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Expert Interviews

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Congenital Syphilis: Diagnosis and Management

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Congenital syphilis expert Dr. Katherine Hsu reviews the complexities of when and how to test neonates for congenital syphilis, actionable differential diagnosis, treatment, and long-term infant outcomes after exposure. The discussion expands on the June 12 Congenital Syphilis Prevention episode.

Topics:

- Syphilis
- congenital syphilis
- sepsis
- diagnostic assays
- STIs
- STDs

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Disclosures

Disclosures for Katherine Hsu, MD, MPH, FAAP
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References

Paper #1 **Paper #2** **Paper #3** **Paper #4**

Transcript

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introduction**[00:00] Introduction**

Dr. Meena Ramchandani
Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STD [sexually transmitted disease] review for health care professionals who are interested in remaining up-to-date on the diagnosis, management, and prevention of STDs.

For the second part of this two-episode series, we welcome back Dr. Katherine Hsu. Dr. Hsu serves as the Medical Director for the Division of STD Prevention and HIV/AIDS Surveillance at the Massachusetts Department of Public Health and is the Director of the [Sylvie] Ratelle STD HIV Prevention Training Center of New England. She is a national authority on both the topic of congenital syphilis as well as congenital syphilis prevention through public health.

In the first episode, we discussed how public health departments can help prevent congenital syphilis and now we are going to discuss the complexities of when and to how to test neonates for congenital syphilis, actionable differential diagnosis, and potential areas of research on long-term infant outcomes after congenital syphilis exposure.

diagnostic-assays**[1:08] Diagnostic Assays**

Dr. Meena Ramchandani
Well, let's jump in and talk a little bit about particular aspects of congenital syphilis management that can be difficult for clinicians. So, the first question I have is if a neonate is born to a parent, let's say with a reactive syphilis test, what type of syphilis testing should be done in the neonate?

Dr. Katherine Hsu
With every infant born to a pregnant individual with a positive trep, treponemal antibody, and non-trep [non-treponemal] antibody test, the recommendation is universal. It doesn't matter what the stage was originally of that woman. That infant needs a titer, a non-treponemal titer, either an RPR [rapid plasma reagin] or VDRL [Venereal Disease Research Laboratory] traditionally in this country, *at* delivery in order to compare it to the mother's titer at delivery. That is the minimum requirement because then, with that information in hand combined with the mother's original stage, the mother's amount of treatment either before pregnancy or during pregnancy, the infant's exam and testing if it's needed in the infant, all of that together can then be

reviewed for a question of how much treatment the infant does or doesn't need, and how much treatment and workup. But the minimum requirement is to do a non-treponemal assay both in mom and baby at the time of delivery.

Dr. Meena Ramchandani
And how important is it to stick with the same non-treponemal test? Like, could you do an RPR in the neonate and a VDRL in the baby parent and compare those two?

Dr. Katherine Hsu
I think that would be very hard to do. The VDRL and the RPR—while relative changes in one of the assays can be used to measure against itself—a VDRL and an RPR are not directly comparable. So you do need the same because the point of the testing both infant and mom at the time of delivery is to ascertain whether the infant's titer is at or below the mother's titer, which simply happens because of translocation of antibody across a placenta, usually protective antibody, which occurs in the last trimester of pregnancy in everyone. And you want to know basically if the infant is mounting a titer defense that's higher than the mother's. That's an indication that potentially the infant is infected no matter what you did with the mother during the course of pregnancy or before that.

The harder thing, I think is RPRs in two different systems. I think one of the difficult downsides to all of these antibody tests is that they are subject to a *significant* amount of what I would call "waffle," which is to say a two-dilution change is what's significant, not a one-dilution change. If a titer is 1:8 and the infant's titer is 1:16, is it significant? Is it not significant? Could it just be lab-to-lab variability? Could it be day-to-day variability, batch-to-batch variability? Even if you're only talking about an RPR or VDRL. Already these questions plague and riddle all of us. The problem is it's not actionable information. So basically, functionally, if you have a two-dilution change, the infant is 1:32, the mother is only 1:8, that counts as significantly different and certainly not fourfold less than the mothers or less than are equal to the mothers, which are what the guidelines are written about.

Dr. Meena Ramchandani
That's really helpful.

congenital-syphilis-workup **[4:45] Congenital Syphilis Workup**

Dr. Meena Ramchandani
That gets me to my next question. Can you describe some of the recommended evaluation? Let's say a neonate does fall in the category of proven or highly probable congenital syphilis, even if they had a normal examination at birth.

Dr. Katherine Hsu
That's a great question, and I think many clinicians do ask this question of the infant looks great, completely well-appearing, and why am I stuck even thinking about LP-ing [doing a lumbar puncture] a beautiful, just newborn, full-term infant? Well, one of the many reasons is the studies back in the '80s, which was the last time we dealt with this problem at the same volume that we're dealing with it now. The studies back in the '80s basically demonstrated that a completely asymptomatic, well-appearing infant who was born to somebody at high risk for reinfection or transmission, so not somebody who had been treated already, not one of those scenarios, they had full evaluations and a handful of those infants actually were shown to have CSF [cerebrospinal fluid] abnormalities when they absolutely had no evidence or any reason to believe that they would. This was Ian Michelow's study that was published in the *NEJM*[*New England Journal of Medicine*]. Basically, they took CSF from apparently well-appearing infants who were, however, born to more high-risk scenarios where the probability of transmission was not improbable, and the only abnormality that was detected was detected through CSF.

So, that's why a total workup is recommended in certain infants, but I think that's the question, right? So, what I do whenever these questions come up is I am sitting there on the Internet with the pediatrician or the

hospitalist or whoever's taking care of the newborn infant, and I say to them, let's go on the Internet together and Google CDC STD treatment guidelines. And, what you're talking about is the *Scenarios 1-4*, right, that basically help us manage the probability of true exposure to the infant and what diagnosis/management/treatment needs to be done in the infant in accordance with the probability [of transmission] accorded around the time of delivery.

Scenarios 1-4 review these beautifully, and usually I go through that, or if the pediatrician is more familiar with the Red Book, these scenarios are very similar to an algorithm that's written about it in tiny, tiny print in the Red Book, and we walk through it together and classify what the approach could be or what the soundest approach could be for any one of these infants. The good thing in Massachusetts is we have such a small volume, 150 to 300 cases a year, we can co-manage them in real-time to have an impact. So, congenital syphilis, it was scenario one, confirm, proven, or highly probable. That's the one where everyone is also supposed to get CSF, complete blood count (CBC), long-bone radiographs, other tests as clinically indicated, basically qualifying if you have an abnormal physical exam. Okay, easy. Almost no one would argue with that, or a change in the titer that indicates that the infant's is fourfold or greater than the mother's titer, which is considered significant or any other reason around confirmed, proven, or highly probable, every single one of those infants is supposed to get CSF. That is correct.

Dr. Meena Ramchandani
Yeah, I find that algorithm really helpful, and I like to go through that as well. I get that question a lot from pediatricians: "If the baby or the neonate looks asymptomatic at birth, do I actually need to do any of this workup?" And the answer is yes.

differential-diagnosis**[8:33] Differential Diagnosis**

Dr. Meena Ramchandani
Are there any features that would distinguish congenital syphilis from, for example, other differential diagnosis if the neonate did have clinical symptoms?

Dr. Katherine Hsu
That's a great question, but I think the question comes up more in the following way: Is there overlap between the signs and symptoms of congenital syphilis or congenital CMV [cytomegalovirus]? Absolutely. Any of the congenital infections, many of them can present with rash, can present with hepatosplenomegaly, can present with eye findings, can present with oddities in the CBC like thrombocytopenia or liver function abnormalities. There's significant clinical overlap. That actually isn't so much the question because the question really becomes, is that actionable information? So, is it to the point where there's so much of a slam dunk for the other infection that you have no reason to treat congenital syphilis if there is a known exposure and there's an indication just in accordance with these guidelines in *Scenarios 1-4*? Would it ever get you off the hook because you had a valid competing diagnosis?

The answer to that question is seldom yes. Because almost always at the outset of life, if there is any reason to believe that the infant would benefit from a single shot of benzathine penicillin or a workup to look harder for syphilis, or 10 to 14 days of IV pen [benzathine penicillin], you're basically going to choose to give it even if there's another competing diagnosis that could explain the rest of the clinical picture. To top it all off, let's say the infant presents asymptomatic. Well, the truth of the matter, right, is there's this incredible statistic which people often forget, which is that, you know, if you're infected with syphilis as an infant, the majority of congenital syphilis infections, they don't present until several weeks after birth with failure to thrive, with more non-specific symptoms, with maybe a more specific symptom of a rash and hepatosplenomegaly, or

So there are not very many reasons to ignore any of the guidance. Even if you have a competing diagnosis, who wouldn't give a round of penicillin treatment or at least a prophylactic dose, depending on the scenario that drives you towards how much treatment and management that you need to do?

Dr. Meena Ramchandani

That's really helpful. So, the baby or the neonate can be asymptomatic at birth but have later features from congenital syphilis, and if you don't implement that treatment right away, then those late features may not be prevented and could have potentially long-term adverse effects or clinical consequences.

Dr. Katherine Hsu
Exactly.

treatment-regimen**[11:41] Treatment Regimen**

Dr. Meena Ramchandani
Can you remind our audience the recommended antibiotic treatment for congenital syphilis?

Dr. Katherine Hsu
Ten to fourteen days of IV penicillin. There are really no data to support any alternative regimens. There are no studies to support the use of any other drugs other than 10 to 14 days of IV penicillin when you actually believe the infant has congenital syphilis or a single shot of 50,000 units per kilo body weight IM [intramuscular] for prophylaxis at the time of delivery if you think the exposure still occurred.

Dr. Meena Ramchandani
Thank you Kathy.

other-antibiotics**[12:20] Other Antibiotics**

Dr. Meena Ramchandani
The neonate might have already been started for possible sepsis on ampicillin, and it's been two to three days, and the RPR comes back, and it's positive. Let's say they have a diagnosis of congenital syphilis. Can the ampicillin be used as part of that treatment course?

Dr. Katherine Hsu
It's a great question. This is where I have actually seen variability across the country and even within my own jurisdiction about the approach. So, at the end of the day, the person writing the orders for the treatment of the infant is the one who's responsible. I have seen people extend, say, a rule-out sepsis course was given for three days, and then you uncover the fact that really the reason the infant was septic-appearing was actually congenital syphilis. I've seen people extend the course of therapy to make sure that it's 10 to 14 days of penicillin that are given.

Dr. Meena Ramchandani
That's helpful to hear of your anecdotal experience in talking to providers because of the lack of data and the fact that morbidity is so great.

Dr. Katherine Hsu
Right.

Dr. Meena Ramchandani
So my recommendation has always been penicillin.

Dr. Katherine Hsu
I think for the most part, people who are in pediatrics or hospitalist care at the front end of somebody's life are very loathe to take chances. So, I'm trying to remember in the cases where this has come up, which surprisingly is not quite as often as you might think, but in the cases where it has come up, have people, on average, erred on the side of giving the extra days of penicillin directly, which is the evidence-based treatment regimen? Yes, that's probably the majority.

potential-long-term-outcomes**[14:02] Potential Long-term Outcomes**

Dr. Meena Ramchandani
You know, alluding to a talk that you gave at the Pediatric Academic Societies, you talked about some research on long-term infant outcomes after congenital syphilis exposure. Can you describe a little bit more about what you presented?

Dr. Katherine Hsu
I was lucky enough to have a pediatric infectious disease fellow from my home institution, Boston University Medical Center, Dr. Amy Triche, who was interested in doing some work at the public health department. And we realized, about five years ago, that we had enough infants (mother-infant dyads) that we could follow for two-year outcomes after delivery. So, we had, at the end of the day, we wound up cleaning the data on about 72 mother-infant dyads. The majority of the time, these mothers didn't actually have infectious syphilis at the time that they were pregnant. Many of them were late latent syphilis or latent syphilis of unknown duration. So that wound up, in effect, being we didn't think a very infectious state of syphilis. As you know, the RPR at that stage, which is thought to be a proxy measure of how transmissible those women are, not particularly high. Some of those women had reported previous treatment in another country but never had it documented, so maybe they were treated with three shots of penicillin, but no one on the clinical teams ever thought that these women were truly very infectious and exposing the infants.

On the other hand, we also had six infants where the mothers had secondary syphilis, most likely during pregnancy. So in comparing the six with the other tens of infants, where there probably wasn't a lot of treponemal, *T. pallidum*exposure, what we were able to identify in the two years of follow-up was that there might be a lower average height percentile at age one year in the infants born to mothers with secondary syphilis, and there might have been a higher rate of developmental delay. Not a lot more referrals to ophthalmology or to ENT [Ear, Nose and Throat] for hearing loss or eye changes, but there was a question of developmental delay that was a little bit more common in *N*=6, two-thirds of the infants, meaning four out of the six, had more developmental delay in the first two years of life versus the infants born to mothers who really had late latent syphilis or latent syphilis of unknown duration, which we really don't think exposed them.

That was a group that only had about a 25% rate of developmental delay as measured by pediatricians and chart reviews when we looked at these 72 mother-infant dyads. That's enough to put, I think, a *huge* question mark and to put a call-out that there is need for research on simply the exposure, even if the exposure occurs in utero when the timing of that exposure is to this bacterial infection may, in fact, impact ex-utero outcomes, even when these mothers were fully treated. These mothers were fully treated for secondary syphilis. No one has previously thought that this would make a difference.

The reason we thought to do this analysis was because, as I think you well know, Meena, there are so many cohorts of well-followed individuals where the mother has HIV or other infections where we track more effectively what the outcomes are even one to two years out. And there are some questions about perinatal HIV exposure and whether or not, even when you cut the risk of transmission to zero, and the infant never acquires HIV, is there developmental delay, or is there a hit the infant takes from the in utero environment and the exposure? That's why we raised the question. We now have a tiny hint of data that maybe this is possible, but again, we're talking *N* of six compared to *N* of tens. So, I think this opens the question and is rather disturbing, right? Because that basically means really to prevent poor outcomes from congenital syphilis, we have to get it even before the woman ever acquires this infection during pregnancy. We need to prevent the acquisition of syphilis before the woman becomes pregnant.

Dr. Meena Ramchandani
It's probably the first data that's come out on this topic, right? I haven't heard or seen anything before.

Dr. Katherine Hsu
Other people tried to look at it, but again, very small cohorts. There was a study where they looked at these longer-term outcomes one to two years out following delivery, but they didn't completely stratify or had such tiny numbers they couldn't stratify for what stage the mother was at and whether or not the mother was

treated completely. So, I think this starts to get at a hint.

Unfortunately, Meena, we're at the point where we have so many exposures and true infection. I mean, there's no question that if you have congenital syphilis and you have to be treated for it as an infant, that is not a hit you want to take early on in life, but the exposure alone in utero, we now have many, many, many more cases because of that 200% rise in reported infections and congenital infectious syphilis. We have so many more cases and mother-infant dyads to follow. At this point, there are cohorts being followed in the U.S. national databases. Ryan Rochat [MD] and others at Texas Children's [Hospital] are doing a study of this very issue.

Dr. Meena Ramchandani
Studies are definitely more needed in this area. I think it just also emphasizes how much we need to do of screening, and then once screening is documented, let's say there is a diagnosis, to getting people into treatment as soon as possible. Thank you so much, Kathy. I've learned so much from you, and I can't thank you enough for being on this episode.

credits**[20:30] Credits**

Dr. Ramchandani
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