Fellow Column: Overview of Syphilis with a Discussion of Four Cases of Congenital Syphilis

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Introduction

Syphilis, caused by the spirochete *Treponema pallidum*, has a long history of human involvement, with recorded outbreaks dating back to the 1400s. (1) The majority of syphilis cases are sexually acquired, but any contact with spirochetes may lead to infection (2). Because syphilis has been recorded for so long, including the pre-antibiotic era, the disease course with and without treatment is well understood. Additionally, the infamous Tuskegee trial followed 431 black men with untreated syphilis, even though there was a known cure.(3)

Treponemal infection elicits both an adaptive and humoral immune response. The duration and progression of infection depend on the immune response mounted. (4) Stronger delayed-type hypersensitivity (DTH) reactions are associated with a better outcome, with total eradication of spirochetes in some cases; however, the majority of untreated cases proceed to prolonged latency. Individuals that respond initially with antibody production or a cytotoxic CD8 response are more likely to progress to secondary and tertiary disease. In primary syphilis, a delayed-type hypersensitivity reaction (DTH) is responsible for a painless well-circumscribed chancre. An initial cytotoxic t-cell response is associated with prolonged infection and progression to tertiary disease.

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Progression of syphilis in adults

Primary syphilis occurs when spirochetes access subcutaneous tissues via microscopic abrasions. (2) The adaptive response consists of an infiltration of neutrophils and antigen-presenting cells that recruit T-Lymphocytes. Often the dendritic cells express the CCR5 receptor, which may explain the link between HIV and syphilis. The humoral response results in the development of antibodies, which are detected early in the disease, thus antibody testing may result in a false positive. This immune response is sufficient to resolve the chancre, but most often cannot prevent the spread of spirochetes. Inflammatory cells are very effective in clearing organisms in primary lesions; however they are much less effective in clearing secondary lesions. Progression to primary systemic syphilis occurs when the spirochetal load is too high to clear when an immune effector blunts the efficiency of the response (e.g., shift toward humoral response with plasma cell infiltration, or if the immune response is dampened before total elimination. In primary systemic syphilis, organisms are disseminated from the site of infection to the lymphatics in a few hours, causing marked lymphadenopathy and splenomegaly. In some cases, mononuclear proliferative vasculitis may occur in various organs resembling a chronic allograft rejection.

Secondary syphilis usually occurs eight weeks after the initial appearance of the chancre. The majority of patients are asymptomatic, though nonspecific systemic symptoms may be seen. In secondary syphilis, the serologic markers are almost always present. Clinical manifestation of secondary syphilis is most commonly cutaneous (81%), but involvement may be seen in the oral mucosa (36%), genitals (20%), and in the CNS (10%). Cutaneous lesions may be urticarial, macular, maculopapular, popular, pustular, or nodular.(5) Patients may also present with alopecia syphilitica, which is a moth-eaten pattern of hair loss commonly seen in syphilis.

Sir William Osler was credited as describing syphilis as the great masquerader because the morphology of secondary syphilis is so broad. (6) conditions secondary syphilis may be mistaken for include alopecia areata, bullous pemphigoid, pemphigus vulgaris, pseudolymphoma, erythema multiforme, leprosy, lichen planus, SLE, mycosis fungoides, psoriasis, and eczema. The mucous patch seen in secondary syphilis is a slightly raised moderately indurated lesion with smooth borders and central necrosis. It is the homologue of the chancre of primary syphilis, and when present on the skin it is termed condyloma latum.

The immune response in primary syphilis is primarily CD4 dominated; however the immune response in secondary syphilis is CD8 dominated and not sufficient for clearing the infection. In response to *T. Pallidum*, vascular adhesion molecules (ICAM-1, VCAM-1, E-selectin) are upregulated, resulting in fibrin deposition and vascular inflammation. This vasculitis contributes to the varied clinical presentation of syphilis.

"Tertiary syphilis only occurs in 1/3 of untreated infected individuals. The onset of tertiary syphilis usually occurs 3-7 years following infection in immunocompetent patients, but may be more rapid in HIV coinfection. (7)"

Tertiary syphilis only occurs in 1/3 of untreated infected individuals. The onset of tertiary syphilis usually occurs 3-7 years following infection in immunocompetent patients, but may be more rapid in HIV coinfection. (7) The formation of a gumma results from an ineffective DTH reaction that results in chronic granulomatous inflammation due to persistent infection. This granuloma has broad irregular acellular zones with central necrosis. Syphilitic granulomas can be differentiated from the granulomas of tuberculosis by the irregular borders and lower cellularity, and from the granulomas of sarcoidosis by the presence of necrosis and plasma cells. Gummas will scar over if the organism is eradicated but may persist for years if treatment is insufficient or immune response is inadequate. Progression to tertiary syphilis can also affect the CNS, as well as any internal organ through vascular damage. (8) Most notable is cardiac involvement in which inflammation of the vasa vasorum of small blood vessels, increases the risk for aneurysm and rupture. "Tree barking" of the vaso vasoum occurs due to heaping up and thickening of endothelium and may speed up ASCVD. Neurovascular involvement leads to meningo-vascular inflammation, inflammation of cerebral vessels, and general paresis. (9) This neurosyphilis has many manifestations, including meningitis, cortical inflammation, and tabes dorsalis due to the demyelination of the posterior column. Renovascular involvement presents a challenge in treatment as increased circulating immune complexes cause nephritis in 10% of patients with neurosyphilis.

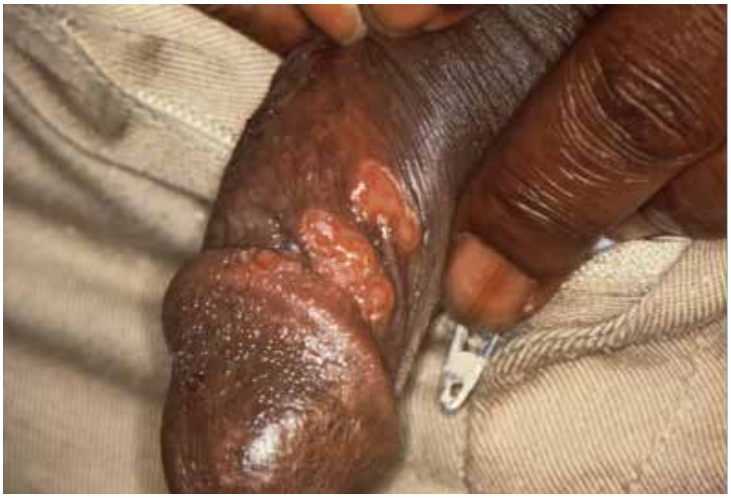

Figure 1 - Primary syphilitic chancre; CDC

Syphilis in pregnancy(10)

The course of syphilis is not significantly changed by pregnancy; however the risk of vertical transmission is increased proportionately to spirochetal load. From 2014 - 2018, primary and secondary syphilis has more than doubled in pregnant women. The highest rates of infection are seen in women age 20-24 (10/100k) and 25-29 (9.4/100k) years old. In 2018 there were 1306 cases of congenital syphilis reported. Of those cases, there were 78 stillbirths and 16 infants died shortly after birth. The incidence of syphilis in 2018 was reported to be 33.1/100k live births, which is a 185% increase since 2014. Syphilis is most common among poor, young (<29), African American women, and those lacking health insurance and prenatal care. (11) Risk factors include drug use, other STDs, living in area w/ high syphilis prevalence, being a sex worker, and having more than one sexual partner in the past year. (12) However, 50% of pregnant women with syphilis do not have any risk factors.

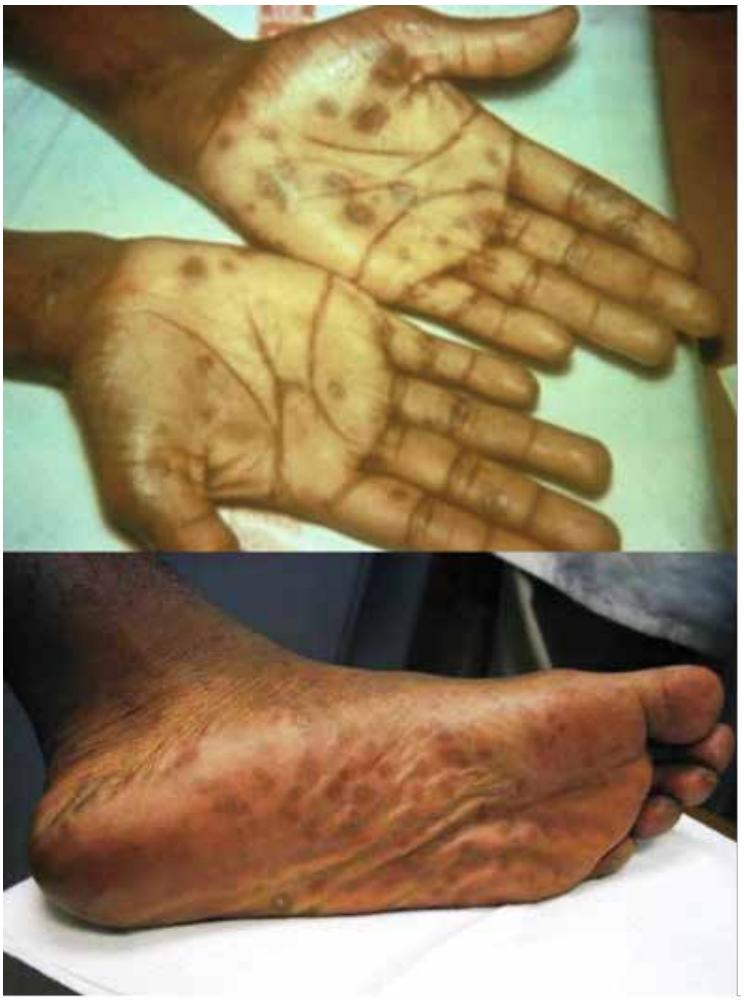

Figure 2- Rash of secondary syphilis; CDC

Because syphilis is so easily treated and screening is so inexpensive, universal antepartum screening is recommended at the 1st prenatal encounter. If the patient has risk factors, screening should be repeated at 28-32 weeks and delivery. Additionally, screening is recommended in all women who have a stillbirth child after 20 weeks. Because HIV is so closely associated with syphilis, all pregnant women should be offered HIV counseling and screening using an opt-out approach.

In order for the diagnosis to be confirmed, spirochetes must be visualized on darkfield microscopy, or two serologic tests (treponemal and non-treponemal) must be positive. Nontreponemal tests include RPR, VDRL, and TRUST, and treponemal tests include FTA-ABS, MHA-TP, TPPA, TP-EIA, and CIA. FT-ABS and RPR must both be positive since RPR may be positive in certain underlying conditions despite no treponemal infection. (13) Causes of false-positive include febrile illness, advanced age, tumor, di-

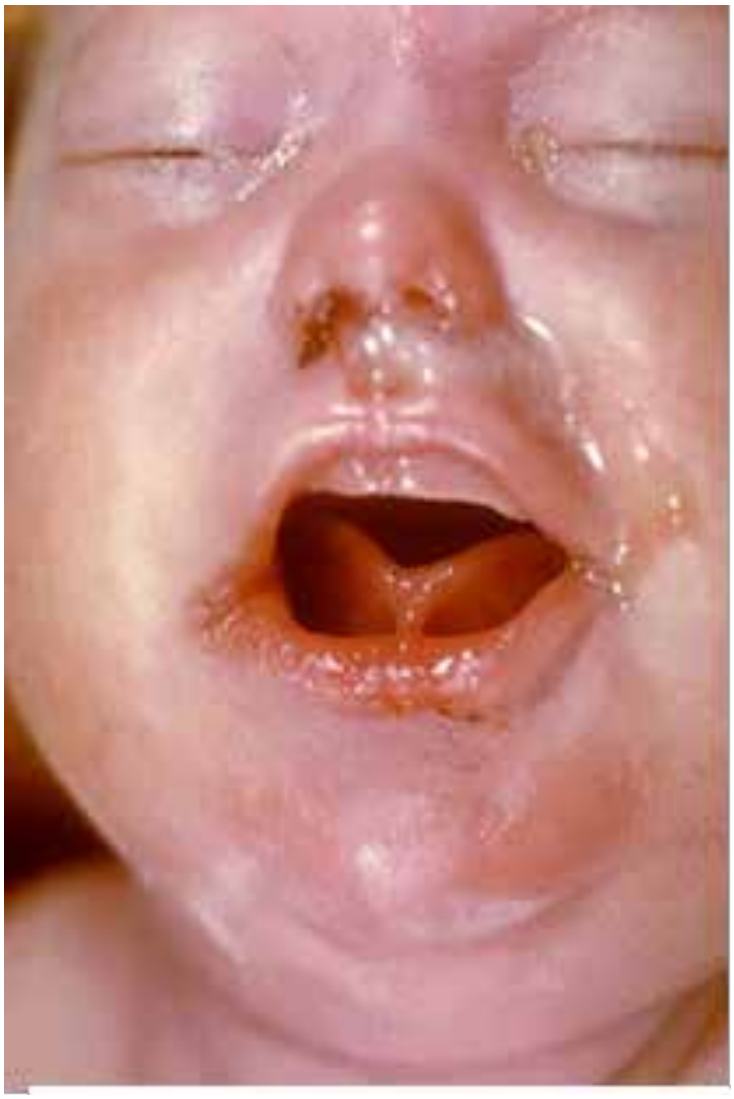

Figure 3- Snuffles; CDC/Dr. Norman Cole

alysis, and autoimmunity. False-positive must be followed up 4-6 weeks following delivery.

The preferred treatment for pregnant women is penicillin.(14) All *T. Pallidum* is sensitive to penicillin, and treatment is effective for maternal disease, preventing vertical transmission, and treating fetal disease. If the mother has penicillin sensitivity, inpatient treatment is recommended with desensitization and subsequent penicillin treatment. In situations where an actual anaphylactic reaction is suspected, consultation of an allergist for skin testing is advised. Mothers should also be monitored for Jarisch-Herxheimer (JH) reaction. (15) JH reactions typically occur within 1-2 hours, peak at 8 hours, and resolves in 24-48 hours. Because of the increased inflammatory response, JH reaction may precipitate uterine contractions, preterm labor, and/or variable heart fetal heart rates. JH may be prevented or blunted by the administration of oral prednisolone(16).

Because penicillin is relatively inexpensive, very efficacious against *T. Pallidum*, and has high beneficence for patients, treatment of syphilis need not be conservative. Penicillin dosing for primary, secondary, or early latent infection is a single dose of 2.4M units Pen G IM, with an optional second dose one week later. For latent or tertiary syphilis, three doses of Pen G 2.4 should be given intramuscular weekly. For both regimens, these doses must be given sequentially and must be restarted if greater than two weeks pass from the last dose. Patients in which verification of treatment cannot be made should receive treatment regardless of symptoms. Presumptive treatment should be administered to all women who have had sexual contact with partners with known syphilis. In order to ensure adequate treatment, titers should be drawn prior to treatment, and treatment should result in at least a fourfold reduction (e.g., 1:16 -> 1:4, 1:32 -> 1:8).

Congenital Syphilis (17)

Congenital syphilis incidence peaked in 1991 at 100/100k births, had a nadir at 8.4 in 2012, and increased to 23.3/100 in 2017. Vertical transmission of syphilis occurs after *T. Pallidum* has infected the placenta, with transplacental transmission occurring as early as 9-10 weeks gestation. The manifestation of congenital infection depends on the state of maternal syphilis, maternal treatment, and fetal immunological response. The highest risk for transmission occurs if the mother has contracted syphilis in the last four years. However, if the mother contracts syphilis late in pregnancy, the risk of transmission increases. Failure to identify and treat is a significant risk factor for transmission. Adequate treatment reduces fetal deaths or stillbirths by 82%, preterm low birth weight by 65%, and clinical disease in infants by 97%.

Fetal abnormalities result from a robust fetal immune response to *T. Pallidum*, which causes damage to the developing fetus. Because the fetal immune system is not well developed until after 20 weeks, signs of fetal infection are not seen until the second trimester. The first sign of fetal infection is hepatic infection/dysfunction, followed by amniotic fluid infection, fetal hematologic abnormalities (anemia, thrombocytopenia), ascites, hydrops, and fetal IgM production. (18)

Ultrasound findings in fetal infection are nonspecific and include early findings of hepatomegaly (liver length >95th percentile), placentomegaly (thickness >2 SD above mean), and late findings of anemia, polyhydramnios, and Ascites or hydrops.

Management of pregnancy includes ultrasound after 20w to look for congenital signs. If signs are present, ultrasound should be repeated weekly to monitor fetal health. Late preterm delivery is warranted if there is a high risk of fetal treatment failure. After delivery, the placenta should be evaluated histopathologically to determine the stage and inform treatment. An untreated placenta is large and edematous and may lead to a negatively impacted fetoplacental exchange of oxygen and nutrients (11).

After birth, congenital syphilis is divided into early congenital syphilis with symptoms occurring before two years, and late syphilis with symptoms manifesting thereafter.

Early Congenital syphilis

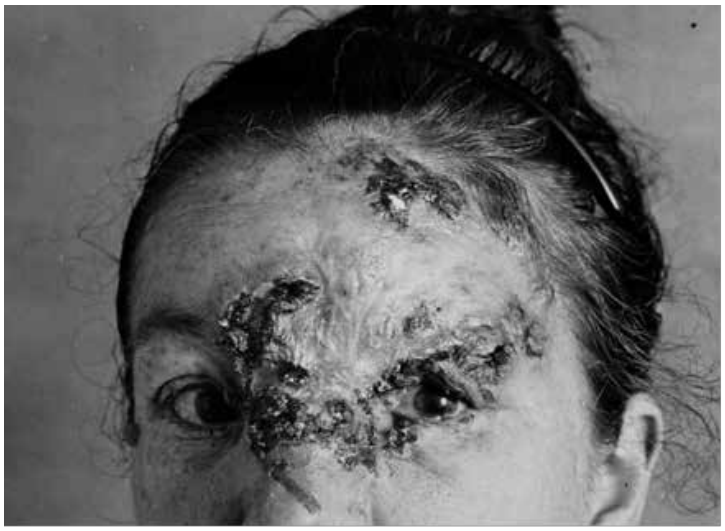

Figure 4 - Tertiary Syphilis; National Museum of Health and Medicine

Clinical manifestations occur before two years of age but are most commonly seen within five weeks – 3 months. 60-90% of infants are asymptomatic at birth, with symptoms depending on the timing of intrauterine infection and treatment.

Only severe cases are clinically apparent at birth. Clinical manifestations of early congenital syphilis include hepatomegaly, jaundice, nasal discharge, rash, generalized LAD, and skeletal abnormalities. The placenta may exhibit necrotizing funisitis, which presents as a large thick and pale, "barber's pole" w/o spiral red and light blue discoloration alternating with steaks of chalky white. (Figure 8) Hepatomegaly and splenomegaly occur in almost all infants, presenting as jaundice and cholestasis with elevated AST, ALT, ALP, Direct Bilirubin, prolonged PT. Snuffles, or rhinitis, usually develops in the first week of life and often heralds the onset of congenital syphilis. The nasal discharge is white and may be bloody if mucosal erosion has occurred.

Figure 5 - Primary syphilitic chancre acquired from mother during birth; CDC/Susan Lindsley

Snuffles is more severe and persistent than viral rhinitis. Care must be taken to not spread infection due to contact with discharge. A rash usually appears within a few weeks, which is most prominent on the back, buttocks, posterior thighs, and soles. The rash progresses for three weeks, followed by desquamation and crusting. The rash may also occur at birth with wide dissemination

Figure 6 - Necrotizing Funisitis; Obstetrical Pathology

and bullous lesions (pemphigus syphiliticus).(19)(20) In addition to hepatosplenomegaly and rash, palpable epitrochlear lymphadenopathy is characteristic of syphilis; however, Generalized lymphadenopathy is commonly seen. Occasionally CNS involvement may be seen but has become less common due to treatment. Acute syphilitic leptomeningitis occurs during the first year of life, most commonly within 3-6months, and resembles bacterial meningitis with vomiting, bulging fontanelle, increased head circumference, and splitting of cranial sutures. However, CSF analysis is more reflective of aseptic meningitis. Chronic meningovascular syphilis occurs toward the end of the first year and presents as progressive hydrocephalus, CN palsies, papilledema, optic atrophy, neurodevelopmental regression, and seizure.

Long bone abnormalities are the most specific finding for syphilis, occurring in 60-80% of infants. They are usually the only findings present at birth but may appear in the first few weeks of life. Congenital syphilis may be associated with pathological fractures and pseudoparalysis. Radiographic findings are usually bilateral, symmetric, and polyostotic (femur, humerus, tibia). Lucent bands, symmetric demineralization, destruction of the medial proximal tibia (Wimberger sign), Metaphyseal serration (Wegener sign), Periostitis, and/or moth-eaten appearance may be seen.

Radiographs are warranted in 1) neonates who have VDRL or RPR titers less than fourfold the maternal titer, a normal physical exam, and a mother who was not treated, treated ≤4weeks, or

had evidence of infection relapse or 2) infants and children with reactive VDRL or RPR with abnormal skeletal findings on physical exam (pain, decreased ROM)

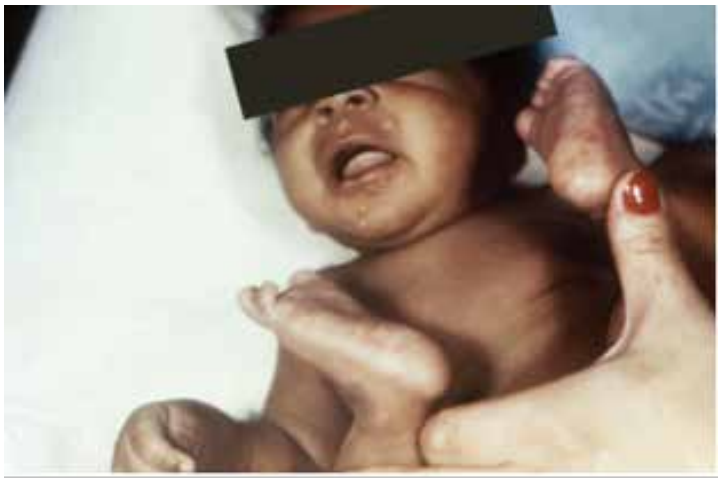

Figure 7 - papular perioral rash and plantar rash; CDC/Susan Lindsley

A radiograph may also reveal a diffuse infiltrative fluffy appearance in all lung areas.

Lab abnormalities include coombs negative hemolytic anemia neonatally, nonhemolytic anemia after neonatal period, thrombocytopenia, and leukopenia. CSF findings include reactive VDRL (54% & 90%), pleocytosis (38% & 88%), and elevated CSF protein (56% & 78%).(19) (sensitivity and specificity respectively)

Late congenital syphilis

Late congenital syphilis is related to scarring or persistent inflammation from early infection, with gumma formation in various tissues. It develops in 40% of infants born to women w/ untreated syphilis during pregnancy and as a wide variety of symptoms.

Late congenital syphilis may also present as neurological abnormalities, which include intellectual disability, arrested hydrocephalus, cranial nerve palsies, and sensorineural hearing loss.

Evaluation and management of congenital syphilis (20)

Because maternal nontreponemal and treponemal IgG antibodies can be transferred through the placenta, serologic tests may not be sufficient to prove the diagnosis if clinical signs are absent. [21] Therefore, treatment decisions must be made on the basis of identification of syphilis in the mother, adequacy of maternal treatment, presence of clinical, laboratory, or radiographic evidence of syphilis in the neonate, and comparison of maternal and neonatal non-treponmal tests. For infants less than one month of age born to mothers with reactive nontreponemal and treponemal tests, the initial evaluation should include Quantitative tests, physical examination with darkfield microscopy of suspicious discharge/lesions, and pathologic examination of the umbilical cord with FT-ABS. Quantitative tests should include treponemal tests (VDRL or RPR) of the infant's serum. Nontreponemal tests of infant serum should be done according to which test the mother received so a direct comparison can be made. All serological tests should be performed on neontatal serum, because umbilical cord blood can become contaminated with maternal blood and yield a false-poisitve result. Subsequent evaluation should be done based on likelihood as follows:

- If congenital syphilis is proven or highly probable syphilis, evaluate with CSF VDRL, cell count, and protein, CBC w/ diff, and any additional warranted tests. , including long bone radiographs, chest radiograph, liver-function tests, neuroimaging, ophthalmologic examination, and auditory brain stem response. CSF tests results obtained during the neonatal period can be difficult to interpret, as normal neonatal CSF may show elevated WBCs or protein. All other possible causes of elevated CSF values must be considered when an infant is being evaluated. Treat with ten days of parenteral penicillin if:

  o Physical exam findings are compatible with congenital

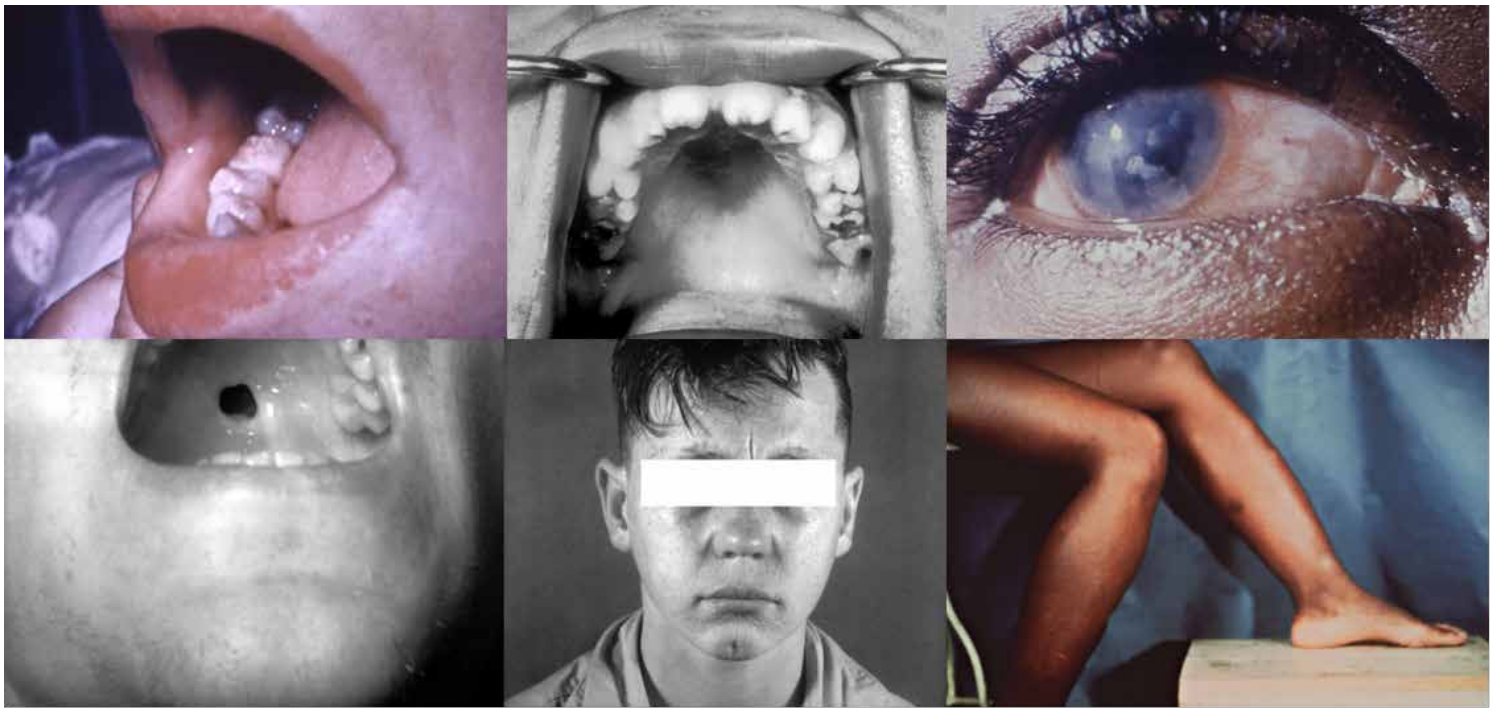

Figure 8 - Left to right top to bottom: Mulberry molars; Hutchinson Teeth; Keratomalacia; Perforated soft palate; Rhagades; Saber shins; CDC/Susan Lindsley and Robert Sumpter

syphilis, regardless of lab results or maternal treatment

- o Baby's titer is fourfold higher than mom's titer
- o Baby has reactive titer (<4x), and mom received inadequate treatment during pregnancy
- o Baby has reactive titer (<4x), and mom showed evidence of relapse (single dose if the neonatal exam is normal, ten days if abnormal)

- If congenital syphilis is possible, evaluate with CSF analysis for VDRL, cell count, and protein. A complete evaluation is not necessary if 10 days of parenteral therapy is administered, but evaluation may be useful. Treat with a single-dose IM benzathine penicillin, procaine penicillin G IM for 10 days, or aqueous crystalline penicillin if:
  - o Baby has reactive titer < fourfold mom and Mom was inadequately treated before or during pregnancy
  - o Baby has a nonreactive titer, but mom was inadequately treated.
  - o Mother received recommended treatment < 4 weeks before delivery
- If congenital syphilis is unlikely, no evaluation or treatment is necessary if:
  - o Baby has nonreactive or less than 4x titer, and mom was adequately treated.

In infants greater than one month of age with serological tests that remain reactive, it is more difficult to know if syphilis is congenital or acquired. Evaluation should include CSF for VDRL, cell count, and protein, CBC w/ diff, HIV screening, and any other tests as clinically indicated. Long bone abnormalities may be helpful in determining whether syphilis is acquired or congenital. The possibility of sexual abuse should be considered as the cause of acquired syphilis

Treatment of congenital syphilis (22)

Effective treatment requires maintaining a minimum inhibitory concentration (MIC) of 0.03 units/mL for ten days. MIC for treponemal treatment with penicillin is approximately 0.004 units. There are multiple options to maintain the specified MIC:

Single-dose regimen

Penicillin G benzathine

Given as 50,000 units/kg intramuscular injection.The benzathine component causes a slow release of penicillin, allowing for extended action. This administration is ideal for patients that may have difficulty following up. This option, however, is contraindicated in asymptomatic infants born to women with inadequate/suboptimal treatment unless labs and imaging are entirely normal. If there are any lab abnormalities, the patient must be treated with the ten-day regimen.

10-day regimens

Aqueous Penicillin G

Given as 50,000 units/kg IV twice daily if under days old, or three times daily if over seven days old. This is the treatment of choice for children >1 month of age or children with acquired syphilis.

Procaine penicillin G

Given as 50,000 units/kg IM QD 10 days. This treatment has been shown to have lower levels of penicillin than IV aqueous penicillin, but this finding has not proven to be clinically significant.

If any signs of neurosyphilis are present, patients must complete a 10-day course to be followed with a single IM dose of 50,000 unit/kg penicillin G benzathine

Adverse effects to infants include a JH reaction that is usually self-limited but may lead to cardiovascular collapse, seizure, or death. If more than one day of therapy is missed in the ten-day regimen, the course must be restarted. As in adults, if the infant is sensitive to penicillin, desensitization should occur.

Follow-up evaluations

During well-child visits, serologically reactive children should be evaluated for signs of congenital syphilis for the first year of life and beyond. Specific attention should be paid to hearing, vision, and neurodevelopmental abnormalities. If diagnosed after infancy, non-treponemal tests (VDRL or RPR) should be performed every 2-3 months. Serology should be repeated until the test becomes non-reactive, or titer has decreased fourfold. If VDRL or RPR fail to decrease or increase within 6-12 months, a lumbar puncture should be obtained and evaluated for VDRL, cell count, and protein, and be treated with ten days parenteral penicillin regardless of previous treatment. Treponemal tests (FTA-ABS, T. pallidum agglutination (TP-PA), microhemagglutination test for T. Pallidum (MHA-TP)) should not be used to evaluate treatment, as they may remain positive despite adequate treatment. Treponemal tests can, however, be used for confirmation of diagnosis if tests at 12-15 months and 18-24 months are positive

Outcomes

Case fatality rates range from 6-8%, with 90% of cases associated with a lack of prenatal care. Certain clinical manifestations, including Interstitial keratitis and saber shins, may occur despite appropriate therapy. Infection may persist for life if spirochetes persist in extracellular loci with no inflammatory response elicited. It is important that patients are instructed that prior infection with syphilis is NOT protective against future infection.

Patient cases

Patient 1

The first patient treated was born at a gestational age of 27 weeks and five days at a weight of 1090g. The infant was admitted to the NICU for prematurity as well as respiratory failure. Throughout the first month of life, the infant repeatedly decompensated, requiring intubation and ventilation. At the time of delivery, the mother presented with a reactive titer of 1:64, and the infant's RPR titer was measured to be 1:128. FT-ABS was reactive in both patients. Radiography showed osteochondropathy of the long bones consistent with congenital syphilis. The infant completed a ten-day course of Penicillin G 50,000 units/kg twice daily. When the infant reached seven days of age, the dose was increased from twice daily to three times daily. Throughout the hospital stay, the patient never exhibited any neurological deficits.

Patient 2

This patient was born at 32 weeks and five days weighing 2060 grams with weight and length between 76-90th percentile, and

head circumference between 51-75th percentile. The mother stated she had received treatment in another country, though her RPR titer was 1:4, and FT-ABS was reactive. The infant's titer was measured to be 1:1. The infant received ten days of penicillin G, while the mother was not re-treated. Because the infant's RPR titer was fourfold less than the mother's RPR titer, imaging was not ordered. This infant did not show any signs of syphilis, including rash or snuffles. The baby did present with jaundice and was borderline LIRZ/HIRZ, which responded well to phototherapy.

Patient 3

Patient three was born at 26 weeks and six days with a birth weight of 990 grams via C-section due to transverse lie and premature rupture of membranes. Following birth, the infant was intubated and given surfactant in the delivery room. The patient was transferred to the NICU and remained intubated for the three weeks of life, and was then slowly weaned to Nasal intermittent mandatory ventilation. Upon screening mother had a urine drug screen positive for amphetamines, a positive GBS and E. Coli blood culture (gentamicin sensitive), and reactive RPR with a titer of 1:8. The infant's RPR was positive with a titer of 1:1 negating the need for long bone imaging. The mother was treated with a 10-day course of penicillin G, and titers improved. The infant's hospitalization was complicated with sepsis, for which the patient was treated with seven days of vancomycin and cefepime. Following treatment for sepsis, a 10-day regimen of penicillin G was started three times daily. The patient did not exhibit any signs of syphilis, including rash, rhinitis, or neurological dysfunction.

Patient 4

Patient 4 was born at 39 weeks gestation with a birth weight of 2105g. Weight, length and head circumference were below the third percentile, consistent with intrauterine growth restriction. The infant was noted to have down facies on delivery, confirmed by karyotype 47 XY + 21. The denied any prenatal care and screened positive for RPR with a titer that was pending at the time of the report. The infant's VDRL titer was nonreactive, RPR titer was also pending, and a survey of the long bones showed no abnormalities. The infant received ten days of penicillin G.

Discussion and Conclusion

Although syphilis is highly infective and has poor outcomes if left untreated, the disease is easily treated with inexpensive and widely available medications. However, despite the treatment being so simple, barriers to care, including lack of insurance, lower socioeconomic status, and lack of health education, prevent pregnant mothers from being treated and syphilis from being eradicated. By ensuring each pregnant woman is screened for syphilis and treated if positive, many of the complications of syphilis can be avoided, thus providing better health and quality of life to both the mother and child.

References

1. *History of syphilis - Wikipedia [Internet]. [cited 2019 Oct 16]. Available from: https://en.wikipedia.org/wiki/History_of_syphilis*
2. *Syphilis: Epidemiology, pathophysiology, and clinical manifestations in HIV-uninfected patients - UpToDate [Internet]. [cited 2019 Oct 12]. Available from: https://www-uptodate-com.proxy.westernu.edu/contents/syphilis-epidemiology-pathophysiology-and-clinical-manifestations-in-hiv-uninfected-patients*
3. *Tuskegee Study - Timeline - CDC - NCHHSTP [Internet]. 2018 [cited 2019 Nov 16]. Available from: https://www.cdc.gov/tuskegee/timeline.htm*
4. *Carlson JA, Dabiri G, Cribier B, Sell S. THE IMMUNOPATHOBIOLOGY OF SYPHILIS: THE MANIFESTATIONS AND COURSE OF SYPHILIS ARE DETERMINED BY THE LEVEL OF DELAYED-TYPE HYPERSENSITIVITY. Am J Dermatopathol. 2011;33:433–60.*
5. *Rash Associated with Secondary Syphilis | NEJM [Internet]. [cited 2019 Nov 16]. Available from: https://www.nejm.org/doi/full/10.1056/NEJMicm1005345*
6. *Revisiting the Great Imitator, Part I: The Origin and History of Syphilis [Internet]. [cited 2019 Nov 16]. Available from: https://www.asm.org/Articles/2019/June/Revisiting-the-Great-Imitator,-Part-I-The-Origin-a*
7. *Syphilis in the HIV-infected patient - UpToDate [Internet]. [cited 2019 Oct 16]. Available from: https://www.uptodate.com/contents/syphilis-in-the-hiv-infected-patient?search=syphilis%20hiv&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1*
8. *Syphilis | NIH: National Institute of Allergy and Infectious Diseases [Internet]. [cited 2019 Oct 12]. Available from: https://www.niaid.nih.gov/diseases-conditions/syphilis*
9. *Neurosyphilis - UpToDate [Internet]. [cited 2019 Oct 16]. Available from: https://www.uptodate.com/contents/neurosyphilis?search=syphilis&source=search_result&selectedTitle=8~150&usage_type=default&display_rank=9*
10. *Syphilis in pregnancy - UpToDate [Internet]. [cited 2019 Oct 16]. Available from: https://www.uptodate.com/contents/syphilis-in-pregnancy?search=syphilis&source=search_result&selectedTitle=6~150&usage_type=default&display_rank=7*
11. *Rac MWF, Revell PA, Eppes CS. Syphilis during pregnancy: a preventable threat to maternal-fetal health. Am J Obstet Gynecol. 2017;216:352–63.*
12. *Moline HR, Smith JF. The continuing threat of syphilis in pregnancy: Curr Opin Obstet Gynecol. 2016;28:101–4.*
13. *Smikle MF, James OB, Prabhakar P. Biological false positive serological tests for syphilis in the Jamaican population. Genitourin Med. 1990;66:76–8.*
14. *Syphilis: Treatment and monitoring - UpToDate [Internet]. [cited 2019 Oct 16]. Available from: https://www.uptodate.com/contents/syphilis-treatment-and-monitoring?search=syphilis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2*
15. *Butler T. The Jarisch–Herxheimer Reaction After Antibiotic Treatment of Spirochetal Infections: A Review of Recent Cases and Our Understanding of Pathogenesis. Am J Trop Med Hyg. 2017;96:46–52.*
16. *Gudjónsson H, Skog E. The effect of prednisolone on the Jarisch-Herxheimer reaction. Acta Derm Venereol. 1968;48:15–8.*
17. *Congenital syphilis: Clinical features and diagnosis - UpToDate [Internet]. [cited 2019 Oct 16]. Available from: https://www.uptodate.com/contents/congenital-syphilis-clinical-features-and-diagnosis?search=syphilis&source=search_result&selectedTitle=5~150&usage_type=default&display_rank=6*
18. *Hollier LM, Harstad TW, Sanchez PJ, Twickler DM, Wendel GD. Fetal syphilis: clinical and laboratory characteristics. Obstet Gynecol. 2001;97:947–53.*
19. *Beeram MR, Chopde N, Dawood Y, Siriboe S, Abedin M. Lumbar puncture in the evaluation of possible asymptomatic congenital syphilis in neonates. J Pediatr. 1996;128:125–9.*
20. *Congenital syphilis: Evaluation, management, and prevention -*

UpToDate [Internet]. [cited 2019 Oct 16]. Available from: https://www.uptodate.com/contents/congenital-syphilis-evaluation-management-and-prevention?search=syphilis&source=search_result&selectedTitle=7~150&usage_type=default&display_rank=8

21. *Congenital Syphilis - 2015 STD Treatment Guidelines [Internet]. 2019 [cited 2019 Oct 12]. Available from: https://www.cdc.gov/std/tg2015/congenital.htm*
22. *Walker GJ, Walker D, Franco DM, Grillo□Ardila CF. Antibiotic treatment for newborns with congenital syphilis. Cochrane Database Syst Rev [Internet]. 2019 [cited 2019 Oct 13]; Available from: http://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012071.pub2/full?highlightAbstract=withdrawn%7Csyphilis%7Csyphili*

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