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## **Congenital Syphilis**

Developed for PedsCases.com by Stephanie Unrau and Dr. Joan L Robinson.

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### **Introduction:**

Hi, my name is Stephanie Unrau, and I am a third year medical student at the University of Alberta. This podcast was developed by myself along with Dr. Joan Robinson, who is a pediatric infectious disease specialist at the Stollery Children's Hospital in Edmonton, Alberta.

*The goals/learning objectives of this podcast will be to:*

1. Summarize the epidemiology and pathophysiology of syphilis
2. Review the potential impacts syphilis can have on a mother and her infant
3. Delineate how prenatal screening for syphilis is completed in Alberta.
4. Review relevant blood work and indications for treatment for both mother and infant
5. Outline the typical follow-up that an infant exposed to syphilis in-utero will require

**CASE: You are a third year clerk one week into your family medicine rotation in Edmonton, Alberta. Your preceptor invites you to go see the first patient of the day, Maria, who is here for a prenatal appointment. Before you go in, your preceptor tells you that the patient is eight weeks pregnant expecting her first child, and this is her first prenatal appointment. Maria has a history of an adequately treated syphilis infection in the last year, and so your preceptor would like you to pay careful attention to whether there is concern for a new infection now. Her last RPR was 1:4 eight months ago (meaning that you could dilute her blood by  $\frac{1}{4}$  and the RPR would still be positive). What are the key points on history and physical exam when you see the patient, and why is detection of a syphilis infection important for this patient and her fetus?**

Whether or not an infant develops congenital syphilis is largely dependent on maternal syphilis stage and prenatal management<sup>1</sup>.

First, let's go over the epidemiology of syphilis: Syphilis is a reportable sexually transmitted infection, with a prevalence of 1 case per 10,000 in Canada in 2017<sup>3</sup>. It is more common in "core populations," meaning communities with highly interconnected sexual networks (for example, men who have sex with men, individuals experiencing lower SES, homelessness, and multiple sexual partners)<sup>2</sup>. However, since 2007 and especially since 2019, Alberta has

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been in a syphilis outbreak, and syphilis rates are increasing in the general population as well<sup>1,4</sup>.

Now, we can move on to pathophysiology and symptoms<sup>2</sup> of a syphilis infection: Syphilis is caused by a type of bacteria called a spirochete, and more specifically, the *Treponema pallidum* spirochete. It is transmitted by contact with certain skin lesions on a sexual partner that are teeming with spirochetes. These skin lesions include chancres, mucous patches, and large, raised, grey-white lesions on moist skin called condylomata lata. They will occur on whatever body part came into contact with the partner's skin lesion. Chancres are the most common form of syphilitic skin lesion, and are usually small and painless so infected people often do not know that they have them. As one might predict, chancres are often in the genital region, allowing transmission to a partner during oral, vaginal, or anal sex. Syphilis can be transmitted to the fetus in-utero if it is in maternal blood, or very rarely from lesions in the birth canal.

As mentioned before, syphilis infection has five stages known as primary, secondary, early latent, late latent and tertiary syphilis.

Think of primary syphilis as the local replication of spirochetes at the site where skin or a mucous membrane has made contact with a partner's infectious lesion. Within 10 to 90 days, the spirochetes typically form a single painless chancre at the site of contact. The infected individual will probably not notice the chancre and will feel well but be very infectious. Chancres disappear without treatment due to the immune response. However, this allows the spirochetes to enter the bloodstream, and four to ten weeks later the host will develop Secondary Syphilis.

Think of secondary syphilis as a diffuse spirochete infection causing immune complex deposition that manifests as a multitude of symptoms. This phase lasts 2-6 weeks and almost always includes skin and mucous membrane involvement. The classic skin manifestation of secondary syphilis is a diffuse maculo-papular rash involving the palms and soles. In fact, whenever you see a rash on the palms or soles of a patient, you should consider the possibility of syphilis. Additionally, the skin manifestations seen in primary syphilis can recur as well. There can be alopecia. Because the bacteria is in the blood, the patient commonly has constitutional symptoms, like low grade fever, malaise, anorexia, weight loss, head ache, and painless and generalized lymphadenopathy. Less commonly there are end-organ infections including meningitis, nephritis, hepatitis, and uveitis. Despite these possible manifestations, the majority of the time secondary syphilis is not diagnosed as the patient is not very sick so does not seek medical advice or clinicians mistakenly think that the patient has a viral illness.

The symptoms of secondary syphilis usually resolve without treatment. However, up to one year after the initial infection, the spirochetes can go back into the blood and cause secondary syphilis manifestations again. This can happen once, several times, or not at all in the first year after initial infection. This stage is known as early latent syphilis. If still untreated, the patient then progresses to late latent syphilis. The patient with late latent syphilis will be clinically well and no longer infectious. Spirochetes are still present in the body but are no longer in the blood, so the patient will have no symptoms. However, slow, granulomatous inflammation around a smaller number of spirochetes in the body continues and after five to forty years, the patient may develop tertiary syphilis.

Tertiary syphilis is the fifth and final stage of syphilis and presents with potentially fatal or debilitating sequelae, such as neurosyphilis, cardiovascular syphilis, and gumma deposition. Neurosyphilis<sup>5</sup> is a term which includes general paresis and dementia, tabes dorsalis meaning sensory ataxia, meningovascular syphilis meaning stroke, retinitis, and meningitis. Cardiovascular syphilis refers to aortitis and associated sequelae. Gummas can deposit on and affect skin, bones, and organs. Although only one third of patients develop tertiary syphilis, it is likely that all patients with latent syphilis would develop it given enough time, but they pass away from other causes first.

Once the clinician suspects syphilis based on history and/or clinical presentation, they must test for it. They should always perform serology. This entails treponemal and nontreponemal tests and will be explained later in greater detail. In addition, if there is a skin lesion, the clinician should perform a direct swab of it for molecular testing with nucleic acid amplification testing (NAAT)<sup>2</sup>.

The only treatment considered to definitively treat syphilis is penicillin, and the number of doses depends on the stage<sup>2,6</sup>. Alternatives have been tried, including doxycycline and azithromycin. However, doxycycline has not been found to be effective for neurosyphilis and can be teratogenic in pregnancy. Additionally, some strains of syphilis are now resistant to azithromycin<sup>2</sup>. Therefore, in the case of penicillin allergy, desensitization therapy followed by penicillin treatment is recommended, and is considered the only definitive treatment for syphilis in pregnancy<sup>6</sup>.

Now that we've got an overview of syphilis out of the way, let's focus on congenital syphilis. The majority of infants diagnosed with early congenital syphilis are asymptomatic at birth. Nonetheless, it is imperative to recognize and treat congenital syphilis as soon as possible to prevent lifelong sequelae. We will organize the symptoms and sequelae by a systems approach<sup>1</sup>:

- Spontaneous abortion, stillbirth, or hydrops fetalis (which is extreme edema of the fetus) occur in approximately 40% of cases where syphilis is acquired DURING pregnancy. Necrotizing funisitis<sup>7</sup> is a rare finding pathognomic to congenital syphilis involving infection and inflammation of the soft tissue of the umbilical cord. The umbilical cord in this situation looks like a "barber shop pole."
- A classic finding of congenital syphilis is a rash that begins as small, erythematous, maculopapular spots that are most prominent on the back, buttocks, posterior thighs, and plantar surfaces of the feet<sup>8</sup>. This rash typically appears 1-2 weeks after birth<sup>8</sup>. Less commonly, infectious lesions full of treponemes like those found on adults can also be found on infants<sup>8</sup>.
- The CNS manifestation of neurosyphilis can be present at birth, or have a delayed presentation<sup>8</sup>. Infants with neurosyphilis can be asymptomatic. On the other hand, they can present like bacterial meningitis, with vomiting, bulging fontanelle, and increased head circumference<sup>8</sup>. Chronic meningovascular syphilis presents with progressive hydrocephalus, cranial nerve palsies, neurodevelopmental regression, and seizures<sup>8</sup>. Cerebral infarction can be caused by syphilitic endarteritis as early as the second year of life!<sup>8</sup>
- There are many eye, ear, nose, and mouth signs and symptoms of congenital syphilis<sup>1,8</sup>. Rhinitis and snuffles are often the first symptoms of congenital syphilis, and especially in conjunction with rash and hepatosplenomegaly should

- make you think of congenital syphilis. Dental changes that may be apparent when the teeth erupt include mulberry molars with extra cusps on them. The front teeth may have notches on them and these are called Hutchinson's teeth. Hearing loss can occur due to involvement of the eighth cranial nerve. Eye and vision can be affected by interstitial keratitis, meaning corneal scarring. Facial features can be altered on a skeletal level, including frontal bossing, poorly developed maxillas, and a collapsed or saddle nose.
- Infection of bones and cartilage leads to painful osteochondritis or perichondritis<sup>1,8</sup>. Shortly after birth, the infant is reluctant to move the limb because it hurts, making it appear like they have paralysis. If not treated, after 2 years of age they may suffer from recurrent arthropathies as well as painless knee effusions, called Colleton's joints. Years later they can develop winged scapulas and sabre shins.
  - Hematological issues may include anemia and thrombocytopenia<sup>1</sup>.
  - GI changes may include hepatosplenomegaly<sup>1</sup>. To emphasize a take home point that was said above, the combination of hepatosplenomegaly, snuffles, and rash in an infant should always make you suspect and investigate for congenital syphilis.

**CASE: Knowing how the various stages of syphilis can present in an adult and how important it is for the fetus to prevent the occurrence and complications of syphilis in pregnancy, you conduct a targeted history and physical exam. You learn that Maria is currently living with her boyfriend of eight months, who she says is the father. They both tested negative for sexually transmitted infections when they started their relationship, and as a result decided not to use any barrier methods during sex. He has been her only sexual partner in the last eight months, and she believes that she is his only partner. Her previous syphilis infection was diagnosed 12 months ago and was acquired from a different partner. Your preceptor had told her that her infection was presumed to be early latent at the time of diagnosis, and had been adequately treated with penicillin. She doesn't remember which symptoms she had during her previous infection. Today, you notice she seems fatigued. You ask around constitutional symptoms and she reports feeling quite exhausted and having headaches in the last few weeks, but assumed it was because of the pregnancy. She hasn't noticed any other changes from her baseline. You briefly explain why it is important to protect her baby from syphilis exposure, and she agrees to let you do a targeted physical exam. You inspect for any kind of lesions on oral mucous membranes, her palms and soles, and her trunk, but don't see anything. Finally you invite your preceptor in so you can do a speculum exam of the genital tract together to rule out lesions in the genital area. This exam and abdominal palpation are both negative. After giving your preceptor a brief summary of the history and exam so far, she asks if you would like to do any tests. If so, which, and is this a trick question? (pause)**

**Answer: This is a trick question, because all pregnant women are screened for syphilis in Alberta at least once, at their first prenatal appointment. Here are the tests that we do, and how they work.**

*Review how Alberta screens prenatally for syphilis:*

Screening for syphilis in all expectant mothers at the first prenatal appointment is recommended worldwide, ideally in the first trimester. This is done as part of routine prenatal bloodwork<sup>1</sup>. The mother is given a requisition for this and other prenatal bloodwork. A small percentage of women in Alberta never seek prenatal care or never go for their bloodwork so are tested only at delivery. In Alberta, an Enzyme Immuno-Assay (EIA) treponemal test is used for screening. If it is positive, the same sample is then tested with another treponemal test, T.Pallidum Particle Agglutination Assay (TPPA) to confirm the results. A non-treponemal test, Rapid Plasma Reagin (RPR) is also run if the EIA is positive. If EIA and TPPA are both positive, a syphilis infection is assumed to be present- although they can remain positive for life even after an infection has been treated. If the mother comes from a resource poor country, there is a small chance that she has a non-venereal treponemal disease such as Yaws, Pinta, and Bejel instead of syphilis<sup>1</sup>. However, we cannot differentiate these from syphilis and do not want to miss the chance to prevent congenital syphilis so always assume that the mother has syphilis. RPR is a quantitative test that allows the physician to monitor disease activity and response to treatment. A higher RPR indicates that there is a more active syphilis infection. The RPR result findings along with history, physical exam, and epidemiological findings are all needed to determine the stage of syphilis infection.

At the time of a positive EIA and TPPA test result in Alberta, Public Health notifies the patient and makes every effort to conduct partner notification and treatment.

**CASE: Given that Alberta tests all pregnant women for syphilis in their first prenatal appointment and Maria's symptoms may be consistent with her pregnancy rather than a new syphilis infection, your preceptor proceeds to order routine prenatal bloodwork and wait on the results. Your preceptor asks Maria to get this done as soon as she can, and lets her know that if she does have syphilis, Public Health will call her directly, and will also need to do contact tracing to treat her source and other people who may be infected. She agrees.**

**Three days later, the clinic receives the results.**

**Maria's EIA and TPPA are both positive, and her RPR titre is reactive, at 1:64. You will remember that it was down to 1:4 when it was last checked. Is this a new infection, or could it still be due to the previous syphilis infection?**

**How will you manage her to prevent pregnancy complications?**

Once we have positive EIA and TPPA, we need to figure out what stage of syphilis a patient has. They will need to be treated unless we find out that they have already been adequately treated<sup>1</sup>. If a pregnant woman has late latent syphilis, we are not worried about transmission to the infant; remember, there are no longer spirochetes in the mother's blood. However, we still want to treat her to prevent progression later to tertiary syphilis<sup>2</sup>. If the mother has primary, secondary or early latent syphilis, we are very worried about the baby and want to treat her as soon as possible<sup>1</sup>. Tertiary syphilis would be super rare in a pregnant woman. When we treat her, we are also treating the fetus as penicillin crosses the placenta. If we treat her at least 4 weeks before delivery AND she has a 4-fold drop in her RPR, we assume that the infant received enough penicillin in-utero so does not require



further treatment<sup>1</sup>. However, you still want to check the mother's RPR at delivery to make sure that it did not go up again, which might mean she was re-infected after finishing treatment and before giving birth<sup>1</sup>. Even if it looks like the mother was adequately treated, the infant still needs a careful physical exam at birth and follow-up blood work<sup>1</sup>. If the mother was treated less than 4 weeks before delivery or her RPR did not drop 4-fold, the infant needs a full assessment including a lumbar puncture<sup>1</sup>. In this case we are worried that the fetus did not get enough penicillin across the placenta and hence the infant requires treatment with penicillin, usually for a full 10 days<sup>1</sup>. If you are unsure whether the infant needs to be treated, always talk to your friendly local pediatric ID specialist!

**CASE: You understand from the rise in her RPR that Maria has again acquired infectious syphilis. You consider that this is most likely secondary syphilis based on Maria's symptoms. Treatment with penicillin is urgent to protect the fetus.**

**Do you remember what RPR drop from 1:64 you are watching for to make sure she has an adequate response to penicillin therapy? (*pause*)**

**If you said you are watching for her RPR to drop fourfold, from 1:64 to 1:16 or lower by 4 weeks before she gives birth, you got it! You should also monitor for reinfection by re-checking Maria's RPR monthly and at delivery.**

**Before the end of your eight week rotation, Maria's titre reaches 1:16. She is very grateful for your help, and her fetus appears well on ultrasound. Not unexpectedly she had found out that her partner had not been monogamous and had given her syphilis. You empathetically listen and support her as best you can, which she really appreciates.**

**7 months pass, and you are now on-call during your obstetrics rotation. You get paged in your on-call room and report to the OR still rubbing the sleep from your eyes. An emergency C-section is going to be performed because the patient has had labour dystocia, an issue of passage and passenger. With a jolt you realize, you recognize the patient! It's Maria! Her RPR had been reordered once since she entered into labor 8 hours ago, but is not back yet. You work with the obstetrics team to assist with the C-section as best you can, and a baby boy with reassuring APGARs is born. You sneak a quick peek at the baby despite the pediatrics team buzzing around him. He appears well! It's out of your hands now, but if you were this family's doctor, what would you do next?**

As we alluded to earlier, infants requiring treatment will receive 10 days of IV penicillin as it is the only definitive treatment for congenital syphilis<sup>1</sup>. The exact dosing differs based on case variables, but these details exceed the scope of this podcast. Treated and untreated infants need syphilis serology done every 3 months<sup>1</sup>. By 6 months of age, their RPR should be non-reactive<sup>1</sup>. If it is not, talk to Peds ID as the infant may need repeat investigations and penicillin. If they have a reactive EIA at 12 months of age, they almost certainly had congenital syphilis<sup>1</sup>. If this is the case and they did not receive 10 days of penicillin earlier on, they should be treated now. If abnormal CSF results indicating neurosyphilis were initially found, repeat CSF studies are sometimes done **at 6 months of age** to ensure that they received enough penicillin<sup>1</sup>.

**CASE: Let's finish off our case! Despite having treated Maria's earlier syphilis infection, the RPR at delivery was 1:128, showing that she was re-infected yet again by the end of her pregnancy. You know that the baby will need to be treated with 10 days of IV penicillin, and receive appropriate serological and clinical follow-up. With all this management in place and a trusting, empathetic relationship between Maria and her doctor to ensure continued follow-up, her baby is expected to have normal growth and development. A trusting physician-patient relationship is especially important for individuals at higher risk of reinfection given chaotic or unstable lifestyles, as the ability for education, prevention, and follow-up depends on trust. Good work managing this case!**

#### PODCAST 5 TAKE-HOME POINTS:

We'd like to give you the following five take-home points so you can do an awesome job identifying and managing congenital syphilis in the future:

1. If you see a baby with chronic snuffles, unexplained hepatosplenomegaly, or unusual rashes (especially ones that look like ringworm or involve the palms or soles) think of congenital syphilis.
2. All pregnant women are screened for syphilis in Alberta as part of their routine prenatal care. If they have infectious syphilis (primary, secondary or early latent) they must be treated as soon as possible in order to prevent adverse fetal events including spontaneous abortion/ fetal demise, neurosyphilis, sensorineural deafness, osteochondritis and perichondritis, all potentially leading to lifelong sequelae.
3. Screening is performed in Alberta with the EIA treponemal test, and if it is positive then this result is confirmed on the same sample with a second treponemal test, TPPA. The nontreponemal RPR test is performed to assess disease activity and monitor response to treatment. Public Health then receives these results, performs contact tracing, and tries to ensure that all appropriate treatment and follow-up are arranged.
4. If a woman had infectious syphilis during pregnancy, the infant will require clinical and serological follow up. If the mother was treated 4 weeks before delivery and had an associated 4-fold drop in her titres with no reinfection by delivery, and the investigations involving the infant are negative, the infant does not require immediate treatment. If these exact conditions are not met, then the infant needs treatment as well as investigations including CBCd, and CSF analysis, long-bone x-rays, and audiological and ophthalmological assessments.
5. If there is any concern that the baby has untreated congenital syphilis, we will treat with IV penicillin for 10 days and continue our clinical observation and monitoring until we are sure that the infant has been adequately treated.

Thank you for listening to the PedsCases' Congenital Syphilis Podcast. Good luck!

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