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REVIEW

eNeonatal Review
Podcast Issue

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HOME

E NEONATAL
REVIEW LIVE

CME/CE
INFORMATION

PROGRAM
DIRECTORS

NEWSLETTER
ARCHIVE

EDIT
PROFILE

RECOMMEND TO
A COLLEAGUE

VOLUME 8 – ISSUE 6: TRANSCRIPT

Featured Cases: Congenital Cytomegalovirus Infection: Diagnosis & Treatment

Our Guest Author is Dr. Richard Whitley, Distinguished Professor, Loeb Eminent Scholar Chair in Pediatrics, and Professor of Pediatrics, Microbiology, Medicine and Neurosurgery at the University of Alabama at Birmingham.

After participating in this activity, the participant will demonstrate the ability to:

- Define the differential diagnosis of a newborn with presumed intrauterine infection,
- Initiate and interpret the diagnostic procedures to confirm that diagnosis, and
- Evaluate the therapeutic options and anticipated outcome.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to Congenital Cytomegalovirus Infection: Diagnosis & Treatment in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 8, Issue 5 eNeonatal Review newsletter—[Congenital Cytomegalovirus Infection: Diagnosis & Treatment](#).

MEET THE AUTHOR



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Unlabeled/Unapproved Uses

The author has indicated that this presentation WILL include off-label discussions of ganciclovir and valganciclovir.

Faculty Disclosure

Richard Whitley, MD, has disclosed that he is serving as a consultant for Gilead Sciences and Chimerix.

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The activity has been developed for neonatologists, NICU nurses, and respiratory therapists working with neonatal patients. There are no fees for this activity.

There are no prerequisites to participate.

Estimated time to complete activity: 30 minutes.

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- **Christoph U. Lehmann, MD** has indicated a financial relationship of honoraria from Mead Johnson and PediatrIX. Dr. Lehmann is also the Editor-In-Chief of Applied Clinical Informatics Journal. He serves on the Board of Directors for the American Medical Informatics Association.
- **Anthony Bilenki, MA, RRT, Edward E. Lawson, MD, Lawrence M. Noguee, MD and Mary Terhaar, DNSc, R** indicated they have no relevant financial relationships with any commercial supporters.

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Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K Modem or better, Windows Media Player 9.0 or later, 128 MB of RAM, monitor settings: high color at 800 x 600 pixels, sound card and speakers, Adobe Acrobat Reader.

MR. BOB BUSKER: Welcome to this *eNeonatal Review*[™] Podcast.

eNeonatal Review is presented by the Johns Hopkins University School of Medicine, and the Institute for Johns Hopkins Nursing. This program is supported by an educational grant from Ikaria and Abbott Nutrition.

Today's program is a companion piece to our Volume 8, Issue 5 *eNeonatal Review* newsletter: Congenital Cytomegalovirus Infection: Diagnosis and Treatment.

Our guest is that issue's author, Dr. Richard Whitley.

This activity has been developed for physicians, nurses, and respiratory therapists caring for neonates. There are no fees or prerequisites for this activity.

The Accreditation and Credit Designation Statements can be found at the end of this podcast. For additional information about accreditation, Hopkins policies, and expiration dates, and to take the post-test to receive credit online, please go to our website newsletter archive – www.eneonatalreview.org – and click on the Issue 6 podcast link.

Learning objectives are, that after participating in this activity, participants will demonstrate the ability to:

- Define the differential diagnosis of a newborn with presumed intrauterine infection,
- Initiate and interpret the diagnostic procedures to confirm that diagnosis, and
- Evaluate the therapeutic options and anticipated outcome.

I'm **BOB BUSKER**, managing editor of *eNeonatal Review*. On the line we have with us Dr. Richard Whitley, Distinguished Professor, Loeb Eminent Scholar Chair in Pediatrics, and Professor of Pediatrics, Microbiology, Medicine and Neurosurgery at the University of Alabama at Birmingham.

Dr. Whitley has disclosed that he is serving as a consultant for Gilead Sciences and Chimerix. His presentation today will include discussion of the off-label or unapproved uses of ganciclovir and valganciclovir.

Dr. Whitley, welcome to this *eNeonatal Review* Podcast.

DR. RICHARD WHITLEY: This is a real privilege for me to discuss the issues surrounding intrauterine infections with you today.

Congenital infections are very common, and as health care providers we must know how to evaluate these babies and consider appropriate interventions for them. Thus, the differential diagnosis, diagnostic procedures, and interventions are extremely relevant to the care that we provide for these babies.

MR. BUSKER: To that end, Dr. Whitley, let's start right in with our first case. If you would, please.

DR. WHITLEY: You are asked to evaluate a 12-hour-old newborn in the well-baby nursery for a rash that was apparent at delivery. On reviewing the obstetrical notes, you learn that the baby was the product of a gravida 2, para1, 29-year old mother and that the gestation was 35 weeks.

On physical examination you find a male who weighs 2,200 grams, clearly both growth-retarded and small for gestational age. When you measure and graph the child's head circumference, you learn that the child is microcephalic. The child has a petechial rash. The liver edge is palpable 5 cm below the right costal margin, and the spleen tip is detected 6 cm below the left costal margin.

The child did not have a heart murmur, and the remainder of the physical examination is unrevealing.

MR. BUSKER: My first question, doctor, is going to sound pretty simple. What do these findings tell the clinician about this child?

DR. WHITLEY: First, we have to recognize what we have learned from the history. The gestational age indicates that the child was born prematurely, a common finding in children with congenital infections.

Next, the child is also small for gestational age, with growth retardation, as indicated by the birth weight adjusted for the gestational age. These findings suggest a placental dysfunction.

The head circumference identifies the child as having microcephaly, reflecting an insult to the developing brain that likely took place very early in gestation.

The breadth of the liver and the spleen indicate that the child has hepatosplenomegaly. The petechial rash suggests that the child could have thrombocytopenia. Importantly, the child did not have a blueberry-muffin rash that is indicative of extramedullary hematopoiesis.

Notably, the child does not have a heart murmur, a finding of relevance in considering the differential diagnosis of children with presumed congenital infections.

MR. BUSKER: That's a lot of information just from the OB's notes and the physical. But is it enough to make the differential diagnosis?

DR. WHITLEY: It certainly goes a long way in helping us sort through the potential differential diagnoses for these children. The clinical findings clearly suggest a congenital infection, one that was the consequence of a maternal infection early in gestation.

Of note, the findings also indicate that it is a symptomatic infection, meaning that the probability of significant morbidity is increased.

With that information, the differential diagnosis would include congenital rubella, toxoplasmosis, congenital herpes simplex virus infection, and congenital cytomegalovirus infection, also known as CMV.

Other diseases can mimic congenital infection, but they are very, very rare.

MR. BUSKER: You've described a wide range of pathogens. What can the clinician do to narrow those down?

DR. WHITLEY: It's exceedingly important for the physician to home in on the most likely diagnosis of this child's illness.

What can we exclude from the differential diagnosis? The findings are not suggestive of congenital syphilis, in that those children usually do not have microcephaly or a petechial rash.

In the absence of a heart murmur, specifically peripheral pulmonic stenosis, the likelihood of congenital rubella becomes very much less. In addition, children with congenital rubella usually

have a blueberry muffin rash, a finding that this child did not have at clinical presentation.

MR. BUSKER: Even so, to refine your differential diagnosis enough to develop a treatment plan, you are going to need additional history. Obviously, that means going to the parents. What would you ask them?

DR. WHITLEY: This is where it is really important for the physician to understand the correct questions to ask Mom and Dad about the potential causes of their child's illness.

First, I would like to know whether the mother received a rubella immunization. It should be expected that most women will be rubella-immune today, but some populations in the United States are not immunized for religious reasons.

Rubella occurs in late winter and early spring, so one would expect a child with congenital rubella infection to be born in late fall. A maternal history of a maculopapular rash associated with fever and arthritis in spring could be suggestive of rubella infection. In this case, however, our mother was rubella-immune before becoming pregnant.

Next, I would ask Mom if she ate raw meat or has an indoor/outdoor cat. Toxoplasmosis is transmitted by one of two methods. First, raw meat, and even undercooked meat that was not previously frozen, can be a source of oocysts responsible for infection.

Second, the oocysts can be found in the feces of indoor/outdoor cats. Pregnant women should not change cat litter because of the risk of acquiring toxoplasmosis if the cat is allowed outdoors and hunts wild animals.

In the 21st century, congenital toxoplasmosis occurs approximately 1 in 10,000 live-borns in the United States. It is more common in other areas of the world, particularly in France, because of their eating habits. This mother neither ate raw meat nor owned a cat.

I would then ask if the parents had a history of recurrent genital vesiculoulcerative lesions, or if the mother had a genital vesiculoulcerative disease associated with fever, dysuria, and pain during her gestation. We would associate such a rash with genital herpes simplex virus infection.

Fortunately, congenital herpes simplex virus infections are very rare, occurring only in 1 in 100,000 live-borns, but they present in a fashion that is identical to all the other congenital infections that we are discussing.

MR. BUSKER: What did you find in the patient you presented?

DR. WHITLEY: Both the maternal and paternal histories were negative for findings suggestive of genital herpes simplex infection. Nevertheless, we need to remember that genital herpes simplex virus infections are usually completely asymptomatic, so a negative history in both parents remains common even in children who present with congenital or neonatal herpes simplex virus infection.

Last, I would ask if the family has a child in day care or if the mother is a day care worker. The most common source of cytomegalovirus infection for parents today is exposure to one of their own children who is in day care.

Because young children experience their environment by mouthing toys and other objects, it is very common for children to transmit infection horizontally in the day care environment.

When cytomegalovirus is isolated from these children in the same day care classroom, a molecular analysis of the virus will demonstrate that the children will excrete exactly the same strain of virus. As many as 85% of children in the same classroom will be infected with the identical virus, and those children can then transmit infection to their parents.

For example, if the mother of one of these children is seronegative for cytomegalovirus and is pregnant, she is at risk for acquiring infection. Similarly, day care providers are at risk for acquiring infection because of exposure to these children.

When congenital syphilis is not a consideration, as in this case, the chart should still be reviewed to determine whether the mother was treated for syphilis and if her serologic responses were documented.

MR. BUSKER: The history certainly suggests CMV infection. But how do you prove that diagnosis? How do you exclude other causes of congenital infection?

DR. WHITLEY: That's an extremely important question, because now we really have to home in on the diagnosis.

First, we would recognize that this child's clinical symptomatology only suggests symptomatic congenital infection. But it is symptomatic and therefore this child is at great risk for hearing impairment and neurologic disability. So we have to consider that in our diagnostic and therapeutic evaluations.

My diagnosis evaluation would begin with establishing microbiologic proof of the etiology of the child's illness. Thus, I would assess the urine for evidence of cytomegalovirus infection. That is really essential.

One of two studies can be performed on the urine, either culture in susceptible tissue culture cell lines, or evaluation of the urine by polymerase chain reaction, which is also known as PCR these days, to detect evidence of viral DNA.

Typically, routine cell culture of the urine for cytomegalovirus can take 4 to 6 weeks. To expedite the identification of CMV, we do a shell vial assay, inoculating urine onto a susceptible cell sheet, then centrifuging the cell sheet. That process concentrates virus in the susceptible cells.

Then, 72 hours later we take the mono layer and stain it with antibodies directed against cytomegalovirus that also has an immunofluorescence tag, looking for immunofluorescent staining of the cell sheet to detect evidence of cytomegalovirus infection.

In the 21st century, many laboratories have moved entirely to molecular tools to diagnose viral infection, and PCR has become the standard. Urine is simply sent to the laboratory to detect DNA associated with CMV infection. (Cytomegalovirus can also be isolated from saliva, tears, and blood and detected by PCR.)

As to the other causes of congenital infection, rubella can be isolated from the saliva in susceptible cell lines. This virus is very difficult to isolate and usually must be done through state health department laboratories.

There are no routinely approved assays to isolate toxoplasmosis in cell culture, although some of us have found evidence of toxoplasmosis in the

cerebrospinal fluid when inoculated on foreskin fibroblasts.

Finally, for herpes simplex infection, vesicles would have to be present so that fluid could be harvested in an attempt to isolate this virus in cell culture.

MR. BUSKER: What about serologic studies? What value might they have here?

DR. WHITLEY: Serologic studies must be considered, there's no two ways about it. Since therapeutic decisions must be made immediately for herpes simplex virus and cytomegalovirus infections, but they are not at all helpful in the acute-care setting. Furthermore, to complicate issues, cytomegalovirus serology in the newborn is fraught with false-positive IgM antibody studies.

If rubella is suspected, both IgG and IgM studies should be ordered. These will likely be enzyme immunoassays, as dictated by your hospital laboratory. Similarly, toxoplasmosis antibodies to both IgM and IgG should be performed on the mother and the baby.

If you are concerned about congenital syphilis, you would order VDRLs on the mother and the baby. For each of these infections, the child will usually have higher antibody titers than the mother if the child has a congenital infection. Follow-up serologic studies will clearly help clarify the diagnosis as antibodies will increase, particularly in the absence of therapy.

MR. BUSKER: While you're waiting for the lab results to come in, what else can you do to help define the extent of the disease in this child?

DR. WHITLEY: That's a great question. We clearly need to begin to do additional laboratory, clinical, and radiologic studies to confirm congenital infection caused by cytomegalovirus. Our goal in doing that is to identify the extent of disease so we can predict a long-term prognosis for this child.

Because the child has petechial rash, a platelet count must be obtained. It will be low in children who have congenital cytomegalovirus, toxoplasmosis, and rubella infections.

Generally the platelet count will be less than 50,000. Some physicians will order routine white blood cell

counts, but I do not find them helpful diagnostically, at least for myself. Nevertheless, a low absolute neutrophil count can be encountered with congenital cytomegalovirus infection.

Because of the hepatomegaly, liver function tests are indicated. With congenital cytomegalovirus infection, the AST and the GGT will both be elevated, as will the direct bilirubin. Usually the direct bilirubin will be in the range of 5 to 10 mg/dL.

Cerebrospinal fluid can also be obtained. Even with brain involvement, the cerebrospinal fluid will reveal a low white blood cell count, all of which will be lymphocytes, and only a slightly elevated protein if the child has congenital cytomegalovirus infection.

In contrast, if the child had congenital toxoplasmosis, we would find an exceedingly high cerebrospinal fluid protein level, usually in excess of 250 mg/dL.

Next, an image of the brain is indicated. An ultrasound will provide evidence of calcifications, and ultrasound can be done very easily. However, I personally prefer to order either a CT scan or an MRI to determine not only the presence or absence of intracranial calcifications, but also evidence of ventricular dilatation, structural abnormalities, and even gray/white matter differentiation. This latter point is important in terms of predicting long-term neurological outcome. Calcifications can be seen with other congenital infections as well, including toxoplasmosis and congenital herpes.

Next, I would do an eye exam. I usually consult with my pediatric ophthalmologists because they are far better at assessing evidence of retinitis than I am. Retinitis will occur in about 35 to 50 percent of children who have congenital cytomegalovirus infection. We also know that toxoplasmosis, rubella, and congenital syphilis cause various forms of retinitis.

Finally, a brain stem evoked response should be performed in the nursery to determine if hearing loss is present at birth. Sometimes a brain stem evoked response is difficult to obtain, but it can be reattempted as an outpatient.

MR. BUSKER: In this specific patient, talk to us about what you learned from the lab results.

DR. WHITLEY: Importantly, the first thing I learned when I assessed the child's laboratory data was that the platelet count was 20,000. The child had an elevated AST and GGT, and the bilirubin totaled 9, 8 of which were direct hyperbilirubinemia.

In addition, when I evaluated the child with an MRI scan, there was evidence of periventricular calcifications, and the lateral ventricles were very enlarged. We succeeded in doing a brain stem evoked response in the intensive care unit of the newborn nursery, which demonstrated evidence of hearing loss. Finally, I consulted with the pediatric ophthalmologist, who determined the child had retinitis.

MR. BUSKER: And your recommendations to treat this child?

DR. WHITLEY: At this juncture, ganciclovir is the only drug for which there is evidence-based medicine for treating congenital cytomegalovirus infection.

The physician can expect that administering ganciclovir at a dose of 12 mg/kg/d in 2 divided doses for 6 weeks will accelerate the resolution of thrombocytopenia, promote growth, and improve head circumference, as compared to babies who received no treatment. The results will be achieved within a short time after the onset of therapy, usually 2 to 3 weeks.

Giving ganciclovir is not at all easy because it requires an indwelling intravenous catheter. Sometimes we have to maintain these children in the hospital for the entire 6 weeks of treatment; other times we treat them at home with educated families who can administer drug in that environment. Clearly we need better alternatives.

MR. BUSKER: Talk to us, if you would, about your expectations from this therapy.

DR. WHITLEY: Our expectations go far beyond the acute events that occur during the first 6 weeks of treatment. Long term, physicians can expect 2 additional benefits. First, since the child has a documented hearing loss, it should either stabilize or improve over time.

Second, the child will achieve improved milestones by Denver Developmental Assessment, again

compared to children who do not receive therapy. But therapy is not without adverse events. Most notably, these children can develop neutropenia that will interrupt treatment or even require its discontinuation. In addition, thrombocytopenia can occur, but late in the treatment course, usually after 4 weeks of drug administration.

MR. BUSKER: Now overall, this child had 6 weeks of ganciclovir therapy. What happens next? How should the clinician follow this child from here?

DR. WHITLEY: In addition to routine pediatric care, the child will require frequent assessments of attainment of developmental milestones.

Rather than use Denver Developmental Assessments, as we have done historically in some of our studies, we currently use Bailey Developmental Assessments to assess neurodevelopment in children with congenital cytomegalovirus infection. Toward this end, the involvement of physical and occupational therapists should be enlisted in the child's care very early in life.

Hearing assessments should be performed at 6-month intervals, since hearing loss can be progressive or can develop after the first year of life.

I really want to stress the latter point. Since hearing impairment can develop as late as 2 to 3 years after the onset of infection, we need to rigorously follow hearing in these children. Any hearing loss requires the involvement of a speech therapist.

Remember that ganciclovir is carcinogenic, mutagenic, and teratogenic in animal models, so long-term follow-up through puberty is required for these children. We have not seen any problems in children we followed here at the University of Alabama at Birmingham, but I think we have a responsibility to these children to follow them through puberty.

MR. BUSKER: We'll be back in a moment with Dr. Richard Whitley from the University of Alabama at Birmingham.

DR. CHRISTOPH LEHMANN: Hello, I'm Dr. Chris Lehmann. I'm the Director for Clinical Information Technology at the Children's Medical and Surgical Center at Johns Hopkins and one of the Program Directors for eNeonatal Review.

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For more information on registration to receive eNeonatal Review without charge, or to look at archived issues, please go to www.eneonatalreview.org. Thank you.

MR. BUSKER: Welcome back to our eNeonatal Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Richard Whitley from the University of Alabama at Birmingham. We're discussing the diagnosis, treatment, and therapeutic options for congenital CMV infections. Dr. Whitley, if you would, please, present us another case.

DR. WHITLEY: This is a child that I saw in the nursery with my attending neonatologist, who was providing care for a 20-week old premature who was now 4 weeks of age. Surprisingly, the child did exceedingly well in our nursery, after an initial episode of respiratory distress syndrome that was managed medically with CPAP. At the time that I evaluated the child, he was only hospitalized for growth.

On rounds, the neonatologist noticed that the child had a respiratory rate of 80 and an oxygen requirement of 82% as demonstrated by a transcutaneous oxygen saturation monitor.

He ordered the chest x-ray and called me over to take a look at it. It revealed peribronchial thickening with a diffuse interstitial infiltrate.

MR. BUSKER: With those findings, what are some of the factors the physician should consider in making the differential?

DR. WHITLEY: When my colleague and I discussed the case, we looked at the chest radiograph and found it most compatible with a viral illness; however, we did remind ourselves that chlamydial disease can present in a similar fashion, although much earlier in life than 4 weeks of age.

The viral respiratory illnesses that we considered included cytomegalovirus, respiratory syncytial virus, human metapneumovirus, influenza, and parainfluenza, among others.

It's important to remember that because of the child's gestational age, no transplacental antibodies crossed the placenta from the mother to the fetus to protect the newborn. Those antibodies would have provided protection against many of the aforementioned organisms.

MR. BUSKER: Other factors to consider?

DR. WHITLEY: The season is summer, a time when respiratory syncytial virus, human metapneumovirus, usually influenza, are active, but we have to remember 2009 H1N1, swine flu, was different last year, and parainfluenza, are not circulating in the community.

Next, the physician should recheck the maternal records for chlamydia to ensure that the test was done and was negative.

We learned that the child received non-frozen and unpasteurized breast milk from his mother beginning at about 1 week of life.

MR. BUSKER: What does that information do to help clarify the diagnosis?

DR. WHITLEY: The unpasteurized breast milk could be a source of infection for this child, because we know that cytomegalovirus exists commonly in breast milk of women who are seropositive for this infection.

The interstitial pneumonitis is most likely caused by cytomegalovirus infection. As I mentioned, breast milk is a known source of CMV infection and is a common cause of infection in newborns, even in term infants who have been discharged from the nursery

and are cared for at home. Because this child did not receive antibodies from mother across the placenta, the child experienced a primary infection.

Saliva and urine can either be cultured or assessed by polymerase chain reaction for evidence of cytomegalovirus infection. In addition, we can do an immunofluorescence assay on a viral respiratory panel. This entails taking a nasal swab, smearing it on a glass slide, and staining the cells from the nose directly for evidence of cytomegalovirus infection. The assay takes only about 2 hours, so it is the most rapid of the tests that can be done. However, it is a little less sensitive than PCR in culture.

Importantly, we should obtain serum from the mother and test it for antibodies directed against cytomegalovirus to make sure she had a previous infection caused by cytomegalovirus.

MR. BUSKER: Talking about treatment options, would you recommend that this child receive antiviral therapy with ganciclovir?

DR. WHITLEY: No evidence-based clinical trials support the value of antiviral therapy for treating interstitial pneumonitis in high-risk prematures. Unfortunately, we don't even have pharmacokinetic data in the very small premature child, like this one, to guide drug administration.

Nevertheless, in infants with an increasing oxygen requirement, many physicians will extrapolate data from older babies in treating these small prematures.

MR. BUSKER: How was this child treated?

DR. WHITLEY: We elected to administer ganciclovir to this child at the same dosage that we would use to treat proven congenital infection. In so doing, the child was weaned from oxygen over a period of 5 days and was back on room air at that time. The child subsequently did well in the nursery and was discharged about 3 weeks later.

MR. BUSKER: Dr. Whitley, thank you for taking us through those two very interesting cases. I'd like to ask you now to give us your thoughts about methods for preventing congenital CMV infection.

DR. WHITLEY: Personally, I really, really want to see improved therapies for cytomegalovirus infections in

all populations. The Institute of Medicine ranked preventing cytomegalovirus infections as the No. 1 target for vaccine development. That report was prepared over a decade ago, and to this day we do not have a licensed vaccine to prevent cytomegalovirus infections.

Let's go back and rethink the issues that surround prevention. We as health care providers can do several things to decrease the risk of infection. First, we must remember that good personal hygiene is essential for health care providers and day care workers. Simply washing hands will go a long way to prevent person-to-person transmission.

Second, for high-risk premature infants in need of blood transfusions, particularly those less than 28 weeks gestation, the type of blood product administered should be carefully considered. Leukocyte-depleted or irradiated blood decreases the risk of acquiring cytomegalovirus from blood products but it doesn't completely prevent it. Obviously, using cytomegalovirus-negative blood, as determined by a simple antibody assay, would prevent transmission of this infection.

Breast milk, as we all know, does contain cytomegalovirus, if the mother has evidence of previous infection as proved by antibodies. Freezing breast milk also significantly decreases the risk of transmission, but freezing is simply not acceptable to some mothers. When mothers choose not to freeze their breast milk, there is a risk of infection to the newborn.

MR. BUSKER: What about potential improvements in therapeutic interventions?

DR. WHITLEY: When we talk about interventions, we need to divide them into three categories: passive vaccination through antibody administration; active immunization, that is, giving a vaccine; or administering a new antiviral drug. Remember, new antiviral drugs are not licensed, so we have to keep that in perspective from what we know and what we don't know.

Let's deal with each one separately. As it relates to passive immunization, Professor Nigro in Italy reported that hyperimmune cytomegalovirus globulin decreased the probability that a child born to a woman with primary infection would develop

symptomatic disease, but that was not a randomized, controlled clinical trial.

Further, the rate of disease in the comparative population in that study was higher than in virtually all other studies that have been performed around the world in similar groups. Thus, the results have been called into question.

Fortunately, a truly randomized, controlled, clinical trial is in process and nearing completion. We will have an answer to the value of this approach, but it will take at least another 18 months before the scientific community knows the results of that trial.

Nevertheless, several pharmaceutical companies are now producing cytomegalovirus monoclonal antibodies for clinical trials with the goal of preventing newborn disease.

When we talk about vaccines, the best data available, at least to my knowledge, come from the study of Bob Pass, my colleague here at the University of Alabama at Birmingham, who administered a subunit glycoprotein vaccine to susceptible postnatal seronegative mothers who had no previous exposure to cytomegalovirus infection.

His data clearly showed that immunized women had a lower incidence of infection for 3 years after they were vaccinated. In addition, the incidence of congenital infection was lower in babies born to immunized mothers, although not significantly. However, that was simply a number issue: not enough women were immunized to evaluate the impact on their children. The persistence of these immune responses needs to be documented over time.

Several attenuated vaccines are approaching clinical trials. Some combine 2 or 3 of the immunodominant antigens of cytomegalovirus into what is known as a DNA vaccine. Other vaccines use an entirely different virus that expresses the same antigens. The value of these vaccines is undetermined at the present time, although clinical trials are in progress.

New antiviral drugs are on the horizon. In fact, the prodrug of ganciclovir, valganciclovir, is being evaluated in a study performed by the NIAID Collaborative Antiviral Study Group to treat congenital cytomegalovirus infection. Valganciclovir avoids the necessity of an indwelling catheter. It also

avoids the potential risks of associated infection with such catheters. This clinical trial is about 70% accrued, and I'm hoping we'll have results within about 18 months to better understand the utility of this approach.

In addition, two other exciting drugs will become available soon. One is the lipophilic derivative of cidofovir that doesn't have cidofovir's toxicity profile, and the other is a cytomegalovirus helicase-primase inhibitor. Both are in clinical trials, but we have no evidence of efficacy at this time.

Personally, I look forward to the time when we have truly safe and efficacious vaccines and therapeutics.

MR. BUSKER: Dr. Whitley, thank you for participating in this eNeonatal Review Podcast.

DR. WHITLEY: You're so very welcome. I certainly appreciate the opportunity to share my thoughts on congenital cytomegalovirus infection with the listeners.

MR. BUSKER: This podcast is presented in conjunction with the eNeonatal Review Newsletter, a peer-reviewed, CME/CE-accredited literature review e-mailed monthly to clinicians caring for neonates.

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Thank you for listening.

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