Moving Closer to Universal CMV Newborn Screening

Recorded December 11, 2019

Presenter: Shannon A. Ross, MD, MSPH

AudiologyOnline.com Course #34162

Partner: Otometrics / Natus

- [Anna] Good morning. Again, this is Anna from Audiology Online, and today, I would like to introduce our speaker, Dr. Shannon Ross. Dr. Shannon Ross is an Associate Professor of Pediatrics and Microbiology in the Division of Pediatric Infectious Diseases at the University of Alabama at Birmingham. Dr. Ross earned her medical degree from the University of Alabama School of Medicine. She completed her pediatric residency and pediatric infectious diseases fellowship at the University of Alabama at Birmingham. During her fellowship training, Dr. Ross also earned an MSPH in clinical research at the University of Alabama School of Public Health. Dr. Ross is an active clinician and researcher with her research focused on the natural history and pathogenesis of congenital cytomegalovirus infection with special emphasis on translational research exploring virological and clinical markers of outcome in CMV-related hearing loss. And now, I'm gonna turn it over to Dr. Ross.

- [Shannon] Thank you Anna, and hello everyone. I'm gonna go ahead and get started, jump right in. I'll start with my disclosures slide. I have done a consultation with Merck and Roche, and also an educational webinar for Meridian, and today, I will discuss the unlabeled and unapproved use of valganciclovir. So the learner outcomes, after this course, you should be able to describe the clinical spectrum and outcomes of congenital CMV, and to describe the appropriate diagnostic test to screen to diagnose congenital CMV in the newborn infant. In addition, this course will help you be able to explain how to evaluate an infant with congenital CMV and understand treatment recommendations for this infection. And finally after this course, learners will be able to describe the difference between targeted and universal newborn CMV screening. So to start with some background, congenital CMV, cytomegalovirus infection, is the most common congenital infection in infants and it occurs in about 20 to 30,000 infants annually in the US. It can result in long-term sequelae including cerebral palsy but the most common long-term outcome is hearing loss, and it has a leading non-genetic cause of hearing loss in children. Overall, approximately 15% of CMV infected children will develop hearing loss, and although less common, children still occasionally will

have severe disease, and actually mortality rate from symptomatic infection is somewhere between five and 10%. So CMV is a congenital infection, so it can be transmitted from the mother to the fetus anytime during gestation. And exposure to CMV in mothers is primarily from young children, but also can be due to sexual activity. The mother may transmit the virus to the fetus when first exposed to CMV, and we call this a primary CMV infection, or a mother who is seropositive prior to pregnancy can acquire a new virus and get re-infected and transmit this virus to the fetus, and we call this non-primary infection. The risk of transmission in primary CMV is approximately 40%, and we really do not know the true risk of transmission in non-primary CMV infection, but we do know from some large epidemiologic studies that approximately 75% of all congenital CMV cases are due to non-primary maternal infection. And it's important to know that maternal seroprevalence, the rate of seroprevalence among women varies greatly by race and age.

So this is some of the most recent data on the congenital CMV epidemiology in the United States, and this is from a study which I will have several slides of data from called the CHIMES study, and this was a large multicenter newborn screening study. My institution, UAB, was the primary site, and there were seven other sites in the US, and as part of the study, newborns were screened for congenital CMV in the nursery and over 100,000 newborns were screened over five years for the study. And from this, we determined that the prevalence in the United States for congenital CMV is 4.5 per 1,000 live births. Now this graph at the bottom shows prevalence based on race, and what this demonstrates is that the prevalence varies greatly depending on the maternal infant race. so the highest prevalence actually occurs in black infants, with around nine per 1,000 live births per year in the United States occurring in black infants. Rates are much lower in both Hispanic and non-Hispanic whites, approximately 2.5 per 1,000 births, and Asians is also lower. So it's important to realize that depending on the population in which you look, the prevalence of congenital CMV can differ. So CMV is an important infection, and when you compare it to other important and common

syndromes or infections in children, congenital C is one of the leading causes of disease in the US. And this is a relatively old study but it's still quite accurate, and what this shows is the annual number of children with long-term sequelae is highest in congenital CMV compared to Down syndrome, fetal alcohol syndrome, and other common infections. And a report in 2000 from The Institute of Medicine estimated that the cost of congenital CMV infection is greater than $1 billion in direct medical care each year so this is a significant disease burden in children.

So as I mentioned, the most common sequelae or outcome of congenital CMV infection is hearing loss, and this is two charts which show etiologies, or causes of hearing loss in children at birth, and then at four years. And what this demonstrates is that congenital CMV is estimated to account for about a fifth of hearing loss in children at birth, and this increases to approximately 25% of hearing loss is due to congenital CMV in children, with other causes of hearing loss primarily being genetic. So CMV is an important contributor to hearing loss in children. So even though I've shown that this is an important infection, a common infection, people just do not know about congenital CMV, and this is a recent report based on lifestyle surveys that the CDC does frequently, and what this shows is both awareness versus the annual incidence of congenital CMV versus, again, some other well-known common conditions in children.

And even though congenital CMV has one of the highest US annual incidences, the awareness of congenital CMV in adults is quite low, and somewhere around less than 10% of adults in the US even have heard of or know about the importance of congenital CMV, so we have a lot of work to do in this area. So let's move on and talk about the disease of congenital CMV. In clinical abnormalities in newborns, so newborns that are born with disease or symptoms that suggest an infection only occurs in about 10% of infants with this infection. In most infants, approximately 90% with congenital CMV have no clinical findings, they look perfectly healthy, and these are termed asymptomatic infants. Among the 10% symptomatic, the newborn disease

can range, it can range from very mild nonspecific findings such as some petechiae or hepatosplenomegaly, or, and this is shown in this infant on the right, or infants can have, and this is less common, multiple organ involvement shown in this infant on the left, this infant has a small head, microcephaly, petechiae, this infant is fairly severely infected. In the literature, there is no standard definition of symptomatic CMV, but we do know that the risk of sequelae is higher in infants who are symptomatic at birth. So this is a publication which looked at clinical findings in symptomatic congenital CMV, and it was a group of about 178 infants and they were either referred to a newborn CMV follow-up clinic, or they were identified with congenital CMV based on a screening program.

And what does shows is that regardless of how they were identified, petechiae is a common finding in about 50 to 75% of infants. Much less commonly, infants will have a purpuric rash. Hepatosplenomegaly can range from 20 to 50% of infants, jaundice, and this is a jaundice with a direct hyperbilirubinemia is fairly common in about 40 to 50% of infants. Microcephaly occurs in about a third to a half of infants, but much less commonly, infants will have seizures. And chorioretinitis which is seen on an ophthalmologic exam occurs in about nine to 20% of infants. And if infants undergo laboratory and neuroimaging, we do see abnormalities in symptomatic infants. Elevated liver enzymes are seen in about 50 to 75%, thrombocytopenia is common, and the most common neuroimaging findings, the classic findings are calcifications, periventricular calcifications, but there are other described neuroimaging abnormalities seen in congenital CMV, and these occur in around 60 to 70% of symptomatic infants.

So let's move on and talk about the most important outcome, hearing loss, and I'm gonna go over several slides which show data from various studies, and this is actually a systematic review of hearing loss outcomes that was put together several years ago by a group that examined several large studies, and they break down hearing loss based on whether an infant was asymptomatic at birth, or symptomatic at birth. And

the overall rate of hearing loss is higher in symptomatic infants, somewhere around 30 to 40%, and approximately 10% of asymptomatic infants will develop hearing loss. The type of hearing loss can differ. Infants with symptomatic infection more commonly will have bilateral hearing loss, and will more commonly have severe to profound bilateral loss, about 65% of infants will have this loss with only about 40% of asymptomatics having this complete bilateral severe to profound hearing loss.

One unique feature of hearing loss in congenital CMV infection is that it can be delayed, it can occur after the newborn period, and this is seen in about 10% of asymptomatic infants and approximately 15 to 20% of symptomatic infants. Hearing loss can actually also fluctuate over time where infants can have loss and then improvements, and then loss again, and this occurs in about a fifth to a quarter of infants. And progression of loss over time is also seen in about 17 to 20% of infants. So as I mentioned, one unique feature of congenital CMV hearing loss is that it can be delayed, it can occur after the newborn period. And this is a large, probably one of the largest cohorts of infants with congenital CMV, approximately 800 infants. And what they showed is that among infants who are asymptomatic at birth, among those who have delayed onset hearing loss, the median age of hearing loss was 44 months in this large cohort. The range is quite large, but again, infants were three to four years of age oftentimes when they develop their hearing loss. Delayed onset loss was also seen in symptomatic infants, but is a bit earlier with a median age of approximately 33 months, so this really underscores the importance of continued hearing monitoring for infants who have this infection.

So what about the degree of hearing loss? And when you compare asymptomatic and symptomatic infants, it's relatively similar. And approximately 20% will have just a mild loss, with over 50 to 60% of infants both asymptomatic and symptomatic having severe to profound hearing loss. Again as I mentioned, fluctuating hearing loss can occur, and this is where you see improvements in threshold levels, and this tends to be

a bit more common in asymptomatic infants, it occurs in approximately 40% of asymptomatic infants, but also seen in approximately a fifth of symptomatic infants. So what about other findings we see in infants with this infection? So as I mentioned, chorioretinitis is a common finding or a classic finding that we see in congenital CMV infection in infants who are symptomatic.

And these are a few recent studies which looked at long-term visual impairments in children. The first study was out of Houston, a cohort of 137 infants, and they reported that 18% of symptomatic children and no asymptomatic children had severe visual impairments long-term. However, moderate visual impairments were seen at a similar rate, approximately six to 7%. A smaller study out of Italy of 48 infants reported that 45% of symptomatic infants had ocular abnormalities, with 22% of these having long-term visual morbidity. Interestingly, among their asymptomatic infants, none had any ocular involvement. We saw a similar finding in the CHIMES study, and we had 77 infants with asymptomatic infection who underwent ophthalmologic exam, and none of our infants were found to have chorioretinitis, and again, these are asymptomatic. So even though chorioretinitis does occur, it is much less common in infants with asymptomatic infection.

So what about cognitive sequelae? Certainly, infants can have long-term cognitive sequelae, and this is seen much more commonly with symptomatic congenital CMV. And looking at a variety of studies with long-term, approximately 25 to 65% of infants with symptomatic congenital CMV will have cognitive deficits, which include an IQ less than 70, and motor deficits, such as cerebral palsy. And consistently, microcephaly and abnormal urine imaging are good predictors, although not 100%, but they are good predictors of a worse cognitive outcome. In asymptomatic congenital CMV, it's not as clear, the long-term cognitive sequelae, and this is because of the challenge of having good controls to do this study. There is a study from a Texas cohort which show that asymptomatic children with normal hearing before two years of age had no differences

in IQ, vocabulary, or academic achievement scores through childhood compared with well-matched controls. However in children with hearing loss, it's not as clear because it's difficult to find good controls, so I think this is where the question remains and more research needs to be done.

So just to sort of review everything we've talked about thus far, so congenital CMV accounts for nearly 25% of childhood hearing loss, and it's important to remember that this hearing loss can be delayed, it can be delayed in onset, and thus not detected by routine newborn hearing screening. It's also important remember that congenital CMV can only be diagnosed in the first three weeks of life. If you test for infants after three weeks of life, it's impossible to know if the virus was acquired intrauterine or postnatally. Newborn CMV screening is the only way to identify CMV-infected infants at risk for hearing loss, particularly delayed onset hearing loss and other sequelae. And the importance of this is that it provides an accurate assessment of the etiology of hearing loss for management and follow up of these infants, and it allows us to counsel parents adequately, and it also alerts clinicians that we need to screen for other potential neurologic sequelae.

So knowing all of this, let's talk about the best way to diagnose congenital CMV. So as I mentioned, the diagnosis of congenital infection requires that you test an infant in the first two to three weeks of life, and this is typically done by looking for viral shedding. If you test after 21 days of life, this could reflect perinatal or postnatal transmission of the virus. Serology is a poor way to test for congenital CMV, and this is due to maternal transfer of IgG, and IgM testing is not sensitive. Viruses shed in the saliva and the urine in very large quantities in congenital CMV infection, and so this is really where the best substrates are to test for this virus. Blood on the other hand has very low levels of virus compared with saliva and urine. Traditionally, viral culture methods of saliva or urine have been the gold standard, and these are labor-intensive and require several weeks. Approximately 30 years ago, there were rapid culture methods that were developed

using monoclonal antibodies to early viral antigens, and these did improve the turnaround time, but they still very labor-intensive, and again require approximately a day or two to have the results back.

So over the past several years, there have been increasing interests in using molecular techniques to screen for congenital CMV. And again, this is data from the CHIMES study that I mentioned, and one of the purposes of this study is to try to determine the best test to screen infants in the newborn period for congenital CMV. And this data shows the utility of dried blood spot PCR for newborn CMV screening. And in all these 20,000 infants that underwent this test, they also underwent a saliva rapid culture, which was considered the gold standard to compare and calculate sensitivity. And sadly, what we found was that the dried blood spot PCR compared to the saliva rapid culture shows poor sensitivity, and approximately 91 infants were positive based on saliva rapid culture, but only 28 infants were positive on dried blood spot, and 64 infants negative on DBS PCR testing, and this calculates out to a sensitivity of less than 40%, so not adequate sensitivity for newborn seen on the screen.

Because saliva rapid culture is the gold standard, we also evaluated the PCR saliva assay, and there's two different methods that we evaluated both liquid and dry saliva, and again, what we found was compared with the rapid culture, the gold standard, the saliva PCR assay is highly sensitive, 97 to 100%, and highly specific for newborn screening. So this is a great easy method to screen newborns is through saliva testing. So what other studies have been done examining dried blood spot versus saliva? The data I just presented again was just from one study, but this is a study more recently published out of China where they screened infants from 2011 to 2013 in two counties in China, and they compared dried blood spot PCR with the wet or liquid saliva PCR and found a similar sensitivity for dried blood spot screening, only 39%. So again, even in other populations, dried blood spot PCR for newborn screening was shown to not be sensitive. And this is why, so this is the viral load level, the amount of virus that is in

both saliva and dried blood spot in infants positive for congenital CMV. And this is the log viral load amount on the left, and as you can see, saliva has a much higher levels of virus compared with the blood in these infants, so six logs median with obviously a high range, but the dried blood spot is only approximately three logs of virus. So the saliva is where the money is, so to speak, because there is just much more virus there. A somewhat issue that always arises when you talk about using saliva for newborn screening is the possibility of contamination of the test due to breastfeeding.

So we know that seropositive women who breastfeed will reactivate CMV in their breast milk. So as part of the CHIMES study, we did not specifically collect this data, but we did try to estimate the contribution of breastfeeding to screening saliva false positives in our study, and so overall we have here 74,000 infants who were screened by both saliva PCR and the gold standard rapid culture, and among these, 23 were false positive. So when the infants were brought back in to confirm, we found these were false positives, so this is a false positive rate of .03%, so very low to begin with. Now if you try to estimate breastfeeding contribution to this rate, what we did is we took, by race, the CMV seroprevalence and the breastfeeding rates to try to determine the number of infants at risk. So for instance, among our black infants, we screened 23,800, we had six false positives. So we know the CMV seroprevalence rate from NHANES data is approximately 80%. We took the breastfeeding rates also NHANES data, and using the infants at risk, we determined the adjusted false positive rate in black infants due to breastfeeding was .08%. And you can see the calculated rates for both white Hispanic and non-Hispanic and Asian, so again, quite low and very acceptable rates of false positive to begin with, but the contribution of breastfeeding to screening saliva false positive is thought to be quite low.

So as I mentioned, urine is also a shedding site in infants with congenital CMV, and although there are many institutes who use urine, there's not previously been a good bit of data showing how urine PCR performs compared to rapid culture. And again, this

is data from the CHIMES study in which we looked at 80 infants with confirmed infection who had both urine PCR in culture and saliva PCR in culture, and what we found was the urine PCR performed as good as the culture if not a little better, there were three infants who were negative on culture but positive by PCR of urine, and similarly in saliva, we had infants who, two infants that were negative by culture, but positive by PCR. So for the diagnosis, meaning if you have a baby you suspect or want to test for congenital CMV, using both urine or saliva PCR is a acceptable and sensitive way to test infants.

And again, this shows why, so these are viral load levels again and these are levels in what we say is screening saliva, so these are saliva samples taken within the first 48 hours of life, and then these are samples taken approximately two to three weeks of age, and as you see, these bars reflect the median viral load levels, but they're very high levels of virus, and it's actually somewhat higher, the saliva compared to the urine. So we've talked about ways to screen infants to test infants for congenital CMV, and the importance of identifying infants early. So many people have started by using targeted approaches much the same as the way newborn hearing screening began, the targeted screening, and this is data again from the CHIMES study looking at a targeted approach to CMV screening, so only screening infants for congenital CMV based on some risk category. And for this, looking at whether or not infants refer on their newborn hearing screening.

So again, this is data from the CHIMES study which shows our just under 100,000 babies that underwent congenital CMV screening and also underwent their newborn hearing screening. And what this shows is among infants who were CMV positive, the hearing refer rate was higher than uninfected infants, so approximately 7%, and this is higher than most national refer rates for infants. So infants with congenital CMV will have a higher rate of refer on newborn screening, so this may be a good way to target our screening, we are able to screen all infants. So will this identify all infants at risk?

So again, this is looking at data from the CHIMES study, and this is infants who were confirmed to have congenital CMV, and this looks at the rates of hearing loss in these infants at birth, so this is only hearing loss at birth. And there were a total of 35 infants who had hearing loss at birth. So among those infants that had confirmed hearing loss, 20 referred on their newborn hearing screening. However, there were 15 infant who passed their newborn hearing screen who on confirmation testing before a month of age had documented hearing loss.

So what this shows is that overall, newborn hearing screen only identified 57% of CMV-related hearing loss in the newborn period. So even among those infants who have hearing loss in the newborn period, the hearing screen did miss some infants who had confirmed hearing loss. So many institutions and states have been screening for congenital CMV, and this is a map on from the National CMV Foundation which tracks this data, and this shows states in the US that have actually legislation components, so laws that mandate either CMV education or CMV screening, or both. The teal-colored states represent states that have screening or education laws enacted, and then the gray and lighter teal and orange states represent ones who either have proposed laws or interest in legislation. So there is and if you looked at this map several years ago, there were less colored states, so there is increasing interest in congenital CMV screening across the country. So let's talk about some data from institutions or states that have actually carried out a CMV screening approach.

And this is data, I know this is a busy figure and I'll walk you through it, but this is data from Utah, which was the first state to mandate targeted CMV screening for infants who refer on their newborn hearing screening. And this is data from the first two years of their program, so they had 103, almost 104 infants who were born under this period. So they had 509 infants that did not pass their hearing screening, and among these, they had 234 who were tested in the first 21 days of life, so that's when you really want to try to test these infants so you will definitively know it's congenital CMV infection.

Among these infants, 14 were identified as CMV positive within 21 days of birth, and six of these infants had hearing loss documented, so 42% of the infants, and these are infants where had this screening program for CMV not been instituted they might not have ever known that CMV was the etiology for their hearing loss. Interestingly, this report shows that regardless of the CMV diagnosis, infants born after this legislation were more likely to undergo their diagnostic hearing evaluation by three months of age. So infants that referred on hearing screen actually were more likely to come back and get their diagnostic hearing test by three months of age. And this is remarkable because certainly, there's a lot of loss to follow-up in newborn hearing screening and it's always a struggle to get these infants back in, and again, this was even among CMV negative infants.

So this is another study that used a targeted approach to CMV screening and this actually was published several years ago and was done in the UK, and for this, their approach was a little bit different, but from 2010 to 2012, at several hospitals among the UK, among infants who referred on their newborn hearing screen, they approached the parents to ask permission to be contacted by a study researcher, and if parents consented, then they were given testing materials to test for congenital CMV. They had about 46,000 infants over this period that had newborn screening, 100, I'm sorry, 1,000 eligible for the study, and they had 951 approached to discuss possible inclusion. Among these, they had 708 who agreed to be contacted and were actually contacted by the study team, and the way they implemented the study is once they agreed to be part of it, they were either given a collection kit in the hospital or they were sent a collection kit, they were sent both a urine and saliva collection kit, and many of these kits were actually sent to the parents at the home for the parents to collect. What they found out, urine and saliva samples collected at home by the parents was quite successful, and 99% of participants returned their saliva sample, however, we all know urine is more challenging to collect in infants, and only 50% returned their urine samples. Using the saliva, they were able to successfully screen 97% of infants within

21 days of life, and among those, they had found 1.5% CMV positive infants among those that they did test by saliva PCR, and because of the quick turnaround in this test, they were able to provide these results within a median of nine days of age. So this was successfully done, this was a successful way to implement screening into the newborn hearing screen program.

Another part of this test was they assessed maternal anxiety, how anxious were mothers that they were adding the screening on, and they assessed this at the time of screening and then three months after, and they found that maternal anxiety was not increased in mothers at infant screening. So these mothers, that's one concern often is that if we screen for more things, we're gonna make parents more anxious, but this study showed that wasn't the case. So what about other data about acceptability? That's certainly an important thing to consider for newborn screening. And this is a very recent study that just came out that was done in Minnesota where sort of general population adults were asked to participate at a health fair, and what they did is they asked these participants if they were, knew of congenital CMV, they did a short education about congenital CMV infection, and then they asked whether or not they would be acceptable to screening, either prenatal or newborn screening for congenital CMV. And what they found is that after the short education, CMV education, they found that over 90% of respondents said that they would be acceptable and think that congenital CMV screening should be offered to newborns. So again, over 90% agreed, and over 80% stated that they would choose for their baby to be screened for congenital CMV were it offered.

So this is something that once parents know about, they want their baby to be screened for. So let's sort of sum up now what we've talked about thus far. So we know that targeted screening, meaning screening for congenital CMV infection based on an infant that refers on their newborn hearing screen will not identify all congenitally infected infants, and only about 60 of those with CMV-related hearing loss will be

identified by this method. So CMV positive children who have late onset hearing loss obviously would be missed by this approach. And the importance of identifying infants as having the etiology is it avoids another diagnostic odyssey for other etiologies, it avoids the genetic imaging, all the other tests. It also allows for earlier intervention to begin with awareness to monitor the child for fluctuating and progressive hearing loss.

So let's look at targeted versus universal screening, meaning screening all babies, based on numbers and the data that we presented so far. So this is based on four million births per year in the US, and we are quoting a rate of five per 10 infants who will have congenital CMV, so 20,000 infants with congenital CMV per year. So we know 10% of these infants will be symptomatic, so based on data I presented earlier, approximately 28% of these will refer on their newborn hearing screen, and 386 will have hearing loss. There's an additional 72% who will pass their newborn hearing screen, but we would hope that because clinically, they are symptomatic, they would be identified, that they would be tested and monitored for their hearing testing. So it's this 90% of asymptomatic infants that are really most important, so this 18,000 infants, and notice it's more infants than the symptomatic, so the 18,000 asymptomatic infants that are born each year. So again, based on data presented, approximately 5% of these infants would refer on their newborn hearing screen. If we did targeted testing, we'd identify these infants, and 423 of these infants would have hearing loss. However, 95% would pass their newborn hearing screen, and unless we did universal screening, we would not identify these infants.

So this is approximately 17,000 infants at risk, and approximately 50% of these infants would be at risk for hearing loss. So if we were not to test them in the newborn period, we would never know their etiology for hearing loss. So certainly this is a large number of infants that are missed by the targeted screening method. So what about cost? Certainly, universal screening would be concerned about a huge cost burden to the healthcare, and even targeted screening, what about cost? And this is a relatively

recent, it was published a few years ago publication, so again, they used CHIMES data to try to estimate, and this is US cost savings of newborn congenital CMV, and it's a busy slide, but I'll show you the important numbers. So based on a targeted screening strategy, if you were to treat CMV infected infants, they factored that into their cost analysis, there would be a net savings of, due to targeted screening, and this is the same for asymptomatic infants based on targeted. And the cost savings for those that are not treated, there would be a small cost, a dollar, but again this is negligible when you consider identifying these infants. What about universal screening? Again, a cost savings across the board for treatment of symptomatic infants, and if you treat asymptomatic infants with hearing loss at birth, again, a cost savings. Among those who you would not treat, there is still a cost savings of universal screening due to earlier identification and monitoring.

So again, even though for targeted screening, there's a small cost, it's a negligible cost compared to other cost savings, and an important thing to know when considering newborn screening. So we're gonna switch gears a little bit now and talk about predictors of hearing loss. As we move closer towards universal newborn screening, which we are, how do we identify those infants at highest risk? Because we know among the asymptomatic infants, not all will develop hearing loss, and can we identify infants who we know may develop hearing loss? And so certainly, there's lots of data in symptomatic infants, they have symptoms and we can look based on their symptoms at the risk of hearing loss, and this is a study published a couple of years ago using a relatively large cohort of symptomatic infants. And they looked at infant symptoms and grouped them based on the severity. So the dark group is infants who had central nervous system involvement, the light gray is transients and meaning these infants have symptoms that would quickly go away, such as hepatosplenomegaly, petechiae, and then we looked at a, there was a group that had only petechiae, which was considered to be a mildly symptomatic group. And if you look at this final data on the right, this is the cumulative hearing loss among this group, and you see that based on

the severity of their infection, there's almost a dose response as far as risk of hearing loss. So among the more severely symptomatic infants with central nervous system involvement, the risk of hearing loss was close to 60%. Infants with transient symptoms, it was lower, approximately 38%, and infants with petechiae only were approximately 20.

So certainly the severity of symptomatic infants correlates with the risk of outcome. So what about neuroimaging specifically? We talked a little bit about you can find your neuroimaging abnormalities in asymptomatic infants, and there's been several studies, there's been lots of small studies, and this is one of the most recent where they developed an MRI score to see if they could sort of grade the severity of findings and look at the risk of outcome. And this was the study out of Italy, and what they found was, and I must note that the higher the number, the more severe the findings, so they had nine children who had a normal MRI, and among these, seven were completely asymptomatic at birth and two had long-term sequelae. So a normal MRI seems to have a good prognosis, although they're not absolute for sequelae. 35 children with an MRI score of greater than zero and 10 were asymptomatic, and eight developed sequelae, so again, not an absolute, but certainly the higher the score, the higher the risk. And then there were 25 symptomatic infants with an MRI score greater than zero, and 20 of these developed adverse neurologic outcome.

So what this shows is that although these neurologic findings on imaging are helpful, they're not absolute at predicting the outcome of these infants. So what about blood viral load? Certainly we use viral load a lot in other populations with CMV, so is it a useful way to predict hearing loss in infants with congenital CMV? And the short answer is no, and this is data from a large cohort of infants who were followed over time in a natural history study, and the chart on the left is asymptomatic infants, the right is symptomatic infants. And these are viral load levels done at various time points in follow up. So children with hearing loss are the circles, and the triangles are children

with normal hearing, and the bars are the median viral load levels, so the amount of blood, the amount of virus in the blood. And what you see is that viral load levels overlap a good bit between the two groups among symptomatic and asymptomatic infants. And this is not, there's not a good viral load level that really is able to predict hearing loss, particularly within the newborn period. So for an individual patient, blood viral load is not a useful predictor of hearing loss. So I'm gonna move on now and finish up with a discussion about treatment of congenital CMV, and unfortunately we only have one available drug to treat this infection, and it's ganciclovir, or the oral drug valganciclovir. This is a drug with known toxicities including bone marrow suppression, which results in neutropenia. And then based on early lab studies, there are potential toxicities. It was shown to be in high, high levels, carcinogenic and gonadotoxic in animals, although we have not had this documented in humans to date.

So this is data from a study that was published years ago that has really established the standard of care for treatment of congenital CMV infection, and this was done by the Collaborative Antiviral Study Group David Kimberlin and others, and what they did is they did a randomized trial comparing six weeks versus six months of valganciclovir in infants with symptomatic infection, so this is only infants with symptomatic congenital CMV. Their primary outcomes were looking at hearing loss at three time points. The primary outcome was at six months, and then other outcomes were looking at hearing loss difference later. And what they found was at 24 months of age, there was a statistical difference with better hearing outcomes in infants who received a six month or longer course of valganciclovir therapy. So here's the adjusted odds ratio. They did not see this difference in the early period, but it was significant at 12 to 24 months. So this is really again the established standard of care for treatment of symptomatic infants.

So as I mentioned earlier, there's no classic definition of symptomatic. We know what general symptoms can be, but there's been variable definitions among the literature.

So several years ago, a large group of international CMV experts got together to write some treatment guidelines for CMV, and they first came up with a classification system to classify congenital CMV infection, and they made four classifications. So the first is symptomatic congenital CMV, and they defined symptomatic as having moderate to severe disease. So these are infants that you see and they clearly have abnormalities, it's readily identified by clinical exam, and they usually have multiple symptoms. Their symptoms were mildly symptomatic disease, these have one or two manifestations, but are considered mild so maybe some petechiae, hepatosplenomegaly, something that's quite mild that will quickly resolve. They classified infants as asymptomatic with hearing loss, so these are infants who look completely normal, but have hearing loss diagnosed by a diagnostic test in the newborn period.

And then the asymptomatic infant, completely normal, completely normal hearing at birth. And based on these classifications, the group recommends symptomatic congenital CMV disease is the only group that is recommended for treatment with valganciclovir, and this is really based on the fact that this is the only group in which was enrolled in the randomized trial that I mentioned, and these are the severely symptomatic infants. Recommendations for six months of oral valganciclovir, the treatment must be initiated in the first month of life, and you need to monitor neutrophil counts and transaminases regularly, and again, the treatment duration is for six months. All other groups that I mentioned, the mildly symptomatic, the asymptomatic with hearing loss, and the asymptomatic, it is not routinely recommended to treat these babies because we really don't have studies to show that it's efficacious. And antiviral therapy is not routinely recommended in pre-term infants, because again, it hasn't been studied in this population.

So even though we're not recommending it in asymptomatic infants, the good news is there are several current studies to look at efficacy in asymptomatic infants, so hopefully in the upcoming years, we will have this data to know if this is also a

population that could be treated. And I think it's important to remember that treatment does not always mean a drug, and for the asymptomatic infant with congenital CMV, there's other important treatment modalities, and these are all slides from my institution's HEAR Center, but it's important to remember that regular audiologic testing with early hearing aids for infants, cochlear implants, in addition to speech therapy and the like are very important treatments, which we know based on the newborn hearing screening and follow-up that these will improve a child's outcome. So these are also important for infants at risk for hearing loss and who have hearing loss with asymptomatic infection.

So I'm gonna just sum up, and then have time for a few questions, so there are approximately 20,000 babies in the US who will be born with congenital CMV, and it is the most common infection. And it's important to remember that prevalence can vary by population, and we know that the higher prevalence in the US is in black infants. Infants can present with symptoms, or most commonly, they look completely healthy. Hearing loss is the most common sequelae of congenital CMV, nearly half is delayed onset and will be missed in the newborn period. And in asymptomatic congenital CMV, unfortunately currently, there are no ways to predict which infant will have hearing loss. Diagnostic testing for congenital CMV must be done in the first three weeks of life. And saliva really, in my opinion, is the preferred method because it's highly sensitive and it's very easy to collect. Urine PCR is also acceptable but it is more challenging, particularly for a infant that's soon to go home. Treatment with ganciclovir or valganciclovir is reserved for infants who are symptomatic, a severely symptomatic infant but remember that hearing aids and speech therapy are important interventions for asymptomatic infants. And that's it, and I will be happy to see if there's any questions.

- [Anna] Okay, at this time, I'd like to direct everybody to send your questions into the Q and A box on the left-hand side of the classroom. We do have one question right

now that says are there precautions nurses working in the nursery NICU that are pregnant or trying to get pregnant should take to avoid developing CMV? And how long are newborns with CMV contagious?

- [Shannon] All right, so children with congenital CMV will shed virus for a long time. So there's actually been data looking at healthcare workers and risk of acquisition of CMV, and healthcare workers are actually not at an increased risk because we as healthcare workers use our standard precautions. So if you are using standard precautions, meaning you're washing your hands after you're touching the body fluids, using gloves, then you're not at an increased risk. It's actually the individuals, we know that daycare workers are those at highest risk because they're not as careful as healthcare workers with using those standard precautions.

- [Anna] I have another question here that says are there any screenings that can be done on pregnant women?

- [Shannon] So that issue is a bit controversial, and ACOG, the American College of Obstetrics and Gynecology does not recommend routine screening for women during pregnancy. And the reason is, there's a lot of reasons why which I really don't have time to go into. So certainly, women can see if what their seroprevalence is, if they're CMV positive or negative during pregnancy, but it's important to remember even if you're seropositive, you can still acquire CMV and transmit it, the risk is lower, but we don't know the risk. But because there's not a treatment modality in pregnancy, ACOG does not routinely screen women for CMV infection. They will screen if there's any sort of risk factors or ultrasound findings that are concerning, however.

- [Anna] I have another question, is saliva PCR readily available in all hospitals?

- [Shannon] So that's a great question, I get that all the time. So PCR is, and you have to ask your lab if they will do it, so most labs will, most virology labs will. And some hospitals have their own virology labs, some send it out, you just have to contact the individual lab, but PCR tests are. But again, urine can be used also, it's just much more harder to collect, but saliva, a PCR test is readily available, you just have to talk with your lab and make sure that they will do it, and the way we typically do it is we just do a swab in viral transport media and send the viral transport media and ask them to do a CMV PCR on it.

- [Anna] Let's see, I have one more question, it just popped in. Would audiologists testing CMV babies or children similarly not be at increased risk of contagion while pregnant? Should they be wearing gloves, washing hands?

- [Shannon] An audiologist who's just doing hearing testing would probably not. Again, it's the contact with the saliva or the urine that's gonna put it at risk, and it's usually in a repeated contact, but I think I would treat a baby with CMV like any other child. I think what's important to realize is that many children acquire CMV after birth and will shed CMV also, so CMV is very common in children, aside from congenital infection, but as healthcare providers, any type of healthcare provider, as long as we use standard precautions, wash your hands before and after, that's the most important thing, but I think an audiologist would probably be even lower risk because you're not doing the same things as far as changing diapers and that sort of thing.

- [Anna] Okay let's see, I have one more that says do you have an update on the status of CMV being added to the routine universal screening panel?

- [Shannon] It is in the works, it's a slow process but they're, actually the National CMV Foundation, several representatives have submitted it and it's, they're going through that sort of the process, but it's in the works, I will say that.

- [Anna] Okay. And you have any long-term studies about the outcomes of infants who have been treated with the valganciclovir?

- [Shannon] Right, so there's starting to be more and more data that's coming out, not a lot of data. Actually, our part from Utah just recently published their data looking at a small cohort of infants who were treated, and there's also been some data from Europe, and what seems to be shown is that it's not a long-term protective benefit. It seems that in some children treated for six months, they may still later, two, three, four years of age develop hearing loss, so it seems to be suggested that it's not a durable effect, but we don't have a lot of good data yet. I think it's gonna be coming out over the next several years we'll see more and more data about that.

- [Anna] Okay, it looks like that's all the questions we have for right now unless I see another one pop in. Other than that, I just want to thank you so much for the presentation today, that was excellent. And as a reminder to our audience, if you're here for the live event, you have seven days to take and pass the test. And if you're listening to this as a recorded course, you have about 30 days. So with that, I'm gonna go ahead and end the meeting and thank everyone for attending.