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Podcast Issue

Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

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VOLUME 10 — ISSUE 4: TRANSCRIPT

Featured Cases: Management Of Bronchopulmonary Dysplasia and Respiratory Distress Syndrome

Our guest author is Bernard Thebaud, MD, PhD, Professor of Pediatrics, at Children's Hospital of Eastern Ontario in Ottawa, Canada.

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

- Describe the current approach to exogenous surfactant administration for the treatment of respiratory distress syndrome in preterm neonates.
- Summarize current therapeutic strategies targeted at reducing the incidence of bronchopulmonary dysplasia.
- Discuss the emerging evidence for the application of stem cell therapies for the prevention of bronchopulmonary dysplasia.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of management of BPD and RDS in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 10, Issue 3 *e*Neonatal Review newsletter— Management of Bronchopulmonary Dysplasia and Respiratory Distress Syndrome.

MEET THE AUTHOR

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Guest Faculty Disclosure

Dr. Thebaud has indicated that he has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of his presentation.

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February 26, 2015

Expiration Date
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⇩ PROGRAM BEGINS BELOW

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- 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.
- Clinicians treating preterm infants may not be fully aware of the most recent developments in optimal management of bronchopulmonary dysplasia and respiratory distress syndrome.

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MR. BOB BUSKER: Welcome to this first *eNeonatal Review*™ podcast.

Today's program is a follow-up to our newsletter on the *Management of Bronchopulmonary Dysplasia and Respiratory Distress Syndrome*. With us today is one of that issue's authors, Dr. Bernard Thebaud, Professor of Pediatrics at Children's Hospital of Eastern Ontario in Ottawa, Canada.

*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:

- Describe the current approach to exogenous surfactant administration for the treatment of respiratory distress syndrome in preterm neonates.
- Summarize current therapeutic strategies targeted at reducing the incidence of bronchopulmonary dysplasia.
- Discuss the emerging evidence for the application of stem cell therapies for the prevention of bronchopulmonary dysplasia.

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MR. BUSKER: I'm Bob Busker, managing editor of eNeonatal Review. Dr. Thebaud, thank you for joining us today.

DR. THEBAUD: Thank you very much for having me.

MR. BUSKER: In your newsletter issue, doctor, you reviewed recent studies about the use of surfactant, antenatal steroids, and Continuous Positive Airway Pressure (CPAP) to stabilize respiration in preterms, oxygen saturation stats, and the new research into stem cell therapies for BPD. Our focus today is on how those new findings can be incorporated into clinical practice. So if you would, Dr. Thebaud — start us off by describing a preterm patient.

DR. THEBAUD: The first case is a female infant born by vaginal delivery at 27 weeks' gestation. The mother had arrived to the hospital with threatened preterm labor a week previously and received antenatal steroids right after admission. Prior to delivery she also received magnesium sulfate for neuroprotection.

MR. BUSKER: The initial stabilization of this infant, doctor — how would you approach that?

DR. THEBAUD: The initial stabilization should follow the classical NRP steps: warming; clearing the airways as necessary; drying and stimulating the baby; reevaluating her condition, heart rate, and breathing; and begin positive pressure ventilation as indicated. The rise in heart rate will remain the most important indicator of PPV or positive pressure ventilation effectiveness. For preterm babies, supplemental oxygen would be started at 0.30 FiO2, guided by pulse oximetry. For this patient born at 27 weeks' gestation, intubation and surfactant administration in the delivery room are not likely; one should try to stabilize this baby with CPAP in the delivery room. In the newsletter I referred to the article reviewed by Schmolzer et al which suggested a good rate of success with CPAP stabilization in this 27 week gestation female baby that received antenatal steroids.[1]

MR. BUSKER: Now what you've described could cause a potential delay in providing surfactant therapy for this infant. Do you have any concerns about that?

DR. THEBAUD: In this infant I would not have concerns regarding the potential delay in surfactant therapy. As mentioned in the Rojas and Reyes article we reviewed in the newsletter, selective surfactant in this case would be preferable to prophylactic administration, which has been shown to decrease BPD or death.[2] This is different from previous analysis indicating that prophylaxis was better, but in the previous studies there was relatively little use of CPAP and antenatal steroid therapy. Since patient management has changed — and it seems in this case the initial stabilization with CPAP is preferable — even if this baby receives surfactant after a few hours of life she will still receive the benefit without risk of unnecessarily intubating her.

MR. BUSKER: So let's say you have a preterm who was initially managed on CPAP. What if, at some

point, intubation is required? Tell us about the recommended intubation criteria.

DR. THEBAUD: This patient would now be transferred to the NICU after initial stabilization and then would be closely monitored for changes mainly in the effort of breathing, the number of apneas, and the FiO2 requirements. The criteria to intubate and provide the delayed surfactant varied in the studies reviewed by Schmolzer in the newsletter,[1] but a requirement of FiO2 above 0.40 or an increased number of apneas would indicate the need for intubation and delayed surfactant administration.

MR. BUSKER: The risk of preterm infants like this developing bronchopulmonary dysplasia — what can be done to reduce that?

DR. THEBAUD: Obviously, prevention of prematurity would be a very effective means of reducing the risk of bronchopulmonary dysplasia, but despite many attempts in the past, this has not been achieved. In this case we have to focus on the factors that today we know contribute to the development of bronchopulmonary dysplasia, for example, mechanical ventilation and oxygen toxicity — the same therapies we use to maintain these babies alive — at the same time contribute to the disease process.

Recent efforts have been made to prevent mechanical ventilation with CPAP stabilization, as we have seen in this case. Recent efforts have also tried to decrease the oxygen toxicity by carefully evaluating how much oxygen a premature baby requires. This paper by Saugstad, et al was also reviewed in the newsletter.[3] Pharmacological therapies have been shown to decrease the incidence of BPD, such as caffeine, which is used to treat apneas of prematurity. Another pharmacological therapy is corticosteroids, which is still very controversial because of their adverse effects on neurodevelopmental outcome. But a recent paper by Doyle that we also reviewed in the newsletter suggests that in infants who have high risk of developing BPD above 50%, late administration of steroids after 7 days of life may be beneficial.[4] In this respect, predicting equations for the risk of BPD can be useful, and one produced by Laughon, et al is available online.[5]

MR. BUSKER: A link to that risk calculator that Dr. Thebaud just referred to is included in the transcript version of this podcast. And we'll return with Dr. Bernard Thebaud from the Children's Hospital of Eastern Ontario 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 eNeonatal Review podcast. I'm Bob Busker, managing editor of the program. Our topic is Management of BPD and RDS. And our guest is Bernard Thebaud, professor of pediatrics at the Children's Hospital of Eastern Ontario in Ottawa.

We've been discussing how some of the new information Dr. Thebaud presented in his newsletter issue can be translated into clinical practice. So to continue: if you would, doctor, please bring us another patient.

DR. THEBAUD: This is a case of a 24 week premature infant born at 540 gm after spontaneous rupture of the membranes. This mother had no time to receive antenatal steroids, she was admitted with 9 cm dilated

and actively contracting, and was anticipated to deliver shortly.

MR. BUSKER: This infant that you've just described is significantly more immature than the one we previously talked about. How would this alter your approach?

DR. THEBAUD: This is correct. In this case we are faced with an extremely premature infant at the limit of viability who has not received antenatal steroids. His lungs are much more immature than in the previous case, so in the resuscitation room one would still do the NRP as we already discussed. However, given the increased immaturity and absence of antenatal steroids, this baby is very likely to require intubation and surfactant in the delivery room.

And here I would like to draw the attention to the limitations of the Cochrane Review by Rojas and Reyes, and also the review by Schmolzer that we analyzed in the newsletter, suggesting CPAP should be the primary mode of stabilization in these babies.[1,2] These studies had a limited enrollment of extremely premature infants and antenatal consent was required, potentially showing a bias for more stable pregnancies and inborn infants. So this baby may very likely require intubation in the delivery room, as he will probably show signs of severe respiratory distress and no signs of initial stabilization with CPAP.

MR. BUSKER: How likely is it that this infant is going to develop BPD?

DR. THEBAUD: This baby has a relatively high risk of developing BPD, based on his gestational age and birth weight. The risk of developing BPD increases with decreasing gestational age and birth weight. This infant is born at 24 weeks' gestation, right at the limit of viability, with extremely premature lungs. In Schmolzer's article reviewed in the newsletter, the incidence of BPD in infants between 500 gm and 699 gm was 85%.[1] This highlights the high risk of developing BPD in these extremely low birth weight infants and our current lack of significant progress in reducing the incidence of BPD; this baby is at the highest risk of developing bronchopulmonary dysplasia.

MR. BUSKER: In the previous case, we talked about current strategies to reduce the risk of BPD. What about new therapies? What shows promise for treating or even preventing BPD in premature infants?

DR. THEBAUD: A very exciting therapy now on the horizon is the use of exogenous stem cells to either prevent or treat bronchopulmonary dysplasia. Different types of stem cells have been studied, such as the mesenchymal stromal cells, or MSCs, or endothelial progenitor cells. The exciting aspects of these mesenchymal stromal cells is that they have a pleiotropic effect that might be advantageous for a multifactorial disease such as BPD. The mesenchymal stromal cells are also potent anti-inflammatory agents that may act on this pathogenesis of BPD.

The interesting preclinical studies of mesenchymal stromal cells that have shown that intravenous or intratracheal administration of these MSCs can prevent lung injury in experimental BPD models.

MR. BUSKER: Preventing BPD in preterms — what's the current clinical evidence for MSC-based therapies?

DR. THEBAUD: The preclinical studies and experimental models of BPD have led to a first phase I trial that tested the feasibility and short-term safety in preterm babies. This trial was performed in nine preterm infants at risk of developing BPD. They had a mild to moderate risk of developing BPD. This was also a dose escalation study in which the investigators tested 10 million cells/kg and 20 million cells/kg. The results of this study showed the feasibility of administering mesenchymal stromal cells derived from the cord blood through the trachea and showed short-term safety of this approach.

Currently the same group has an ongoing phase II trial testing the efficacy and safety of this approach. Long-term follow-up studies are planned and are obviously crucial for this type of cell-based therapies.

MR. BUSKER: So as these studies proceed — what factors would you like to see the investigators focus on regarding an MSC therapy for BPD?

DR. THEBAUD: Clinical trials with mesenchymal stromal cells are starting. It is a very new therapy, so for the very first trials one would want to first test the safety of this approach in a high-risk patient population with established BPD. Once the safety of this novel therapy has been shown, one may want to

move toward the more at-risk patient population and provide the mesenchymal stromal cells to patients who have evolving BPD to prevent this disease.

MR. BUSKER: Thank you for that information, doctor. Now, if you would, let's look at one more patient.

DR. THEBAUD: This is a one month old male who was delivered by C-section at 29 weeks' gestation because of maternal gestational hypertension. There was a significant growth restriction, with a birth weight of 670 gm.

This baby required intubation for respiratory distress and received one single dose of surfactant shortly after birth. He was successfully extubated by three days of life and weaned from biphasic support to CPAP. He has a current FIO2 requirement of 30%. However, attempts to discontinue CPAP have not been successful at one month of age.

He is tolerating full feeds of fortified mother's own milk and gaining weight adequately.

MR. BUSKER: Fetal growth restriction — how does that alter an infant's risk of developing BPD?

DR. THEBAUD: This baby is not that premature as he was born at 29 weeks gestation, but deleterious effects of his growth restriction, 670 gm, likely because of maternal gestational hypertension, affected his lung growth and maturation in utero. This baby did not have severe respiratory distress at the beginning; he just required one dose of surfactant and was quickly extubated, but now at one month of age he still requires respiratory support with CPAP and 30% oxygen. This is likely a reflection of antenatal fetal growth and fetal lung growth restriction, and he probably harbors a phenotype of BPD due to decreased lung growth and lung vascular growth.

MR. BUSKER: As you discussed in your newsletter issue, there's been an increased interest, and an increased concern, about determining appropriate provision of oxygen to neonates. So let me ask you specifically: what role does supplemental oxygen play in the pathogenesis of BPD? What does the evidence show?

DR. THEBAUD: Oxygen does play indeed a role in the pathogenesis of BPD, even though some premature babies will require additional oxygen to survive. But oxygen also leads to oxidative stress and free radicals that can damage the immature lung. As a consequence, several trials have been performed either in the delivery room or also during later NICU stay, to determine the lowest possible oxygen saturation that is safe for premature babies.

In the delivery room, numerous trials have been performed that have suggested the benefit of room air resuscitation in term infants; however, for premature babies it is still recommended to start with at least 30% oxygen in the delivery room until further trials have been performed.

In the most recent trials outside of the delivery room, such as the BOOST trial or the COT trial reviewed by Saugstad, et al in the newsletter, these studies suggest that safe oxygen saturation target for premature babies lies between 90% and 95% oxygen.[3]

MR. BUSKER: Talk to us a little more, if you would, doctor, about what Saugstad's group reported.

DR. THEBAUD: The Saugstad study was a very important meta-analysis of five multicenter, randomized, controlled trials to look at the optimal oxygen saturation for premature babies. The trials that were reviewed were the SUPPORT trial, the BOOST trial, and Canadian Oxygen Trial. These trials showed that in the low-targeted oxygen saturation — that means oxygen saturation between 85% and 89%, there was a reduced risk of severe retinopathy of prematurity, but an increased risk of necrotizing enterocolitis compared to the high-targeted oxygen saturation group, which was between 91% and 95% oxygen saturation.

In addition, there was an increased mortality in the low-targeted saturation group, prompting early termination of two of the BOOST-2 trials. Based on these findings, the current recommended oxygen saturation target for infants born less than 28 weeks' gestation should be 90% to 95%.

MR. BUSKER: Thank you for today's cases and discussion, doctor. Let me switch gears on you now, and ask you to look to the future for us. What do you see happening in — oh, let's say the next five years — to improve the treatment of BPD?

DR. THEBAUD: I think the treatment of BPD will remain a challenge, especially as we improve the

management of extremely premature babies, we will also push back the limits of viability to earlier gestational ages. As a consequence, the challenge of protecting the more and more immature lung from BPD will be increasing. We will certainly improve our use of careful oxygen delivery, optimize the use of CPAP to avoid mechanical ventilation, and discover new pharmacological therapies that can prevent BPD. But the challenge of preventing BPD in more and more immature babies will be very high.

I also think that mesenchymal stromal cell therapy holds tremendous promise in preventing BPD in these high-risk babies because of their pleiotropic effects that can attenuate the inflammation and the oxidative stress, but at the same time promote lung growth, which no medication so far has been able to accomplish.

MR. BUSKER: Thank you for sharing your insights, doctor. I'd like to wrap things up now by reviewing our learning objectives and how they were addressed in today's conversation. So to begin: the current approach to exogenous surfactant administration for the treatment of respiratory distress syndrome in preterms.

DR. THEBAUD: Case one highlighted the selective approach preferred over prophylactic surfactant administration in this 27 week gestational premature infant who had received antenatal steroids. Unlike previous studies had shown, today it seems that initial CPAP stabilization and delayed surfactant administration, if required, is superior to the prophylactic approach.

Case two described a baby with a higher risk of developing respiratory distress and requiring intubation. This baby was 24 weeks' gestation and had no antenatal steroids, which highlights the need for caution when generalizing the results of published studies and meta-analyses in which fewer of these extreme premature babies were enrolled, so we have less knowledge about the use of CPAP stabilization in the delivery room in this patient population.

In addition, at these extremely premature ages, 24 weeks' gestation with no antenatal steroids, it is likely that this baby will require intubation in the delivery room and may benefit from prophylactic or very early surfactant.

MR. BUSKER: And our second learning objective: therapeutic strategies to reduce the incidence of bronchopulmonary dysplasia?

DR. THEBAUD: In case one we discussed current strategies that can decrease the incidence or severity of BPD. These include avoiding mechanical ventilation by stabilizing the baby on CPAP and decreasing the need for additional oxygen. We also talked about pharmacological therapies such as caffeine and postnatal steroids.

In case three we discussed the role of oxygen in the pathogenesis of BPD and the recent completed randomized, controlled trials that suggest a thoughtful approach to supplemental oxygen, and the current knowledge suggesting that a saturation target of 90% to 95% is reasonable in this patient population.

MR. BUSKER: And finally: the emerging evidence for stem cell therapies for the prevention and treatment of BPD.

DR. THEBAUD: In case two we reviewed the preclinical evidence to support stem cell-based therapies for the prevention and/or treatment of BPD, and first clinical trials are clinically ongoing. We briefly reviewed the first phase 1 study published that showed the feasibility and safety of administration of mesenchymal stromal cells in extremely premature infants.

Mesenchymal stromal cells represent a very promising therapy for the prevention of BPD in extreme premature infants and the coming decade will show whether these cells hold their promise.

MR. BUSKER: Dr. Bernard Thebaud from the Children's Hospital of Eastern Ontario, thank you for participating in this *e*Neonatal Review Podcast.

DR. THEBAUD: Thank you very much for having me. I hope your listeners will enjoy this *e*Neonatal Review podcast.

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