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## **Congenital Infections**

Developed by Mackenzie Heidel and Dr. Rupeena Purewal for PedsCases.com.  
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### **Introduction:**

Hi, my name is Mackenzie Heidel and I am a fourth-year medical student at the University of Saskatchewan. This podcast was created in collaboration with Dr. Rupeena Purewal, a Pediatric Infectious Disease Physician in Saskatoon and the creator of the Canadian Infectious Disease podcast, The Canadian Breakpoint. In this episode of PedsCases, we aim to contribute to your understanding of the broad topic of congenital infections. While the acronym TORCH is currently used to refer to congenital infections (Toxoplasmosis, other infections, Rubella, Cytomegalovirus, and Herpes Simplex Virus), we have chosen not to use it in this episode to focus the discussion. In the first half of this podcast, we will explore when you should think about including congenital infections on your differential diagnosis, and discuss Cytomegalovirus or CMV, and Herpes Simplex Virus or HSV, including clinical manifestations, diagnosis, management, and follow-up for these infections. In the second half we will welcome Dr. Purewal who will provide us with some clinical pearls on other less common congenital infections, including Toxoplasmosis, Rubella, Hepatitis B, and Varicella. While Syphilis is on the rise, we will not cover it in this episode for the sake of time. We encourage you to check out the existing PedsCases episode on Congenital Syphilis for more information on this important topic. It is important to note that information on congenital infections is always evolving, and the Canadian Pediatric Society Position Statements are a great and regularly updated source for current information. The current CPS statements were the main source of information used to create this episode.

This episode has five objectives. By the end of the podcast, you should be able to:

- 1) Highlight the importance of congenital infections, specifically cytomegalovirus, Neonatal Herpes Simplex Virus, Toxoplasmosis, Rubella, Hepatitis B, and Varicella.
- 2) List the signs and symptoms of certain congenitally acquired infections.
- 3) Describe when testing for congenital infections is warranted.
- 4) Outline what management and follow up might look like for certain congenital infections.
- 5) Discuss when you should consider involving an Infectious Disease expert to assist with diagnosis and management of congenital infections.

Alright, let's jump right into talking about congenital infections!

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## **Approach to Congenital Infections**

Congenital infections are infections that are vertically transmitted, meaning they are transferred from the birthing parent to the baby. Given the potential sequelae for the infant, this is an important topic for providers to be aware of and it's crucial to have an organized approach to congenital infections.

When approaching a patient with a potential congenital infection, first start by gathering a history from the birthing parent. We want to ask questions to help us determine the likelihood of congenital infection. This can include symptoms of both the birthing parent and the child. Include prenatal travel, diet, medication or recreational drug use, exposures including exposure history to risk factors such as cat litter, sexually transmitted infections including if they were tested or treated, immunization status, and past or recent infections.

Next, examine the baby. There are many signs and symptoms that should prompt you to add congenital infections to the differential diagnosis. These include: microcephaly, rash which can be petechial or maculopapular, intrauterine growth restriction, jaundice, hepatosplenomegaly, seizure, poor feeding, lethargy, fever, and irritability. These signs and symptoms should prompt you to investigate further. Generally, for congenital infections, the initial workup should include:

- CBC & differential to look for thrombocytopenia, anemia, and neutropenia.
- If there is hepatosplenomegaly on exam you should consider ordering liver enzymes & liver function tests.
- If you are considering a specific infection, then you should order initial and confirmatory testing.
  - For example: if you suspect CMV infection in the first weeks of life, you should consider ordering a urine PCR.
- Additional investigations could include: head ultrasound to look for calcifications commonly seen in congenital infections, and/or abdominal ultrasound to rule in/out hepatosplenomegaly and detect other lesions/nodules, and/or referral for ophthalmological exam to look for cataracts or chorioretinitis which is also seen in congenital infections
- Consider consulting Infectious Diseases for advice on ordering specific tests. If testing for a specific infection returns positive, you should also strongly consider consulting Infectious Diseases who can help you determine management.

So, you've collected a thorough history from the birthing parent and performed a physical exam of the newborn. Your findings have led you to include congenital infections on your differential diagnosis and you've completed a general workup, but which congenital infection is the most likely?

## **Cytomegalovirus (CMV)<sup>1</sup>**

First, let's explore congenital Cytomegalovirus or CMV. This is currently the most common congenital infection and the leading cause of non-genetic sensorineural hearing loss in newborns! Depending on the centre you are practicing in, CMV could be detected through

universal screening through the newborn screen or through targeted screening or testing which is based on prenatal history and patient signs and symptoms. Birthing parents with crowded housing situations or who have had intimate contact with body fluids during pregnancy are at higher risk. Many patients who have CMV are asymptomatic; however, symptomatic congenital CMV can present at birth with microcephaly, intrauterine growth restriction, hepatosplenomegaly, petechial rash, jaundice, and seizures. Characteristic lab findings include low platelets, elevated ALT, and increased conjugated bilirubin. Head imaging abnormalities are also seen such as ventricular or periventricular calcifications, ventriculomegaly and cerebellar, ependymal, or parenchymal cysts. Newborns that fail their hearing screen should also be tested for CMV. If you suspect congenital CMV, the newborn's urine or saliva should be tested using CMV rapid viral cultures or, more commonly, PCR-based assays. Testing for CMV is ideally done before the baby is 21 days old as after this, a positive test is not conclusive for congenital CMV and could represent perinatal or postnatal infection. Babies with symptomatic congenital CMV can be further classified as asymptomatic, mildly symptomatic, and moderate-to-severely symptomatic. Those with mildly symptomatic congenital CMV have mild or transient abnormalities in two or fewer organ systems without chorioretinitis or CNS involvement. Moderate to severe CMV involves  $\geq 3$  organ systems and includes CNS disease, chorioretinitis, and severe single organ disease.

All symptomatic CMV cases should be referred promptly to a Pediatric Infectious Disease expert for assistance with risk stratification, management, and treatment. If treatment is considered this would include oral valganciclovir for 6 months. Neonates with congenital CMV can develop CNS sequelae, including retinitis, sensorineural hearing loss, developmental delay, and periventricular calcification, so prompt testing and treatment of CMV is crucial to minimize long-term consequences. Follow-up for children with congenital CMV should include regular hearing, neurodevelopmental, and ophthalmological exams to monitor complications of infection.

### **Neonatal Herpes Simplex Virus (NHSV)<sup>2</sup>**

Next, we will discuss neonatal Herpes Simplex Virus, also known as NHSV. This infection can be acquired through intrauterine, perinatal, or postnatal transmission, with perinatal acquisition being most common. Babies with NHSV can be asymptomatic, or they can present with irritability, poor feeding, lethargy, skin vesicular rash, fever, or seizures. In most cases of NHSV, initial symptoms develop in the first 4 weeks of life. However, if an infant is less than 2 months old and is presenting with these symptoms, even if it's just a fever, you should consider NHSV. Initial symptoms can be non-specific and given the significant morbidity and mortality, when there is clinical suspicion, prompt diagnosis and early treatment is very important to improve outcomes. Remember that if the birthing parent does not have a known history of genital herpes, this does not exclude a diagnosis of NHSV, so all infants can potentially be at risk. As well, transmission can occur whether the birthing parent with HSV is asymptomatic or symptomatic, if the infection is present in the birth canal at the time of delivery. It's a great idea to consult Infectious Diseases for help with risk stratification, management, and treatment of NHSV if it's on your differential. NHSV is classified as disseminated NHSV when multiple organs are involved (like the liver and lungs), we call it CNS NHSV when the brain is involved, or skin, eyes, and mucous

membrane infection also known as SEM infection when these areas of the body are involved. PCR testing of the CSF, blood, skin lesions, and mucous membranes (eye, mouth, rectum) is preferred to diagnose NHSV and to determine which organs are involved. Management of NHSV includes intravenous acyclovir and supportive care. Left untreated, NHSV can result in high morbidity or mortality, with disseminated NHSV being the most dangerous. NHSV that is limited to the skin, eyes, or mouth is treated for 14 days. CNS or disseminated NHSV infection is treated for a minimum of 21 days and IV acyclovir can be transitioned to oral acyclovir for suppressive therapy. Follow-up of NHSV includes a monthly complete blood count, urea, and creatine to monitor for the adverse effects of acyclovir. The dose of acyclovir should also be adjusted for growth. Long-term follow-up for children with NHSV should include regular hearing, neurodevelopmental, and ophthalmological exams to monitor complications of this infection. If you are interested, we recommend checking out the Canadian Pediatric Society position statement on NHSV cited in our references. This statement provides guidance on managing asymptomatic term infants who might have been exposed to HSV during delivery, which is outside the current scope of this podcast.

### **Q&A with Dr. Purewal**

I would now like to welcome Pediatric Infectious Diseases Physician Dr. Rupeena Purewal to answer some of our questions about Toxoplasmosis, Rubella, Hepatitis B virus, and Varicella.

Question: It's known that pregnant people should not clean cat litter, could you please explain to us why that is?

*Answer: Yes, this is a very important recommendation that is given to all pregnant woman and those with an underlying immunodeficiency to prevent the acquisition of Toxoplasmosis.<sup>3</sup> Toxoplasmosis is a parasite that can be obtained from eating undercooked meat, unwashed vegetables that are grown where an infected cat has left droppings, or by touching infected cat droppings. The reason we are worried about this in pregnancy is because the baby can get Toxoplasmosis. The risk is higher when the infection is acquired in the first trimester and the birthing parent receives no treatment.*

*Clinical manifestations of Toxoplasmosis:<sup>3</sup>*

- *Most infants are asymptomatic*
- *If they do develop signs and symptoms, these range from:*
  - *Less severe: infants have hepatosplenomegaly and lymphadenopathy.*
  - *More severe:*
    - *Neurological complications: intracranial calcifications*
    - *Ophthalmological manifestations: chorioretinitis, microphthalmia, strabismus*
    - *Growth issues: SGA, IUGR*
    - *Hematologic abnormalities: thrombocytopenia, anemia,*
    - *Skin manifestations: petechiae, maculopapular rash*

*Congenital Toxoplasmosis can lead to long term sequelae e.g. Developmental delay, blindness, and learning disorders.<sup>3</sup>*

*I will just touch on the treatment options in pregnancy, although they would be considered after consultation with adult and pediatric infectious diseases. In pregnancy, we have a few options.<sup>3</sup> In general, if toxoplasmosis is diagnosed before 18 weeks of gestation and the fetus is likely not infected, then guidelines would suggest giving a medication called spiramycin. This acts to reduce the transmission to the fetus and is most effective when given early to mother. If there are concerns that the fetus is infected (abnormal ultrasound findings, distress, or toxoplasmosis PCR is positive on amniotic fluid that is usually obtained after 18 weeks gestation, OR maternal infection was acquired after 18 weeks gestation, then treatment options would include pyrimethamine, sulfadiazine and leucovorin. For the sake of time, I will not go into further details regarding each of these medications, but this treatment would be done in consultation with infectious disease and OBGYN specialists, as I mentioned prior.*

*Therefore, we recommend that pregnant women try to avoid or limit their exposure to this parasite e.g. Cooking meat completely, washing and peeling all fruits/veggies before eating them and wearing gloves when gardening or handling sand in the sandbox.<sup>4</sup> Also, we would recommend that someone else change the litter box, but if pregnant parents must change it, wear disposable gloves and wash your hands with soap and water afterwards. Also, it's advisable to change the litter box daily because the parasite does not become infectious until 1-5 days after it is shed in the feces.*

Question A newborn baby presents to the clinic with a positive infant Rubella IgM titre. Can you explain some clinical pearls for congenital Rubella infection and how congenital Rubella can be prevented?

Answer:

- *Fortunately, due to immunization (MMR) that was licensed back in 1969, we do not see many cases of Rubella as it was eliminated from the US in 2004.<sup>5</sup> So annually we don't see a very high number of cases except for those imported from travel/immigration.*
- *Of note, humans are the only source of the infection and transmission is through direct, or droplet contact from nasopharyngeal secretions.*
- *A pregnant woman who contracts the virus can be asymptomatic but if symptomatic will have non-specific flu-like symptoms (muscle aches, low grade fever, cough, sore throat, runny nose, headaches), enlarged neck lymph nodes, they may have joint pain and finally a rash that is described as maculopapular (pink/red spots). The rash starts on the face and neck and spread down to the rest of the body*
- *The infectious period is 7-8 days before to 7-8 days after the onset of the rash*
- *Congenital Rubella is very serious. Rubella in pregnancy can cause spontaneous abortions, fetal death or congenital Rubella syndrome.*
- *Early detection of maternal infection is key– prenatally is important if mom does have Rubella like illness develop. If infection occurs before 18 weeks of gestation – maternal counselling of termination of pregnancy is discussed.*



- *Congenital Rubella syndrome: similar to many congenital infections, risk is highest when acquired in early pregnancy (first 12 weeks) where there is an 85% chance of congenital defects which decreases to 25% if acquired late in pregnancy.<sup>6</sup>*
- *Congenital Rubella can present with:<sup>7</sup>*
  - *Congenital heart defects eg. PDA, peripheral pulmonary artery stenosis*
  - *SNHL*
  - *Ophthalmologic findings (cataracts, chorioretinitis)*
  - *Neurologic findings: microcephaly, calcifications*
  - *Hematologic abnormalities: thrombocytopenia, dermal erythropoiesis causing this classic blueberry muffin rash*
  - *Other changes: low birth weight, interstitial pneumonitis, bony abnormalities*
- *Management of congenital Rubella: management is supportive for congenital Rubella syndrome, there is no cure.<sup>7</sup>*
- *Prevention is key. This includes:<sup>7</sup>*
  - *Making sure all women of childbearing age are vaccinated with MMR (live vaccine, so can't get in pregnancy)*
  - *Maternal screening: checking if maternal titres are adequate in early pregnancy*
  - *Preventing spread: if someone is positive for Rubella, pregnant woman should not be around them. Ensure appropriate isolation protocols to mitigate spread.*
  - *Note: children with congenital Rubella are considered contagious until at least one year of age unless two negative cultures are obtained one month apart after 3 months of age – therefore while handling urine and other secretions, proper hand washing and hygiene is important*

Question: Moving on to Hepatitis B now. While most newborns with congenital Hepatitis B virus are asymptomatic at birth, this virus can have long-term consequences like chronic infection and disease. What are the ways to prevent transmission of hepatitis B virus to a newborn?

*Answer: To prevent Hepatitis B transmission, all infants born to Hepatitis B surface antigen positive birthing parent are given Hepatitis B immune globulin and start their Hepatitis B vaccine series at birth. Ideally this is given within 12 hours of birth.<sup>8</sup> Without this timely postexposure prophylaxis, 90% of infants born to Hepatitis B surface positive parent will acquire chronic Hepatitis B virus infection, and of those 1/4<sup>th</sup> (25%) will eventually die from chronic liver disease.<sup>9</sup> Hence the importance of this intervention. It's very important to remind health care providers monitoring pregnancy women to ensure they know the Hepatitis B status of the birthing parent prior to delivery. Screening and offering treatment to the parent is another important part of preventing transmission.*

Question: Finally, we are on our last congenital infection to explore today, varicella. Varicella Zoster virus (VZV) is the virus responsible for chickenpox. When is the baby at highest risk for congenital Varicella infection and how is infection prevented?

*Answer:*

### *Congenital Varicella Syndrome:*

- *When a pregnant woman has chickenpox in the first 20 weeks of her pregnancy, there is a 1/50 chance that the baby will have this syndrome develops.<sup>10</sup> The highest risk time is between 13-20 weeks.*
- *Congenital Varicella syndrome is not very common- 41 cases per year in US, 4 cases per year in Canada since 1947.<sup>11</sup>*
- *This syndrome includes: scarring, microcephaly, seizures, limb abnormalities include hypoplasia, atrophy or malformed digits, and ocular defects (chorioretinitis, cataracts).<sup>10</sup>*

### *Prevention is key!*

- *All pregnant women should know their immune status for VZV (some have had natural disease and others vaccinated). Of note, the vaccine was approved in 1995.*
- *If someone of childbearing age did not have natural disease, prior to becoming pregnant they should consider VZV vaccine. It is a live vaccine, so cannot be given in pregnancy.*
- *If non-immune, birthing parents should avoid exposure to someone who has clinical findings consistent with chickenpox.*

Thank you so much Dr. Purewal for donating your time and expertise to teach us all about congenital infections!

### *In summary:*

- Congenital infections are on the rise.
- CMV is the most common congenital infection and is one of the leading causes of sensorineural hearing loss in newborns exposed to CMV. While universal screening is becoming more common in Canada, testing and consultation with an Infectious Disease expert is crucial to managing long-term consequences of infection.
- Neonatal HSV has a high mortality and morbidity. It is important to recall signs and symptoms of this infection and if the diagnosis is suspected to send off PCR testing empirically start treatment with acyclovir.
- Toxoplasmosis is transmitted through the fecal-oral route and can cause long-term CNS consequences so pregnant women should avoid cleaning cat litter or eating undercooked meat.
- Rubella infection can be prevented through administration of the MMR vaccine.
- Providing a Hepatitis B vaccination and immune globulin to babies born to Hepatitis B positive parents can help prevent the long-term sequelae of the disease.
- Babies are at the highest risk of congenital Varicella 5 days before and 2 days after delivery.
- Always consult an Infectious Disease expert if you suspect your patient has a congenital infection!
- And finally, consider reading the Canadian Pediatric Society statements on each of these infections to learn more.

That concludes this episode of PedsCases on congenital infections. After listening, you should have an understanding of the importance of congenital infections and knowledge of

the signs and symptoms of certain congenitally acquired infections. You should also have an awareness of when testing for congenital infections is warranted, as well as what management and follow up might look like. Finally, you should know when to involve an Infectious Disease expert to assist with diagnosis and management.

Thank you to Dr. Purewal for your expertise, the Canadian Pediatric Society for your clinical guidance, and PedsCases for the opportunity to host an episode. And thank you so much for tuning in!

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