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neonatal INTENSIVE CARE

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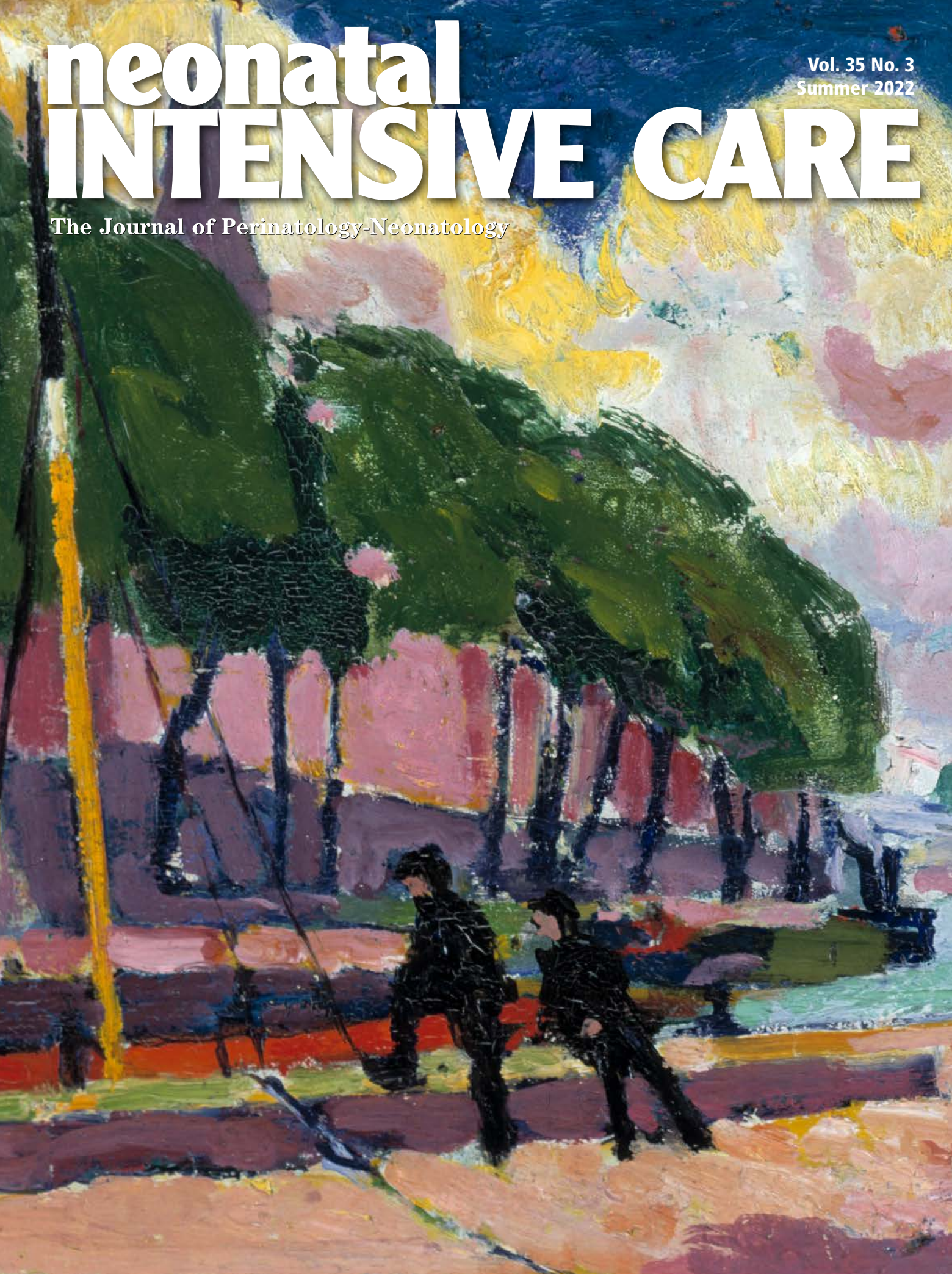

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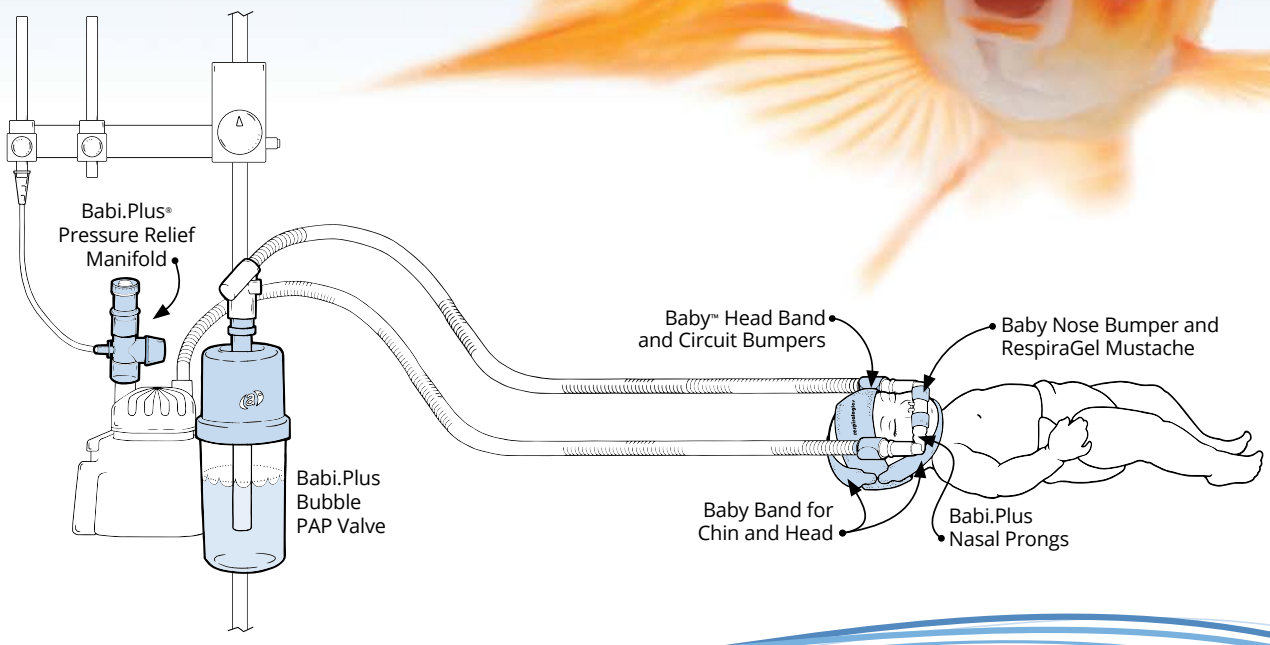

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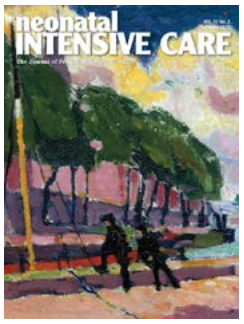

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☐ Summer 2022

Sentynl Therapeutics Announces Launch of Patient Access Program

Sentynl Therapeutics, Inc. (Sentynl), a US-based biopharmaceutical company focused on bringing innovative therapies to patients living with rare diseases, owned by Zydus Lifesciences Ltd. (formerly known as Cadila Healthcare Ltd.), today announced the continued availability of NULIBRY (fosdenopterin) for Injection and the launch of Sentynl Cares. NULIBRY is approved by the US Food and Drug Administration (FDA) to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A, an ultra-rare, life-threatening pediatric genetic disorder. Sentynl Cares provides a comprehensive set of support programs dedicated to helping children with MoCD Type A in the United States gain access to NULIBRY. Recognizing that most patients with MoCD Type A experience delayed or missed diagnoses that may affect patient outcomes, Sentynl plans to advance initiatives aimed at providing an earlier diagnosis and treatment of the disease. These initiatives include: Supporting the development of a novel newborn screening test, including facilitating the collection of whole blood samples from patients with MoCD Type A disease for assay development and validation, with the aim of universal screening for all babies in the first days of life. Also, advocating for the inclusion of the MOCS1 gene to the commercially available genetic test panels that will aid in the diagnosis of MoCD Type A patients. Plus, launching Sentynl Cares a comprehensive set of support programs dedicated to helping children get access to our therapies. Sentynl Cares also provides tools and resources to help facilitate the access process. Sentynl's Chief Executive Officer, Matthew Heck, said, "Early diagnosis and therapeutic intervention is critical to MoCD Type A disease patients and their caregivers. Our company is proud to advance initiatives that are aimed at earlier diagnosis and treatment of rare diseases like MoCD Type A." Speaking on the development, Dr. Sharvil Patel, Managing Director, Zydus Lifesciences Ltd., said, "These initiatives align with our core purpose to empower patients suffering from rare disease with the freedom to live healthier and fulfilled lives. Zydus is proud that NULIBRY (fosdenopterin) is now among its portfolio of rare disease treatments designed improve outcomes for patients and their caregivers." MoCD Type A is an autosomal recessive, inborn error of metabolism caused by mutations in the molybdenum cofactor synthesis 1 gene and characterized by a deficiency in molybdenum cofactor production, leading to a lack of molybdenum-dependent enzyme activity. The lack of activity leads to decreased sulfite oxidase activity with buildup of sulfite and secondary metabolites (such as S-sulfocysteine) in the brain, which causes irreversible neurological damage. MoCD Type A is an ultra-rare disease. The incidence and prevalence of MoCD Type A in the United States are not known, but the estimated incidence is 1 per 100,000 live births. Based on these estimates, MoCD Type A is likely to be underdiagnosed, with an estimated 22 to 26 missed diagnoses per year in the United States and European Union. The most common presenting symptoms of MoCD Type A are seizures, feeding difficulties and encephalopathy. Patients with MoCD Type A who survive beyond infancy typically suffer from progressive brain damage, which presents in characteristic patterns on magnetic resonance imaging (MRI). This damage leads to severe psychomotor impairment and an inability to make coordinated movements or communicate with their environment.

Second-Trimester Blood Test Predicts Preterm Birth

A new blood test performed in the second trimester could help identify pregnancies at risk of early and very early spontaneous

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preterm birth (sPTB), based on a prospective cohort trial. The cell-free RNA (cfRNA) profiling tool could guide patient and provider decision-making, while the underlying research illuminates biological pathways that may facilitate novel interventions, reported lead author Joan Camunas-Soler, PhD, of Mirvie, South San Francisco, and colleagues. "Given the complex etiology of this heterogeneous syndrome, it would be advantageous to develop predictive tests that provide insight on the specific pathophysiology leading to preterm birth for each particular pregnancy," Dr Camunas-Soler and colleagues wrote in the American Journal of Obstetrics and Gynecology. "Such an approach could inform the development of preventive treatments and targeted therapeutics that are currently lacking/difficult to implement due to the heterogeneous etiology of sPTB." Currently, the best predictor of sPTB is previous sPTB, according to the investigators. Although a combination approach that incorporates cervical length and fetal fibronectin in cervicovaginal fluid is "of use," they noted, "this is not standard of care in the USA nor recommended by the American College of Obstetricians and Gynecologists or the Society for Maternal-Fetal Medicine." Existing molecular tests lack clinical data and may be inaccurate across diverse patient populations, they added. The present study aimed to address these shortcomings by creating a second-trimester blood test for predicting sPTB. To identify relevant biomarkers, the investigators compared RNA profiles that were differentially expressed in three types of cases: term birth, early sPTB, and very early sPTB. Among 242 women who contributed second-trimester blood samples for analysis, 194 went on to have a term birth. Of the remaining 48 women who gave birth spontaneously before 35 weeks' gestation, 32 delivered between 25 and 35 weeks (early sPTB), while 16 delivered before 25 weeks' gestation (very early sPTB). Slightly more than half of the patients were White, about one-third were Black, approximately 10% were Asian, and the remainder were of unknown race/ethnicity. Cases of preeclampsia were excluded. The gene discovery and modeling process revealed 25 distinct genes that were significantly associated with early sPTB, offering a risk model with a sensitivity of 76% and a specificity of 72% (area under the curve, 0.80; 95% confidence interval, 0.72-0.87). Very early sPTB was associated with a set of 39 genes, giving a model with a sensitivity of 64% and a specificity of 80% (area under the curve = 0.76; 95% CI, 0.63-0.87). Characterization of the two RNA profiles offered a glimpse into the underlying biological processes driving preterm birth. The genes predicting early sPTB are largely responsible for extracellular matrix degradation and remodeling, which could, "in terms of mechanism, reflect ongoing processes associated with cervical shortening, a feature often detected some weeks prior to sPTB," the investigators wrote. In contrast, genes associated with very early sPTB are linked with insulinlike growth factor transport, which drives fetal growth and placentation. These findings could lead to development of pathway-specific interventions, Dr Camunas-Soler and colleagues suggested.

Furosemide Seen as Safe for Preventing Newborn Lung Disease

A medication used to reduce fluid retention can also safely be used to prevent a dangerous lung condition that affects newborns, particularly those born premature, according to a new study. Furosemide (Lasix) — which can reduce excess fluid in the body caused by heart failure, liver disease, and kidney trouble — is commonly used off-label to prevent bronchopulmonary dysplasia (BPD), a disorder that causes irritation and poor development of lungs in premature infants. But until now, researchers have not studied its safety in this setting. BPD often affects babies born more than 2 months early and can sometimes result in breathing difficulties into adolescence and young adulthood. "There are so few drugs that have been tested for newborns and there are very little data to help neonatologists decide if certain medications are safe and effective," said Rachel Greenberg, MD, MHS, a neonatologist and member of the Duke Clinical Research Institute, Durham, North Carolina. "We found there was no greater risk of safety events for newborns given furosemide." Greenberg presented the findings at the 2022 Pediatric Academic Societies meeting in Denver.

For the 28-day randomized controlled trial, Greenberg and colleagues enrolled 80 preterm newborns, born at less than 29 weeks' gestation, at 17 centers within the Eunice Kennedy Shriver National Institute of Child Health and Human Development Pediatric Trials Network. Of those, 61 received furosemide and 19 received a placebo. Although babies given furosemide had more problems with electrolytes — an expected outcome from the use of diuretic medications — the researchers observed no greater risk for more serious issues, namely hearing loss or kidney stones, Greenberg said. "The mechanism here is we know that extra fluid can damage the lungs and can cause you to have to use more respiratory support and more oxygen," she said. "The thought from a physiological standpoint is using a diuretic can decrease fluid in the lungs and lead to improvements in lung outcomes." The researchers did not observe a reduction in BDP or death in babies who received furosemide, but Greenberg said the study was underpowered to detect such an effect.

Nafcillin Therapy a Safe Alternative to Vancomycin for Infants With Late-Onset Sepsis

A change in treatment guidance to reduce the use of vancomycin in the neonatal intensive care unit (NICU) for late-onset sepsis was safe, sustained, and resulted in similar mortality outcomes, a study of three Ohio NICUs found. In the retrospective review of over 350 infants who received an empirical antibiotic course for possible late-onset sepsis, use of vancomycin fell from 84% in 2013-2014 to 25% in 2017-2019 following vancomycin reduction guidelines for those without a history of methicillin-resistant *Staphylococcus aureus* (MRSA). And the proportion of infants receiving nafcillin jumped from 16% to 75% between the two study periods, reported Jacqueline Magers, PharmD, of Nationwide Children's Hospital in Columbus.

Award Handed Out For Research Into Human Milk Science

The International Conference on Human Milk Science and Innovation (ICHMSI) announced that Dr Alecia-Jane Twigger is the fourth recipient of the Ruth A. Lawrence Investigator Award for Research in Human Milk Science. Established by ICHSMI in 2016, the Ruth A. Lawrence Investigator Award goes to outstanding contributors advancing human milk science and breastfeeding medicine through original research. It is named in honor of Dr. Ruth A. Lawrence, MD, a pioneer in the field of lactation and breast milk. Twigger's research, published in *Nature Communications* and titled "Transcriptional Changes in the Mammary Gland During Lactation Revealed by Single Cell Sequencing of Cells From Human Milk," was selected by an independent panel of expert judges. Twigger's research found over 110,000 viable or living cells from human milk and breast tissue, which may offer clues to the interplay between pregnancy, lactation, and breast cancer. "As we continue

to advance the scientific and clinical innovations of human milk, we rely on research such as Alecia-Jane Twigger's and are looking forward to how her findings will further our goal of raising awareness on the scientific potential and benefits of human milk," Lawrence said. Twigger's findings may have significant implications for the industry, with her study demonstrating the power demographic factors such as age and parity have on the composition of the adult mammary gland and how this might influence long-term breast cancer risk. "I have always been fascinated by cells in milk and think they hold the key to helping us understand human milk production," Twigger said. "This work has taken over four years to complete, but it was well worth it. I hope the findings will advance our understanding of how to optimize milk products to support long-term maternal and infant health outcomes." Twigger will accept the award and present her research at the eighth-annual International Conference on Human Milk Science and Innovation in Vienna on June 10-11, 2022. She will also receive a $10,000 award and travel expenses to attend the event. Twigger is currently a research associate in the Department of Pharmacology at the University of Cambridge, Wellcome-MRC Cambridge Stem Cell Institute. She received her bachelor's degree from The University of Western Australia and received her Ph.D. in cell biology, biochemistry, and human nutrition from the School of Chemistry and Biochemistry at The University of Western Australia. Throughout her career, Twigger has been awarded several prestigious recognitions, including the Federation of American Societies for Experimental Biology (FASEB) Junior Investigator Award, the Seed Funding grant of the UHU collaborative network, and a postdoctoral fellowship at Helmholtz Zentrum München, to name a few. The current research that has earned the Ruth A. Lawrence Award has also been covered in several prominent media outlets, including Medical News Today, SciTechDaily, and ScienceDaily.

Neonatal Hypoglycemia Doesn't Affect Childhood Academics

Children at risk of neonatal hypoglycemia who were screened and treated if needed showed no difference in educational achievement from controls at age 9-10 years, based on data from 480 children. Previous studies have shown an increased risk of poor executive and visual-motor function in children with neonatal hypoglycemia, but the effect on later childhood academic performance remains unclear, wrote Rajesh Shah, PhD, of the University of Auckland, New Zealand, and colleagues. In a prospective cohort study published in JAMA, the researchers enrolled moderate to late preterm and term infants born at increased risk for hypoglycemia; those with episodes of hypoglycemia were treated to maintain a blood glucose concentration of at least 47 mg/dL. The study population was enrolled between 2006 and 2010 at a regional perinatal center in New Zealand, and their educational achievement was assessed 9-10 years later. The primary outcome of low educational achievement was defined as performing below the normal curriculum level in standardized tests of reading comprehension or math. The researchers also identified 47 secondary outcomes related to executive function, visual-motor function, psychosocial adaptation, and general health. Rates of low educational achievement were not significantly different for children with and without neonatal hypoglycemia (47% vs. 48%, adjusted risk ratio 0.95). No significant differences appeared between the two groups for any secondary outcomes, including reading comprehension, math, behaviour manifestations of executive function, fine motor function, autism traits, and overall well-being, the researchers noted. However, children with

neonatal hypoglycemia were significantly less likely to be rated as below or well below reading curriculum level by teachers compared to those without neonatal hypoglycemia (24% vs. 31%). The researchers cited a previous study of the same patient cohort at age 4.5 years, which suggested an association between adverse neurodevelopmental outcomes and infant hypoglycemia. However, the reason this association did not persist at age 9-10 years remains unclear, the researchers wrote in their discussion. "Early disturbances in brain development may have diminishing effects over time due to neuroplasticity, that is, reorganization of neural networks, or delayed maturation with mid-childhood catch-up in neurocognitive function," they said. The study findings were limited by several factors including the lack of data on several measures of cognition, notably processing speed, and a lack of adjustment for intelligence quotient at age 4.5 years, the lack of data on any treatment for developmental impairment, and the inclusion of a population with well-managed hypoglycemia, the researchers said. However, the results were strengthened by having a sample size large enough to detect associations, the prospective design, and the accurate measure of neonatal glycemic exposure, they said. Although the results suggest that at-risk children reach similar endpoints by the end of primary school, "efforts to prevent and optimize adverse pregnancy conditions remain important, and developmental surveillance after birth should be considered for at-risk infants," they concluded.

Preterm C-Sections, Induced Deliveries Dropped During COVID-19 Pandemic

Premature births from cesarean (C-section) and induced deliveries dropped abruptly by 6.5% from the projected number in the first month of the COVID-19 pandemic and stayed at the lower rate consistently throughout the year, researchers have found. Results of the study, led by Daniel Dench, PhD, assistant professor at the Georgia Institute of Technology School of Economics in Atlanta, were published online in Pediatrics. The authors say their findings help answer the question of whether numbers of preterm (less than 37 weeks gestation) C-sections and induced deliveries would change if women didn't see their physicians during pregnancy as often, especially in person, and raise the question of whether some birth interventions by physicians may not be necessary. The pandemic gave researchers a natural, ethical way to study the question. The researchers found that in March 2020 – the start of business closures and stay-at-home orders around the country – preterm births from C-sections or induced deliveries immediately fell from the forecast number for the month by 0.4 percentage points. For the rest of 2020, the number remained on average 0.35 percentage points below the numbers predicted. That means 350 fewer preterm C-sections and induced deliveries per 100,000 live births, or 10,000 fewer overall, the authors said. Dr Dench told this publication the numbers for those births had been steady from January 2010 to February 2020, but the pattern "diverges from this trend very clearly beginning exactly in March 2020 and does not return to trend by December 2020." Meanwhile, during the study period, the number of full-term cesarean and induced deliveries stayed steady and started to increase slightly in 2020. Researchers also adjusted for seasonality as, for example, preterm births are higher on average in February than in March. So far, Dr Dench said in a press release, it's not clear whether the lower numbers mean physicians didn't deliver babies that ended up surviving in the womb anyway or if they missed some that would die in the womb without intervention. To better understand those implications, Dr Dench says he is turning to fetal death records for March-December 2020 and he said he expects to have those results analyzed by the end of the year. If there was no change in fetal deaths at the same time as the drop in preterm births, Dr Dench said, that could point to physician interventions that may not have been necessary.

No Adverse Effect of mRNA Shot for Pregnant Women, Newborns

According to the European Medicines Agency (EMA)'s COVID-19 task force (ETF), a growing body of evidence suggests that messenger RNA (mRNA) COVID-19 vaccines do not cause pregnancy complications for expectant mothers and their babies. The ETF undertook a detailed review of several studies involving around 65,000 pregnancies at different stages and did not find any sign of an increased risk of pregnancy complications, miscarriages, preterm births or adverse effects in the unborn babies following mRNA COVID-19 vaccination. Despite some limitations in the data, the EMA stated the results appear consistent across studies looking at these outcomes. The studies also highlighted that COVID-19 vaccines are as effective at reducing the risk of hospitalisation and deaths in pregnant people as they are in non-pregnant people. In addition, the most common side effects in pregnant people are the same as those in the overall vaccinated population. These symptoms, including pain at the injection site, tiredness, headache, redness and swelling at the site of injection, muscle pain and chills, are usually mild or moderate and improve within a few days of vaccination.

Company Awarded Patent on International Women's Day

Ultrasound AI, Inc., an artificial intelligence company dedicated to improving women's health, announced that they were awarded their first patent on International Women's Day for the software powering their groundbreaking predictive diagnostic medical technology, Preterm AI (PAI). PAI combines the power of ultrasound with artificial intelligence to predict preterm birth. The US patent application states PAI's software has been applied to real-world data obtained from a clinical context and has been shown to consistently produce a positive predictive value *(the AI predicts a preterm birth, and the mother then delivers preterm)* above 90% and a negative predictive value *(the AI predicts a normal birth, and then the mother delivers the baby at full term)* above 90%. "This technology has the potential to revolutionize obstetric care as well as accelerate research to develop new interventions to prevent both premature births and miscarriages," said Dr Garrett K. Lam, FACOG, Chief Medical Officer at Ultrasound AI. Preterm birth is when a baby is born before 37 weeks of pregnancy. In 2020, preterm birth affected one in 10 infants born in the United States. Preterm birth complications are the leading cause of death among children under five years of age, responsible for approximately one million deaths annually. Premature births often result in emotional trauma for families, prolonged stays in specialty care nurseries, and profound health consequences for preterm infants. Many women who deliver prematurely have no known risk factors or early symptoms of complications. "Doctors assume 280 days until birth, and they may be able to label someone as 'at risk,' but that isn't necessarily accurate. The ability to accurately predict if a baby will be born early and how early are non-existent using ultrasound imaging. The current blood tests are limited in use and accuracy, and can be expensive," explains Robert Bunn, President and Founder of Ultrasound AI. Bunn is the pioneering expertise behind this discovery. After he and his wife experienced nine miscarriages

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and the happy arrival of four daughters over time, he knew he wanted to "make a huge dent in every serious affliction that only impacts women." He used AI to analyze the data from 400,000+ de-identified ultrasound images. The AI learned patterns from those images and was eventually able to recognize patterns in images and associate them with birth outcomes. "There's a lot of noise in the images in ultrasound, so humans have difficulty seeing the image and understanding it. Our AI software is trained to do what we can't and see things that we can't see. Most people wouldn't even consider this possible," shared Bunn. Now, after four years of cutting-edge research and development, this revolutionary new AI software shows the promise to change the lives of countless families around the world. PAI has the power to give providers and patients timely, accurate information to make better-informed decisions and improve the wellbeing of babies and mothers.

BridgeBio Pharma and Sentynl Therapeutics Announce Asset Purchase Agreement

BridgeBio Pharma, Inc., a commercial-stage biopharmaceutical company that focuses on genetic diseases and cancers, and Sentynl Therapeutics, Inc., a US-based biopharmaceutical company focused on bringing innovative therapies to patients living with rare diseases owned by Zydus Lifesciences Ltd. (formerly known as Cadila Healthcare Ltd.), announced the execution of an asset purchase agreement (the Agreement) for the sale of BridgeBio's NULIBRY (Fosdenopterin) for Injection. NULIBRY is approved by the US Food and Drug Administration (FDA) to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A, an ultra-rare, life-threatening pediatric genetic disorder. The closing of the asset purchase is subject to customary closing conditions. "Sentynl's focus on meaningful treatments for serious rare diseases is further enhanced by the acquisition of Fosdenopterin. We will leverage our existing platform of ultra-rare pediatric disease initiatives to facilitate early diagnosis and treatment by enhancing awareness, newborn screening, genetic testing and patient support across multiple products and rare diseases. By partnering with BridgeBio, we hope to reach even more patients born with MoCD Type A as quickly as possible with the hope of reducing the risk of mortality and progression of this devastating disease," said Matt Heck, CEO of Sentynl. Under the Agreement, Sentynl will acquire global rights to NULIBRY and will be responsible for the ongoing development and commercialization of NULIBRY in the United States and developing, manufacturing and commercializing Fosdenopterin globally. BridgeBio will share development responsibilities for Fosdenopterin through approval of the marketing authorization application already under accelerated assessment with the European Medicines Agency and through approval of its regulatory submission with the Israeli Ministry of Health. Sentynl will provide cash payments upon the achievement of certain regulatory milestones. BridgeBio will be eligible to receive commercial milestone payments as well as tiered royalties on adjusted net sales of NULIBRY. "Sentynl is an ideal partner given its expertise in the rare pediatric neurodevelopment space and its relationships with physicians who diagnose and treat children with MoCD Type A," said Neil Kumar, Ph.D., founder and CEO of BridgeBio. "Focused execution means reducing the scope of our internal activity. We will continue to advance high-quality programs in our pipeline while expanding our reach to patients in need of options."

New Faces on Company's Board

Nonin Medical announced the appointment of five new members to the company's board of directors. The new directors bring a diverse and unique set of experiences, along with a passion for growth and innovation in the medical device and healthcare sectors. Together, they will provide Nonin with strategic guidance and support the company's continued growth.

The new board members are:

- Waqaas Al-Siddiq, Founder and CEO of Biotricity
- Larry Betterley, President and CEO of Lexington Advisors, LLC
- Angela Dillow, Strategic Consultant and Board Director at Regions Hospital
- Laura Gillund, Corporate Board Director and Global Human Resources Executive
- Robert Rajalingam, President, US Medical Products & Distribution, Cardinal Health

"We have assembled a team of world-class board members with successful track records in the industry who will provide valuable business insights as we accelerate our growth trajectory and serve customers across the globe. Looking to the future of Nonin, we are confident the new board members are uniquely qualified to support the next growth phase of the company," stated Phil Isaacson, Executive Chairman, Chief Technology Officer and Founder, Nonin Medical. With healthcare technology playing a major role in the management of the global pandemic, the Nonin leadership team recognized the need for a new board of directors to help the company address rapidly changing market needs and meet the demands of providers, payors, and other audiences using health-driven digital and data solutions. Phil Isaacson will continue in his board role. The biographies of the new board are available at Nonin.com.

No Adverse Effect of mRNA Shot for Pregnant Women, Newborns

According to the European Medicines Agency (EMA)'s COVID-19 task force (ETF), a growing body of evidence suggests that messenger RNA (mRNA) COVID-19 vaccines do not cause pregnancy complications for expectant mothers and their babies. The ETF undertook a detailed review of several studies involving around 65,000 pregnancies at different stages and did not find any sign of an increased risk of pregnancy complications, miscarriages, preterm births or adverse effects in the unborn babies following mRNA COVID-19 vaccination. Despite some limitations in the data, the EMA stated the results appear consistent across studies looking at these outcomes. The studies also highlighted that COVID-19 vaccines are as effective at reducing the risk of hospitalisation and deaths in pregnant people as they are in non-pregnant people. In addition, the most common side effects in pregnant people are the same as those in the overall vaccinated population. These symptoms, including pain at the injection site, tiredness, headache, redness and swelling at the site of injection, muscle pain and chills, are usually mild or moderate and improve within a few days of vaccination.

ART Associated With Less Risk of Preterm Birth in Large US Study

Over the past decade, data have suggested that antiretroviral therapy (ART) may be associated with an increased risk for adverse pregnancy outcomes, namely, preterm birth (PTB). But a combination of methodologic challenges, demographic gaps, and spotty clinical data has left the question unresolved, especially for pregnant women with HIV who reside in developed countries. "Given that a lot of the emerging data has come out of resource-limited settings where patient and clinical characteristics are different from developed world settings like the United States, we felt that this was an important question to address," Kartik Venkatesh, MD, PhD, a high-risk obstetrician and perinatal epidemiologist at the Ohio State Wexner Medical Center, said. In a prospective cohort study of US women with or at risk for HIV, Venkatesh and his colleagues found that ART exposure (including highly active antiretroviral therapy [HAART]) was associated with as much as an 80% decline in the likelihood of PTB (defined as birth <34 weeks). The study was published in the upcoming special April issue of *HIV Medicine*, devoted to women and HIV. Venkatesh and his team analyzed self-reported birth data of women with singleton live-born pregnancies enrolled in the ongoing, multicenter, prospective observational Women's Interagency HIV Study (WIHS) from October 1, 1995, to March 31, 2019. "We first looked at women with HIV vs without HIV, [who were] matched on many clinical and sociodemographic characteristics and at similarly high risk of some of these obstetrical outcomes like PTB," explained Venkatesh. "We then looked at the relative impact of antiretroviral therapy amongst women living with HIV compared to no antiretroviral therapy." ART regimens were classified as none, monotherapy, dual therapy, or HAART. (HAART was defined as more than three antiretrovirals, including at least one protease inhibitor [PI], nonnucleoside reverse transcriptase inhibitor, integrase inhibitor, or entry inhibitor.) In this cohort, for 63.5% of women receiving ART, therapy was initiated before pregnancy (mean duration of HAART, 6 years), and most were virally suppressed. Among the 4944 women assessed in the WIHS

Continued on page 52…

AMAZON Action Plan for Postnatal Growth

Viviana Juarez, MD, Michelle Benjamin, MD and Shabih Manzar, MD

Neonates admitted to the NICU need close monitoring of their growth. Based on the birth weight they are classified into appropriate for gestational age (AGA), small for gestational age (SGA) and large for gestation age (LGA). SGA is defined as a birth weight (BW) of less than 10th percentile for gestational age, while large for gestation age (LGA) as BW > 90th percentile.[1] Babies born SGA or LGA are prone to increased metabolic risk in later life as compared to AGA.[2] Rapid weight gain during the catch-up growth phase in SGA infants has been associated with childhood obesity, type 2 diabetes, hypertension, and cardiovascular disease.[3] Similarly, LGA infants are at a considerable cardiovascular and metabolic risk.[4] It is therefore very important to closely follow the growth of these babies. We describe the acronym AMAZON (assess growth velocity (GV), monitor weight gain ratio (WGR), adjust calories, z-score difference, offer support to the family, nutritional follow-up) to follow postnatal growth for AGA, SGA and LGA infants (Table 1). AMAZON has three measurable (GV, WGR, Z-score difference) and three action components (adjusting calories, family and nutritional support).

For example, we examine an AGA infant for whom we need to know the growth for last 7 days (Figure 1). The current weight is 2225 grams, 50% corresponding weight is 2750 grams, and z-score is –0.32. The previous weight, 7 days prior, was 2055 grams, 50% corresponding weight was 2200 grams, and z-score was –0.26. This infant has poor growth and needs application of the action plan. The poor growth is shown by low GV, low WGR and negative z-score. If we follow the action plan, the patient requires adjusting caloric intake, offering family support and nutritional follow up.

For AMAZON calculations, the growth velocity (GV) formula is obtained from the previous study by Patel et al [5]. The formula is simplified as: current weight in grams – previous weight in grams ÷ average of weight in grams (average weight is calculated by current weight plus previous weight divided by 2) × 1000, divided by the number of days. For weight gain ratio (WGR), the formula is adapted from the study of Rochow et al.[6] The formula is: current weight in grams minus previous weight in grams divided by the 50% reference weight difference. The 50% reference weight points are obtained by drawing a line at the current and previous weight to the 50% and looking at the corresponding weight (Figure 1, red arrows, and red dotted lines). For z-score difference, the formula is: current z-score – previous z-score. We obtained z-scores from the electronic growth chart by placing the cursor on the weight (z-score could be calculated from the website (https://peditools.org/olsen2010/index.php).

The reason to use more than one method to monitor growth stems from the previous reports.[6,7] Rochow et al[6] found weight gain ratio as an important adjunct to the z-score for appropriate growth monitoring in neonates. Similarly, Simon et al [7] compared Z-score with the growth velocity and found Z-score to be more suitable for analyzing growth.

In conclusion, we describe AMAZON action plan to monitor postnatal growth. Following this plan would help in better assessment and quick action plan to improve postnatal growth.

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Author contribution
Dr Manzar, Dr Juarez and Dr Benjamin conceptualized the study and wrote the manuscript.

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Conflict of interest
None

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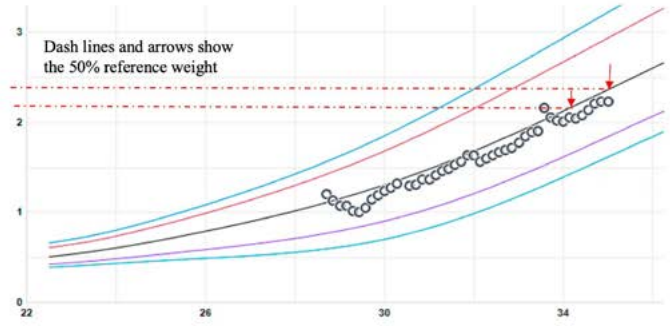
Table 1. Amazon Action Plan. AMAZON [asses growth velocity (GV), monitor weight gain ratio (WGR), adjust calories, z-score difference, offer support to the family, nutritional follow up]

AMAZON Action Plan		Adequate Indicator
A-Asses Growth Velocity	Growth velocity (GV) (g/kg/d) = Current Wt – Previous Wt /Average Wt*/ Days	10-15 g/kg/d
M - Monitor WGR	Weight Gain Ratio (WGR) = Current Wt – Previous Wt divided by 50% reference Wt difference **	1
A - Adjust Calories	Add fortifier, protein supplement, MCT oil	120-130 Kcal/kg/d
Z - z-score Difference	Current z-score – Previous z-score	Positive number
O - Offer family support	Encourage feedings/ Reassurance	
N - Nutritional follow up	Consult Dietician	

Wt: Weight in grams, kg: kilogram, d:day
*Average Wt = Current Wt + Previous Wt ÷ 2
** 50% reference weight is obtained by drawing a line from the weight to the 50% percentile on the growth curve (see Figure 1)
Z-score could be autogenerated or calculated (https://peditools.org/olsen2010/index.php).

Figure 1. Shows the example of AMAZON action plan.



Current Weight = 2225 grams
Corresponding 50% weight = 2750 grams
Current Z-score = – 0.32

Corresponding weight is provided by electronic system on placing the cursor on the growth chart point

Previous Weight = 2055 grams
Corresponding 50% weight = 2200 grams
Previous Z-score = – 0.26

Corresponding Z-score is provided by electronic system on placing the cursor on the growth chart point

A-Asses Growth Velocity = 11 g/kg/d, low
M- Monitor WGR = 0.3, low
A-Adjust Calories = YES
Z-z-score Difference = – 0.06, negative
O-Offer family support = YES
N- Nutritional follow up = YES

Growth Velocity = 2225 – 2055 = 170/ 2225 +2055/2 x 1000
= 170 / 2140 x 1000 = 79 g/kg
= 79 /7 = 11 g/kg/d (divided by 7 days)
Weight Gain Ratio = 2225 – 2055 / 2750 – 2200 = 0.30
Z-score Difference = (Current z-score) – (Previous z-score)
= (– 0.32) – (– 0.26)
= – 0.32 + 0.26 = – 0.06

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Hyponatremia, Hyperreninemia and Hypertension in a Neonate

Syeda Areeba Afzal, MD and Shabih Manzar, MD

Summary
Hyponatremia hypertension syndrome has been described with renovascular disease in children. We present a case of hyponatremia and hypertension in a neonate secondary to transient hyperreninemia. The case is supported by literature review.

Background

Hyponatremic hypertensive syndrome has been described in pediatric patients in association with renal vascular disease.[1] We describe a neonate who manifested hyponatremic hyperreninemic hypertension with microscopic hematuria and normal renal vasculature. We did not find any match on an extensive literature search.

Case

A preterm infant was born at 32-3/7 weeks of gestation via cesarean section to a 41-year-old gravida 5, para 1 mother. The pregnancy was complicated by pre-eclampsia, anemia, and group B streptococcus urinary tract infection. Prenatal ultrasound revealed normal anatomy. She received betamethasone and magnesium sulphate prior to delivery. Infant at birth required continuous positive airway pressure (CPAP) and was transferred to the NICU. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively.

Upon admission to the NICU, patient was placed on bubble CPAP which was gradually weaned off. Infant was started on feeds which were well tolerated. Infant did not require caffeine or antibiotics. On day 14 of life, blood pressure readings taken multiple times with the appropriate cuff size, became elevated in all 4 limbs. Urine analysis was remarkable for 3+ protein, 3+ occult blood (Table 1), and laboratory work up was notable for hyponatremia and elevated renin level of 1600 ng/mL/h (Figure 1 A and B). BP readings continued to be > 99th percentile (Figure 1 C). Due to continued hypertension, pediatric nephrology was consulted and cardiac echography, and renal doppler ultrasound were also completed. Echocardiogram was notable for a muscular VSD, but otherwise normal, and renal US Doppler was also normal. Serum creatine and urine output were noted to be normal (Figure 1 A, Figure 2). As per nephrologist recommendation, amlodipine 0.2 mg/kg/day was initiated followed by nicardipine 0.5 mg/kg/min. After two doses, amlodipine was switched to labetalol 1 mg/kg/day in BID dosing. Infant's BP gradually normalized and stayed normal off all medications. Mother was counselled on how to check blood pressure. The infant was discharged home with pediatric nephrology follow-up.

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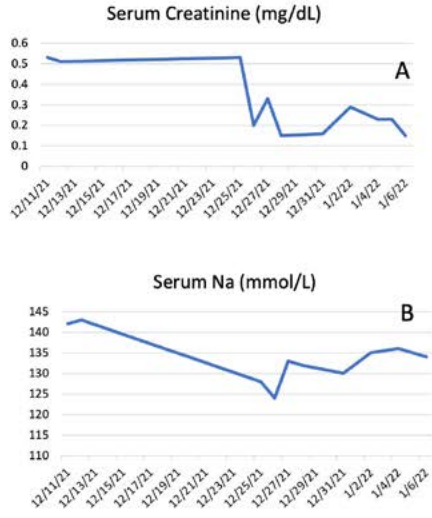
Discussion

Renal injury could be a plausible cause for hypertension with hematuria and natriuresis, but the case was unique as it did not fit into the classical diagnosis of acute kidney injury.[2] Infant had low serum creatinine and good urine output (Figure 1A and 2). Also, fractional excretion of sodium (FeNa) of 0.9% (Table 1), suggested prerenal disease rather than renal. Isosthenuria (normal ranges of urine specific gravity), ruled out vasopressin excess as the reason for hypertension and inappropriate ADH secretion causing dilutional hyponatremia.

Hypertension, high serum renin level with microscopic hematuria, and hyponatremia pointed towards the possibility of renovascular disease but renal ultrasound and doppler for both kidneys were normal. Follow up renin level dropped from 1600 ng/mL/hr to 63 ng/mL/hr, suggesting a transient process deterring the need of renal nuclear or CT scans. We postulated that renal hypoperfusion due to unidentified cause led to activation of renin-angiotensin-aldosterone pathway causing hypertension and hypervolemia that in return led to natriuresis and hematuria. Kovalski et al[1] described four pediatric patients with similar pathophysiology with unilateral renal artery stenosis causing secondary hyperfiltration, pressure diuresis, and sodium loss. Bergstein et al[3] in their series of 229 patients evaluated for asymptomatic hematuria, twelve patients were found to have hypertension. The finding of hyponatremia in the setting of low urinary Na excretion could be explained by two factors: pressure natriuresis at glomerulus and proximal tubules due to hypertension was compensated by aldosterone release which resulted in increased absorption of NaCl at the collecting ducts and ADH release resulting in dilutional hyponatremia (Figure 3).

Diminished renal blood flow resulting from decreased intravascular volume may be seen in compromised placental blood flow, as a result of maternal and neonatal exposure to certain medications.[4] As infant manifested hypertension after 14 days of life, maternal or placental causes are less plausible. Infant did not receive any caffeine, ibuprofen, ampicillin, and gentamicin.



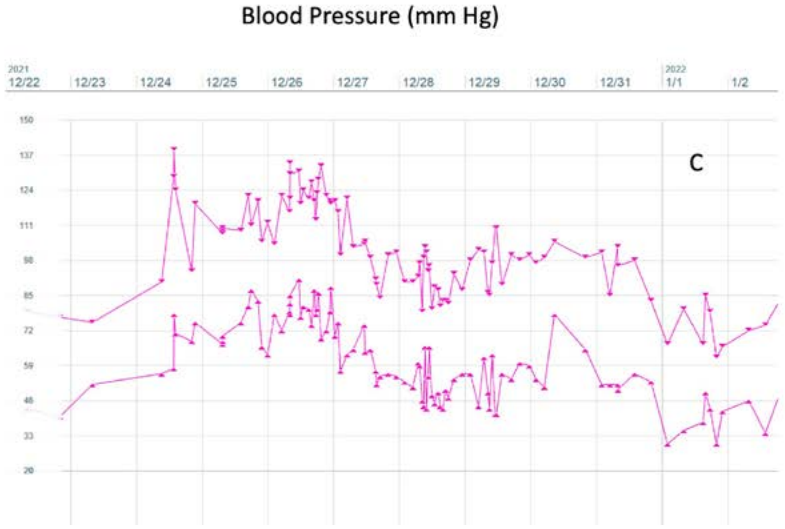


Figure 1 A. Serum Creatinine Trend

Figure 1 B. Serum Sodium Trend

Figure 1 C. Blood Pressure Trend

12/27/21:

Renin Activity = 1600 ng/mL/h (reference range 1.4-7.8 ng/mL/h)

11-Deoxycortisol = 161 ng/dL (Range < 344 ng/dL)

Cortisol (am) = 9.7 mcg/dL (range 7-25 mcg/dL)

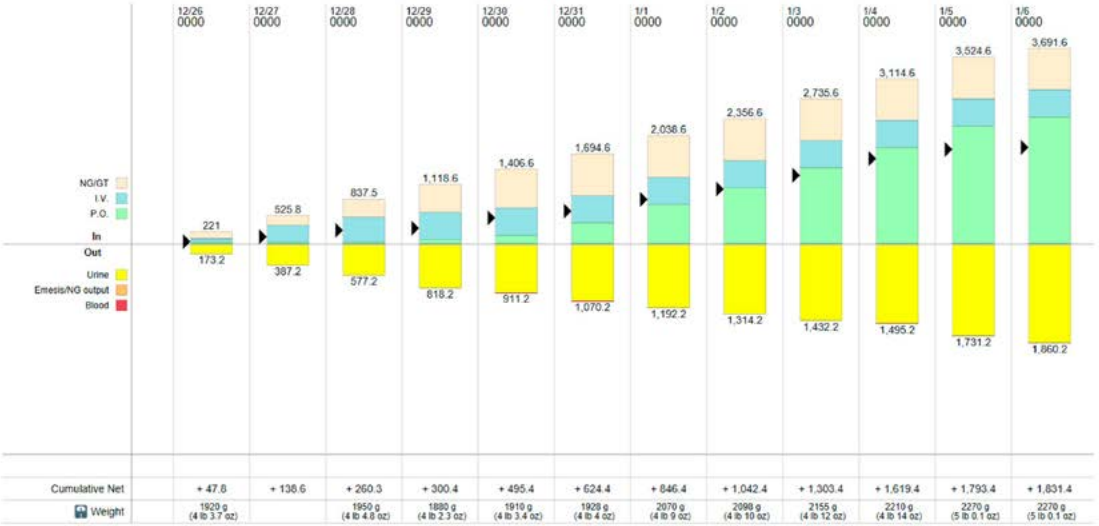


Figure 2. Fluid Intake Output Trend

We went through an extensive list of other possible causes for hypertension, as described Giri et al[5] but did not find any risk factors for our patient described in the review. Other possible causes for hyperreninemic hypertension described in the literature could be renal artery stenosis, pheochromocytoma or urinary tract infection.[6-8] Infant had a normal abdominal ultrasound, normal renal Doppler and urine culture was negative ruling out transient pseudohypoaldosteronism with hyponatremia.

In conclusion, we describe a unique neonatal case of hyponatremic hyperreninemic hypertension with no evident pathology. We postulated renal hypoperfusion as the possible reason for the condition.

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Figure 3. Suggested Pathophysiology

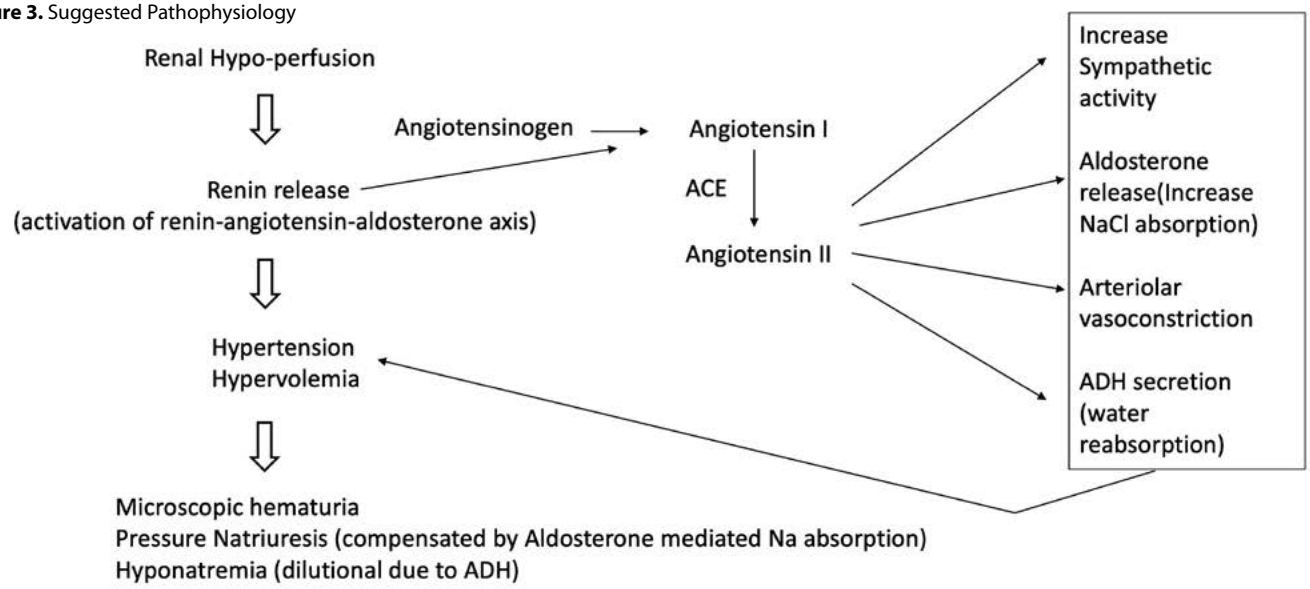

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Table 1. Serial Urine Analysis

	12/25/202	12/26/2021	12/27/2021	12/28/2021	12/31/2021
Color	Yellow		Yellow	Yellow	Yellow
Appearance	Clear		Clear	Clear	Cloudy
Specific Gravity	1.010		1.010	1.010	<=1.005
pH	6.0		8.0	6.0	6.0
Protein	3+		2+	2+	Trace
Glucose	Negative		Trace	Negative	Negative
Ketones	Negative		Negative	Negative	Negative
Occult Blood	3+		2+	2+	Trace
Nitrate	Negative		Negative	Negative	Negative
Urobilinogen	Negative		Negative	Negative	Negative
Bilirubin	Negative		Negative	Negative	Negative
Leukocytes	Negative		Negative	Negative	Negative
RBC	44		73	5	15
WBC	3		1	2	1
Bacteria	Negative		Negative	Negative	Negative
Squam Epithelial	52		16	14	18
Hyaline Casts	2		0	1	0
Chloride, Urine		82			
Creatinine, Urine		<13.0			<13.0
Protein, Random		206			30
Sodium, Urine		71			8
Potassium, Urine		39			
Osmolality, Urine		294			

Fractional Excretion of Sodium (FENa) = 0.9 % (calculated with 12/26/21 lab values.

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NIV in the NICU and the Importance of Monitoring

Dr Oliver Götz, Senior Physician, Clinic For Pediatrics, Adolescent Medicine and Neonatology, Kempten Hospital, Germany, discusses the important role of monitoring for NICU patients on noninvasive forms of ventilation.

Introduction

It's a great pleasure for me to talk to you today about the *Importance of Monitoring In The Neonatal Intensive Care Unit During Non-Invasive Ventilation*. I'd like to talk today about the principles of treatment in neonatal patients, the challenges and changes of airway management, the measurement of CO_2 in the neonatal intensive care unit, and the selection of patients — which is quite interesting — a bit about monitoring equipment, and finally, some conclusions.

I come from Kempten, in Bavaria, Germany. We are a perinatal center of the highest level, with about 2,600 to 2,800 deliveries and about 50 to 60 preterm babies below 1500 grams.

In regards to the principles of treatment in neonatal patients, our first, and overall, aim is to avoid complications, particularly those major complications that we are all afraid of: intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, etc.

Our other aim is to discharge our preemies in good condition, both in the immediate short-term, at discharge, as well as longer-term over the years. The long-term outcome — such as neurological and motor development — is a very important aim in our treatment, and in all the things we do in the NICU.

Pillars and Correct Treatment in the NICU

Everything we do in the NICU is based on two pillars.

The first pillar is the *close observation* of patients: Monitoring the heart rate, the breathing rate, saturation, blood examinations, ultrasounds, X-rays and more.

The second pillar is the *correct treatment* of the phenomena of premature birth and related diseases. Not every preterm baby is a *sick* preterm baby. Some premature babies are healthy. What we need to determine is the truly correct treatment. For example: What is the correct treatment of the surfactant deficiency disease? *When* should we give CPAP therapy? *When* do we give surfactant therapy?

There are standard procedures in every hospital, and this question may come up in every meeting, in every discussion: *What* is the correct treatment? With every treatment, we know that there are adverse effects and possible complications of the treatment itself, perhaps on the lung, on the brain, we may see anemia, we may have gastrointestinal side effects. Every decision we make, must come with the understanding that we may also create problems with our babies.

How does this affect ventilation strategies? When we are talking about changes in therapy guidelines, we may have come to a point where we know that the invasive ventilation has an effect on our babies; for instance, we are afraid of bronchopulmonary dysplasia.

And we now know that there is a benefit, a real benefit, in non-invasive ventilation modalities. Talking about non-invasive ventilation, we could use the example that many of our preterm babies need surfactant. They may have surfactant deficiency disease. There are now well-established and available possibilities to administer surfactant without intubating, even without invasive ventilation. And so we see a real trend to more non-invasive ventilation, CPAP therapy, and a movement away from invasive ventilation.

It's also clear that a surfactant therapy without CPAP, without administering PEEP, does not work well, which means we need CPAP and PEEP, at least. In many non-intubated preterm babies, we will need non-invasive ventilation.

The effect of less-invasive surfactant application and of non-invasive ventilation is now both well-documented and well-established. The methods are safe, and the developmental outcomes are good. One new publication, in Acta Paediatrica in 2021, shows that this (noninvasive ventilation) is perhaps a better way to protect babies from neurodevelopmental problems.

Fundamentals of Respiratory Support

When we are talking about breathing and respiratory support, we know babies need sufficient oxygenation and sufficient ventilation, To assess this sufficiency, we look for normal pO_2 and pCO_2 levels in arterial blood, to avoid hyper-and-hypocapnia, and hyper-and-hypoxemia.

Methods of Measurement

We know the problems of the oxyhemoglobin dissociation curve: if you have 100% saturation, you really don't know if your partial pressure of oxygen is 80mmhg or 180mmhg, which illustrates an additional need to measure pO_2 and pCO_2. The standard

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A transcription of Dr Götz's 20-minute webinar discussion on the important role of monitoring for NICU patients on noninvasive forms of ventilation. Transcribed by rev.com. Edited for clarity and brevity.

procedure for this measurement is, of course, the arterial blood sample, which provides an exact measurement. However, it is a spot measurement where you get an exact result in *this* moment when you've taken the blood. You'll either need an arterial line or you have to perform a blood draw, and in either method there will be a loss of blood.

Noninvasively, we also have the saturation of peripheral oxygen through pulse oximetry, which is routinely done, well-established—everyone does it in the NICU. It's also a continuous measurement. It's very helpful, but you're measuring the O_2 saturation, not the partial pressure of oxygen. Additionally, you have no idea what's going on with carbon dioxide. So, you can't detect hypercapnia or hypocapnia.

Another noninvasive method is the transcutaneous measurement of pCO_2, allowing for the continuous detection of hypercapnia and hypocapnia.

The benefit of transcutaneous monitoring is that it is an easy and safe detection of hyper- and hypocapnia. With a continuous measurement, you have not only a spot measurement, but visibility to your patient's CO_2 for the duration of their ventilation—both noninvasive or invasive methods.

With continuous information, you can take action to prevent additional damage of the lung, atelectasis or overdistension of the lung, and you can prevent BPD. You can also prevent additional damage to the brain by preventing them from hyper or hypocapnia

Another benefit is the reduction of blood loss from reducing ABGs, and a less frequent need for transfusions. We must keep in mind that the blood volume of a preterm baby is low, about 80 to 100 milliliters per kilogram. So, if you have this baby for 8, 10, or 12 weeks in the NICU you end up with a lot of blood loss and may have a need for transfusion. If you can save blood, you have a real benefit for your baby.

With continuous monitoring, you also can avoid pain to the baby. We know that there is a pain-brain connection, that babies remember, in a sense, the painful things we do with them, and if we can avoid sticking them too often, that's a real benefit for the babies.

Determining Patients for Transcutaneous Monitoring

When determining which baby needs transcutaneous monitoring, or close observation of CO_2 in the blood, focus should be on the babies with respiratory distress or failure, which realistically means most of our babies in the NICU. Every baby with mechanical respiratory support also needs very close observation. With mechanical ventilation, *we* are intervening, and we are now responsible for what's going on with this baby. The proportion of babies requiring this level of support depends a bit on the gestational age, but, with preemies below 28 weeks of gestational age, generally more than 90% of them will need respiratory support and very close observation.

So, which forms of observation do we have? This depends a bit on the type of ventilation.

With an intubated baby, the large clinical decision has already been made. The tube is in the baby, you can monitor, you can see, control, and change the parameters of the respirator, which can include conventional ventilation, high frequency, etc.

In a non-invasively ventilated baby, you have to stay very close to them. It must be mentioned that non-invasively ventilated babies are often more unstable than the intubated ones. You have not yet made the decision if an intubation is needed or not, so you must monitor closely, and, importantly, the changes in treatment should not be delayed. You should not wait until the next blood gas analysis. You should make your decision in real time. For this reason, continuous monitoring is very, very important.

In an invasively-monitored baby, you have the tidal volume, you have the minute volume, you have the dCO_2 or perhaps the $ETCO_2$. These are all things you *do not* have in non-invasively ventilated patients , but you still need a way to be very close to these babies and make your decisions quickly. You don't want to be too late with your decisions and interventions.

And those decisions are diverse: you may reduce your CPAP therapy, your non-invasive ventilation, to prevent a pneumothorax, for example. On the other side, if you see that CO_2 levels are rising under your non-invasive ventilation, you may learn you have to change your strategy, and you may even have to intubate the baby after all.

Transcutaneous Monitoring Limitations

Are there challenges with this kind of monitoring? Yes, but only minor ones. You may have a bit of problem, at the beginning, in the selections of your patients for transcutaneous monitoring. You do need to routinely change the site of the sensor. There are skin lesions possible in extremely low birth weight babies, which I haven't seen when only measuring carbon dioxide, which needs a heating temperature of only 41 degrees C. You'll be wondering about differences in transcutaneous values and blood gas values, and this is a learning curve you will have, but it's not difficult to overcome. And the additional benefit you receive when monitoring the therapy you are doing is real, and the side effects of transcutaneous measurement are very small.

In very sick babies, you may have reduced skin and tissue perfusion when they are undergoing sepsis, if you're using catecholamines, or if monitoring during a hypothermia treatment. Transcutaneous monitoring still works in these children, but the results may be not as exact as in a baby with normal perfusion. In extremely low birth weight babies, the skin regions may be a bit too small to place the sensor on the skin. Healthy babies may cause some issues by moving too much, but that's a *good* sign.

Every other therapy, every other monitoring system has limitations and problems in neonatology. That's nothing new. There is no absolutely-best way to treat neonatal patients, in any field of problems.

Transcutaneous Monitoring Best Practices and Use-Cases

With transcutaneous monitoring, it's important not to respond to a single value. You want to see the trend of the CO_2, of the carbon dioxide levels. And in this case, the trend is your friend and not only one value. Your equipment has to be safe, accurate, easy, and integrate with PDMS systems.

In addition to the NICU, we use transcutaneous monitoring in the operating room, and in transport. In the operating room

you have a real benefit in the surveillance of your baby, and the accuracy of the measurement is well-proven.

Case Illustration

Here is an example from theory to practice:

When you're looking at a preterm baby of 28 weeks of gestational age, with a moderate APGAR, pH 7.18, you will start in the delivery room with a recruiting maneuver using non-invasive ventilation.

You may stabilize the baby and then transport it with non-invasive ventilation to your NICU. There, you see that you need to give surfactant, which you perform using the LISA technique, and then you continue with non-invasive ventilation.

You take an initial blood gas analysis, which is not so good, not so bad. So, you don't know: is this patient heading in the right direction, or the wrong direction? In this example, you can see how important a continuous CO_2 measurement is.

If you see that with this respiratory support, your CO_2 levels are decreasing, you may reduce your non-invasive ventilation. You can go to CPAP therapy, and you perhaps can take a blood gas analysis in 6 to 10 hours with a target pH of perhaps more than 7.25.

If you're on the other side, if you're seeing that your CO_2 levels are increasing, you may increase the frequency of non-invasive ventilation, or if it's going worse, you may even intubate the baby.

In both situations, you can delay your blood gas analysis, and can instead look to your transcutaneous CO_2 levels.

Without CO_2 monitoring, you need to do a blood gas analysis perhaps every one to three hours, in these first hours of life of the baby. And with transcutaneous monitoring, you may be able to reduce your blood gas analysis to once or twice per day, which is a real benefit.

The overall reduction of blood gas analysis in our NICU is about 30% with transcutaneous monitoring. It depends a little bit on the gestational age and on the exact clinical situation, but there is a real reduction of blood gas analysis.

Conclusions

Let me conclude by saying that optimal observation is the basis for optimal treatment of a preterm baby. Regarding oxygenation and ventilation, only measuring the oxygen saturation is not enough. With a trend toward more CPAP and non-invasive ventilation, high-quality monitoring is even more important. With transcutaneous monitoring, you may monitor your patients very closely and you can make your decisions based on fact, and in real time: you don't have to wait for the next blood gas analysis.

Taking too many spot-blood samples is not helpful, because of the need for an arterial line, blood loss, pain, and the infection risk that comes with sticking a preterm baby.

I think the transcutaneous measurement of pO_2 and especially CO_2 is useful for even extremely low birth weight preterm babies and is a well-established method in monitoring this group of patients.

Lastly, providing great care in neonatology is done by doing many things a little bit better. There's not just one method. There is not one single therapy or strategy, which will be the best for all kind of problems. You cannot only specialize in ventilation, or stimulation, or skin integrity. And transcutaneous monitoring is something that helps us to do a few of these things a little bit better for our patients.

Thank you very much for joining this webinar. I'm really looking forward to your questions.

Q&A

Moderator: Thank you so much, Dr. Götz. Our first question is how is NICU SIMV delivered in both transport from delivery to the NICU, as well as in the NICU? Are you using a nasal mask? Are you delivering the breaths manually? How are you treating that? Or how are you working with that?

Oliver Götz: That depends a bit on the gestational age. In babies with about 28, 30 weeks, 32 weeks of gestational age, we have a transport incubator. We are putting on the nasal cannula or the CPAP mask. Support is always given pressure-controlled with a respirator and never manually. And for babies more preterm below 28 weeks of gestational age, for example, we need a shuttle system with the incubator, where the baby can stay the whole time, with a respirator, where we can put the same CPAP therapy, the same non-invasive ventilation as we do on our NICU — so we don't have to change the systems. So, in the very preterm babies, we use a shuttle system, and I think that's the best way to handle the baby with care.

Moderator: Do you have any best practices or any advice to get a whole NICU team on board with transcutaneous monitoring for new adopters or new users?

Oliver Götz: You have to use it. I think that's the best way. I think you should not begin with the very tiny 500 gram babies for example. This is not really the best baby to get some experience with transcutaneous monitoring. I think you should begin with a baby of perhaps 28 or 30 weeks of gestational age, test this method for one or two days, and then you will see that after some issues at the beginning, you'll get comfortable with the technology. Learning by doing is the best way. You have to teach your team. You have to tell them very clearly that there may be problems in the beginning, but then you have to just do it, learning by doing.

Moderator: And how long has your NICU been using transcutaneous monitoring?

Oliver Götz: Oh, for years. German guidelines require us to use transcutaneous systems, and we decide on usage from case to case. We don't use it in every baby, that's unnecessary. But we have had the systems for more than 10 or 12 years at least and use them commonly.

Moderator: Are you aware of any evidence or any data that shows that transcutaneous monitoring could help reduce the rate of bronchopulmonary dysplasia? Or have you seen that in your own NICU?

Oliver Götz: I think it's a bit difficult to get a study which shows specifically that transcutaneous monitoring reduces BPD. BPD is a very wide field. There are many input factors to create

BPD. So, I think, it's a bit difficult to say, this is the one method that is reducing BPD. As I said, transcutaneous monitoring is a small part. You have to be better in many small parts. And if transcutaneous monitoring is helping you to reduce the intensity of your invasive or non-invasive ventilation, this is a *real* benefit to prevent BPD.

Moderator: Do you apply the transcutaneous sensor in the labor and delivery unit or right when the baby is born, or do you wait until they're in your NICU?

Oliver Götz: At our hospital, we are placing the sensor in the NICU and not the delivery room, but that's part of our strategy. We don't spend too much time in the delivery room.

We also, for example, do the umbilical cord catheters in our NICU and not in the delivery room because our NICU is close by. We stabilize the baby in the delivery room, go quickly to our NICU, and there, we put the umbilical cord catheters and the transcutaneous sensor. So our time in the delivery room is very short.

Moderator: Do you use transcutaneous monitoring to help manage the risk of IVH and PVL at all?

Oliver Götz: Yes, of course. I think you have many beneficial aspects in transcutaneous monitoring. Today, we only talked about or mainly talked about preventing BPD, about CO_2 monitoring, but there are many side effects and positive side effects of the transcutaneous monitoring.

You won't protect only the lung. You want to protect the whole baby. And this is a very complex system of things working together in a preterm baby. You can't only work on the lung or on the brain or on the abdominal side. And so you have positive impact in the whole baby.

Moderator: Do you have preferred sites when you're monitoring the very small preterm infants, as they have so many other things going on in limited body space? Do you have any recommendations there?

Oliver Götz: You have the front side and the backside in this very tiny space. And it's a question of importance. The space is enough even on a tiny baby, even on a 500- or 600-gram baby, it's possible to place the sensor on the baby. I think you understand that it's very important to protect *especially* the very low birth weight babies from additional damage. There are very, very tiny babies where it's perhaps a bit difficult, or if you have perhaps some skin lesions, but normally it works quite well.

And if you have these very tiny babies on non-invasive ventilation, as I told you, you have to be very close to the baby. Especially in those babies, I think it's really important to continuously see the CO_2 levels, where are they going to, for the brain, for the lung, for the whole baby. So that works quite well.

Moderator: Do you find it beneficial to monitor the transcutaneous CO_2 to see improvement in the ventilation or lung volumes after you administer surfactant, especially during high frequency ventilation?

Oliver Götz: Yes, of course. In every kind of mechanical support, you want to reduce support as fast as possible. That's a part of the strategy to prevent BPD! And during high frequency oscillation, it's very comfortable because it doesn't have so many parameters on the ventilator to monitor your CO_2 level. So transcutaneous monitoring is well-established under high frequency ventilation. Also under high frequency ventilation, you try to reduce your mean pressure, for example, you can reduce your intensity of mechanical support, and therefore you can reduce the risk for getting BPD.

Moderator: Thank you so much, Dr. Götz, for your presentation and the interesting discussion.

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Eliminating Bacterial Colonization of Infant Bathtubs Through the Use of Disposable Liners and Disinfecting Wipes

Timothy R Wolfe, MD

Abstract

Background: Patient wash basins are frequently contaminated with pathologic organisms that may lead to hospital acquired infections. This study assessed the TurtleTub™ infant bathtub with the TurtleTub™ disposable liner to determine if the system could reduce the risk of patient cross-contamination.

Methods: The study was conducted in a lab setting where a worst-case contamination situation could be achieved. Three tubs (study group) were grossly contaminated with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella aeruginosa* and *Escherichia coli*. Two additional tubs served as positive and negative controls. Thirty minutes after contamination all the tubs except the positive control had their liners discarded, were wiped out with a disinfecting cloth for 30 seconds and were allowed to dry for 3 minutes. All devices were then extracted to determine bacterial concentrations.

Results: The positive control tub cultures grew 1.66×10^9 organisms. The negative control and all three study tubs grew no contaminating organisms.

Conclusion: Despite gross contamination, simply removing the TurtleTub disposable liner followed by brief disinfection and drying led to complete elimination of bathtub contamination. This data suggests that the TurtleTub disposable liner and simple disinfection procedures can markedly reduce the risk of patient cross-contamination with the TurtleTub.

Keywords: Bath Basin, disposable liner, Cross contamination, hospital acquired infection, infant bathtub

Introduction

Infant bathing in the hospital is a parent friendly activity with the emotional impact of being the infant's "first bath." In the NICU, an infant bath can be one of the few typical parenting activities for the family. Tub bathing techniques such as immersion bathing and swaddled immersion bathing decrease temperature loss and decrease motor stress for infants during bathing: however, a bath basin can be a potential source for nosocomial infections. This study was designed to assess whether the TurtleTub cleaning and disinfecting system, which includes its own disposable liner, is sufficient to avoid the risk of cross- contamination and HAIs with this device.

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Background

Healthcare-Associated Infections (HAI) are defined as infections that patients acquire during the course of receiving healthcare treatments for other conditions.[1] HAIs are a major problem in US hospitals. They are estimated to occur in 5 to 10% of admitted patients, are the most common complication seen in hospitalized patients and cost billions of dollars a year to treat.[2-4] The result of these potentially preventable infections is higher resource consumption as well as increased morbidity and mortality.[4] In fact it is estimated that deaths from HAIs are in the top 10 causes of hospital mortality.[4]

In the early 2000's the National Quality Forum and Centers for Medicare & Medicaid Services (CMS) introduced patient care guidelines designed to reduce patient harm from preventable errors including some HAIs.[5] CMS refers to these errors as "never events" because these events are preventable if basic evidenced-based guidelines are followed. However, CMS is also aware that evidence based guidelines provide insufficient motivation for hospitals to introduce meaningful change. Therefor they have introduced a more motivating item: Money. Substantial financial penalties are incurred by the institution should a "never event" occur, including denying payment for portions of the hospital stay.[6,7] Some private insurers, such as United Health Care, have adopted similar non-payment criteria.

A potential source of HAI is the bath basin. Conventional bath basins are known to harbor human pathogens and are potential sources of nosocomial infections as shown in two prior studies.[8,9] Johnson et al cultured ninety bath basins in 3 separate hospitals on a single predefined date. They found 98% of the basins were contaminated with bacteria, including enterococci, gram negative bacteria, staph aureus (including methicillin resistant Staph Aureus - MRSA), Vancomycin resistant enterococci (VRE), Pseudomonas aeruginosa and Escherichia Coli (E coli). These authors also noted that some of the human pathogens found in the bath basins were not present on the patient on admission (MRSA and VRE) but were later found in surgical wounds of the patients, suggesting the basin may have been the fomite that led to the patients' infections. These wound infections are often considered "never events" by CMS, and their presence could result in denial of payment for portions of the hospital stay. A few years later, Marchaim and colleagues revisited the issue, culturing 1103 bath basins from 88 hospitals in the USA

and Canada. They looked only for serious pathogens, such as MRSA, VRE, E coli, and Pseudomonas and found that 62% of all basins were contaminated with these serious pathogens. Both authors conclude that current conventional bath basins are used improperly to store various materials in the patients' rooms (such as items used for incontinence episodes, emesis and indwelling catheter care), that they are cleaned, disinfected and stored improperly, and that they are reservoirs for transmission of pathogenic bacteria and a potential cause of serious HAIs. These authors suggest that greater awareness of this issue is necessary and recommend adoption of more evidence based guidelines for bath basin cleaning and storage to deal with this problem.

The current CDC recommended evidence based guidelines for bath basin cleaning and disinfection are based on the "Spaulding classification."[10] In these guidelines, devices are divided into three categories based on their infectious risk to the patient: Critical, Semi-critical and Noncritical. Bath basins and infant bathtubs are considered noncritical because they primarily come into contact with intact skin. While noncritical items pose a low risk of HAI, they still need to be treated as potential sources of HAI because at times they may contact semi-critical areas such as non-intact skin (diaper rash, abrasions, etc.), surgical wounds or mucous membranes. Therefore, they require appropriate cleaning, disinfection and storage to reduce the possibility of introducing a nosocomial infection. Failure to follow these simple steps should be avoided.[8,9]

The literature makes it clear that bath basins are often potential sources of nosocomial infections due to improper cleaning and storage. This study was designed to assess whether an infant bathing system with its disposable bath liner and the recommended cleaning process, was adequate to overcome the limitations of traditional bath basins. The study was conducted in a lab setting where it was possible to create a worst-case contamination situation with highly pathogenic microorganisms. The study goal was to determine if the cleaning and disinfecting Instructions-For-Use (IFU) were sufficient to avoid the risk of cross-contamination and HAIs with this device.

Methods

The FDA requires all critical product disinfection procedures to be validated prior to sale of a device. Microchem Laboratory, Round Rock Texas, is an approved laboratory that conducts disinfection validation studies which comply with the FDA guidelines for medical device reuse. Given Microchem Laboratory's expertise and lack of conflicts of interests, they were commissioned to develop a validated study design and conduct the study outlined here. All data presented is from their lab testing and was not influenced by the manufacturer.

Study procedure: See Table 1 for overview of the procedure

Creation of the solution containing infectious contaminants: *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 15422, *Klebsiella aeruginosa* ATCC 4352, and *Escherichia coli* ATCC 11229 cultures were initiated in Tryptic Soy Broth (TSB) and allowed to incubate at 36±1°C overnight before use in testing. The test microorganisms were pooled into an inoculum solution with an estimated concentration greater than 1×10^9 (1 billion) colony forming units per ml (CFU/ml). See table 2 for the micro-organism concentrations determined at the start of the study procedure.

Device sterilization and preparation: Infant bathtubs and disposable liners (TurtleTub, Catapult Products LLC, Salt Lake City Utah, USA) were disinfected with alcohol spray and allowed to rest under UV light for approximately 15 minutes per side before use in testing. The liners were then aseptically put onto the tub in a manner simulating use prior to the testing. Five bathtubs and liners were prepared in this fashion—three test devices, one positive control and one negative control.

Device contamination procedure: The assembled bathtubs and liners were inoculated with 1.5 milliliters (ml) of the infectious solution. The solution was then spread across the bathtub and rubbed into the liner using a sterile gloved fingertip. The area of the seat, head and indicator strip were the focus of this rubbing. The device and its contaminated liner were then allowed to dry for 30 minutes. After drying, the infant bathtub cleaning instructions for use (FDA/Spaudling compliant) were followed: The liner was removed and discarded, the bathtub was wiped for 30 seconds using a disposable wipe (PDI Super Sani-cloth, PDI HealthCare, Woodcliff Lake, NJ, USA) and the bathtubs were allowed to dry for approximately 3 minutes.

Extraction of contaminants from the test devices: (Extraction is a technical microbiology lab term that refers to the collection of any microorganism contaminants in a sample in an effort to determine the intensity or concentration of contaminants present.) After the tubs were dried, bacterial contaminants were extracted using the following method: 100 ml of Letheen broth was swabbed onto the surface of the tub in four areas using 2 inch by 3 inch swatches of the brush. The fluid was then collected, vortexed and diluted as needed back to 100 ml for culturing. These dilutions were plated onto agar plates designed to enhance growth of each of the four contaminants to determine the amount of contamination present.

Extraction of contaminants from the positive control device: The positive control device differed only in that the liner was not removed, no disinfection wipe was used, and it was extracted 4 times rather than a single time in order to plate each microorganism concentration individually for comparison to the test devices.

Extraction of contaminants from the negative control device: The negative control device differed only in that the liner was never contaminated with the infectious solution. Otherwise the procedure was identical to the test devices.

Calculation of the extent of contamination: The percentage of contamination and the $\log_{10}$ reductions of contamination were calculated based on the number of surviving microorganisms recovered from the extraction of each device compared to the positive control device.

Criteria used for defensibility of cleaning: The Association for the Advancement of Medical instrument technical information report 2020 (AAMI tir12:2020) criteria are an industry standard used by the FDA to validate cleaning and storage of re-usable medical devices. The following criteria are required to be met to scientifically defend the cleaning process:

- The average number of bacteria recovered from the positive control sample must exceed 1×10^6 (1 million) CFU.
- The efficacy of the extraction procedure must be ≥ 70%
- The positive control must demonstrate growth of the

appropriate test microorganisms
- The negative control must demonstrate no growth.
- In order to pass the disinfection test, the test devices must demonstrate a ≥ 6 $\log_{10}$ reduction of four vegetative microorganisms when compared to the positive control for that organism.

Table 1. Study Procedure overview

Culture Growth Media	Tryptic Soy Broth
Inoculum Supplement	5% Fetal Bovine Serum
Test Surface	Liner of infant bath basin
Inoculation Technique	Micropipette
Contact Timed	30 Seconds
Recovery Fluid	Letheen Broth
Extraction Technique	4 swatches, 2" x 3"
Culture Growth Time	19 hours, 44 minutes
Test Device	Infant bath basin, Liner Inoculated
Inoculation Area	Base of Seat, Indicator Strip, Head Area
Inoculum Dry Time	30 minutes–36 minutes
Contact Conditions	Ambient
Recovery Volume	100mL

Results

Tables 2, 3 and 4 validate the reliability of the test design and its compliance with regulatory guidelines. Table 2 demonstrates the test culture concentrations of each microorganism showing that all were in excess of 1 billion CFU/ml with the exception of *S. aureus* which reached a concentration just over 400 million CFU/ml.

Table 2. Test Culture Concentrations

Test Microorganism	CFU/ml
S. aureus ATCC 6538	4.05E+08
K. pneumoniae ATCC 4352	1.67E+09
P. aeruginosa ATCC 15442	1.68E+09
E. coli ATCC 11229	2.22E+09
Pooled Inoculum	1.66E+09

Table 3 confirms the validity of the positive control for comparison as it demonstrates a nearly 98% recovery efficiency of the extraction (over 70% is the required efficiency).

Table 3. Extraction Efficiency of Positive Device Control

Positive Sample ID	CFU/Surface	Recovery Efficiency
Positive Device Control Extraction 1	1.10E+09	97.81%
Positive Device Control Extraction 2	1.72E+07	
Positive Device Control Extraction 3	5.45E+06	
Positive Device Control Extraction 4	2.02E+06	

Table 4 shows that the control solutions and organism cultures all remained intact and uncontaminated so any results from the device cultures shown in Table 6 are be reliable.

Table 5 is the actual results of test device culturing. The negative control showed no growth (limit of accuracy to less than 100 CFU – 1×10^2). The positive control was grossly contaminated with over 1 billion CFU on the surface (1.1×10^9). The three test device bathtubs also showed no growth (limit of accuracy to less than 100 CFU – 1×10^2) with a $\log_{10}$ reduction of microorganism greater than 1×10^9. The combination of these results comply with industry standards and confirm that the bathtub cleaning instructions result in a safe, reusable device that is not contaminated with any detectable bacteria despite gross exposure to billions of microorganisms.

Table 4. Incubation Time and Sterility Observations

Sample ID	Incubation Conditions	Control Result
Letheen Broth Sterility	43 hours, 20 minutes at 36°C	Sterile
PBS (dilution) Sterility		Sterile
Nutrient Agar Sterility		Sterile
FBS Sterility		Sterile
S. aureus ATCC 6538		Pure, Adequate Growth
K. pneumoniae ATCC 4352		Pure, Adequate Growth
P. aeruginosa ATCC 15442		Pure, Adequate Growth
E. coli ATCC 11229		Pure, Adequate Growth

Discussion

Reduction or elimination of hospital acquired infections (HAIs) should be a major focus of hospitals for two primary reasons. First and foremost it will improve patient outcomes by decreasing the number of patients who unnecessarily develop nosocomial infections. The result will be shorter overall lengths of stay, less consumption of medical resources and improved morbidity and mortality for the patients. A second major reason to reduce HAIs is the financial implications it has for the institution (and the patient and their insurance). Since the introduction of the "never event" rulings, hospitals may be denied payment for a patient's hospital stay should an HAI occur. This is a substantial financial penalty that needs to be avoided when at all possible.

Older model bath basins are proven fomites and could lead to HAIs.[8,9] However, this study shows that bathtub contamination and bacterial transmission can be easily and inexpensively avoided. Despite contamination with billions of pathogenic bacteria, using the test device bathtub and disposable liner, combined with the disinfecting procedure as outlined by the manufacturer, pathogen contamination of the bathtub is completely eliminated. This prevents the device from introducing a nosocomial infection to a patient. The minor costs associated with the disposable liner and the disinfection wipes pale in comparison to revenue that will be lost from a reimbursement denial resulting from a preventable HAI.

Given that traditional bath basins are known reservoirs of pathologic bacteria, it is imperative that the caretaker has confidence that the bath basin they use, especially if used on multiple patients, is safe. This study used a worst-case contamination scenario by covering the bathtub liner with over a billion pathogenic bacteria. Despite this contamination, simply removing the disposable liner followed by 30 seconds of wiping a disinfectant cloth and allowing 3 minutes to dry led to complete elimination of detectible pathogens.

Conclusion

Removal and disposal of the TurtleTub single use bathtub liner

Table 5. Device culture results: Number of colony forming units cultured from each device.

Sample ID	CFU/Surface	Log_{10} Reduction From Positive Device Control	Percent Reduction From Positive Device Control
Negative Device Control	< 1.00E+00[2]	NA	
Positive Device Control	1.10E+09		
Test Replicate 1	<1.00E+00[2]	>9.04	>99.99999991%
Test Replicate 2	<1.00E+00[1,2]	>9.04	>99.99999991%
Test Replicate 3	<1.00E+00[2]	>9.04	>99.99999991%

[1]Single external contaminant was noted on filter plate. Not thought to affect study outcome, not included in results of this study.
[2]Values fell below the limit of detection. As a result, the limit of detection (1.00E+00) was used in calculations.

followed by brief disinfection of the TurtleTub completely eliminates pathogenic bacterial device contamination even under a worst-case scenario where billions of bacteria are placed on the liner. These results provide compelling evidence that when properly used and disinfected, this infant bathtub system will not result in cross-contamination of patients. Caregivers can offer infants the benefits of swaddle bathing and immersion bathing, which include decrease in temperature loss and decrease in stress, knowing that the system is safe from cross-contamination.

Conflicts of interest

This research was funded (i.e. the research lab fees required to conduct the lab study) by Catapult Products, the manufacturer of the TurtleTub infant bathing system which was the bath basin product evaluated in this research study. The study lab that conducted the microbiologic testing was paid a standard fee but has no conflict in terms of the results of the testing they conducted. Tim Wolfe, the author of this paper, is a retired academic clinician and businessman. He has no financial conflict of interest related to this research and was not paid any fees nor provided any form of compensation. However, he is associated with the owners of Catapult Products through prior business dealings a decade in the past and he agreed to write the paper as a friend who has the academic credentials and skill set to do so.

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The Benefits of Using AI in Predicting Birth Outcomes

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Robert Bunn, President and Founder of Ultrasound AI, which uses the power of artificial intelligence to advance research in women's health.

Can you give us some background on yourself and what led you to the founding of Ultrasound AI?
I have been a software developer, data scientist, and artificial intelligence researcher for 20 years now. I actually enjoy doing all of these things even in my spare time. I also have four young daughters who keep me on my toes. About five years ago I realized I needed to create my own startup if I really wanted to innovate my way and change the world. So, I then began developing ideas that might be worthwhile to bring to the world.

What made you want to look into creating technology like Preterm AI?
I am well aware of the power AI would likely have when applied to medical problems. I figured I could just start obtaining medical datasets, learn about them, and see if I could do anything valuable with them.

One of the datasets I obtained contained fetal ultrasounds along with corresponding information about preterm birth. I mentioned to more than one doctor that I was trying to create an AI that could look at ultrasounds and predict if a baby would be born preterm or not. I was advised that such a thing would likely not be possible (for the general population anyhow) because they had been looking at ultrasounds for a long time and if such information were present, they would have noticed it already. There are some specific circumstances currently known, such as a short cervix, that have some predictive capability, but they are not highly accurate.

I see it as a challenge when people tell me something is impossible. So I immediately set out to prove them wrong and, in the process, revolutionize the field of Obstetrics—having zero knowledge about the field of Obstetrics! It took two years to learn the basics of this field and to figure out how to solve this problem, but it was an amazing feeling to see something work after spending so much time on it.

Robert Bunn has over 20 years of experience working in software development, data science, and artificial intelligence. As founder & president of Ultrasound AI, he leads the development of revolutionary artificial intelligence technologies for women's health. Bunn is deeply passionate about creating lifesaving and accessible products that help women live longer and healthier lives. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

What was the inspiration for this undertaking?
Preterm birth is the #1 cause of death for children under 5 worldwide, at 1 million deaths per year. As a parent, I feel that the death of a child must be the worst possible thing that could ever happen. I considered giving up on more than one occasion, but simply couldn't bring myself to stop trying. The problem was too important to give up on, and I didn't.

Can you describe/explain the Preterm AI technology and what it does exactly/how it functions?
The type of AI used is called deep learning. In this scenario, images are fed into a large neural network which then learns to identify patterns of pixels in the image, resulting in a prediction of whether the baby will be born preterm or not. This description is a huge simplification of the actual process necessary, but conveys the important concepts.

What sets the Preterm AI technology apart from other Ultrasound technologies?
There are many other algorithms that identify conditions that can be seen in ultrasound images. However, our technology doesn't only tell us what is true now, but also makes a prediction about a future medical event ie, preterm birth. We can make predictions up to six months in advance for this particular type of event. However, our technology is not limited to predicting when a preterm birth will happen. We can also predict when other medical events may happen in the future. One example would be Preeclampsia which is a serious blood pressure condition that develops during pregnancy. We look forward to revealing our research around other conditions in the near future.

What data/testing was done/used in developing Preterm AI?
We started with a dataset containing about 400,000 fetal ultrasounds, and we're currently working on a university partnership to obtain millions more to increase accuracy even further. The partnership will allow us our first independent validation opportunity, which we believe will go a long way toward convincing the obstetrics community about the capabilities of this technology.

What do you envision for the future of the Preterm AI technology and its usability as a MedTech device?
I believe that Preterm AI can become a universal diagnostic test available to every pregnant woman. Access to this technology would help them identify which pregnancies are at risk of

preterm birth, along with relevant clinical information, which would then allow doctors to create customized interventions to improve the eventual outcome.

How about the future of Ultrasound AI?
We believe our technology can extend far beyond premature births. Developing partnerships with researchers will allow us to extend this technology to a wide variety of other medical conditions. I look forward to exploring future collaborations on innovative research. I'm confident we haven't even scratched the surface of what this technology has to offer.

Why do you think this technology is life-changing/ revolutionary?
Right now, there is no way to predict the actual number of days early a baby will be born. There are techniques to estimate the risk of a preterm birth, but the output doesn't reveal the severity of the situation. For an obstetrician to have a tool that indicates a baby will be born 100 days early instead of 30 has enormous implications in the field of Obstetrics. The AI can also show the doctor what anatomical areas are driving adverse predictions so they can develop customized interventions. It should also be noted that having a quantitative prediction during each scan allows the obstetrician to have an objective measurement of improvement.

Now that you have secured a patent what are the next steps to get Preterm AI approved and ready for the MedTech market?
We are currently working on the FDA approval process which will take some time, obviously. We are also working on public and private partnerships to validate the technology and optimize the clinical effectiveness.

How do you think this technology is going to make an impact and pave the way for the future of Ultrasound medical devices and technology?
This application shows that combining AI with ultrasound can create technology with enormous lifesaving potential. Preterm birth costs the United States $30 billion dollars a year and we believe having an accurate and accessible method to predict it will allow a significant reduction in NICU stays and other lifelong health effects. Once the medical community is able to see the profound capabilities that AI applied to ultrasound can deliver to them it should encourage even more collaborations in the future.

Why is it important to detect preterm birth?
All unborn babies deserve a fighting chance for a healthy life. Losing a child due to prematurity is an enormous tragedy for the parents — in some cases, a tragedy that can be avoided. Being able to predict preterm birth allows doctors and patients to take steps to prevent this from happening. It's hard to imagine anything more important than this.

More information about Ultrasound AI can be found on the website https://www.ultrasound.ai.

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Newborn Pulse Oximetry Screening for Critical Congenital Heart Defects

Sophie Jullien

Abstract

We looked at existing recommendations and supporting evidence addressing the effectiveness of pulse oximetry effective for detecting critical congenital heart defects (CCHDs) in newborns. We also looked at the impact of timing of oximetry and the site of testing in the accuracy of screening, and at the potential harms and limitations of pulse oximetry screening.

We conducted a literature search up to the 13th of August 2019 by using key terms and manual search in selected sources. We summarized the recommendations and the strength of the recommendation when and as reported by the authors. We summarized the main findings of systematic reviews with the certainty of the evidence as reported. Current evidence supports consistent accuracy for detection of CCHDs in newborns by pulse oximetry screening in addition to antenatal ultrasonography and clinical examination. Overall, early diagnosis of CCHD with pulse oximetry is judged to be beneficial and cost-effective, and potential harms associated with false-positive tests are not serious, while missing CCHDs and other serious diseases detected by hypoxaemia in absence of pulse oximetry screening can lead to serious consequences. The site of testing (post-ductal versus pre- and post-ductal) had no significant effect on sensitivity nor specificity for detection of CCHDs.

Keywords: Screening, Congenital heart defects, Pulse oximetry, Newborn

Background

Introduction

The World Health Organization (WHO) European Region is developing a new pocket book for primary health care for children and adolescents in Europe. This article is part of a series of reviews, which aim to summarize the existing recommendations and the most recent evidence on preventive interventions applied to children under five years of age to inform the WHO editorial group to make recommendations for health promotion in primary health care. In this article, we looked at existing recommendations and supporting evidence addressing the effectiveness of pulse oximetry effective for detecting critical congenital heart defects (CCHDs) in newborns. We also looked at the impact of timing of oximetry and the site of testing (post-ductal versus pre- and post-ductal) in the accuracy of screening, and at the potential harms and limitations of pulse oximetry screening.

Why is screening for critical congenital heart defects important?

CCHD is defined as any cardiac lesion from which infants die or require surgery or cardiac catheterization within the first 28 days of life to prevent death or severe end-organ damage.[1,2] Early detection of CCHD before acute cardiovascular collapse leads to improved cardiopulmonary and neurological outcomes.[3] However, most newborns are asymptomatic at birth. Newborn screening for CCHD can help identifying some cases to allow prompt diagnosis and treatment, and may prevent disability or fatal outcome.[4]

Context

Congenital heart defects (CHDs) constitute the most common group of birth defects, with a prevalence of around 6 to 11 per 1000 live births for moderate and severe cases.[2,5-8] They account for up to 10% of all infant deaths, and 46% of deaths related to congenital malformations.[5,9] About 25% of CHDs are life-threatening CCHDs. Antenatal ultrasound screening and newborn clinical examination are already established methods to detect malformations such as CCHDs. However, it was estimated that antenatal ultrasound can detect around two thirds of CCHDs (sensitivity of 68.1%; 95% confidence interval [CI] 59.6 to 75.5%), and that the newborn examination also has a low detection rate.[5,6] Indeed, detection of hypoxaemia by visual assessment of the newborn colour has limitations, and cardiac murmurs are not always present in cases of CCHDs and accidental murmurs can be heard in up to 60% of healthy newborns.[6] The combination of antenatal ultrasonography and clinical examination of the newborn lead to sending home up to 30% of cases of CCHDs before diagnosis, with mortality rates up to 50%.[5,6] Several studies have reported that adding routine pulse oximetry (PO) to the antenatal ultrasound screening and clinical examination of the newborn can potentially improve the detection of CCHDs.[10] PO is a simple, non-invasive and painless tool that measures oxygen saturation, and therefore could detect CCHDs with ductal-dependent systemic or pulmonary blood flow that usually present with hypoxemia. Seven severe lesions have been identified as primary targets for screening by PO; those are hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, and truncus arteriosus.[11]

Sophie Jullien, Barcelona Institute for Global Health, University of Barcelona, Barcelona, Spain.

Table 1 Included manuscripts for revision

Sources	Final selected manuscripts
WHO	None
USPSTF	None
PrevInfad	None
AEP	• The Spanish National Neonatal Society Recommendations [6]
CDC	• Fact sheet and recommendations [4]
NICE	None
AAP	• AAP Policy statement, with 2011 recommendations [10] • Newborn screening for CCHD. Recommendations and resources [3]
RCPCH	• Congenital heart disease (Section in the book chapter of Physical examination) [5]
UK NSC	• 2014 recommendations [14] • Consultation on the use of pulse oximetry as an additional test in the Newborn and Infant Physical Exam (Cover note) [15]
Cochrane Library	• Plana 2018 – Pulse oximetry screening for critical congenital heart defects (Systematic review) [9]
Others	• Evans 2016 – Newborn Pulse Oximetry Screening Pilot. End Project Report [16] • Kemper 2011 – Strategies for implementing screening for critical congenital heart disease [11] • Martin 2013 – Implementing recommended screening for critical congenital heart disease [17]

Abbreviations: *AAP* American Academy of Pediatrics, *AEP* Spanish Association of Paediatrics (Asociación Española de Pediatría), *CDC* Centers for Disease Control and Prevention, *NICE* National Institute for Health and Care Excellence, *PrevInfad* PrevInfad workgroup from the Spanish Association of Primary Care Pediatrics, *RCPCH* Royal College of Paediatrics and Child Health, *UK NSC* UK National Screening Committee, *USPSTF* US Preventive Services Task Force, *WHO* World Health Organization

Key questions

1. Is PO effective for detection of CCHDs in newborns?
2. Does timing of oximetry have an impact in the accuracy of screening?
3. Is pre- and post-ductal more effective than post-ductal measurement for detection of CCHDs?
4. What are the harms and limitations of PO screening?

Cost-effectiveness of the implementation of PO screening and acceptability to parents and health workers are beyond the scope of this summary but were assessed by others.[6,9,11,12]

Search methods and selected manuscripts

We described the search methods, data collection and data synthesis in the second paper of this supplement (Jullien S, Huss G, Weige R. Supporting recommendations for childhood preventive interventions for primary health care: elaboration of evidence synthesis and lessons learnt. BMC Pediatr. 2021 https://doi.org/10.1186/s12887-021-02638-8). The search was conducted on the 13th of August 2019, by manual search and by using the search term "congenital heart" OR "congenital cardi*". We did not find any recommendations from the WHO. No document was identified from the US Preventive Services Task Force (USPSTF) (published recommendations or recommendations in progress) or the PrevInfad workgroup (Spanish Association of Primary Care Pediatrics), but we did include the consensus document with recommendations from the Spanish National Neonatal Society, Spanish Association of Paediatrics (AEP, from acronym in Spanish). We did not find recommendations from the National Institute for Health and Care Excellence (NICE) other than the physical examination of the newborn that should include 'heart; check position, heart rate, rhythm and sounds, murmurs and femoral pulse volume'.[13] From the Centers of Disease Control and Prevention (CDC) website, we included a fact sheet and recommendations addressing this topic. We also included the 2011 recommendations from the American Academy of Pediatrics (AAP) and their comprehensive website within the "Program to Enhance the Health & Development of Infants and Childre"'. The Royal College of Paediatrics and Child Health (RCPCH) included this topic within their chapter on "Physical examination." Finally, we also included the recommendations stated by the UK National Screening Committee (NSC) in their recommendations report from 2014-15, and their current update on this matter.

The search in the Cochrane library by using the search strategy 'congenital heart OR congenital cardi*' in titles, abstracts or keywords returned 41 reviews and three protocols. By screening the titles and abstracts, we included one systematic review and two protocols. However, one protocol entitled 'Routine screening by echocardiography to reduce morbidity and mortality from congenital heart disease in neonates with Down syndrome' dated from 2005, and the other one, entitled 'Clinical assessment for diagnosing congenital heart disease in newborn infants with Down syndrome' was out of date and consequently withdrawn from the authors and editors of Cochrane Neonatal. Therefore, we did not contact authors from any of these two protocols and only included one Cochrane review published in 2018. By looking at references from included manuscripts and by hand search, we identified two documents endorsed by the AAP for inclusion (one published by Kemper et al in 2011, and one published by Martin et al in 2013) and one report from a pilot study conducted in the UK (published by Evans et al in 2016).

All the included manuscripts for revision in this article are displayed in Table 1.

Existing recommendations

We summarized the existing recommendations and the strength of recommendations as per their authors in Table 2.

Existing evidence

Short history of PO used for newborns screening

In 2009, the AAP and the American Heart Association (AHA) published conjointly a statement of evidence on the routine use of PO in newborns for detection of CCHDs.[1] The evidence

Table 2 Summary of existing recommendations

Source	Ref	Date	General recommendations for newborn pulse oximetry screening for CCHDs
AEP	[6]	2018	"There is sufficient evidence to recommend neonatal screening by pulse oximetry in the first hours post birth, in addition to prenatal ultrasound and the physical examination." (Level of evidence A) "The timing of screening affects its sensitivity, with a higher sensitivity the earlier it is performed." (Level of evidence A) "Early screening, within 24h of birth, reduces the risk of onset with severe or very severe symptoms in CCHD at the expense of a greater number of false positives, although most of the latter are indicative of other disorders that may also require observation, diagnosis and treatment, so early screening is preferable to late screening (>24 h). Very early screening (<12 h) may result in an excessive number of false positives, an issue that needs to be weighed at the local level. In case of very early discharge, screening should be performed before discharge, regardless of timing. It is recommended that the screen be performed between 6 and 24 h post birth." (Level of evidence B)
CDC	[4]	2018	The CDC recommends screening of all newborns in well-baby nursery at ≥24 hours of age or shortly before discharge if <24 hours of age, with a subsequent algorithm according to findings (reported by Kemper et al. [11]). In addition, it is recommended that 'Pulse oximetry screening should not replace taking a complete family health history and pregnancy history or completing a physical examination, which sometimes can detect a critical CHD before the development of low levels of oxygen (hypoxemia) in the blood.'
NICE		2015	"heart; check position, heart rate, rhythm and sounds, murmurs and femoral pulse volume"
AAP	[3, 10]	2019	• "All newborns at risk for undetected CCHD should be screened. In other words, the only babies who do not need to be screened are those who are already known to have CCHD, such as those identified by prenatal ultrasound or who have already had an echocardiogram." • "Screening should begin after 24 hours of age or shortly before discharge if the baby is less than 24 hours of age. Waiting until 24 hours of life will decrease the false-positive results." • "The screening should occur in the right hand and either foot. If using only one pulse oximeter, test one right after the other." • "CCHD screening should be conducted by individuals who have pulse-oximetry testing within their scope of practice, who are trained in the use of pulse oximetry and the CCHD algorithm, and who regularly use pulse oximetry for other purposes." • "In the event of a positive screening result, CCHD needs to be excluded with a diagnostic echocardiogram. Infectious and pulmonary causes of hypoxemia should also be excluded."
RCPCH	[5]	2019	"Until the result of this study [using PO in 15 NHS Trusts in England] are available, it [PO] cannot be recommended as a routine addition to the existing newborn physical examination tests within 72 hours of birth."
UK NSC	[14]	2014	• "A systematic population screening programme is not recommended." • "The UK NSC recommends piloting the use of the pulse oximetry test to evaluate the potential benefits of its use as a new screening test for congenital heart disease."
	[15]	2019	• "Recommendation against using pulse oximetry as an additional test in the newborn and infant physical exam"

Abbreviations: *AAP* American Academy of Pediatrics, *AEP* Spanish Association of Paediatrics (Asociación Española de Pediatría), *CCHD* Critical congenital heart defect, *CDC* Centers for Disease Control and Prevention, *NHS* UK National Health Service, *NICE* National Institute for Health and Care Excellence, *PO* Pulse oximetry, *RCPCH* Royal College of Paediatrics and Child Health, *UK NSC* UK National Screening Committee, *USPSTF* US Preventive Services Task Force

supporting this document was mainly based on two studies (de Wahl 2009 and Riede 2010), both included in the Cochrane systematic review by Plana et al. Although the document showed benefits of PO screening, it was concluded that "future studies in larger populations and across a broad range of newborn delivery systems are needed to determine whether this practice should become standard of care in the routine assessment of the neonate". Based on this document, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) recommended that CCHDs to be added to the recommended uniform screening panel (RUSP). After this, the SACHDNC in collaboration with the AAP, the AHA, and the American College of Cardiology Foundation convened a work group to elucidate how to implement this screening safely and with efficiency. The working group evaluated the new findings of large population-based screening activities in Sweden and England, and published their updated recommendations in 2011, which are the basis for the AAP and CDC current recommendations.[11] Previously called "cyanotic congenital heart diseases", this group recommended renaming the target conditions of the PO screening as "critical congenital heart disease" (CCHD), as "many newborns with the targeted congenital heart defects do not develop clinically appreciable cyanosis until after nursery discharge, and some lesions (e.g., hypoplastic left heart syndrome) may present with significant cardiovascular compromise without apparent cyanosis." As a conclusion, "the work-group members found sufficient evidence to begin screening for low blood oxygen saturation through the use of pulse-oximetry monitoring to detect CCHD in well-infant and intermediate care nurseries", however they identified research gaps, mainly regarding some specifics populations and delivery strategies. Therefore, "the

Secretary of the US Health and Human Services has directed an interagency work group to develop a plan to address these critical gaps before recommending that CCHD be a part of the recommended uniform screening panel".[11] The CCHD newborn screening was added to the RUSP in 2011, and two years later, another document was published, addressing some of the implementation challenges.[17]

While routine PO screening for detection of CCHDs in all newborns has been introduced in the US, other countries have been conducting similar assessments to evaluate the potential harms and benefits of introducing the screening at a national level. In the UK, a pilot study was conducted in 2015 in order to elucidate effectiveness and feasibility of the implementation of the CCHD newborn screening (findings below). In addition, "Public Health England undertook a review of the extent to which PO met the UK NSC criteria for screening, particularly focussing on the harms and benefits of potential for over-diagnosis, over-treatment, false-positives, false reassurance, uncertain findings, and complications".[15] Based on the pilot study and the review conclusions, the UK NSC recently recommended against the introduction of routine PO screening, which is disputed by others.[18] In May 2019, the UK NSC "announced a public consultation on its decision not to introduce routine PO for CCHD in all newborn babies".[15] By the time this review got published, this public consultation revealed that despite the national recommendation against newborn PO screening, 96/189 (51%) neonatal units were currently using it.[19] Of them, 75 (78%) neonatal units felt that screening did not increase unnecessary investigations, and 10 (10%) felt "that any small increase was justified and offset by the benefits of identifying considerable cardiac and non-cardiac pathology".[19] Findings of this survey call for unified national recommendation.

Accuracy of PO for detection of CCHDs

Threshold for considering PO result pass or failed

As mentioned by Kemper et al, "selecting the threshold for a positive pulse-oximetry monitoring result is challenging, because it must trade-off the harm of missing CCHD against the harm of false-positive screen results".[11] Several institutions currently agree on the following criteria to consider a screen failed: any oxygen saturation measure less than 90% in the initial screen or in repeated screens; oxygen saturation less than 95% in the right hand and foot on three measures, each separated by one hour; or an absolute difference in oxygen saturation of three percentage points between the right hand and foot on three measures, each separated by one hour.[3,4,6,11,20]

Studies reporting accuracy of PO for detection of CCHDs

Accuracy of PO for detection of CCHDs was assessed by one Cochrane review,[9] and by one project conducted in the UK.[16] The Cochrane review conducted by Plana et al assessed the diagnostic accuracy of screening with PO compared to echocardiography or clinical follow-up in the first 28 days of life for detection of CCHD in asymptomatic newborn infants.[9] The literature search was conducted up to March 2017. Twenty-one studies were included (16 prospective cohorts and five retrospective cohorts), published between 2002 and 2017, mainly from Europe (UK, 5 studies; Italy, 2 studies; Germany, Norway, Poland, Sweden, Switzerland, and Turkey, 1 study each), but also from other settings (US, 3 studies; Australia, China, Mexico, Saudi Arabia, and South Africa 1 study each). Across the included studies, data was provided for 457,202 newborns and several pulse oximeters models were used. Different thresholds were used to establish a pass or failed screening: post-ductal saturation <95% (8 studies), post-ductal saturation ≤95% (3 studies), pre- and post-ductal saturations <95% (6 studies), pre- and post-ductal saturations ≤94% (1 study), post-ductal saturation <96% (1 study). The applicability concerns were judged as low for all included studies per the review authors.

In 2013, the UK NSC decided to assess the feasibility and impact of PO screening in a wide context, and started a multicentric pilot study across England.[16] This took place from July to December 2015, and it consisted in taking pre- and post-ductal measurements between 4 and 8 hours of life.

Main findings

Plana et al considered <95% or ≤95% as a threshold to include studies for primary analysis.[9] From 19 studies (n = 436,758), they found that PO for detection of CCHDs had a sensitivity of 76.3% (95% confidence interval [CI] 69.5 to 82.0%) and a specificity of 99.9% (95% CI 99.7 to 99.9%) with a false-positive rate of 0.14% (95% CI 0.07 to 0.22).[9] Summary positive and negative likelihood ratios were estimated at 535.6 (95% CI 280.3 to 1023.4) and 0.24 (95% CI 0.18 to 0.31), respectively. As detailed by the review authors and considering a median prevalence of 0.6 per 1000 newborns, 'these results showed that out of 10,000 apparently healthy late preterm or full-term newborn infants, six will have CCHD'; 'screening by PO will detect five of these infants as having CCHD and will miss one case' and 'screening by PO will falsely identify another 14 infants out of the 10,000 as having suspected CCHD when they do not have it'.[9] The certainty of the evidence was graded as high for specificity and low for sensitivity, downgraded due to serious imprecision (due to small number of cases with CCHD included) and serious risk of differential verification bias ('diagnosis was established by echocardiography in test positive cases however test negatives were usually confirmed by clinical follow-up or by accessing congenital malformation registries and mortality databases').[9]

Main findings from the English pilot study showed that among the 32,836 newborns screened, there were 239 cases (0.73%) with a positive screen, out of which eight were CCHD cases.[16] The screening was performed within the target time of 4 to 8 hours for half (52%) of the participants, within 12 hours for 78%, and after 24 hours for 8.5%. More in detail, around half the newborns with a positive screen were admitted to the neonatal unit. Among those not admitted, 97% had transitional circulation and 2 cases had culture negative sepsis. Among the 114 newborns admitted to the neonatal unit, eight (7%) had a CCHD, 86 (75%) had a 'significant illness which required medical intervention', and 22 (9% of newborns with positive screen, 0.07% of all newborns screened) were healthy babies. From these findings, investigators interpreted that 'earlier screening (within 24 hours) results in a higher proportion of babies detected with a clinical condition but at the expense of a slightly higher screen positive rate'. Two CCHD cases were missed by a negative screen result. These two newborns also passed the antenatal ultrasonography screening and the clinical examination screening without detecting anomalies. One of them had a fatal outcome, and the other one presented with cardiovascular collapse. Overall, authors concluded that 'the pilot has demonstrated that in general, it is feasible to introduce PO screening in an NHS environment, however there are important clinical considerations' and that 'the routine introduction of PO screening could be considered once these issues have been satisfactorily resolved.'

Accuracy considering different thresholds

Different thresholds were considered by two studies included in the Cochrane review.[9] According to the review authors, one study used a threshold of ≤94% and found a sensitivity of 100% (95% CI 29 to 100) and specificity of 100% (95% CI 100 to 100); and another study used a threshold of <96%, and found a sensitivity of 100% (95% CI 3 to 100) and specificity of 100% (95% CI 100 to 100), respectively.[9] While it is difficult to understand 100% for both sensitivity and specificity, we noted some inconsistencies between the findings of this systematic review on this aspect and what is reported in the original included papers. We have contacted the review authors for clarification but have not received any reply.

Accuracy considering antenatal diagnosis

The review authors looked whether antenatal diagnosis could have an impact in the findings and found that both sensitivity and specificity did not change significantly when newborns with suspicion of CHD by antenatal ultrasound screening were included versus excluded.[9]

Accuracy considering risk of bias

The Cochrane review authors also looked at the impact of risk of bias in the findings.[9] For the 'flow and timing domain', nine studies were judged at unclear risk of bias and 10 studies at low risk of bias. It was found that risk of bias for this domain had no significant effect on sensitivity, but that studies classified at unclear risk of bias had higher specificity than those judged at low risk of bias (100% [95% CI 99.9 to 100%] versus 99.7% [95% CI 99.3 to 99.8%]; P = 0.016).

Accuracy considering other factors

Other factors that could impact the findings of pulse-oximetry in the detection of CCHDs have been reported. Algorithm and cut-offs for pass or failed PO screening were based on studies conducted at low altitude. As oxygen saturations are lower at higher altitudes, using the same algorithm in newborns at high altitudes might lead to higher false-positive rate. While there is global awareness around this question, there is a lack of data to support modification of the current algorithm on PO screening.[3,11] The altitude where screening was performed was not reported in the studies included in the Cochrane review.[9]

Performing the screening in alert newborns was associated with lower false-positive rates, 'possibly by reducing the likelihood of low oxygen saturations caused by hypoventilation in deep sleep', although this was reported from anecdotal reports.[11] Performing PO screening around the time of the hearing screening was also associated with an improved efficiency, 'assuming that the hearing screening is conducted after 24 hours or immediately before discharge'.[11]

Conclusions on accuracy of PF for detection of CCHDs

Current evidence supports consistent accuracy for detection of CCHDs in newborns by pulse oximetry screening in addition to antenatal ultrasonography and clinical examination.

Timing of PO screening

With the closure of the arterial ductus and other physiologic changes after birth, timing might have an impact in the findings of PO screening. A recent study estimated the median ductal closure time to be 27 hours in boys and 45 hours in girls.[5] However, the cut-off considered in the studies is usually 24 hours, which coincides with timing discharge of apparently healthy neonates without maternal complications leading to performing neonatal examination and screening within the first 24 hours of life. In the review conducted by Plana et al (primary analysis), PO screening was performed within the first 24 hours of life in eight studies, with an overall sensitivity of 79.5% (95% CI 70.0 to 86.6) and specificity of 99.6% (95% CI 99.1 to 99.8).[9] Among the 11 studies that performed the screening test after 24 hours of life, the overall sensitivity was 73.6% (95% CI 62.8 to 82.1) and specificity 99.9% (95% CI 99.9 to 100). There were no significant differences on sensitivity between performing the screening before versus after 24 hours of life, but the false-positive rate for detection of CCHDs was significantly lower among the group of newborns screened after 24 hours of life (0.06% [95% CI 0.03 to 0.13] versus 0.42% [95% CI 0.20 to 0.89]; P = 0.027).

The Spanish National Neonatal Society affirmed the opposite: "The timing of screening affects its sensitivity, with a higher sensitivity the earlier it is performed" with a level of evidence judged as A. From the supporting evidence provided by the consensus document, authors argued that "an analysis of late screens (>24 hours) demonstrated that half of CCHDs manifest in the first 24 hours and 20% do so with cardiovascular compromise", but no data was given on direct comparison between screening before versus after 24 hours of life. However, there is a general agreement in the literature that early screening leads to an increased rate of false-positive cases, although it is highly valuable to detect most of these cases, as most of them are indicative of other severe disorders that may also require prompt diagnosis and treatment. Indeed, in the UK, early screening of around 26,000 newborns led to a screening positive rate of 0.8%, with the detection of nine CCHDs cases and within the false-positive cases, 79% had a significant medical condition.[21] Conversely in the US, late screening of around 73,000 newborns led to a very low false-positive rate of 0.04%, at the expenses of a low number of CCHDs cases detected (three cases). As reflected by Ewers et al, "the likelihood is that in the US cohort, many infants with CCHD presented before screening took place".[21] These considerations are the main rationale why early screening is finally recommended by several associations, such as the Spanish National Neonatal Society, as it is judged that benefits outweigh risks.

Conclusions on timing of oximetry

- The timing of pulse oximetry screening had no significant difference on sensitivity, but the false positivity rate was significantly lower among newborns screened after 24 hours of life, when compared with newborns screened within the first 24 hours of life.
- There is some evidence – and wide acceptance among physicians – that early screening leading to early detection of CCHDs allows timeliness of appropriate medical intervention and therefore reduces the risk of onset with severe or very severe symptoms, with subsequent better outcome.
- Newborns with false-positive screening results might undergo unnecessary additional tests such as echocardiogram. However, early screening allows detection of hypoxemia due to other clinically severe conditions that benefit from prompt intervention.
- Overall, benefits of early screening are judged to be greater than the potential negative impact of the increased rate of positive rate by some societies, but this is not the position of other institutions such as the United Kingdom National

Screening Committee and the Royal College of Paediatrics and Child Health.

Post-ductal versus pre- and post-ductal screening

A pulse oximeter device can measure pre-ductal oxygen saturation when the probe is placed on the right hand, and post-ductal oxygen saturation when used on either foot. Eleven studies included in the Plana et al (primary analysis) review measured post-ductal oxygen saturation only for the detection of CCHDs, with a sensitivity of 81.2% (95% CI 70.9 to 88.4), a specificity of 99.9% (95% CI 99.7 to 100), and a false-positive rate of 0.13% (95% CI: 0.05 to 0.31%).[9] Pre-ductal and post-ductal screening was performed in 8 studies, with a sensitivity of 71.2% (95% CI 58.5 to 81.3), a specificity of 99.8% (95% CI 99.5 to 99.9), and a false-positive rate of 0.17% (95% CI 0.06 to 0.46). It was found that the site of testing (post-ductal versus pre- and post-ductal) had no significant effect on sensitivity nor specificity.

Conclusions on site of testing

The site of testing (post-ductal versus pre- and post-ductal) had no significant effect on sensitivity nor specificity for detection of CCHDs.

Potential harms of PO screening

PO is a safe and harmless tool. Newborns with a false-positive screen will however receive additional testing such as an echocardiography or a chest radiography, and might be referred or admitted to a neonatal unit. This has the potential to cause discomfort to the newborn, although additional tests are very unlikely to be invasive. Authors from the pilot study conducted in the UK concluded that "there was little evidence of additional significant harm to the majority of babies who had a screen positive outcome. It is possible however, that some babies underwent unnecessary admission and investigation as a result of testing screen positive, particularly some of those with culture-negative sepsis, these are likely to be in a minority".[16] In settings where echocardiography is not available within a short period, the delay in performing the test for confirmation or exclusion of the CCHDs diagnosis might increase parental anxiety, in addition to increase the workload for health workers performing echocardiography and additional potential admissions until the test is performed. Indeed, like any screening of a potential severe disease, CCHDs screening might raise unnecessary parental anxiety. However, clinical practice and available literature suggests good acceptability to mothers and no increased anxiety among mothers given false-positive results compared to mothers given true-negative results.[12]

However, it was found that the number of false-positive results generated by PO screening was lower than those generated by clinical examination alone, which is worth to consider when balancing benefits and harms of PO screening.[22]

In addition, it is important to note that detection of hypoxemia that is not due to CCHDs allows the identification of many cases of clinically significant conditions that cause hypoxemia such as pneumonia or sepsis, that benefit from early recognition and management.[6,16] As neonates with a clear non-cardiac diagnosis are unlikely to require an echocardiography, the number of false-positive cases lead to a lower number of echocardiography needed. In the UK, health staff were not aware of any increase in the number of echocardiograms during the period of the pilot study introducing PO screening.[16]

Conclusions on harms and limitations of PO

Overall, early diagnosis of CCHD with pulse oximetry is judged to be beneficial and cost-effective, and potential harms associated with false-positive tests are not serious, while missing CCHDs and other serious diseases detected by hypoxaemia in absence of pulse oximetry screening can lead to serious consequences.

Summary of findings

- Current evidence supports consistent accuracy for detection of CCHDs in newborns by pulse oximetry screening in addition to antenatal ultrasonography and clinical examination.
- Overall, early diagnosis of CCHD with pulse oximetry is judged to be beneficial and cost-effective, and potential harms associated with false-positive tests are not serious, while missing CCHDs and other serious diseases detected by hypoxaemia in absence of pulse oximetry screening can lead to serious consequences.
- Timing of oximetry:
  - The timing of pulse oximetry screening had no significant difference on sensitivity, but the false positivity rate was significantly lower among newborns screened after 24 hours of life, when compared with newborns screened within the first 24 hours of life.
  - There is some evidence – and wide acceptance among physicians – that early screening leading to early detection of CCHDs allows timeliness of appropriate medical intervention and therefore reduces the risk of onset with severe or very severe symptoms, with subsequent better outcome.
  - Newborns with false-positive screening results might undergo unnecessary additional tests such as echocardiogram. However, early screening allows detection of hypoxemia due to other clinically severe conditions that benefit from prompt intervention.
  - Overall, benefits of early screening are judged to be greater than the potential negative impact of the increased rate of positive rate by some societies, but this is not the position of other institutions such as the United Kingdom National Screening Committee and the Royal College of Paediatrics and Child Health.
- The site of testing (post-ductal versus pre- and post-ductal) had no significant effect on sensitivity nor specificity for detection of CCHDs.

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Author's contributions

SJ was identified as the researcher in the development of the synthesis of evidence and writing the report. For each selected topic on preventive interventions, SJ defined the key questions,

established and run the literature search, screened the returned manuscripts for eligibility, extracted data and summarized the existing recommendations and supporting evidence. The principal advisors of this project were Dr. Gottfried Huss, MPH General Secretary of ECPCP, Project-Coordinator and Prof. Ralf Weigel, Friede Springer endowed professorship of Global Child Health, Witten/Herdecke University (scientific advice). The author(s) read and approved the final manuscript.

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More Effort Needed to Protect Neonatal Intensive Care Patients from Noise

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Dr Andrew Unger, a neonatologist and neonatology researcher, and Medical Advisor to NEATCap Medical LLC.

Neonatal Intensive Care: Why is noise protection important in the NICU?
Dr Andrew Unger: Basically, for two reasons: sleep and stress.

We want to encourage *sleep* because REM sleep is critical for brain development and non-REM sleep for growth hormone secretion. Noises — particularly loud, transient noises — disrupt sleep.

We want to reduce noise-induced *stress* because it raises neonates' heart and respiratory rates, as well as their steroid levels. This causes a higher metabolic rate — and slower growth. Of course, we also don't want NICU's to be so loud on average that they might damage hearing itself — but nowadays that almost never is the case.

NIC: Are there neonates for whom effective noise protection might be particularly important?
AU: Yes: Infants with Narcotic Abstinence Syndrome, infants receiving potentially ototoxic drugs such as gentamicin, furosemide, or vancomycin, and extremely premature infants who will be exposed to abnormal sounds for long periods of time. Also, infants that are simply having trouble sleeping.

We also want to protect the hearing of infants undergoing transport and/or MR examination. Those are the medical environments where hearing damage from loud noise actually remains a possibility. In addition, a critical task during neonatal transport is maintaining patient stability until definitive care can be rendered at the new location — preferably without the need for sedation or neuromuscular blockade. Noise is a deterrent to this goal.

Similarly, during MRI exams, neonatal patients often experience noise-induced agitation, and may require sedation or even general anesthesia to get through the exam. This limits both the quality and availability of MR imaging.

NIC: Hasn't Single Family Room (SFR) architecture solved the noise problem for hospitalized neonates?

AU: Yes and no. Single family room designs — when available — certainly have greatly reduced the risk of NICU patient hearing loss from excessive noise. In addition, common sense modification of caregivers' behavior and improved monitor design has reduced the background noise level of most NICU's to a safe level, at least with respect to hearing loss.

SFR design has done nothing, however, to address the issue of the transient, very loud and stressful noises typically associated with patient care. In addition, SFR's may be too quiet — some exposure to human voice is essential for normal language acquisition. So SFR's aren't a panacea.

NIC: In your article in the recent Winter Edition of Neonatal Intensive Care, you state that "appropriate and effective hearing protection" should be considered a standard aspect of neonatal care. What about earmuffs and ear plugs? They've been around for decades. Don't they work?
AU: Ear plugs don't work if they aren't used, and caregivers have traditionally been reluctant to jam things that might be hard to remove into tender, tiny ear canals. Earmuffs would work — if they had sufficient sound dampening properties, were correctly sized, sturdy, usable over reasonably long timeframes without replacement, and could be snugly applied over an infants' external ears without causing skin damage.

Unfortunately, currently the most used neonatal earmuffs are single-size and only modestly acoustically effective. In addition, they bond directly via adhesive to the premature infant's skin, resulting in a risk of skin breakdown when removed.

DREAMIES are the first neonatal earmuffs that meet the size, durability, patient safety, and ease-of-use requirements of modern NICU care — and actually are effective at blocking out loud noises. In short, they fit well, stay on, and don't hurt the baby.

NIC: So, what's so special about DREAMIES? How come they work?
AU: First, DREAMIES were designed by a team including professional neonatal clinicians — present company included. Besides a sophisticated, transparent, chiral earmuff design that fits the infant skull well, the major advantages of DREAMIES are twofold: (1) They are available in 4 (soon to be 5) patient sizes appropriate for patients weighing 500 grams to 5 kilograms, and (2) most importantly, they are secured without the use of adhesive by a patented headband that distributes the stabilizing

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Dr Unger is a board-certified neonatologist with expertise in clinical trial processes — particularly Informed Consent — having chaired St Luke's University Health Network's Institutional Review Board from 1998 to 2012. He currently is in active clinical practice in New Jersey. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net

forces around the infant skull in such a manner that it does not cause injury to the skull or the skin.

NIC: What are the advantages of DREAMIES T-M — the product for Transport and MRI?
AU: The noise environments of neonatal transports and MR imaging are different from that in a typical NICU. Sturdier earmuffs are needed for these shorter use cases. Nurses have observed infants transported with DREAMIES T-M have been more content than those without hearing protection, and they actually often sleep through noisy transport — making the job of patient monitoring much easier.

MRI studies that often had to be cut short because of patient movement now are easier to complete with DREAMIES T-M hearing protection. This is particularly useful when trying to obtain diffusion-weighted-imaging studies to detect PVL among premature infants soon to be discharged.

NIC: What do NICU nurses think about DREAMIES?
AU: Not to brag — but in every NICU so far that's used them, the nurses love them. DREAMIES are easy to learn how to put on, and they calm babies down. Nursing documentation is minimal. DREAMIES for the NICU selectively block out high-frequency noises such as those annoying alarms but allow a significant amount of voice volume — especially the lower, soothing voice frequencies to pass through. When parents come to visit, if completely unimpeded vocal interactions with the baby are desired, the earmuffs can be easily removed — and then replaced when it's time for baby to go back to sleep.

NIC: What benefits do we hope to see with effective hearing protection of neonatal patients? What more research is needed?
AU: Faster growth and shorter hospitalization among premature infants and infants with NAS. Calmer neonatal transports, with reduced use of sedation. Better imaging and reduced use of sedation among patients receiving MRI's.

There already have been numerous studies of hearing protection in neonatal patients that have suggested these effects — but all have been subject to criticism because of their small size and single NICU character, as well as possible observer bias.

The first study on the effect of neonatal hearing protection on sleep as monitored by EEG — with blinded analysis — has just been published (Ref) and demonstrates increased sleep with DREAMIES use.

Other blinded, randomized studies of the effect(s) of comprehensive noise control on NICU patients' outcomes coordinated among a group of NICU's serving a varied patient population are urgently needed. Such studies are under discussion.

Similar studies of infant MR imaging quality with and without DREAMIES use should be relatively easy to perform- and these studies are being actively pursued.

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To Pump or Not to Pump? That is the Question for Clinicians and Families

Darlene N. Silver MSN, RN, IBCLC

To Pump or not to Pump? That is the Question for Clinicians & Parents. Challenges related to breastfeeding at the time of delivery and during the first few days or weeks after delivery are a reality. Initiating milk expression for the mother of an infant in the Special Care Nursery (SCN) or Neonatal Intensive Care Unit (NICU) is paramount to meeting breastfeeding goals. Ideally this should be done within an hour of delivery utilizing a pump with technology that can mimic the human infant during breastfeeding, particularly because these mothers are often pump-dependent if their infants are NPO (nothing by mouth), very or extremely preterm at birth (Meier 2012). Healthcare providers and nurses caring for families with an infant or even a mother requiring specialized or intensive care understand the need to support the initiation of milk expression, as their separation means skin-to-skin contact and the initiation of breastfeeding is delayed. In these clinical situations, the reasons for delayed lactogenesis II are clear. However, for infants who do not require resuscitation or those infants who respond quickly to interventions in the delivery room and are able to room-in with their families, the need to initiate expression may not be as obvious. This holds true for the mother with a complicated delivery who responded well to interventions in the delivery room and does not require a higher level of care which would separate her from her newborn. When the dyad is not separated and "rooming-in" the family may not be aware of risk factors which could lead to suboptimal milk supply or milk transfer. This has the potential for long-term repercussions and a family weaning sooner than planned.

Counseling families and providing guidance based on risk factors or actual versus perceived milk insufficiency is essential to normalizing breastfeeding and meeting long-term breastfeeding goals. Clinicians should support direct and exclusive breastfeeding over the first few weeks of life and beyond, adding milk expression and supplementation with expressed human milk based on maternal and neonatal risk factors or when clinically indicated (Kellams, Harrel, Omage, et. al, 2017).

The following are risk factors which may lead to suboptimal milk supply or milk transfer. Although not inclusive, they are frequently seen in clinical practice.

Darlene N. Silver is the Lead Lactation Consultant at the George Washington University Hospital in Washington, DC. She has over 30 years of perinatal nursing experience and 20 as an International Board Certified Lactation Consultant. She is also a consultant for Medela, LLC.

Maternal Risk Factors
Advanced maternal age
Primipara
Diabetes (Gestational, Type 1 & Type 2)
Pre-gravid BMI => 30
History of low milk supply or negative experience with breastfeeding
History of breast surgery or surgery/trauma to the chest wall
Hypovolemia r/t shock (hemorrhagic, septic)
Hypertension (chronic, gestational)
Pre-eclampsia, HELLP syndrome, DIC
Postpartum hemorrhage (particularly those requiring a transfusion or iron transfusion)
Retained placental fragments
Chorioamnionitis
Cesarean birth/operative vaginal birth
Multiples
Painful latch or nipple trauma

Neonatal Risk Factors
Near-term and preterm infants (late, moderate, very, extremely)
Hypoglycemia
Prolonged second stage
Forceps or vacuum assist
Facial bruising
Cephalohematoma
Caput
Hyperbilirubinemia
Meconium stained fluid
Neonatal resuscitation interventions (suctioning, PPV, CPAP)
Ongoing respiratory support
Uncoordinated suck

From the neonatal perspective, the neonate's presentation at birth, ongoing assessments, bilirubin levels, weight loss and output along with their trends over the first 4-5 days of life are important indicators for initiating milk expression. The BiliTool™ at www.bilitool.org is helpful in the management of hyperbilirubinemia and can guide the clinician in assisting the mother with the initiation of milk expression and supplementation, as appropriate (Flaherman & Maisels, 2017). Another evidence-based tool, NEWT (Newborn Weight Tool) at www.newbornweight.org was developed to evaluate neonatal weight and can be accessed by clinicians, as well as parents. The tool can be used to trend the infant's weight in order to guide and modify the infant's feeding plan and recommend milk expression and supplementation if indicated to prevent complications or hospital readmission (Kellams, Harrel, Omage, et. al, 2017).

For mothers and neonates at-risk, particularly those with multiple risk factors ensure a clinician with expertise in

human lactation observes the neonate feeding directly from the breast to provide guidance with optimal positioning and latching techniques or evaluate whether a nipple shield would be beneficial. A clinician with expertise in lactation can also ensure the mother is using the pump safely and effectively, particularly for those mothers who are relying on the pump to initiate and maintain their milk supply. This includes assessing the breast shield (flange) fits the mother correctly, as well as using the pump program, features and settings to optimize the volume expressed while preventing discomfort, pain, engorgement or abrasions.

Initiating milk expression, pumping based solely on the mother's request so she can "…see if anything is coming out" or if she states, "I want to see how much the baby is getting." compounds misconceptions about the physiology of milk production and unnecessary. In fact, it may lead to more challenges. Initiating milk expression when the latch is comfortable, the neonate is demonstrating bursts of nutritive sucking, has an adequate number of feeds per day along with adequate output and normal weight loss may lead to oversupply, engorgement, plugged ducts, mastitis or overactive milk ejection reflex (OMER). Bear in mind, there are mothers who choose to exclusively pump. They do not wish to directly breastfeed. They may have had a negative experience breastfeeding a previous infant or this is their personal preference. Discuss their decision using a nonjudgmental approach, assist them with expression, as soon as possible post-delivery. Encourage the family to see a clinician who specializes in human lactation during their hospital stay when possible and on an outpatient basis, as initiating and maintaining an adequate supply solely through expression is challenging.

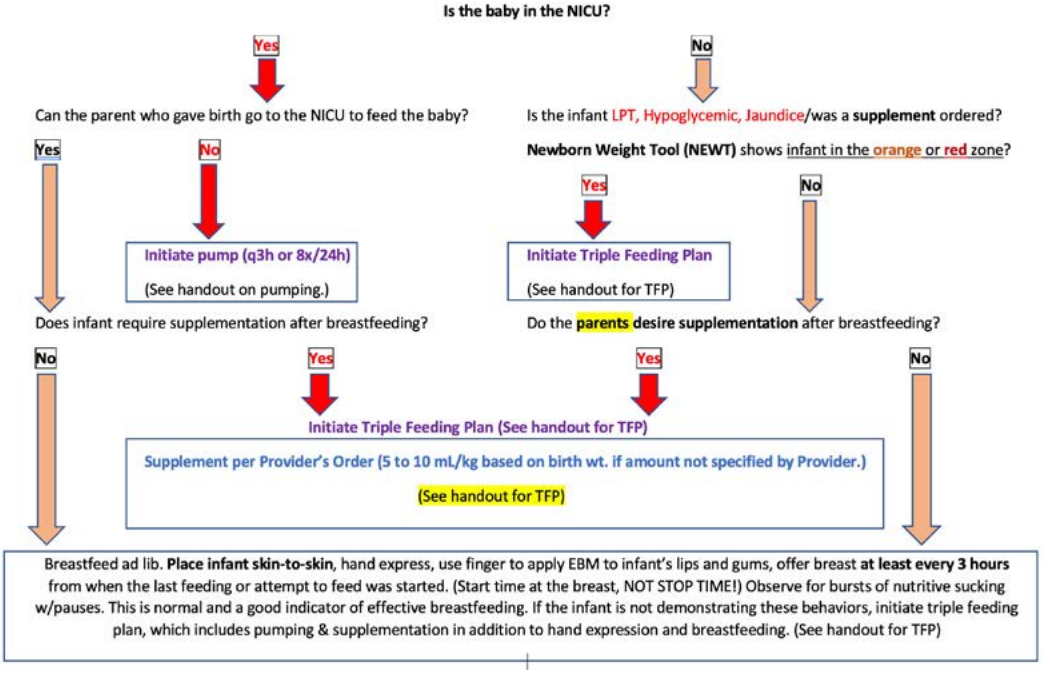
Developing a decision-making tree or tool to assist the healthcare team in determining if it would be advisable for the mother to initiate milk expression can be helpful. Questions to consider in a clinical decision-making tool for breastfeeding families might include:

- Have the mother and infant been separated?
- Is the mother able to go to the SCN or NICU to place the baby skin-to-skin and offer the breast?
- Is the infant NPO?
- Is the mother stable and able to safely breastfeed?
- Has the mother been transferred to another unit for a higher level of care?
- Is the infant having issues related to glucose regulation or hyperbilirubinemia?
- Is the infant's weight loss outside of normal limits?
- Is the infant's urine output or number of stools/24h inadequate?

Developing a tool for frontline clinicians, particularly registered nurses in labor & delivery or on the mother-baby/postpartum unit can help improve initiation of milk expression when indicated for at-risk families, thereby improving breastfeeding outcomes and long-term breastfeeding rates. This is critical as only 25.6 percent of infants in the United States are exclusively breastfed at 6 months of age (CDC, 2020). The support provided to families in the first few days of life during the family's hospital stay is crucial, particularly when we consider the challenges accessing professionals with expertise in human lactation as we navigate an unprecedented pandemic and taxed healthcare delivery system (WHO, 2020).

The following is a sample of a decision tree being developed and piloted to support clinicians, particularly those assigned to the mother-baby unit. Although still in development, it can certainly spark discussion and ideas for a tool that meets the needs of healthcare teams in other facilities caring for mothers and neonates at-risk for suboptimal lactogenesis, milk supply and milk transfer.

Supporting Breastfeeding Families when Pumping & Supplementation is Indicated



Ultimately, initiating appropriate interventions to help meet breastfeeding goals requires a multidisciplinary collaborative approach supporting the mother's plans and goals related to feeding her newborn. Helping parents make informed decisions about when and how to initiate milk expression is essential for all families, but particularly for those with multiple maternal and neonatal risk factors. For families whose feeding plans include expression and supplementation at the time of discharge, ensuring they have tools and supplies needed prior to discharge and secured outpatient lactation follow-up is essential for meeting goals.

Developing a decision-making tree can be helpful for initiating expression in a timely and optimal manner. Ongoing assessments of the mother and neonate by a clinician with expertise in human lactation, as well as discharge planning are an integral part of

the plan of care. This is because pumping and supplementation routines can be exhausting for the parents and family, particularly the mother. Outpatient support will assist the family in transitioning to exclusive breastfeeding or establishing a maintenance pumping routine that is sustainable. Collaborating with case management, social work and community-based lactation centers is an integral part of meeting breastfeeding goals for families at risk and should be incorporated into the discharge plan. An evidence-based collaborative approach, keeping maternal and neonatal risk factors at the forefront along with ongoing maternal and neonatal assessments improves the initiation human milk feedings and a family's ability to meet with breastfeeding goals on their breastfeeding journey.

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Premature Babies' Survival Rate is Climbing, Study Says

Ruthann Richter

A comprehensive new study of premature babies in the United States is helping to redefine what it means for a premature infant to survive.

The study looked at 10,877 babies born between 2013 and 2018 and found a significant improvement in survival of those born between 22 and 28 weeks, compared to the past. Some 78% lived, compared to 76% of those born between 2008 and 2012. Two percent translates into many hundreds of infants saved each year.

This study showed that even the babies delivered at 22 weeks — 18 weeks early — had a chance of living. With active treatment, about 28% of them survived; among those born at 23 weeks, 55% survived.

"When I was in residency in the mid-1980s, babies born at 500 grams [about 1.1 pounds] and 25 weeks didn't survive; it just didn't happen. Now we see the borderline of viability dropping to 22 weeks," said Krisa Van Meurs, MD, neonatologist at Stanford Children's Health and a Stanford Medicine emerita professor of pediatrics and study co-author. "With all of these new treatment strategies we've developed, we've seen an amazing impact."

This analysis shows infants even at the lowest gestational ages — 22 and 23 weeks — might live if they are actively resuscitated, said Susan Hintz, MD, medical director of the Fetal and Pregnancy Health program at Stanford Children's Health, a Stanford Medicine professor of pediatrics and a co-author on the paper. "There has been a shift toward considering a more active initial treatment in prenatal discussions with families over the past several years in light of increasing data to support this approach," she said.

This study appeared in the *Journal of the American Medical Association*. The work is a product of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network and included scientists at 18 institutions across the United States. The lead author is Edward Bell, MD, of the University of Iowa, and the senior author is Abhik Das, PhD, of RTI International, in Rockville, Maryland. Hintz is the lead principal investigator for the Neonatal Research Network's follow-up studies, which track how babies fare after going home from the neonatal intensive care unit.

Ruthann Richter has been writing about medical issues, including HIV/AIDS, since the early 1980's. She holds a Master's degree in journalism from Stanford University and has received awards for her reporting from the American Cancer Society, the Association of American Medical Colleges, the Council for Advancement and Support of Education and the National Alliance for the Mentally Ill.

Tracking babies

The researchers studied the neurosensory, developmental and functional progress of babies born at 22-26 weeks of gestation, conducting evaluations when the children were 2 years old. Overall, about half had mild or no signs of neurodevelopmental problems, while 29% had moderate disabilities. About 21% of the children had severe impairments, including approximately 1.5% with blindness and 2.5% with severe hearing loss. Some 15% of the children used a mobility aid such as an orthotic, brace or walker, while 8% had moderate to severe cerebral palsy. About half had been re-hospitalized after being discharged from the NICU.

"It is encouraging that half of the children had no or minimal neurodevelopmental impairments at 2 years of age. But moderate to severe neurodevelopmental challenges are not uncommon in this group, particularly for those born at the lowest gestational ages," said Hintz. "We also explored other important outcomes, like feeding challenges and equipment and medication needs, which inform complex care preparations and counseling."

Improving outcomes

In the past 20 to 30 years, researchers have discovered myriad approaches to improve the survival and care of premature infants, Van Meurs said. That includes using surfactant, a mix of protein and fat that aids lung development, as well as steroids in pregnant mothers, which helps the baby's lungs and other organs mature and minimizes the risk of breathing problems, bleeding in the brain and other complications, she said.

Clinicians also have enhanced the environment in which preterm infants are treated, creating a womb-like atmosphere with low lighting, and minimal noise and disruption. They are also using CPAP devices, which help keep the airways open and are a gentler way of supporting breathing, instead of using ventilators, which can damage the lungs, Van Meurs said.

Parents are also being included in the treatment process — it's been shown that regular parental touch and especially skin-to-skin "kangaroo care" can increase weight gain, decrease the

chance of sepsis — a severe blood infection — and improve survival and neurodevelopment, she said.

Van Meurs said Stanford Medicine uses innovative neuromonitoring devices to monitor brain activity and oxygen levels in the brains of fragile newborns to minimize brain injury in the neonatal intensive care unit. "That's the focus for the next decade — how can we protect the brain and improve outcomes for these children," she said.

According to Hintz, investigators in the National Institute for Child Health and Human Development Neonatal Research Network, a group of 18 academic medical centers funded by the institute, are continuing to follow some of the children born extremely preterm through 5-7 years of age. "At an early school age, we can better understand abilities and challenges over a range of more detailed neurologic and cognitive skills, behavioral and social interactions and functional outcomes," said Hintz, who is the lead investigator for the research network's follow-up activities.

Continuing care at home

With the increasing probability of survival for extraordinarily preterm infants, Hintz said, more emphasis needs to be placed on life beyond the hospital.

"We need to shift our focus from the NICU hospitalization to far beyond that period, investing in parents and the family, launching interventions and support strategies to improve outcomes that are important to families," Hintz said. "We have made enormous strides and are doing amazing things for children in the NICU. Now it's time for us to take a truly life-course view — listening to families, integrating the concerns and outcomes important to them in research and quality improvement efforts. This is how we will help families and children to live their best lives."

Aerodigestive Changes and Considerations in the Neonate: a Three-Part Series

Part One: Swallowing and Feeding Following Extubation in the Neonatal Intensive Care Unit (NICU)

Catherine S Shaker, MS/CCC-SLP, BCS-S

This article is the first in a three-part series addressing potential aerodigestive changes and considerations in the preterm and sick-term infants in the neonatal intensive care unit (NICU). During this series, the articles will address potential impacts on feeding and swallowing as related to intubation and tracheostomy. The prevalence of aerodigestive challenges leading to feeding and swallowing difficulties is high for sick-term and preterm infants in the NICU.[1,2] Establishing full, safe oral feeding in the setting of complex co-morbidities requires a collaborative infant-guided approach.[3] Problem-solving critical decisions about developmental expectations and cautious opportunities to feed are essential to optimizing feeding outcomes after the NICU.[4] Some of the more common feeding-related challenges following intubation in the NICU are discussed below.

What are your current practices regarding oral feeding for NICU infants who have been recently extubated?

I am part of the team in a large level IV NICU which serves sick newborns and the sickest and the most fragile preterms, some born at 22 weeks gestational age. Intubation and ventilation are avoided, when possible, with a goal of stabilization on non-invasive positive pressure ventilation (NIPPV) or continuous positive airway pressure (CPAP) in the delivery room.

NICU infants, when extubated, often require levels of respiratory support that continue to delay oral feeding. Once an infant is stable on NIPPV, the neonatal therapist can support feeding readiness for infants with complex co-morbidities, including prolonged intubation and/or sequelae, especially respiratory; and/or neuro; gastrointestinal (GI); airway; cardiac; and/or neuromotor processes.[5]

Unfortunately, well-intentioned oral feedings for which the infant is not ready may wire the brain away from eating, lead to later feeding aversions, and adversely affect the already fragile infant-parent relationship.[6] The literature on feeding outcomes in former preterms includes a high percentage of former preemies with enduring feeding problems, far beyond their NICU stay.[3] Care must be taken to match readiness with opportunities to progress to oral feeding.

Even sick newborns who require intubation and ventilation are fragile, once extubated, and may have sequelae that adversely affect oral feeding. Fragile preterms, had they not been born early, would have experienced motor learning and oral-motor learning in utero. Their oral-motor patterns would have evolved in the context of the containment provided by the uterus, with their hands on the face and in the mouth while alternating with touching the placenta. During all infant-guided feeding readiness experiences, careful attention and watchful vigilance are required for signs of physiologic stability or instability, especially the impact on work of breathing and respiratory rate.[1] Progression from sucking on their own hands to pacifier sucking, offered via rooting response with co-regulated pacing, is followed by tiny droplets of expressed breastmilk on a pacifier offered for purposeful swallows — building non-nutritive suck-swallow-breathe synchrony on the infant's own timeline of skill progression.

In the NICU, every experience matters, especially every feeding experience. Well-planned therapeutic experiences will best support underpinnings for eventual opportunities for coordinated feeding and airway protection.

How safe is feeding on HFNC (High Flow Nasal Cannulae) or CPAP (Continuous Positive Airway Pressure)? There is pressure to feed infants and get them home. How do we minimize risk and navigate dialogue with physicians?

Unfortunately, often the conclusion regarding the "safety" and the "tolerance" of NICU infants feeding on CPAP is determined by volume and perhaps lack of overt or symptomatic decompensation. Recent studies were done on the effect of CPAP under videofluoroscopy.[7,8] In one study, their preliminary findings regarding aspiration were so worrisome that the neonatologists stopped the research project. The study determined that "oral feeding while on CPAP significantly increases the risk of laryngeal penetration and tracheal aspiration events," and recommended caution when initiating oral feedings on CPAP. Unfortunately, the conclusions did not focus on changes in swallowing physiology under CPAP, which would have been instructive. It is not only aspiration

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that is worrisome; altered swallowing physiology increases risk for airway invasion. It is not uncommon for neonates to evidence changes in swallowing physiology due to respiratory co-morbidities, even when stable on less respiratory support or indeed on unassisted room air.

Many of our former preterms do indeed learn to feed orally when respiratory co-morbidities better permit, such as once weaned from HFNC, and, in my experience, do so more safely with much less physiologic stress.

NICU technology has advanced such that infants as early as 22 weeks gestation are surviving, and many infants born extremely premature may require extended periods of CPAP and HFNC. Those infants with the greatest respiratory co-morbidities, often those born ≤ 28 weeks gestation and BW ≤ 1000 grams,[5] are most likely to require CPAP and/or HFNC at those post-menstrual ages when oral feeding is often attempted. Sick newborns may also present similar issues, secondary to their co-morbidities.

If a neonate has such respiratory needs that CPAP or HFNC is required, one must ask if oral feeding is really a priority at that time. The neonate's ability to safely reconfigure the pharynx from a respiratory tract and back to an alimentary tract with precise timing and coordination surrounding each swallow is already fragile. Under these conditions, it is worrisome. When we look objectively in radiology during an instrumental assessment of swallowing physiology, our data suggest that even neonates with respiratory co-morbidities who are stable on unassisted room air often have altered or impaired swallowing physiology. The bolus misdirection and resulting aspiration we often observe is, unfortunately, typically silent.

A neonate with increased work of breathing and "air hunger" may have the need for an "urgent breath." This may then predispose the infant to difficulty maintaining glottic closure throughout the duration of the swallow. This uncoupling of swallowing and breathing may lead to airway invasion.[6]

We cannot conclude that feeding under these conditions is "safe," without objective data on the impact of CPAP or HFNC on an infant's swallowing physiology. If your NICU's protocol includes feeding infants on CPAP or HFNC, safety may be optimized by one to two very brief, cautious oral feeding experiences with the neonatal therapist for interval motor learning. Infant-guided interventions (swaddled elongated side-lying, slow flow nipple, strict co-regulated pacing, and resting) should be used, with watchful vigilance.[3] Then, this would be followed by an instrumental assessment of swallowing physiology in radiology to objectify the impact of HFNC or CPAP on airway protection and swallowing physiology.

Even if there is no witnessed aspiration during a dynamic swallow study, the infant may aspirate during a true feeding; the swallow study is a moment in time.[9] Our focus during a swallow study needs to be on physiology because altered physiology and its etiologies may create conditions during a true feeding under which bolus misdirection may or does occur. These "conditions" may include intermittent changes in position, sucking rate and length, variations in timeliness and depth of breathing, and caregiver's feeding approach. Analysis of radiologic data would occur in the setting of that infant's unique history and co-morbidities. From there, we would dialogue with the team to support safety and neuroprotection.[1]

What is common practice in your unit to support the oral and pre-feeding skills for the infants with delayed introduction to oral feeding?

I like to conceptualize the feeding-related services neonatal therapists provide in the NICU as "feeding readiness" and "supporting safe and functional oral feeding" to help neonatal nurses and neonatologists understand how we are uniquely prepared to support both preterm and sick term infants in the NICU. We begin early to foreshadow for parents the swallowing, breathing, and postural skills needed, and help families through guided participation support those components in simple ways during interactions with their infant.[6,10]

If they were not born too soon, preterm infants would be in utero integrating their structurally intact aerodigestive system as early as 17 weeks of life, swallowing several ounces of amniotic fluid per day. Intrauterine motor learning and oral-motor learning provide the underpinnings that support oral feeding in the delivery room for term infants. That means full-term newborns (40 weeks gestation) have had 23 weeks of intrauterine motor learning prior to "using" those skills at birth. For our preterm infants, every week early is an additional seven days of intrauterine learning lost. Even at term-equivalent, the preterm infant remains at a disadvantage.

In the NICU, we carefully structure experiences outside of the uterus that most closely align with the ideal intrauterine sensory-motor environment, create a positive oral-sensory environment, promote the oral-sensory-motor components that underpin future oral feeding, and provide cautious infant-guided experiences that support therapeutic swallowing experiences.[3] Sick term and post-term newborns also may have co-morbidities that delay onset of oral feeding and create the need for therapeutic support.

Postural control and alignment, swaddled side-lying, elongation of the trunk for optimal tidal volume, facilitated capital flexion to promote the motor learning for hands to face and mouth, while maintaining physiologic stability, is the foundation. Once the infant is tolerating a dry pacifier with physiologic stability utilizing co-regulated pacing, therapeutic pacifier dips can provide opportunities for creating the motor maps for swallowing needed for future oral feeding.[1]

A tiny droplet of mother's milk or formula is placed on the tip of the pacifier and then offered via the infant's rooting response. We rest the infant to rebuild reserves and offer co-regulated pacing

to assure that respiratory stability is fostered from moment to moment via a stable burst-pause pattern. Based on the infant's responses, we progress to oral feeding with very small amounts via a slow flow nipple. Careful titration of bolus size, support for the swallow-breathe interface, and physiologic stability all become essential components of our intervention that support infant-guided learning as co-morbidities permit. The infant's physiologic and behavioral communication should always guide us.[11]

Summary

Addressing some of the more prevalent challenges faced in the NICU as it pertains to feeding considerations following intubation, this discussion provides an overview of protocol and therapeutic interventions. With the prevalence of aerodigestive challenges leading to feeding and swallowing difficulties in sick term and preterm infants in the neonatal intensive care unit (NICU), this discussion challenges the clinician to use a problem-solving, critical thinking approach with an emphasis on individualizing the treatment plan with neonates. Continue to follow this series as more questions related to feeding and swallowing considerations following tracheostomy will be addressed in Part Two in the next NeoNatal INTENSIVE CARE issue.

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HeRO: AI with Evidence

Will King

For the past decade, HeRO has been proving that AI is ready to impact care in the NICU. The latest published peer-reviewed journal reports demonstrate that HeRO monitoring during the NICU stay reduced both death[1] and death-or-neurodevelopmental impairment at 18-22 months.[2]

Here, we will review the physiological basis for HeRO, how the AI was developed, and how it brings about such dramatic improvements in care and cost.

Infection, Inflammation, and Cytokines

Early in infection, cytokines are released. These chemicals mediate the inflammatory response, evoking responses throughout the body. Bone marrow produces more white blood cells, the body becomes febrile and muscles feel achy.

The cytokines also change the way the heart responds to the autonomic nervous system.[3,4] In a healthy neonate, the heart rate is always fluctuating as the heart's pacemaker, the SA node, responds to conflicting inputs it receives from the sympathetic (fight-or-flight) and parasympathetic (rest-and-digest) branches of the autonomic nervous system.

In the presence of cytokines, the SA node changes the way it reacts to the autonomic nervous system, as seen in Figure 1. The heart rate tends to become more consistent, like a flat line. When it does change, it's a deceleration and then return to baseline, but rarely are there any accelerations.

Heart Rate Characteristics (HRC)

We observed that these abnormal patterns of reduced baseline variability and transient decelerations were occurring in the days and hours *prior to* infection, and we developed specific statistical measures that capture and quantify the degree to which these abnormal patterns are present.[5,6] We called these measures heart rate characteristics.

Will King studied signal processing and statistical pattern recognition, and now has 25 years of experience in technology transfer with the last 20 concentrating on predictive physiological monitoring for neonates. He has personally collaborated with academic researchers, developed and coded real-time algorithms to predict deterioration in neonates based on physiological monitoring data, managed the database of the largest randomized controlled trial of a medical device among premature infants, raised millions from investors, obtained FDA and other regulatory approvals, developed an FDA compliant quality system, and sold devices to customers throughout the world.

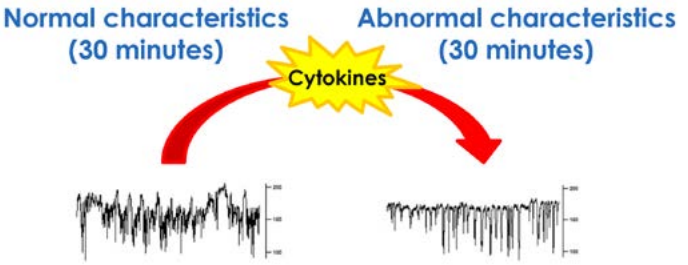

Figure 1. Normal neonatal heart rate variability from a healthy patient on the left. On the right, the same patient's heart rate immediately prior to diagnosis of sepsis.

Predictive Analytics

We then developed an artificial intelligence model to predict impending infection based on the degree to which abnormal HRC were present. The model is called the Heart Rate Characteristics index (HRCi), or HeRO Score. In a supervised learning environment, we collected a training set of heart rate and clinical data from hundreds of patients, and labeled all heart rate data in the 24 hours leading up to a positive blood culture as *sick*, and all other time periods as *well*. We excluded from the training dataset the 10-day period *after* a positive blood culture (Figure 2). We then trained a model that used the HRC data to predict whether or not the patient was *sick* or *well*.

Hence, the HeRO Score is an AI prediction, based on the degree to which abnormal heart rate characteristics are present in a

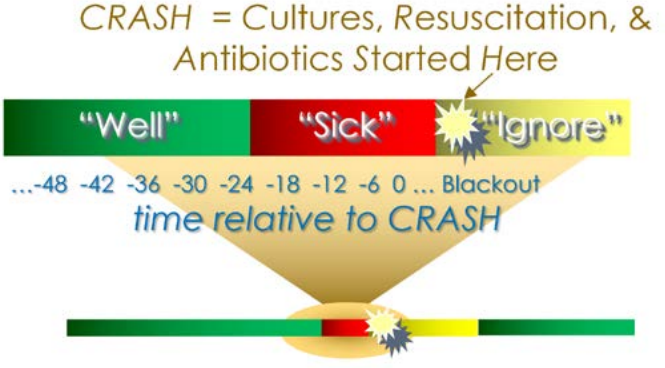

Figure 2. The HeRO AI algorithm was trained by collecting heart rate data from NICU patients. HR data in the 24-hours prior to sepsis was labelled "Sick". Data for 10 days after the culture was removed from the training set. Remaining data was labeled "Well".

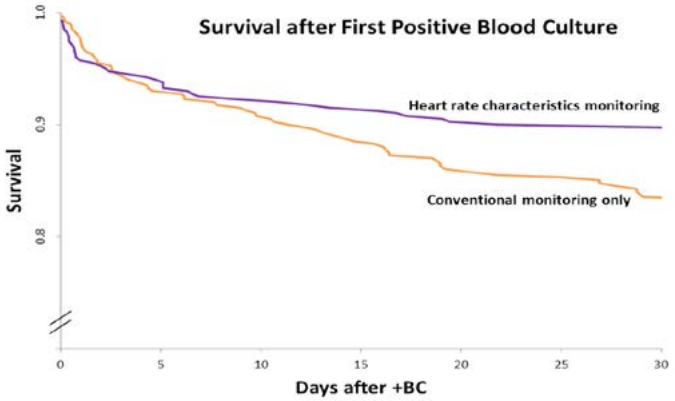

Figure 3. Survival curve in the days after a positive blood culture by study arm. HeRO-monitored patients experienced 40% reduction in mortality.

patient's heart rate, that the patient will have a positive blood culture within the next 24 hours.[5]

Putting it to the Test: the Randomized Controlled Trial

It is all well and good to be able to predict an event such as neonatal sepsis, but does that mean that the outcome can be changed? While it seemed plausible—it has been well established that delays in treatment lead to poor outcomes, so it would stand to reason that an improvement in the timing of treatment might lead to a better outcome—there were legitimate concerns that a prediction of decline might lead to more testing and more antibiotics *without* any improvement to patient outcomes.

In order to answer these questions, we conducted the largest ever randomized controlled trial among premature babies, where 3,003 very low birthweight infants at eight study centers were randomized to receive either standard of care monitoring, or standard of care monitoring *plus HeRO*. It was a pragmatic study design, meaning that there were no mandatory interventions based on the HeRO Score. Instead, the HeRO Scores were displayed to the clinicians for half the patients, and then outcomes were tracked.

Among all patients in the RCT, those randomized to HeRO display experienced a 22% reduction in all-cause mortality (Number Needed to Treat to save one life: 48). There was no significant increase in testing or antibiotic usage.[7]

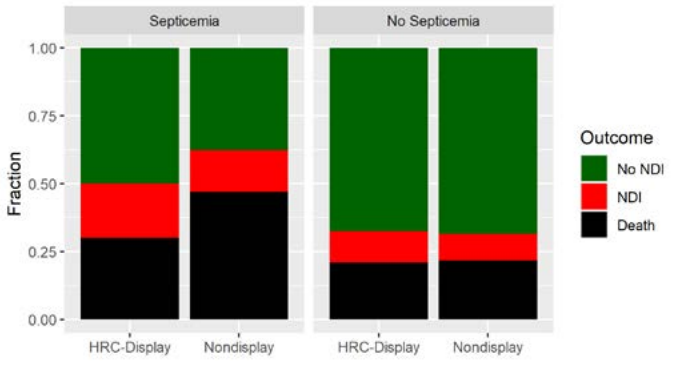

Figure 4. Differences in neurodevelopmental outcomes by study arm and sepsis status. Among patients that did not experience sepsis, HeRO display did not alter outcomes. However, among patients that experienced sepsis, outcomes were statistically significantly improved with HeRO-display.

Among patients that experienced sepsis during their NICU stay, there was a 40% reduction in mortality (NNT: 16, Figure 3).[8]

A follow-up study was conducted at three of the study centers where Bayley assessments were routinely conducted among Extremely Low Birthweight (ELBW) patients. In this subgroup, those randomized to HeRO display maintained the improved survival to their follow-up at 18-22 months.[1] And among those patients in the follow-up study that experienced sepsis during their NICU stay, the outcomes of both death and death-or-neurodevelopmental impairment were improved at 18-22 months for patients that had been randomized to HeRO display (Figure 4).[2]

Method of Action: Early Warning

While clinicians were only able to see and act upon HeRO Scores for half the patients in the RCT, HeRO Scores were generated but not displayed for the other half. From this, we can see that HeRO Scores were significantly higher in patients randomized to non-display *for a full week* prior to the overt clinical deterioration that prompted the blood culture.[8]

Think of it this way: if the HeRO Score is an alarm bell signaling deterioration, nobody could hear the alarm when patients were randomized to non-display.

And even more striking, spikes in the HeRO Score were more likely to be shortly followed by treatment in the HeRO-display group than the non-display group.[9] In other words, clinicians reacted to a deteriorating patient *earlier* when the HeRO Score was available, leading to earlier diagnosis, earlier treatment, and better survival.

HeRO Monitoring at the Bedside

The most basic implementation of HeRO is as a standalone, bedside monitor. HeRO *solo* is the one bed version for single-bed rooms, while HeRO *duet* is a two-bed version, more suitable to open bays (Figure 5). In both cases, the HeRO device consists of a 10-inch tablet screen that can be mounted on a roll-stand, desktop, or rail channel. It is cabled to the existing multi-parameter monitor to acquire heart rate data. There is no networking connection, so installation consists of plugging it in and turning it on.

For NICUs desiring central monitoring and automated upload of HeRO Scores into the EMR, we offer HeRO Symphony. In this case, a server is installed in the hospital data center that collects heart rate data via the monitoring network and calculates the HeRO Scores. Central monitors showing HeRO Scores are installed throughout the NICU (Figure 6), and any workstation in the hospital can access the HeRO user interface. Finally, HeRO Scores are automatically sent from the HeRO Symphony server to the EMR via HL7.

For customers that utilize Philips MX700 through MX850 multiparameter monitors, these monitors can be ordered or upgraded with an internal PC (iPC) option. In such cases, HeRO ES

Figure 5. HeRO duet.

Figure 6. HeRO Symphony central monitor.

can be installed on the iPC, and screens on the MPM configured to show the HeRO numeric and trend right alongside the vital signs. And for NICUs that desire both a bedside HeRO display within the physiological monitor along with central monitoring and automated upload of HeRO Scores into the EMR, HeRO ES can be combined with HeRO Symphony.

Clinical Protocol

In keeping with the spirit of the pragmatic RCT design, we do not tell new customers how they must implement HeRO monitoring in their unit, although we are certainly willing to share how other customers utilize HeRO, and work with new customers to develop an appropriate protocol. The most typical usage scenario is for the nursing staff to document and review HeRO Scores at the same frequency that they are documenting other vitals on a particular infant. The first time the HeRO Score rises above 2, or if it rises more than 2 points in a 24-hour period, then the nurse will advise the neonatologist, and a physical exam is performed, lab tests are ordered, and the clinical staff and parents have a discussion about how the patient is doing. If any of these are abnormal, then is treatment initiated.[10]

The Future of Predictive Analytics

While the AI algorithm underpinning HeRO was trained to predict sepsis specifically, we have found that elevated HeRO Scores are associated with other inflammatory events, including meningitis, urinary tract infections,[11] and other focal infections, necrotizing enterocolitis,[12,13] respiratory decompensation,[9,14] neuro trauma,[15,16,17] and neurodevelopmental impairment (Figure 7).[18,19]

We have recently developed models to predict extubation readiness and extubation success, available on our website at www.heroscore.com/extubation. Although the models perform better with HeRO, even without HeRO, clinicians can use them to understand patients' chances of a successful extubation.[20]

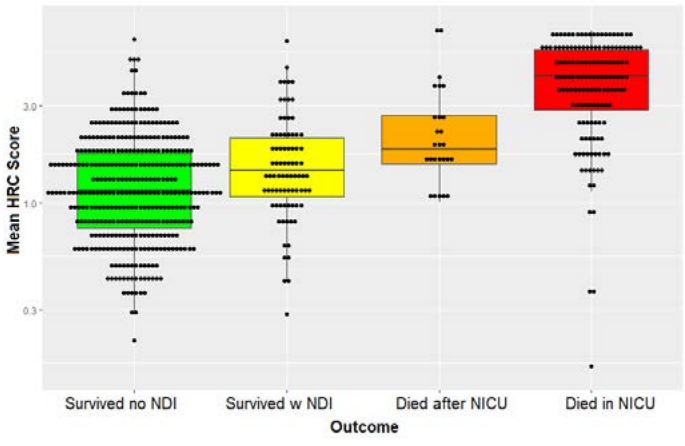

Figure 7. Boxplot of mean HeRO Score during the entire stay by outcome. Each patient is represented by one point.

We have also developed models to predict subsequent death or neurodevelopmental impairment (Figure 8),[18] and are working to make them available to clinicians as well.

We see the future of predictive analytics at the neonatal bedside to include these predictive models as well as new models for growth and nutrition, the hemodynamic significance of the PDA, adequate oxygenation, etc., and are actively working to bring these new models to the bedside.

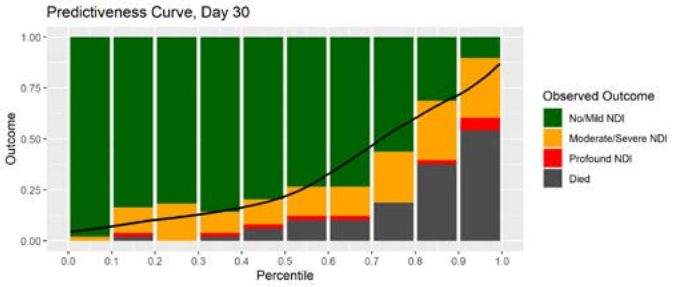

Figure 8. Predictiveness curve of Day-30 model to predict neurodevelopmental outcome. The smooth black line is the model's predicted risk of death-or-moderate/severe/profound NDI.

Conclusion

HeRO is an AI algorithm that has been proven to benefit patients and hospitals with the highest level of evidence available: an RCT. Not only will HeRO improve your ability to provide care today, it is an investment in the future of bedside predictive analytics.

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trial, 74% (3,646) had HIV. In total, 383 women had 488 singleton deliveries, including 218 women with HIV (272 deliveries) and 165 without HIV (216 deliveries). Sociodemographics in both cohorts were well matched. For most participants, the mean age was 40–41 years at delivery, most were non-Hispanic Black persons, and the mean pregnancy body mass index was ≥29 kg/m^2. Of the women with HIV, 33% had chronic hypertension; of those without HIV, 42.1% had chronic hypertension; 4.7% and 5.0%, respectively, had pregestational diabetes.

Hydrocortisone Fails to Prevent Bronchopulmonary Dysplasia in Preemies

Systemic hydrocortisone (HC) does not reduce the risk for bronchopulmonary dysplasia (BPD) or for a composite endpoint of BPD or death in very preterm infants receiving mechanical ventilation, a randomized trial shows. However, a planned secondary analysis suggests that HC may reduce the risk for death when analyzed as an endpoint on its own. "Our study shows that HC does not reduce BPD. Our finding that it does reduce death is somewhat surprising, although trials on prophylactic HC use indicated that this might be a benefit from HC," senior author Anton H. van Kaam, MD, PhD, from the department of neonatology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, the Netherlands, said. Wes Onland, MD, PhD, from the department of neonatology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, the Netherlands, and colleagues published their findings online January 29 in *JAMA* for the Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants (SToP-BPD) Study Group. Dexamethasone is effective at reducing the risk for death or BPD in this patient population. "However, this benefit may be outweighed by an increased risk of neurodevelopmental impairment. As a result, clinicians started using dexamethasone less frequently, in lower doses, and at later postnatal ages. Furthermore, international guidelines recommended investigating whether hydrocortisone would be an effective and safe alternative to dexamethasone," the authors write. The researchers conducted a double-blind, placebo-controlled randomized trial to determine whether systemic hydrocortisone treatment started between 7 and 14 days after birth decreased the incidence of death or BPD at 36 weeks' postmenstrual age in ventilator-dependent very preterm infants. The study included 372 infants (mean gestational age, 26 weeks; 55% male) in 19 neonatal intensive care units with a gestational age of less than 30 weeks and/or birth weight below 1250 g. The infants were randomly assigned to receive systemic hydrocortisone (cumulative dose, 72.5mg/kg; n = 182) or placebo (n = 190) for 22 days. One infant treated with hydrocortisone was withdrawn from the study by the parents.

Neurodevelopmental Disorders Prevalent With Extremely Preterm Birth

A large registry-based cohort study in Sweden has revealed that 75% of children born before 24 weeks of gestation had neurodevelopmental disorders, including intellectual disabilities and autism, and required habilitative services. In addition, somatic disorders such as asthma and failure to thrive/short stature were diagnosed in 88% of the cohort. The findings, published in Acta Paediatrica, emphasize the need for further study of this population, especially as survival rates continue to increase. "The primary aim of this large, retrospective, national study was to report clinical diagnoses registered after children born before 24 weeks were discharged from neonatal care," explained lead author Eva Morsing, MD, PhD, of Lund (Sweden) University, and colleagues. Data on diagnoses of neurodevelopmental disorders and selected somatic diagnoses were obtained from national Swedish registries. Study participants' individual medical files were also examined by the researchers. The study cohort comprised 383 infants born at a median of 23.3 weeks of gestation (range, 21.9-23.9 weeks). The median birthweight of participants was 565 grams (range, 340-874 grams), with a median birthweight standard deviation (SD) of –0.40 (range, –3.63–3.17). The majority (75%) of infants had a neurodevelopmental disorder, including speech disorders (52%), intellectual disabilities (40%), attention-deficit/hyperactivity disorder (30%), autism spectrum disorder (24%), visual impairment (22%), cerebral palsy (17%), epilepsy (10%), and hearing impairment (5%). With respect to gender, a greater number of boys than girls born at 23 weeks had intellectual disabilities (45% vs. 27%; $P < .01$) and visual impairment (25% vs. 14%; $P < .01$). Moreover, 55% of the participants were referred for habilitative services. With respect to somatic diagnoses, failure to thrive/short stature was diagnosed in 39% of the cohort, and it occurred more often in those born at 21 and 22 weeks than in those born at 23 weeks (49% vs. 36%; $P < .05$). In addition, asthma and childhood bronchopulmonary dysplasia, pulmonary hypertension, and vocal cord paresis were diagnosed in 63%, 12%, and 13% of participants, respectively.

Neonatal Hypoglycemia Doesn't Affect Childhood Academics

Children at risk of neonatal hypoglycemia who were screened and treated if needed showed no difference in educational achievement from controls at age 9-10 years, based on data from 480 children. Previous studies have shown an increased risk of poor executive and visual-motor function in children with neonatal hypoglycemia, but the effect on later childhood academic performance remains unclear, wrote Rajesh Shah, PhD, of the University of Auckland, New Zealand, and colleagues. In a prospective cohort study published in JAMA, the researchers enrolled moderate to late preterm and term infants born at increased risk for hypoglycemia; those with episodes of hypoglycemia were treated to maintain a blood glucose concentration of at least 47 mg/dL. The study population was enrolled between 2006 and 2010 at a regional perinatal center in New Zealand, and their educational achievement was assessed 9-10 years later. The primary outcome of low educational achievement was defined as performing below the normal curriculum level in standardized tests of reading comprehension or math. The researchers also identified 47 secondary outcomes related to executive function, visual-motor function, psychosocial adaptation, and general health. Rates of low educational achievement were not significantly different for children with and without neonatal hypoglycemia (47% vs. 48%, adjusted risk ratio 0.95). No significant differences appeared between the two groups for any secondary outcomes, including reading comprehension, math, behavior manifestations of executive function, fine motor function, autism traits, and overall well-being, the researchers noted. However, children with neonatal hypoglycemia were significantly less likely to be rated as below or well below reading curriculum level by teachers compared to those without neonatal hypoglycemia (24% vs. 31%). The researchers cited a previous study of the same patient cohort at age 4.5 years, which suggested an association between adverse neurodevelopmental outcomes and infant hypoglycemia. However, the reason this association did not persist at age 9-10 years remains unclear, the researchers wrote in their discussion.

"Early disturbances in brain development may have diminishing effects over time due to neuroplasticity, that is, reorganization of neural networks, or delayed maturation with mid-childhood catch-up in neurocognitive function," they said.

Neotech Turns 35

Neotech Products LLC is excited to celebrate its 35th year developing and manufacturing innovative medical devices. Neotech Products is an essential brand in hospitals worldwide. Products include the RAM Cannula, Little Sucker suction tips, NeoShades Phototherapy Eye Shields, NeoBar ET Tube Holder, and more. Neotech made its mark as a neonatal company, but its reach extends beyond the NICU into pediatrics, children's oncology, home healthcare, and more. They even offer products for adults, like EZCare trach ties and NeoSucker suction tips. "I think I am most proud of the impact we've made as a company over the last 35 years," said Craig McCrary, Neotech President. "Impact to employees, impact to clinicians, and impact to patients and parents. "We've done things that have made a positive difference in many lives around the globe." McCrary, who has been with Neotech for over 30 years, credits company success to: Simple, unique products; clinician-driven products that fill a need, and products made in the USA. "Made in the US has truly set us apart," McCrary said. "Especially this past year when so many companies have experienced supply chain issues." Neotech is a proud Certified B Corporation that continues to expand its international presence by developing simple solutions to medical needs. To learn more about Neotech and its products, please visit neotechproducts.com.

Study Shows Benefits of Human Milk-based Fortifiers

An independent, head-to-head study from Neuburg, Germany, shows extremely low birth weight preterm infants fed Prolacta Bioscience 100% human milk-based fortifiers (HMBF) as part of an Exclusive Human Milk Diet (EHMD) had reduced incidences of life-threatening comorbidities and experienced shorter stays in the neonatal intensive care unit (NICU), compared to those fed cow/bovine milk-based fortifiers (CMBF), offsetting the higher therapeutic costs of HMBF. The study, "Nutrition of Infants with Very Low Birth Weight Using Human and Bovine Based Milk Fortifier: Benefits and Costs," was published in Neonatal and Pediatric Medicine and is the first head-to-head clinical trial of nutritional fortifiers conducted within Germany's national health care system. The findings corroborate the results from more than 20 peer-reviewed studies demonstrating the benefits of Prolacta's 100% human milk-based fortifiers, compared to cow-milk based fortifiers. The study compared whether preterm infants benefited from Prolacta's human milk-based fortifier supplementation compared to cow/bovine milk-based fortifiers and whether the higher purchase costs were economically viable for hospitals. It found that preterm infants tolerate human milk-based fortifiers significantly better than bovine-based fortifiers, and while the human milk fortifiers entail higher therapeutic costs, they are offset by shorter in-hospital stays and fewer morbidities. The objective of the independent study was twofold: 1) To determine whether extremely low birth weight preterm infants benefit from a HMBF compared to CMBF regarding food tolerance and common comorbidities of prematurity; and 2) To evaluate whether the higher purchase costs associated with HMBFs are economically viable for Germany's hospital NICUs. The study included 23 preterm infants of < 32 + 0 gestational weeks, born weighing less than 1,000 g (2.2 Ibs), admitted to the NICU at KJF Klinik St. Elisabeth, Neuburg an der Donau, Germany, between January 2019 and December 2020.1 The study allowed parents to choose between HMBF or CMBF supplementation; there were no other differences in the remaining nutrition and care. Based on the total number of events observed in the study, typical morbidities in the HMBF group were significantly less frequent (30%) than in the CMBF group (77%, P = 0.04). Due to the small sample size, individual comorbidities did not reach statistical significance. All comorbidities were higher in the CMBF group. As such, the study concluded the group of infants fed Prolacta's human milk-based fortifier had significantly fewer preterm neonate morbidities over the entire clinical course compared with preterm infants given the cow milk-based fortifier. Additionally, fecal calprotectin values in the stools of preterm infants – a marker for gastrointestinal tract inflammation – were significantly lower in the HMBF group than the CMBF group at days 35 (P = 0.02) and 42 (P = 0.03), suggesting improved gastrointestinal tolerance and reduced inflammation. Even though the HMBF group was smaller at birth, weight gain was as good as the CMBF group and resulted in fewer comorbidities. The study reported that preterm infants given HMBF were discharged from the hospital a median of 75.5 days versus 80 days in the CMBF group. This resulted in a revenue gain of €5958.20 ($6,758.65 USD) per patient in the HMBF group. Making the same calculation for the CMBF group, this resulted in a per-patient revenue loss of €346.00 ($392.48 USD), respectively. Likely due to the small number of comorbidities throughout the study, the revenue gain in the HMBF group was negated by the cost of the fortifier. Larger centers with higher case numbers may see a distinct economic advantage due to earlier discharge of preterm infants and decreased morbidities. Furthermore, earlier discharge creates additional capacity in NICUs, resulting in a positive impact on cost-effectiveness. "The German study reaffirms, in a head-to-head trial, that not only is early fortification with human milk fortifiers better tolerated by the smallest neonates, but it is also the key to achieving healthy growth and reduced complications among these infants," said Melinda Elliott, MD, chief medical officer at Prolacta and a practicing neonatologist. "Human milk is a complex, dynamic bioactive fluid with a myriad of compounds that make it the preferred nutrition for extremely low birth weight preterm infants to support their immunity, growth, neurodevelopment, and overall long-term health. The resulting benefit of Prolacta's fortifiers, as part of an EHMD, to preterm infant health and the reductions in the cost of care, as demonstrated in this study, are being replicated worldwide by institutions using Prolacta's feeding protocol in the first days of life."

Article Looks at Homogenization of Human Milk-based Products

Prolacta Bioscience, the world's leading hospital provider of 100% human milk-based nutritional products for premature, critically ill infants, announced the publication of a journal article that summarizes existing evidence on the impact of homogenization on human milk-based nutritional products. The article focuses on changes to the macromolecular structure of the milk fat globule (MFG) and the subsequent impact on digestion and was published in December in the peer-reviewed journal Current Developments in Nutrition. Authored by Sarah M. Reyes, Ph.D., MSc, and colleagues, "The Impact of Homogenization on Donor Human Milk and Human Milk-Based Fortifiers and Implications for Preterm Infant Health" uses published data to create a conceptual framework for the potential implications of homogenized human milk-based nutritional products on preterm infant health

and suggests avenues for future research. "Homogenization disrupts the milk fat globule, which may lead to premature digestion of bioactive components, including sphingolipids and long-chain polyunsaturated fatty acids (LCPUFAs), linked to favorable neurological outcomes. The implications of these changes for infant health are unknown," according to Reyes, scientific liaison, human milk and clinical research, at Prolacta. Homogenization is a process that evenly disperses two liquids to create a single uniform mixture. In the dairy industry, homogenization is used to improve cow milk's taste, consistency, and appearance, as well as to extend its shelf life. Dairies homogenize cow milk to disperse fat droplets and prevent the cream from rising to the top. Human milk is a complex, dynamic bioactive fluid with a myriad of compounds that make it the preferred nutrition for infants to support their immunity, growth, neurodevelopment, and overall long-term health. "The well-established clinical benefits of human milk-based nutritional products only apply to currently available non-homogenized products. The safety and efficacy of homogenized human milk-based nutritional products have not been established," Reyes wrote. "Human milk-based nutritional products are not created equally," said Melinda Elliott, chief medical officer for Prolacta, practicing neonatologist, and a study co-author. "As human milk researchers and medical professionals, it is our opinion that the use of industrial processing techniques such as homogenization, with or without high-heat processing, should be avoided for human milk-based nutritional products until their safety and efficacy have been established."

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