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Podcast Issue

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VOLUME 10 — ISSUE 2: TRANSCRIPT

Featured Cases: Optimal Methods For Preventing And Treatment Of Necrotizing Enterocolitis

Our guest author is Josef Neu, MD, Professor of Pediatrics at the University of Florida in Gainesville, Florida.

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

- Summarize the difficulties impeding progress against NEC, including lack of a clear definition of the disease, inappropriate animal models, and multifactorial pathophysiology.
- Discuss challenges in the expeditious diagnosis of and treatment of NEC.
- Describe some of the modalities being currently used for prevention of NEC as well as ones that are under development.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of Optimal Methods for Prevention and Treatment of Necrotizing Enterocolitis in the format of case-study scenarios for the clinical practice. This program is a follow up to th Volume 10, Issue 1 *eNeonatal Review* newsletter— Optimal Methods for Prevention and Treatment of Necrotizing Enterocolitis.

MEET THE AUTHOR

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Guest Faculty Disclosure
Josef Neu, MD has indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

Unlabeled/Unapproved Uses
Josef Neu, MD had indicated that he has received grant funding from and served on a scientific advisory panel for Medela, and has served as a consultant to BioGaia/Infant Microbial Therapeutics.

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⇩ PROGRAM BEGINS BELOW

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Nutrition

- Physicians may not be aware of recent evidence-based recommendations on recognizing and treating GERD in neonates.
- Current neonatal nutritional management practices may be enhanced to optimize and meet the specific needs of low birth weight preterm infants.
- Current neonatal nutritional management practices may be enhanced to optimize and meet the specific needs of low birth weight preterm infants.
- Clinicians who treat neonates are uncertain of optimal strategies for prevention and early recognition and treatment of necrotizing enterocolitis.

Respiratory-Related Issues

- Clinicians may be unfamiliar with some of the newest evidence-based approaches for treating neonatal persistent pulmonary hypertension.
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HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP/7 or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K or better modem, Windows Media Player 9.0 or later, 128 MB of RAM, sound card and speakers, Adobe Acrobat Reader, storage, Internet connectivity, and minimum connection speed. Monitor settings: High color at 800 x 600 pixels.

MR. BOB BUSKER: Welcome to this first *eNeonatal Review*™ podcast of our 10th volume of the program.

Today's discussion is a follow-up to our newsletter topic, *Optimal Methods for Prevention and Treatment of Necrotizing Enterocolitis*. Joining us today is that issue's author, Dr. Josef Neu, Professor of Pediatrics at the University of Florida in Gainesville.

*e*Neonatal Review is jointly presented by the Johns Hopkins University School of Medicine, and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from Abbott Nutrition, Ikaria, and Mead Johnson Nutrition.

Learning objectives for this audio program include:

- Summarize the difficulties that impede progress against NEC, including the lack of a clear definition and the multifactorial pathophysiology.
- Discuss the challenges clinicians face in the expeditious diagnosis and treatment of NEC.
- Describe some of the modalities currently being used, as well as those that are under development, for the prevention of NEC.

Dr. Neu has disclosed that he has received grant funding from and served on a scientific advisory panel for Medela and has served as a consultant to BioGaia/Infant Microbial Therapeutics. Dr. Neu has indicated that there will be no references to the unlabeled or unapproved uses of drugs or devices in his presentation today.

MR. BUSKER: I'm Bob Busker, managing editor of *e*Neonatal Review. Dr. Neu, thank you for joining us today.

DR. NEU: Thank you for inviting me. I'm glad to be here.

MR. BUSKER: In your newsletter issue, doctor, you reviewed some of the relevant literature about why necrotizing enterocolitis — which is the most common GI emergency in the preterm neonate — why NEC remains so difficult to prevent, diagnose, and treat. What I'd like to do today is discuss how some of that new information can be translated into practice in the NICU. So if you would, doctor — start things off for us by describing a patient.

DR. NEU: A 24 week gestation infant born three days ago presents with sudden abdominal distention, he was not being fed, and was receiving indomethacin for intraventricular hemorrhage prophylaxis and hydrocortisone for hypotension refractory to fluid boluses and dopamine.

MR. BUSKER: This infant's presentation — as you've described him, is this typical of NEC?

DR. NEU: No, this is not a typical presentation of necrotizing enterocolitis. Most babies who develop necrotizing enterocolitis, if they are at 24 weeks' gestation, do not develop it within the first couple of days after birth; in fact, they develop it several weeks later. Some babies who are less premature, for example, babies who are born at 27 or 28 weeks' gestation, may develop it at only two to three weeks after birth, whereas a 24 week gestation preterm baby tends to develop it four to six weeks after birth. So there appears to be a window where necrotizing enterocolitis that is dependent on postmenstrual age is much more common. This is some time between approximately 29 and about 32 weeks postmenstrual age. The etiology of this remains unclear, but we see this fairly commonly in what we would consider the more classic form of necrotizing enterocolitis.

This particular baby developed an intestinal perforation within three days after birth, and the combination of using indomethacin and hydrocortisone in a baby with low blood pressure is probably strongly associated with the development of this disease because the studies have shown a very strong association when both of these drugs are used together, much more so than when either one of these drugs is used alone.

MR. BUSKER: The lack of feeding, does that suggest an alternative diagnosis to NEC?

DR. NEU: Yes, the lack of feeding would make one think more that this is not the classic form of necrotizing enterocolitis. The majority of babies who develop necrotizing enterocolitis are receiving some enteral feedings, whereas a spontaneous intestinal perforation occurs very early in the course of the disease, and many of these babies who have spontaneous intestinal perforation have either never been fed or are getting very small amounts of enteral feeding.

MR. BUSKER: So overall, differentiating between NEC or a different process — what key factors should the clinician consider?

DR. NEU: The fact that this occurred so early in a baby at this low gestational age, with the combination of not being fed and receiving a combination of drugs, makes one think very strongly toward spontaneous intestinal perforation. However, one cannot tell with 100 percent certainty unless one examines the bowel in this situation, but the likelihood that this is spontaneous intestinal perforation rather than necrotizing enterocolitis is very high.

Of interest is that in the late 1970s at Columbia University, a rodent model for necrotizing enterocolitis was developed. This includes induced hypoxia, ischemia, cold stress, introduction of potentially pathogenic microorganisms, and feeding the infant animals by tube with a formula rather than providing their own mother's milk to them. These animals developed necrosis of the intestine, which in many studies has been related to the human form of necrotizing enterocolitis. However, when one considers what I said previously about most of the babies who develop the classic form of necrotizing enterocolitis, they developed it later, not right after birth, and rarely do they have severe hypoxic ischemic insults right before the development of the disease, as seen in the rodent model.

So whether this rodent model is representative of the disease seen in preterm babies is highly questionable, and one needs to consider this in terms of the studies that have been done using this model.

MR. BUSKER: Based on the research and your own clinical experience, how is NEC diagnosed?

DR. NEU: The diagnosis of necrotizing enterocolitis is usually made by a combination of clinical criteria, laboratory criteria, and imaging studies, radiographic studies. In terms of clinical presentation, most of these babies present with a distended abdomen. Sometimes there will be erythema around the umbilical cord. These babies also frequently become lethargic and develop systemic signs such as increased apnea and bradycardia. They may not tolerate their feedings as well as previously and along with this, radiographs of the abdomen are often done. What is diagnostic of necrotizing enterocolitis is portal venous gas in the liver or pneumatosis intestinalis, which is air in the bowel wall, and then we have some nonspecific laboratory features that may suggest an inflammatory response such as very low white blood cells, a shifted immature white blood cell to mature white blood cell ratio, elevated C reactive protein, and low platelet counts, but unfortunately these laboratory results are highly nonspecific and may represent another inflammatory process such as late onset sepsis.

MR. BUSKER: Let's assume the clinician is pretty sure that NEC is an accurate diagnosis. What's the standard treatment?

DR. NEU: Depending on what is seen in the baby, if it is considered to be medical necrotizing enterocolitis, and by medical necrotizing enterocolitis I mean a baby that has some of the clinical signs of necrotizing enterocolitis such as abdominal distention, severe feeding intolerance, and some of the radiologic manifestations such as pneumatosis intestinalis or portal venous gas without signs of intestinal perforation, which would be free intraperitoneal air. Those babies are usually placed what we call NPO, or *nulla per os*, in other words, they are not fed anything through the gastrointestinal tract for several days; the usual course is somewhere between five to 14 days of not feeding these babies. They are placed on broad spectrum antibiotics, largely because many of these babies also have severe systemic inflammation and may actually translocate microbes through their gastrointestinal tract into their bloodstream and have a systemic sepsis-like picture. The bowel is decompressed by placing a tube into the stomach to suction, and their laboratory results and radiographic signs are followed closely to ensure that they are not proceeding to a worsening stage of the disease.

In terms of surgical treatment, if the medical and surgical team believe that the baby is not improving and may not even have free intraperitoneal air, sometimes these babies are taken to surgery. Usually free intraperitoneal air is considered to be an indication for surgery. Two main types of surgical interventions are undertaken. One is a laparotomy, where the surgeons will open the abdomen and examine the intestine for signs of necrosis; if the area of bowel is severely necrotic, that is usually removed. The other form of treatment is to place a peritoneal drain into the abdominal cavity and observe the baby for several days to see if the baby improves with

that intraperitoneal drain. Occasionally babies will improve with the intraperitoneal drain, but oftentimes the babies do not improve and may require additional surgery.

MR. BUSKER: Thank you, doctor. And we'll return with Dr. Josef Neu in just a moment.

DR. MAUREEN GILMORE: Hello. I'm Maureen Gilmore, assistant professor of pediatrics and director of neonatology at Johns Hopkins Bayview Medical Center. I'm one of the program directors of *e*Neonatal Review.

*e*Neonatal Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to neonatologists, respiratory therapists, neonatal nurses and nurse practitioners, and other health care practitioners whose work/practice includes treating neonates.

Bimonthly podcasts are also available as downloadable transcripts, providing case-based scenarios to help bring that new clinical information into practice in the delivery room and at the bedside.

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MR. BUSKER: Welcome back to this *e*Neonatal Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Josef Neu, from the University of Florida in Gainesville. And our topic is Optimal Methods for Prevention and Treatment of NEC. We've been discussing how the information Dr. Neu presented in his newsletter issue might be used in the NICU — so to continue, Dr. Neu, let me ask you to describe for us another patient.

DR. NEU: A 27 week gestation, three week old male receiving nasal prong positive pressure ventilation presents with increased gastric residuals from 2 cc to 4 cc, increased abdominal circumference, hemoglobin positive stools increased C reactive protein, and an increased white blood cell count. He received a blood transfusion two days previously but has been fed throughout with 150 mL/kg/day donor milk and has tolerated these feedings well. Abdominal radiographs reveal slightly distended loops of bowel but no pneumatosis intestinalis or portal venous gas.

MR. BUSKER: Based on what you've just described, doctor, does this baby have NEC?

DR. NEU: Definitive diagnosis of NEC cannot be made based on this information because this baby does not have pneumatosis intestinalis or portal venous gas or a perforation of the bowel based on abdominal radiograph or observation at the time of surgery.

MR. BUSKER: So without a definitive diagnosis of NEC, how should this baby be monitored?

DR. NEU: This baby needs to be observed very closely. The baby should have repeat laboratory investigations such as platelet count, abdominal radiographs, white blood cell count, and C reactive protein and should have very close observation by the nursing and medical teams.

MR. BUSKER: Now as you described it, this baby has been fed throughout his time in the NICU. Should these feedings be stopped?

DR. NEU: In cases such as this it is probably reasonable to decrease the amount of feeding, but the fact that the baby is not showing definitive signs of necrotizing enterocolitis suggests that it is probably reasonable to maintain some level of enteral feeding to prevent atrophy of the bowel, to prevent some of the complications that are associated with only giving parenteral nutrition to babies such as this for a prolonged period of time. Thus, continuation of feedings, at least small feedings, is probably reasonable in this case, along with close observation.

MR. BUSKER: In your newsletter issue, doctor, you reviewed a 2014 paper on biomarkers. Talk to us a little more, if you would, about biomarkers that may be potentially diagnostic for NEC.

DR. NEU: I previously mentioned some biomarkers such as C reactive protein, white blood cell count, and platelet count. These are highly nonspecific signs of systemic inflammation and thus are not specific biomarkers for the disease. Other biomarkers are being developed that are considered to be potentially diagnostic biomarkers. Some of the recent literature suggests that intestinal fatty acid binding protein, which is found elevated in the bloodstream and urine of individuals who have intestinal epithelial damage may be a biomarker. Another biomarker seen in the literature that might be useful in the future is claudin 3 (CLDN3). CLDN3 is one of the proteins that maintains integrity of the tight junctions between intestinal epithelial cells. It is also a water-soluble protein that can be found in the bloodstream and urine. Other biomarkers found in the feces of these babies, such as calprotectin or S100A12, if elevated may suggest the development of necrotizing enterocolitis. However, sometimes these babies will not pass stool at the will of the physician and thus this may make the fecal studies somewhat limited. These biomarkers were addressed in the newsletter issue.

MR. BUSKER: Thank you, doctor, for that case and discussion. Let me ask you, now, to bring us one more patient, if you would, please.

DR. NEU: A 27 week gestation preterm infant who is now three weeks old has recently been transferred to the level 2 step-down unit. She has a history of mild respiratory distress that resolved in the first week and only needed CPAP ventilatory support. She still has intermittent bradycardic spells and is receiving caffeine. At 3:00 the patient's nurse notes that the baby, who had been on full donor milk feedings with fortifier, develops increased apnea and bradycardia, a distended and discolored abdomen with periumbilical erythema. She vomits around the nasogastric tube and is having increased respiratory distress. The baby's respiratory status deteriorates, she is intubated, and mechanical ventilation is begun. Abdominal radiograph reveals no pneumatosis intestinalis, no free air, but also no bowel gas with severe distention and complete abdominal opacity.

MR. BUSKER: The absence of pneumatosis and the absence of free intraperitoneal air — do those rule out NEC?

DR. NEU: This does not rule out the diagnosis of necrotizing enterocolitis. Unfortunately, at this time we do not have biomarkers that can differentiate a questionable situation such as this from one that is not as questionable, where you have pneumatosis intestinalis or portal venous gas. This baby may have a severe form of necrotizing enterocolitis which is not observable by radiograph. Occasionally we may not be able to pick up the stage of pneumatosis intestinalis or portal venous gas where there is a perforation and considerable fluid leaks into the abdominal cavity and free air is not readily noticeable. So this could potentially be a case of necrotizing enterocolitis and we would have to do additional studies to determine whether or not this is the case.

MR. BUSKER: Those additional studies — talk to us a little more about them, if you would, please. Which diagnostic procedures might be helpful in this case?

DR. NEU: Sometimes repeat abdominal films, especially left lateral decubitus, may layer out the fluid and show that there is some free air in the peritoneal cavity. This would be very helpful in terms of being able to make the diagnosis of perforation having occurred. Abdominal ultrasound may be helpful to determine if some of this fluid is extraintestinal. Abdominal paracentesis may be helpful to determine if the fluid in the abdominal cavity is intestinal content, and sometimes a repeat evaluation of some of the nonspecific biomarkers I previously mentioned such as CRP, white blood cell count, and platelet count may be helpful if you see a deterioration in these numbers.

Another laboratory evaluation that might be helpful in this situation is to look at the blood pH. If the metabolic acidosis continues to worsen, this is also an indicator that there may be ischemia occurring; with this ischemia you see increased metabolic acidosis.

MR. BUSKER: How would you determine when surgery should be considered?

DR. NEU: In this situation it is very important to work as a team with the neonatologists and the pediatric surgeons. This is a situation that may require surgery, and the earlier the pediatric surgeon is on board and helping in the decision-making process, the better will be the likely outcome for a patient like this.

MR. BUSKER: And what are the surgical options that might be considered in a patient like this?

DR. NEU: It was mentioned before that there are two different surgical options. One is to place a drain, which would help determine whether there is a perforation. When a drain is placed, frequently material comes out of the abdominal cavity and into the drain itself. This may help decompress the bowel, and in some cases may be all that is needed. However, many of these cases also proceed to requirement for additional surgery.

As in one of the articles that was discussed, the pros and cons of peritoneal drains versus laparotomy were discussed. One of the concerns I had about the drains is that in many cases, drains are placed and no additional studies such as a laparotomy are done, Sometimes these babies will die without a laparotomy being performed. This is largely in situations where the babies are so unstable that the pediatric surgeon is highly reluctant to operate because the baby may die in surgery. This is a real conundrum we have in terms of doing a laparotomy versus just placing a drain.

The other approach is to do an immediate laparotomy. This obviously has some advantages and some disadvantages. The advantage is that one can determine very early if the infant does have a piece of necrotic bowel which can be immediately removed and that baby can then proceed onto the next step, which is recovering. However, sometimes this is very difficult because subjecting a baby to anesthesia and surgery is also very stressful and can have its complications as well. This is not an easy situation, and the decision made by the pediatric surgeon and the neonatologist is not an easy one.

MR. BUSKER: Doctor Neu, thank you for today's patient cases and discussion. Let me ask to go to an overview perspective now, and my question is: What you believe needs to happen to improve clinicians' ability to accurately diagnose and treat necrotizing enterocolitis?

DR. NEU: First, I think a better understanding of the cause of the more classic form of the disease is necessary. That means we also need a good definition so we can define classic necrotizing enterocolitis, because as I mentioned, what we are calling necrotizing enterocolitis is probably a mixture of different diseases and different pathophysiologies, so we have to define the most common pathway toward this disease.

Once we have that, we will have a much better feel for areas where we might be able to intervene. There have been some studies evaluating different nutritional regimens such as arginine, glutamine, omega-3 fatty acids. These are all agents that may be involved in preventing the inflammatory response. Some more recent studies that have raised a lot of excitement include probiotics but we still do not know which is the most appropriate probiotic to use. In fact, the neonatologists who are using probiotics still do not have a basis from one strong properly powered study with one agent to base this therapy on. We have to make sure this is truly safe, and we need to do studies to ensure safety of any probiotic agent we use.

That being said, it appears that the microbial ecology of the gastrointestinal tract is something we could focus some attention on, and microbial therapeutic measures may be very important in the future.

One thing that may help us improve the microbial ecology of the gastrointestinal tract is not to use as many antibiotics as we are using in these preterm babies. Heavy use of antibiotics in very low birth weight infants may cause a dysbiosis in the gastrointestinal tract, leading to microbes that are much more pathogenic and are actually a prelude to the development of necrotizing enterocolitis. Putting some food into the gastrointestinal tract early instead of keeping these babies NPO for prolonged periods of time may also improve bowel function and improve the microbial ecology of the gastrointestinal tract. So learning how to feed these babies appropriately and what to feed them, most likely something like the baby's own mother's milk, and focusing on trying to get the baby's own mother's milk into their gastrointestinal tract early will be potentially very helpful.

We have a lot of modalities, but a lot of questions remain that we need to use and study, but we should try to base this on the best science possible.

MR. BUSKER: Thank you for sharing your thoughts, doctor. I'd like to wrap things up by reviewing what we've discussed today in light of our learning objectives. So to begin: the difficulties that impede progress against NEC.

DR. NEU: The first issue is having a good definition of the disease. Second, we need a better understanding of the pathophysiology, especially the multifaceted

pathways toward development of intestinal necrosis. Some of these may include what we are feeding the babies, such as a situation where certain proteins that may cause a reaction in the gastrointestinal tract are being fed to the baby either through human milk or through a formula, which causes bleeding and even pneumatosis intestinalis, but this may not be the same as the classic form of the disease. So we need a better understanding of some of the pathophysiologic pathways that lead to intestinal necrosis and determine which of these we will term necrotizing enterocolitis.

MR. BUSKER: And our second learning objective: the challenges in the expeditious diagnosis and treatment of NEC.

DR. NEU: Necrotizing enterocolitis can present with very few symptoms and the baby can progress to full-blown symptoms and death within a fairly short period of time, sometimes less than 24 hours. This leaves us with a true dilemma in expeditious treatment of this disease, and because of this it is mandatory that we have better biomarkers for a diagnosis of this disease. And having biomarkers that will allow us to do surveillance of high risk babies may help us catch this disease before it becomes a full blown disease.

MR. BUSKER: And finally: the modalities — both current and those under development — being used for prevention of NEC.

DR. NEU: So there may be some modalities that are currently used to prevent necrotizing enterocolitis that may actually cause harm. One example is placing babies NPO, or *nulla per os,* for long periods of time, and this may actually be the exact wrong thing to do, because this predisposes to intestinal atrophy, predisposes to intestinal dysbiosis.

Another modality that we need to be very careful about that can cause harm is the use of antibiotics. There's a high prevalence of antibiotics use in preterm babies, and we need to reevaluate this because several studies now show that prolonged use of antibiotics may predispose to the development of necrotizing enterocolitis by causing a dysbiotic microbial environment in the intestine.

One factor that may be very helpful in preventing the disease is the use of human milk. The baby's own mother's milk appears to be highly preferable to donor milk or formula. A baby's own mother's milk has numerous protective factors including, a set of microbes that may be preventive for the pathogenesis of necrotizing enterocolitis by promoting good microbial environment in the gastrointestinal tract.

Using probiotics may be a reasonable approach, but as mentioned, considerable work is needed to ensure safety and efficacy of any single probiotic preparation.

MR. BUSKER: Dr. Josef Neu from University of Florida, thank you for participating in this *e*Neonatal Review Podcast.

DR. NEU: Thank you very much, Bob. It's a real pleasure and honor to be asked to do this. I hope that this information will be helpful to the people listening to this podcast.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.eneonatalreview.org/test.

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