Congenital Infections: Syphilis, CMV

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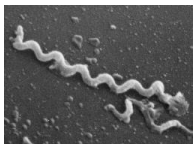
- I have nothing to disclose

Congenital Syphilis

Microbiology

- Treponema pallidum



- Spiral shaped
- Spin around their long axis in a corkscrew manner.
- Cannot be cultured in vitro
- Cannot be viewed by normal light microscopy

Pathogenesis

- Penetration:
  - T. pallidum enters the body via skin and mucous membranes through abrasions during sexual contact
  - Transmitted transplacentally from mother to fetus during pregnancy
- Dissemination:
  - Travels via the circulatory system (including the lymphatic system and regional lymph nodes) throughout the body
  - Invasion of the central nervous system (CNS) can occur during any stage of syphilis.

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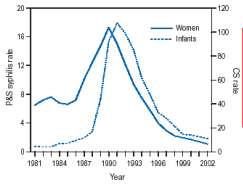
Congenital Syphilis Epidemiology

- Incidence increasing since 2005
  - "The World Health Organization estimates that 1 million pregnancies are affected by syphilis worldwide. Of these, 460,000 will result in stillbirth, hydrops fetalis, abortion, or perinatal death; 270,000 will result in an infant born preterm or with low birth weight; and 270,000 will result in an infant with stigmata of congenital syphilis."
- United States
  - After 14 years of decline in the United States, the rate of congenital syphilis increased 15.4% between 2006 and 2007 (from 9.1 to 10.5 cases per 100,000 live births). In 2007, 430 cases were reported, an increase from 373 in 2006. This increase in the rate of congenital syphilis may relate to the increase in the rate of P&S syphilis among women that has occurred in recent years.

Congenial Syphilis Epidemiology

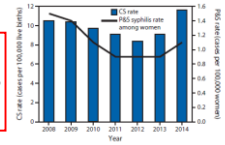
FIGURE 1. Rates of congenital syphilis (CS) among infants* and primary and secondary (P&S) syphilis among women†, by year — United States, 1981–2002



* Per 100,000 live-born infants.
† Per 100,000 population.

The incidence of congenital syphilis corresponds to the incidence of disease in women.

FIGURE. Congenital syphilis (CS) rate* among infants aged <1 year and rate of primary and secondary (P&S) syphilis among women† — United States, 2008–2014§



* CS rates during 2008–2013 were calculated by using annual live birth data as denominators. Available at http://wonder.cdc.gov/natality-current.html.
† P&S syphilis rates during 2008–2013 were calculated by using bridged race U.S. Census population estimates as denominators. Available at http://wonder.cdc.gov/bridged-race-v2013.html.
§ The CS rate and P&S syphilis rate for 2014 were calculated by using 2014 case counts and 2013 denominators.

www.cdc.gov

Congenital Syphilis-Increase in the US, MMWR Nov. 2015

- In the US, the rate of CS decreased during 1991–2005 but increased slightly during 2005–2008.
- To assess recent trends in CS, CDC analyzed national surveillance data reported during 2008–2014, calculated rates, and described selected characteristics of infants with CS and their mothers.
- The overall rate of reported CS increased to 11.6 cases per 100,000 live births in 2014
  - highest CS rate reported since 2001

Congenital Syphilis-Increase in the US, MMWR Nov. 2015

TABLE 1. Number and rate* of congenital syphilis (CS) cases by race/ethnicity of mother and region of birth of infant — United States, 2008–2014†

	2008		2009		2010		2011		2012		2013		2014	
Characteristic	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
Race/ethnicity of mother														
White, non-Hispanic	67	2.9	65	2.9	63	2.9	50	2.3	50	2.3	61	2.8	80	3.7
Black, non-Hispanic	226	35.9	216	35.1	216	36.3	211	35.9	189	32.1	185	31.4	225	38.2
Hispanic	135	13.0	128	12.8	91	9.6	73	8.0	80	8.8	92	10.2	110	12.2
Asian/Pacific Islander	7	2.9	11	4.6	9	3.8	14	5.7	6	2.3	9	3.5	18	7.0
American Indian/Alaska Native	6	13.8	5	11.8	1	2.5	2	5.0	2	5.1	5	12.8	5	12.8
Other	1	N/A	2	N/A	3	N/A	3	N/A	4	N/A	3	N/A	7	N/A
Unknown	4	N/A	4	N/A	4	N/A	5	N/A	3	N/A	4	N/A	13	N/A
Region of birth of infant§														
Northeast	37	5.5	30	4.5	26	4.0	23	3.6	17	2.7	17	2.7	30	4.8
Midwest	37	4.2	41	4.7	46	5.3	41	4.9	57	6.8	53	6.4	71	8.5
South	265	16.4	263	16.7	253	16.6	234	15.5	206	13.7	213	14.1	234	15.5
West	107	10.1	97	9.5	63	6.4	60	6.2	54	5.5	76	7.9	123	12.8
Total	**446**	**10.5**	**431**	**10.4**	**387**	**9.7**	**358**	**9.1**	**334**	**8.4**	**359**	**9.1**	**458**	**11.6**

* CS rates during 2008–2013 were calculated as cases per 100,000 live births by using annual live birth data as denominators. Available at http://wonder.cdc.gov/natality-current.html.
† The CS rates for 2014 were calculated by using 2014 case counts and 2013 denominators.
§ *Northeast*: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; *Midwest*: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; *South*: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia; *West*: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming.

Congenital Syphilis-Increase in the US, MMWR Nov. 2015

Clinical Results

- Among 428 CS patients born alive in 2014, 28 (6.5%) had one or more clinical sign or symptom of CS infection
- The most commonly reported signs were:
  - syphilitic rash (n = 8)
  - jaundice (n = 8)
  - hepatosplenomegaly (n = 5)
- An additional 49 (11.4%) had other evidence of CS infection:
  - long bone x-ray findings consistent with CS
  - reactive cerebrospinal fluid (CSF) venereal disease research laboratory test
  - elevated CSF white blood cell count or protein level in the absence of another etiology

Congenital Syphilis-Increase in the US, MMWR Nov. 2015

Clinical Results

- CDC recommends that all pregnant women be screened for syphilis at their first prenatal visit.
- Women at increased risk for syphilis and women living in high-morbidity geographic areas should also be screened at the beginning of their third trimester and again at delivery.

TABLE 3. Characteristics of infants with congenital syphilis (CS) and their mothers — United States, 2008–2014

Characteristic	2014 (N = 458) No. (%*)
Infant	
Symptom status of infants born alive	
Total born alive	428 (100.0)
Signs or symptoms of CS[†]	28 (6.5)
Asymptomatic	343 (80.1)
Unknown	57 (13.3)
Treatment regimen of infants born alive	
Total born alive	428 (100.0)
Aqueous or procaine penicillin (10 days)	301 (70.3)
Benzathine penicillin (1 dose)	50 (11.6)
Other	33 (7.7)
No treatment	42 (9.8)
Unknown	2 (0.5)
Mother	
Mother received prenatal care	
Yes	314 (68.6)
No	100 (21.8)
Unknown	44 (9.6)
Treatment status among mothers who received prenatal care	
Total receiving prenatal care	314 (100.0)
Adequate treatment[§]	43 (13.7)
Inadequate treatment: <30 days before delivery	78 (24.8)
Inadequate treatment: Nonpenicillin therapy	3 (1.0)
Inadequate treatment: Not enough penicillin for mother's stage of infection	13 (4.1)
No treatment	135 (43.0)
Unknown	42 (13.4)

* Percentages might not sum to 100% because of rounding.
† Signs and symptoms of CS in an infant or a child aged <2 years included condyloma lata, snuffles, syphilitic rash, hepatosplenomegaly, jaundice/hepatitis, pseudoparalysis, or edema (nephrotic syndrome, malnutrition, or both).
§ Treatment is considered adequate if mothers are treated with a course of benzathine penicillin G appropriate for their stage of syphilis infection and treatment is initiated ≥30 days before delivery. Syphilis treatment guidelines are available at http://www.cdc.gov/std/tg2015/syphilis.htm.

Congenital Syphilis-Increase in the US, MMWR Nov. 2015

Summary

What is already known on this topic?

The rate of congenital syphilis (CS) in the United States decreased during 1991–2005 but increased slightly during 2005–2008.

What is added by this report?

Although the rate of CS steadily decreased during 2008–2012 (10.5 cases to 8.4 cases per 100,000 live births), the rate increased during 2012–2014 (11.6 cases per 100,000 live births in 2014), reflecting an increase in the national rate of primary and secondary syphilis among women. The 2014 CS rate is higher than seen in over a decade.

What are the implications for public health practice?

CS and its complications can be prevented by rapidly responding to syphilis increases among women of reproductive age and men who have sex with women, and by quality prenatal care, which includes screening and treatment for syphilis.

Congenital Syphilis-Increase in the US, MMWR Nov. 2015

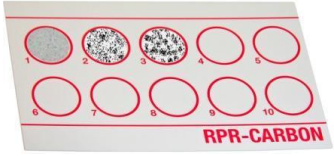
CDC Provider Letter 2015-Recommendations

- This recent increase in congenital syphilis is evidence of missed opportunities for prevention within the public health and the health care systems. As public health and medical officials, you should:
  - Be aware of syphilis trends in women and MSW, and local congenital syphilis trends.
  - Public health departments can reduce syphilis transmission within the community through partner services and screening programs for women and MSW.
  - Take a sexual history.
    - Talk to your patient and provide counseling about STD prevention.
  - Know who to test and when:
    - Screen all pregnant women for syphilis at the first prenatal visit.
    - Repeat screenings for women at high risk and in areas of high morbidity early in the third trimester and again at delivery.

CDC Provider Letter 2015-Recommendations

- If she has syphilis, take immediate action by treating her according to CDC's STD Treatment Guidelines.
- Test and treat her sex partner(s) to avoid reinfection.
- Report all cases of syphilis and congenital syphilis to your local or state health department.
- Before discharging the mother or infant from the hospital, make sure the mother has been tested for syphilis at least once during pregnancy or at delivery.
  - If she tests positive, manage the infant appropriately.
- Many cases of congenital syphilis are due to a lack of prenatal care. Even among those receiving some prenatal care, the detection and treatment of maternal syphilis often occurs too late to prevent congenital syphilis. Women who are uninsured or underinsured, and women with substance use issues have been found to be at increased risk for receiving inadequate or no prenatal care, placing their unborn babies at increased risk for congenital syphilis.
- Any woman who delivers a stillborn infant should be tested for syphilis.

Syphilis Testing



Laboratory Diagnosis

- Identification of Treponema pallidum in lesion exudate or tissue
  - Darkfield microscopy
- Serologic tests to allow a presumptive diagnosis
  - Nontreponemal tests
  - Treponemal tests

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Darkfield Microscopy

- What to look for
  - T. pallidum morphology and motility
- Advantage
  - Definitive immediate diagnosis
  - Rapid results
- Disadvantages
  - Requires specialized equipment and an experienced microscopist
  - Possible confusion with other pathogenic and nonpathogenic spirochetes
  - Must be performed immediately
  - Generally not recommended on oral lesions
  - Possibility of false-negatives

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Serologic Tests for Syphilis

- Two types
  - Treponemal (qualitative)
  - Nontreponemal (qualitative and quantitative)
- The use of only one type of serologic test is insufficient for diagnosis
  - False-positive nontreponemal test results occur with various medical conditions
  - Treponemal tests stay positive long after syphilis has been treated adequately and can be false positive with other spirochetal diseases

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Nontreponemal Serologic Tests

- Principles
  - Measure antibody directed against a cardiolipin-lecithin-cholesterol antigen
  - Not specific for T. pallidum
  - Titers usually correlate with disease activity and results are reported quantitatively
  - May be reactive for life, referred to as "serofast"
- Nontreponemal tests include VDRL and RPR

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Nontreponemal Serologic Tests

- Advantages
  - Rapid and inexpensive
  - Easy to perform and can be done in clinic or office
  - Quantitative
  - Used to follow response to therapy
  - Can be used to evaluate possible reinfection
- Disadvantages
  - May be insensitive in certain stages
    - Early primary syphilis, latent acquired syphilis of long duration and late CS
  - False-positive reactions may occur:
    - EBV, hepatitis, varicella, measles
    - Lymphoma
    - TB
    - Malaria
    - Endocarditis
    - Pregnancy
    - Connective tissue disease
    - IV drug abuse
    - Laboratory error
    - Wharton jelly contamination from the umbilical chord (not a recommended source of blood)
  - Prozone effect may cause a false-negative reaction (rare)

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Treponemal Serologic Tests

- Principles
  - Measure antibody directed against T. pallidum antigens
  - Qualitative
  - Usually reactive for life
  - Titers should not be used to assess treatment response
- Treponemal tests include TP-PA, FTA-ABS, TP-EIA, and TP-CIA
- Not 100% specific for syphilis
  - Positive tests occur in patients with other spirochetal diseases
    - Yaws
    - Pinta
    - Leptospirosis
    - Rat-bite fever
    - Relapsing fever
    - Lyme disease

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Syphilis Testing

- CDC recommends syphilis serologic screening with a nontreponemal test and confirmation with a treponemal test
- Some institutions use a "reverse sequence screening" approach
  - A treponemal test first and confirming with the non-treponemal test
  - CDC has reaffirmed its recommendation not to use the reverse sequence screening as this can lead to high rates of false-positive results
  - "The traditional algorithm performs well in identifying people with active infection who require further evaluation and treatment while minimizing false-positive results in low-prevalence populations"

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Congenital Syphilis Clinical Manifestations

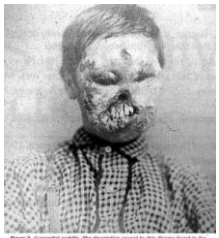

Figure 2. Congenital syphilis. The devastation caused by this disease found in the prepenicillin era was horrible.[3]

Congenital Syphilis

- Occurs when T. pallidum is transmitted from a pregnant woman to her fetus
- Congenital syphilis lack a primary stage
  - disseminated through blood
- May lead to stillbirth, neonatal death, and infant disorders such as deafness, neurologic impairment, and bone deformities
- Transmission can occur during any stage of syphilis
  - risk is much higher during primary and secondary syphilis
- Fetal infection can occur during any trimester of pregnancy
- Wide spectrum of severity exists; only severe cases are clinically apparent at birth
  - 60% of patients are asymptomatic

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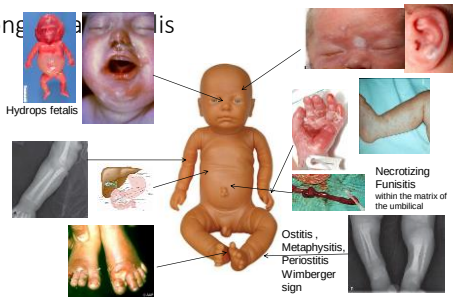
Early Congenital Syphilis

- Clinical Manifestations before the age of 2 years
- 2/3rds of infants with congenital syphilis are asymptomatic at birth
  - Most will present with symptoms by 3 months of age
- Approximately 40-60% of symptomatic infants at birth have at least one of the following:
  - HSM
  - Nasal discharge
  - Mucocutaneous Lesions/Desquamation
  - LAD
  - Skeletal abnormalities
  - Hydrops Fetalis
  - Hemolytic Anemia/Thrombocytopenia

Musculoskeletal Manifestations

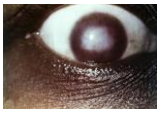
- Pseudoparalysis of Parrot: lack of movement of an extremity due to pain associated with bone lesion
- Long-Bone Radiographs:
  - Bilateral, symmetric and polyostotic (femur, humerus and tibia)
  - Diaphyseal Periostitis: Irregular periosteal thickening with new bone formation
  - Wegner sign: Metaphyseal serration (sawtooth metaphysis)
  - Wimberger sign: Demineralization and osseous destruction of the upper medial tibia
  - Irregular areas of increased density and rarefaction (moth-eaten appearance)

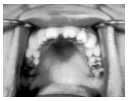
Cong[illegible]is



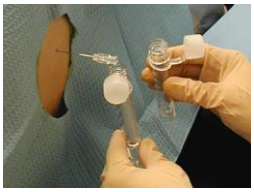
Late Congenital Syphilis

- Hutchinson teeth, mulberry molars
- Interstitial keratitis (5–20 years of age)
- Eighth cranial nerve deafness (10–40 years of age)
- Bowing of shins and Clutton joints





Congenital Syphilis Evaluation



Evaluation of Newborn with Congenital Syphilis

- Physical Examination
- Quantitative non-treponemal serologic test of serum from the infant for syphilis (not from cord blood)
- VDRL and cell count, protein, glucose from CSF
- Long bone X-rays
- Complete blood cell and platelet count
- Other tests include:
  - Chest X-ray
  - LFTs
  - neuroimaging
  - Eye Exam
  - ABR Hearing test

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Who Should Be Evaluated? Treated?

Evaluation of Newborn with Congenital Syphilis

- Must know mother's serological status for syphilis and history of prior treatment
  - Blood cord testing is inadequate for screening (could be non-reactive even when the mother is +)
- Infants born from seropositive mothers require a careful examination and a quantitative non-treponemal test (same test should be performed on the mother)
- Once this information is obtained, follow the decision making tree…

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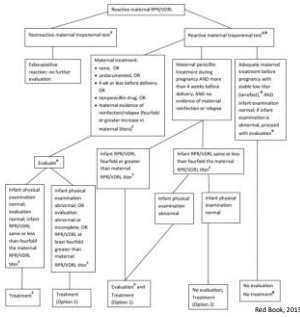

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RPR indicates rapid plasma reagin; VDRL, Venereal Disease Research Laboratory; TP-PA, *Treponema pallidum* particle agglutination; FTA-ABS, fluorescent treponemal antibody absorption; TP-EIA, T pallidum enzyme immunoassay; MHA-TP, Microhemagglutination test for antibodies to T pallidum.
* TP-PA, FTA-ABS, TP-EIA, or MHA-TP.
† Test for human immunodeficiency virus (HIV) antibody. Infants of HIV-infected mothers do not require different evaluation or treatment.
‡ A fourfold change in titer is the same as a change of 2 dilutions. For example, a titer of 1:64 is fourfold greater than a titer of 1:16, and a titer of 1:4 is fourfold lower than a titer of 1:16.
§ Women who maintain a VDRL titer 1:2 or less or an RPR 1:4 or less beyond 1 year after successful treatment are considered serofast.
‖ Complete blood cell (CBC) and platelet count; cerebrospinal fluid (CSF) examination for cell count, protein, and quantitative VDRL; other tests as clinically indicated (eg, chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brainstem response).
¶ Treatment (Option 1 or Option 2, below), with many experts recommending Treatment Option 1. If a single dose of benzathine penicillin G is used, then the infant must be fully evaluated, full evaluation must be normal, and follow-up must be certain. If any part of the infant's evaluation is abnormal or not performed, or if the CSF analysis is rendered uninterpretable, then a 10-day course of penicillin is required.
# Some experts would consider a single intramuscular injection of benzathine penicillin (Treatment Option 2), particularly if follow-up is not certain.
Treatment Options:
(1) Aqueous penicillin G, 50 000 U/kg, intravenously, every 12 hours (1 week of age or younger) or every 8 hours (older than 1 week); or procaine penicillin G, 50 000 U/kg, intramuscularly, as a single daily dose for 10 days. If 24 or more hours of therapy is missed, the entire course must be restarted.
(2) Benzathine penicillin G, 50 000 U/kg, intramuscularly, single dose.

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Who Should Be Evaluated for Congenital Syphilis?

- If mom is:
  - untreated, inadequately treated, or treatment not documented
  - Treated with a non-penicillin regimen (i.e.,erythromycin)
  - Appropriately treated with PNC, but without the expected decrease in treponemal titers
  - Syphilis treated < 1 month prior to delivery
  - Syphilis treated before pregnancy but with insufficient serologic f/u to assess response
  - Maternal evidence of reinfection/relapse
    - maternal titers have increased to > 4 fold
  - Infant's titer is 4 fold greater than the mother's titers
  - Infant's titer is less than 4 fold greater than mother's titer but exam is abnormal

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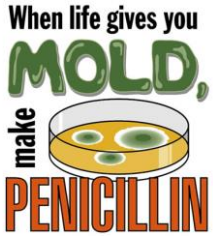
Congenital Syphilis Treatment



Maternal Syphilis Diagnosis and Treatment

- Test During Pregnancy :
  - All women should be screened for syphilis with a non Treponemal test – RPR / VRDL – early in pregnancy and preferably again at delivery .
  - In high risk areas testing at the beginning of 3rd Trimester is also recommended.
  - All Positive tests should be confirmed with a Treponemal test FTS-ABS /TPPA.
    - Some hospitals do a reverse screen in which they perform the Treponemal test first and confirm with the non Treponemal test.
- For women treated during pregnancy follow up serology testing is necessary to assess efficacy of therapy.
- Treatment with penicillin is the gold standard.
  - maternal treatment with penicillin is 98% effective at preventing CS

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Maternal Syphilis Diagnosis and Treatment

- A single dose of Benzathine Penicillin therapy for early disease is only appropriate when it is possible to document that there was a non reactive Syphilis test within the last Year.
- Some give a second dose of Benzathine Penicillin 1 week after the first to improve the likelihood of a serology response in early disease.
- In all other cases the disease should be consider Latent syphilis of unknown duration for which 3 doses of Benzathine penicillin at weekly intervals are recommended.
- Follow up titers at 1,3,6,12 and 24 months decreases fourfold by 6 months and becomes negative by 12-24 months. Failure to decrease titers is likely to be failure of treatment or reinfection.

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Syphilis Treatment

- Times you have to desensitize patients to PCN as Parenteral penicillin G is the only documented effective therapy for these patients:
  - Syphilis during pregnancy
  - Neurosyphilis
  - Congenital Syphilis
- Skin testing for penicillin hypersensitivity with the major and minor determinants is reliable in identifying people at high risk of reacting to PCN
  - Only the major determinant PCN G tests are made commercially
  - If only test against major determinants, will miss 3-10% of allergic patients at risk of serious or fatal reactions

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CS Treatment: Infants in First Month of Age

- For proven or probable congenital syphilis:
  - Aqueous crystalline penicillin G, administered IV x 10 days
  - 1-7 day old: 50,000 U/Kg q 12 hours
  - >= 8 days old: 50,000 U/Kg q 8 hours
  - If more than one day of therapy is missed, the whole 10 day course should be repeated.
- If neonate is at risk of CS because of inadequate maternal treatment or response to treatment during pregnancy but the neonate's PE/imaging/labs are normal:
  - Most recommend 10 days treatment but some would give one dose of penicillin G benzathine (50,000 U/Kg IM)

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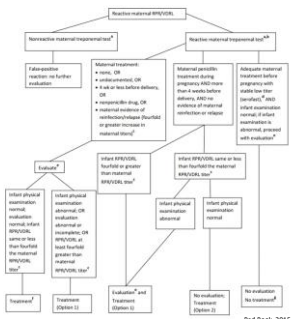
CS Treatment: Infants in First Month of Age

- Infants with normal PE and RPR less than fourfold higher than the maternal titer are at minimum risk of syphilis if:
  - They are born to mothers who completed appropriate PCN tx for syphilis during pregnancy and more than 4 weeks prior to delivery AND
  - Mother had no evidence of reinfection or relapse
  - Treat these patients with the single IM penicillin G benzathine
  - May want to examine patient monthly until RPR returns to normal
- Infants with normal PE and RPR either the same or lower than the maternal RPR AND
  - Whose mother's treatment was adequate before pregnancy AND
  - Whose mother's RPR remained low and stable before and during pregnancy and at delivery
  - Require NO evaluation
  - If follow up is uncertain, some would treat with one dose of IM penicillin G benzathine

Red Book, 2015 Report of the Committee of Infectious Diseases



Red Book, 2015 Report of the Committee of Infectious Diseases

CS Treatment: Older Infants and Children

- Any infant older than 1 months who possible have CS or who have neurologic involvement should be treated with IV aqueous crystalline penicillin x 10 days.
- Also use above treatment for children older than 2 years who have late and previously untreated CS.
  - Some experts advise to give a dose of IM penicillin G benzathine after the 10 days IV penicillin course
  - If the patient has no clinical manifestations of disease, the CSF examination is normal and the CSF-VDRL is negative, some experts treat with 3 weekly doses of IM penicillin G benzathine

Red Book, 2015 Report of the Committee of Infectious Diseases

CS Follow Up (normal CSF)

- CS:
  - Receive careful follow-up evaluations during well-child visits at 2, 4, 6 and 12 months of age
  - RPR should be performed every 2-3 months until it becomes NR or the titer has decreased at least fourfold
    - CDC recommends following RPR until the titer is NR
  - In the neonate who was not treated because congenital syphilis was considered less likely or unlikely, RPR should be decreased by 3 months of age and should be NR by 6 months of age.
    - if the RPR is still reactive at 6 months, the infant is likely to be infected and should be treated
  - The serologic response after therapy may be slower for infants treated after the neonatal period
  - Patients with increasing titers or persistent stable titers at 6-12 months after initial treatment should be reevaluated, including CSF, and treat with a 10 day course of IV penicillin

Red Book, 2015 Report of the Committee of Infectious Diseases; CDC Congenital Syphilis Treatment Recommendations

CS Follow Up (abnormal CSF/positive CSF VDRL)

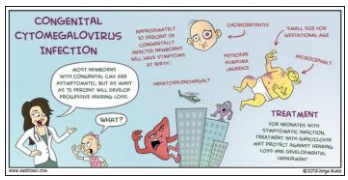
- Follow already outlined testing for RPR, AND
- Repeated clinical evaluation and CSF examination at 6 month intervals until their CSF examination is normal.
  - A reactive CSF VDRL test or abnormal CSF indices at the 6 month interval are indications for retreatment
  - Repeat neuroimaging should be considered

Red Book, 2015 Report of the Committee of Infectious Diseases

Congenital Syphilis Conclusions

- The incidence of congenital syphilis corresponds to the incidence of disease in women.
- All pregnant women should be tested 1st trimester and in the beginning of 3rd Trimester and at delivery if at increased risk.
- All positive test should be confirmed with a Treponemal Test , treat and follow up titers as per protocol.
  - Some institutions use a "reverse sequence screening" approach, testing the treponemal test first and confirming with the non-treponemal test
- Documentation is an important aspect in the evaluation of treatment.
- If CS is suspected, please consult with and pediatric infectious diseases specialist and/or follow treatment protocols provided by the AAP (2015 Red Book) or the CDC.

Congenital CMV



Virology

- Largest virus to infect humans
- Member of the human herpesvirus group
  - HHV-5
- All members of the herpesvirus family share common characteristics including
  - a genome of double-stranded linear DNA
  - virus capsid of icosahedral symmetry
  - viral envelope
  - Biological properties including latency and reactivation
- CMV replicates slowly
  - Can take as long as 24 hours to produce virus progeny in infected cells
  - several days to weeks to produce visible cytopathic effect in laboratory cell lines

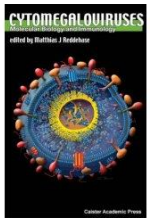
Principles and Practice of Infectious Diseases, 6th Edition

Virology

- CMV genome
  - Linear, double-stranded DNA molecule
  - 225-230 kbp
  - Encodes 230 proteins
    - CMV DNA polymerase
      - Target of ganciclovir
    - UL97 (phosphotransferase protein)
      - Phosphorylates ganciclovir to make it active
- No distinct serotypes of CMV exist
  - strain differences can be detected by molecular analysis of DNA
    - provides a classification of genotypes

Virology

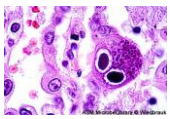
- CMV Structure
  - Nucleoprotein core
    - Wraps CMV double-stranded DNA
  - Matrix proteins
    - Surrounds nucleoprotein core
  - Lipid envelope
    - surrounds the matrix and inner core
    - Contains viral glycoproteins important for viral entry

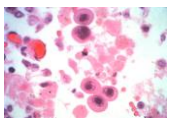


Principles and Practice of Infectious Diseases, 6th Edition

CMV Infection

- CMV infects cells by endocytosis
- CMV genome is uncoated within cell
- DNA protein core is transported to the nucleus of the cell
- Viral DNA polymerase is synthesized and CMV replication occurs in the nucleus
  - Inclusion bodies are aggregates of replicating CMV nucleoprotein cores
- New virus is created and sent to infect new cells





Principles and Practice of Infectious Diseases, 6th Edition

Epidemiology

- In developing countries, most children are infected by 3 years of age
- In developed countries, as many as 60 to 80 percent of the population will be infected with CMV by adulthood

Epidemiology

- CMV is the most common congenital viral infection
- Acquisition of CMV in the infant can occur two ways
  - Prenatal infection in utero = Congenital CMV
    - Can occur secondary to primary or reactivation of CMV in the mother
  - Perinatal infection via delivery, blood transfusion or breastfeeding
- Congenital CMV (cCMV) occurrence estimated to 0.6% of all deliveries in the developed world
  - US = approximately 40,000 infants infected annually

Cytomegalovirus, Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th ed, 2014.

Epidemiology

- Estimated that approximately 40% of women with primary CMV infection during pregnancy will transmit virus to her fetus
  - Infants more likely to have symptomatic infection and have a high risk to develop sequelae
- Women with CMV immunity will transmit virus to her fetus in approximately 1% of all pregnancies
  - Typically, infant infection will by asymptomatic with little neurodevelopmental morbidity
- Women who are seropositive for CMV can be infected with a new strain of CMV creating a new primary CMV infection

Rev Med Virol. 2007;17(4):253

Congenital CMV

- Most newborns with cCMV appear normal and are asymptomatic
  - 5 to 15 percent newborns with cCMV will have symptoms at birth
- Both primary and recurrent infection of CMV in the mother during pregnancy can result in congenital infection of the infant
  - rate of transmission is higher for mothers with primary infection (40% versus <1 % transmission)

Rev Med Virol. 2007;17(4):253

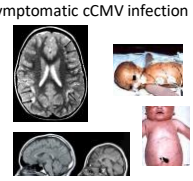
Congenital CMV

- Infants born congenitally infected with CMV as a result of a primary maternal infection also are much more likely to have symptoms at birth
  - Mortality rate = 30% (in infants with Cytomegalic Inclusion Disease)
  - Severe neurologic morbidity = 80%
- The societal costs for surviving infants and children with cCMV infections is approximately 1.9 billion/year (in 1992 dollars)

Yow et al, New England Journal of Medicine: 1992

Cytomegalic Inclusion Disease (CID) of the newborn

- Occurs in 50% of newborns with symptomatic cCMV infection
- Symptoms
  - Jaundice (67%)
  - Hepatosplenomegaly (60%)
  - Petechial rash (76%)
  - Multiple organ involvement
  - CNS
    - Microcephaly
    - Chorioretinitis
    - Periventricular calcifications
    - Poorer prognosis if have brain and ocular abnormalities



Cytomegalic Inclusion Disease (CID) of the newborn

- Laboratory Abnormalities
  - Thrombocytopenia
  - Anemia
  - Increased AST/ALT
  - Bilirubinemia
- Can see lethargy, respiratory distress and seizures after birth
- HSM and jaundice may subside
- Neurologic sequelae, microcephaly and MR persist

Neurological Complications

- Brain
  - Multiple abnormalities can occur including calcifications, PVL, ventriculomegaly, vasculitis and hydranencephaly
  - Sequelae most often is mental retardation
- Sensorineural hearing loss
  - Seen in up to 65% of infants with symptomatic infections
  - Hearing loss is progressive and occurs over the 1st six years of life
    - Etiology of progressive hearing loss is unknown
      - Reactivation of virus
      - Immunologic response of the host to the virus
      - Delayed clinical appearance of damage already present

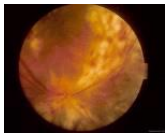
Michaels et al, PIDJ: 2003

Neurological Complications

- Ocular Abnormalities
  - Can see chorioretinitis, retinal scars, optic atrophy and central vision loss
  - Visual impairment is more common in symptomatic infections vs. asymptomatic infections
    - CMV retinitis can occur up to 25% of infants with severely symptomatic cCMV and approximately 1% of infants with silent infections
  - Retinitis usually does not progress after birth if the infant is otherwise immunocompetent
  - Most experts would treat CMV retinitis if it is an actively progressing necrotizing retinitis
    - Goal is to stop the spread of the retinitis before central vision is lost or retinal detachment occurs

Barampouti, Br. J. Ophthalmol: 2002

Brushfire Retinitis



- Typical ocular lesion found in cCMV
- White perivascular infiltrate with hemorrhage

Asymptomatic Infection

- The majority of infants with cCMV are asymptomatic
- Some of these infants are picked up on routine hearing screens
  - Sensorineural hearing loss can appear in up to 10% of infants who present as "silent" cCMV
    - Multiple studies in the 1970-1980's show that not only can silent infection cause hearing loss, but this can interfere with learning abilities
    - Bopanna et al, 2005 Pediatrics
      - Showed that among children with silent disease, those with hearing loss had a significantly greater amount of CMV in urine (P = .03) during infancy than those with normal hearing.
      - Infants with < 5 x 10(3) cfu/mL of urine CMV and infants with < 1 x 10(4) copies/mL of viral DNA in blood were at a lower risk for hearing loss.

Perinatal Infections

- Usually asymptomatic
- Occurs when already infected mother passes virus to infant during…
  - Delivery
  - Breastfeeding
    - Concerning for low-birth premature infants
  - Less commonly, blood transfusion
- Subtle effects on hearing and intelligence have been reported

Diagnosis

- Confirmation of cCMV occurs when there is isolation of the virus in urine or saliva in the first 2-4 weeks of the infants life
  - Preferred diagnosis is Urine CMV PCR (much faster)
  - Viral Cutlure:
    - `Actual viral culture can take up to 6 weeks of incubation time for the result
    - Shell Vial Assay
      - Concentrate clinical specimen by spinning in centrifuge
      - Place concentrate on a cell monolayer
      - Following incubation in tissue culture, cells are stained with a monoclonal antibody to a CMV-specific antigen
      - Positive shell vial assay is presumptive evidence of active CMV disease
- Important to obtain urine for PCR or shell vial prior to the infants 4 week birthday
  - A positive result after the 4 weeks could represent perinatal infection with CMV

Diagnosis

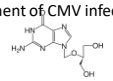
- Serology
  - CMV IgM is too non-specific to reliably diagnose congenital CMV alone
    - Vary in accuracy for identification of primary infection in the neonate (Red Book, 2015)
  - If there is positive CMV IgM serology, it is optimal to have a positive CMV shell vial assay in addition

Treatment

- Ganciclovir??
- Valganciclovir??
- Nothing???

Ganciclovir

- First compound licensed specifically for treatment of CMV infections
  - Treatment of choice for severe CMV infections
- Synthetic acyclic nucleoside analog
  - Structurally similar to guanine
- Requires phosphorylation for antiviral activity
- After phosphorylation, ganciclovir triphosphate metabolite exerts the antiviral effect by inhibition of CMV polymerase



Schleiss; Seminars in Pediatric Infectious Diseases; 2004

Ganciclovir Side Effects

- Myelosuppression
  - Leukopenia (30-40%)
    - Neutropenia = 14%
  - Anemia (20-25%)
  - Thrombocytopenia (6%)
  - Usually dose-limiting in newborns
- Neuropathy (8-9%)
- Elevated liver transaminases
- Nephrotoxicity

Schleiss; Seminars in Pediatric Infectious Diseases; 2004
Lexi-comp

Congenital CMV and Ganciclovir

- First report of ganciclovir use for cCMV infections were in the late 1980's
- Shown to be generally safe and tolerated in newborns
- Useful in treating severe CMV end-organ disease
  - Pneumonitis, hepatitis, sight threatening retinitis
- Does ganciclovir provide any long-term benefit for infants with cCMV infection?

Congenital CMV and Ganciclovir

- A phase II, randomized controlled multicenter clinical trial evaluated using ganciclovir for treatment of symptomatic cCMV
  - Study showed there was a decreased viral load found in urine during antiviral administration
    - Viuria returned once ganciclovir was stopped
  - 16% of infants had stabilization or improvement of hearing at the 6th month follow-up appointment

Whitley et al, JID: 1997

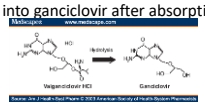
Congenital CMV and Ganciclovir

- A phase III, randomized clinical trial of ganciclovir therapy in infants with cCMV and at least one neurologic symptom
  - 84% of ganciclovir treated infants showed stable or improved hearing
  - 59% of the control group showed stable or improved hearing
  - Suggested that treatment with ganciclovir prevented worsening hearing at the six month follow-up appointment
    - Limited data because only 42% of subjects (25 treated and 17 control) returned for the 6 month follow-up appointment
    - Also, neutropenia was seen in 63% of ganciclovir treated infants versus 21% of control infants

Kimberlin et al, Journal of Pediatrics: 2003
Prober et al, Journal of Pediatrics: 2003

Valganciclovir (VGCV)

- Valine ester of ganciclovir
- Great oral bio-availability
- Metabolized quickly into ganciclovir after absorption



- Side Effects
  - Identical to ganciclovir

Schleiss; Seminars in Pediatric Infectious Diseases; 2004

Congenital CMV and Valganciclovir

- Neonates with symptomatic cCMV (with or without CNS disease)
  - Improved audiologic and neurodevelopmental outcomes at 2 years of age with treated with oral valganciclovir x 6 months
    - 16 mg/kg/dose BID
    - Should adjust dose monthly for weight gain
    - Should monitor CMP/CBC monthly for side effects
      - Significant neutropenia occurs in 1/5 of infants
- Neonates with asymptomatic cCMV should not receive antiviral treatment.

2015 Report of the Committee on Infectious Diseases
Kimberlin, n engl j med 372;10, 2015

CMV Neonatal Screening???

- Utah was the first state to require all babies who fail NB hearing screening undergo CMV testing within the first 3 weeks of life (unless parents decline).
  - Identified 14 CMV-positive infants
    - 6 had true hearing loss by ABR
- CHIMES Study (CMV and Hearing Multicenter Screening)
  - Approximately 100,000 babies had CMV testing and newborn hearing screening (NHS) over 7 US medical centers
    - Saliva PCR is screening test with urine PCR as confirmatory test
  - Among cCMV infants who failed NHS, diagnostic testing confirmed that 65% of those had SNHL
  - Targeted screening identified the majority of infants with CMV-related SNHL at birth.
  - However, 43% of infants with CMV-related SNHL in the neonatal period and cCMV infants who are at risk for late onset SNHL where not identified by NHS.
    - Targeting screening misses some cCMV neonates
    - Universal Screening???
  - CHIMES researchers found that both universal and targeted screening would be cost effective.

Pediatrics 2017;139:e20162128

CMV Neonatal Screening???

- Problems with cCMV screening:
  - States would need new infrastructure to collect and test saliva or urine
    - Current bloodspots aren't as sensitive and specific for picking up CMV
    - New studies going on by CDC and the Minnesota Department of Health and the University of Minnesota
  - Need more data/outcomes on using valganciclovir in neonates with asymptomatic Congenital CMV
  - Remember-up to 80% of CMV-positive newborns don't lose their hearing

Clinical Laboratory News, AACC.org, April 2017

Conclusions

- cCMV is the most common viral congenital infection
- Infants with symptomatic congenital CMV can (I think should) be treated with antivirals.
  - a combination of IV ganciclovir and PO valganciclovir
    - Use if patient unable to use GI tract
  - PO valganciclovir
- Treatment duration is 6 months
- Screening for cCMV may be the way of the future