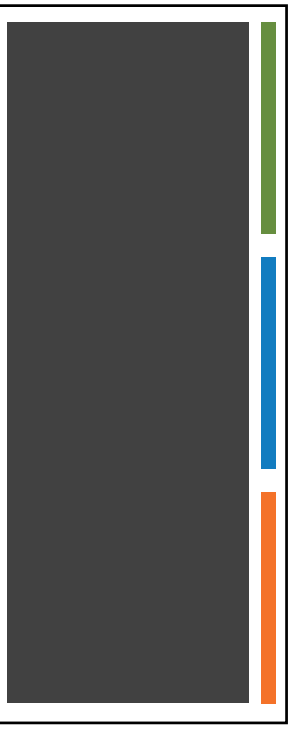
Proportions of infants with abnormal results

(76 CS INFANTS, CSF RIT: 17 POS, 59 NEG)



Michelow et al. NEJM, 2002

Courtesy of Pablo Sanchez, MD



Long bone Xray

Courtesy of Pablo Sanchez, MD

CDC Clinical Scenarios

Scenario 1: "Proven or Highly Probable Congenital Syphilis"

- Abnormal **physical exam** consistent with congenital syphilis

OR

- Serum VDRL/RPR **titer 4-fold higher** or more than maternal titer

OR

- Positive **darkfield or PCR** of lesions or body fluids (or placenta)

➢ **Full work-up and 10 days treatment recommended**

Courtesy of Jessica Kim, MD UCSF

"Full" Evaluation for Congenital Syphilis

- Careful physical exam
- CSF analysis for VDRL, cell count and protein
- CBC with differential
- Other tests as indicated, including:
  - X-rays (long bone and chest)
  - Liver function tests
  - Ophthalmologic exam
  - Neuroimaging
  - Auditory brainstem response

Courtesy of Jessica Kim, MD UCSF

Scenario 2: "Possible Congenital Syphilis"

Normal physical exam, Nontrep Titer = or < 4-Fold Maternal Titer
AND

- **Maternal factors:**
  - Not treated, inadequately treated, or no documentation of treatment OR
  - Treatment with erythromycin or other nonstandard regimen OR
  - Maternal treatment less than 4 weeks prior to delivery
- **Work-up/Rx:**
  - Complete evaluation if 10 days treatment not planned
  - Complete evaluation not necessary if 10 days treatment given
  - If complete evaluation is normal and infant follow-up certain, single dose benzathine PCN, 50,000 U/KG IM may be given

Courtesy of Jessica Kim, MD UCSF

Scenario 3: "Congenital Syphilis Less Likely"

Normal physical exam, Nontrep Titer = or < 4-Fold Maternal Titer
AND

Maternal factors:

- Treated during pregnancy, treatment was appropriate and administered > 4 weeks prior to delivery AND
- No evidence of reinfection or relapse

- **Work-up/Rx:**
  - No evaluation needed, but single dose benzathine PCN 50,000 U/KG IM recommended

Courtesy of Jessica Kim, MD UCSF

Scenario 4: "Congenital Syphilis Unlikely"

Normal physical exam, Nontrep Titer = or < 4-Fold Maternal Titer
AND

Maternal factors:

- Treated adequately before pregnancy AND
- Low and stable non-trep titers before and during pregnancy and at delivery (VDRL < 1:2, RPR < 1:4)

- **Work-up/Rx:**
  - No evaluation needed, no Rx required (but some experts would give single dose benzathine PCN 50,000 U/KG IM, particularly if follow-up uncertain)

Courtesy of Jessica Kim, MD UCSF

Congenital Syphilis: Treatment for Neonates

- **Aqueous crystalline penicillin G** 100,000-150,000 units/kg/d, given as 50,000 units/kg/dose IV q12 hours x 7 days, then q8 hours x 3 days **(total 10 days)**
  OR
- Procaine penicillin G 50,000 units/kg/dose IM qd x 10 days (only for neonates) *current drug shortage

- Single dose (ONLY for scenario 2 w/normal work-up, scenario 3 and 4): Benzathine penicillin G 50,000 units/KG/dose IM in a single dose

Congenital Syphilis: Follow-up for neonates

- Serologic testing **(RPR) every 2-3 months** (whether treatment given or not) until test becomes nonreactive
  - Non-treponemal titer should decline by 3 months and be non-reactive by 6 months if treated adequately or uninfected
  - Re-evaluate and treat if titer persists at 6-12 months
- If initial CSF is abnormal, repeat at 6 months.
  - If abnormal at 6 months, retreat

Evaluation and treatment of infants and children >=1 month*

Get an RPR!

If RPR positive

- CSF analysis
- CBC, differential
- HIV screen
- Other tests as indicated (long bone xray, CXR, LFT, Abd U/S, etc).

Treatment:

Aqueous crystalline penicillin G **200,000-300,000** units/kg/day IV, administered as 50,000 units/kg IV q4-6 hours x 10 days

If all tests normal, can consider BPG 50,000 U/kg **IM x 3 in weekly intervals**

What would you do if….

CASE 1

- Infant born at 39 weeks gestational age.
  - MOB - RPR at first prenatal visit 1:128. + palmer rash. Dx secondary syphilis. Received BPG x 1. (RPR 1:128 at time of treatment). No risk of reinfection. RPR at 32 weeks 1:8
  - MOB - RPR at Delivery: 1:4. No s/sx
- What would you do first?
  - Infant – Normal Physical Exam. RPR 1:1
- What scenario is this?

CASE 1: Scenario 3

- **Work-up/Rx:**
  - **No evaluation needed,** but single dose benzathine PCN 50,000 U/KG IM recommended
  - Another approach: no treatment; provide close serologic follow-up Q2-3months for 6 months
    - Only for infants whose mother's non-trep titers decreased 4-fold after appropriate therapy for early syphilis, or remained stable for low titer latent syphilis – VDRL <1:2, RPR<1:4)

CASE 2

- Infant born at 37 weeks gestational age.
  - MOB – No prenatal care, + RPR at Delivery: 1:16. No s/sx. History of syphilis and treatment unknown
- What would you do first?
  - Infant – Normal Physical Exam. RPR 1:32
- What scenario is this?

CASE 3: Scenario 2

- **Work-up/Rx:**
  - **Complete work up is recommended (CSF, long bone, CBC)**
    - Complete work up is not necessary if 10 days of parenteral therapy is administered.
  - **10 days IV penicillin**
  - Single dose benzathine PCN 50,000 U/KG IM if work up is normal and follow-up is certain

CASE 3

- Infant born at 38 weeks gestational age.
  - MOB – No prenatal care, + RPR at Delivery: 1:16. No s/sx. History of syphilis and treatment unknown
  - Infant and MOB discharged to home before RPR results available.
  - Infant located 2 months later.
- What would you do first?
  - Infant – Normal Physical Exam. RPR 1:32
- What scenario is this?

CASE 3
Evaluation and treatment of infants and children >=1 month*

If RPR positive

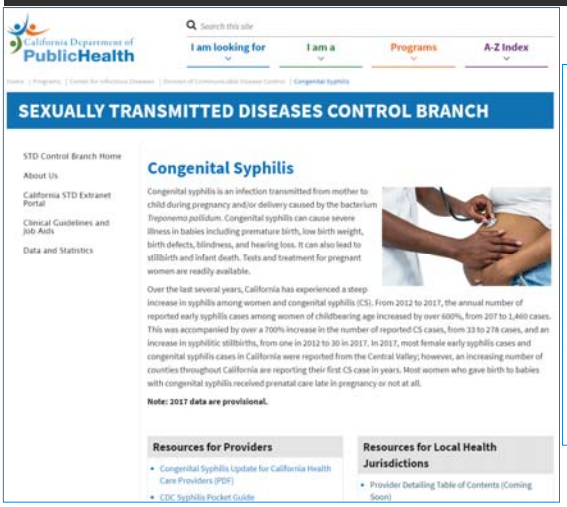
- CSF analysis
- CBC, differential
- HIV screen
- Other tests as indicated (long bone xray, CXR, LFT, Abd U/S, etc).

Treatment:

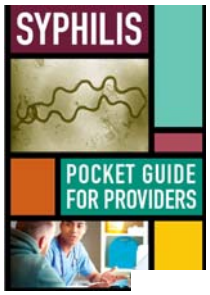
Aqueous crystalline penicillin G **200,000-300,000** units/kg/day IV, administered as 50,000 units/kg IV q4-6 hours x 10 days

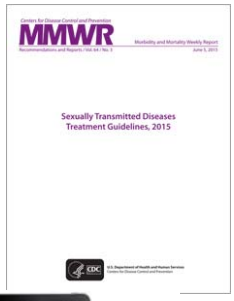
If all tests normal, can consider BPG 50,000 U/kg IM x 3 in weekly intervals

Online resources @ STD.ca.gov



More resources



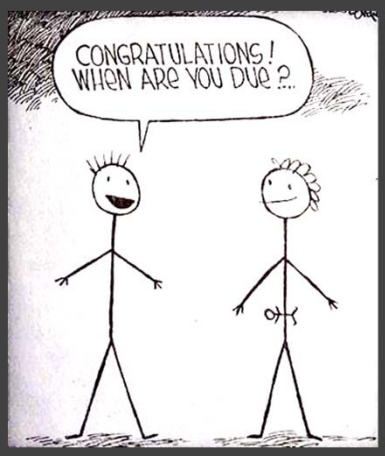


https://www.STDCCN.org

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

Questions? Comments?

Acknowledgments: Heidi Bauer MD MS, Ashley Dockter MPH, Jennifer Harmon MPH, Nicole Burghardt MPH



Thank you

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