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Winter 2023

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The Journal of Perinatology-Neonatology

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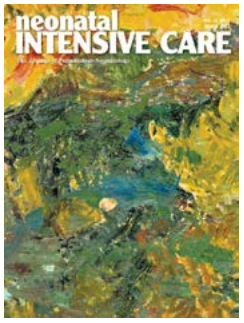

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'New Era' for Company With Breastfeeding Device

Neotech Products announced the acquisition of the Bridge Breastfeeding Assistance Device. The Bridge features a silicone nipple cover with a built-in channel, which attaches to a syringe that can hold and deliver breastmilk or formula. It helps babies latch to the breast and helps promote milk production. It can be used in most circumstances in which a bottle would traditionally be used. The Bridge was invented by Kate Spivak, a Physician Assistant and an International Board Certified Lactation Consultant. "I created the Bridge because there was a lack of solutions for the most common issues I was seeing in practice," Spivak said. "I consistently saw babies who were being supplemented with a bottle due to low supply and issues with latch. Theoretically, the solution was simple: keep the baby at the breast as much as possible. Realistically, there was no efficient way to do that until the Bridge was created." The Bridge Breastfeeding Assistance Device: Provides a surface for baby to latch and allows supplementation while breastfeeding which helps to stimulate natural milk production; can be used to provide colostrum, expressed milk, fortified human milk, or formula; allows precise control of supplement flow, rate, and timing. A large percentage of mothers experience breastfeeding challenges, including difficulty with infant feeding at the breast, pain, and milk quantity. "Neotech is primarily known as a NICU company, but the Bridge is a natural progression into the Mother Baby market," Craig McCrary, Neotech President said. "We have a few other products in the works for the Mother Baby space. The Bridge marks the start of a new era for Neotech."

New Prospective Study Evaluates the Accuracy of Monitoring During Elective Cesarean Section

Masimo announced the findings of a prospective study published in the Egyptian Journal of Anesthesia in which Dr Mohamed Ibrahim Beleta and colleagues at Cairo University evaluated the accuracy of noninvasive, continuous hemoglobin monitoring with Masimo SpHb on patients undergoing elective cesearan section (CS) with antepartum hemorrhage. The researchers found significant positive correlations between SpHb and invasive hemoglobin (Hb) values, and concluded, "In patients undergoing CS with antepartum hemorrhage, continuous SpHb through Masimo Pulse CO-Oximetry demonstrated clinically acceptable accuracy of Hb measurement compared with invasive Hb, even at low hemoglobin levels." The authors note that antepartum hemorrhage is associated with adverse maternal and neonatal outcomes and that blood transfusion is also associated with a variety of risks, but that invasive laboratory hemoglobin measurement, while a crucial factor in transfusion decisions, yields intermittent and often delayed results. The researchers thus sought to evaluate whether use of noninvasive, continuous hemoglobin monitoring might "enable a more rapid detection of clinically significant blood loss, improve perioperative transfusion practices, allow patient condition to be assessed more quickly and blood management more adequately, and perhaps even reduce needless transfusions." They enrolled 60 pregnant women, aged 18-45, scheduled for elective CS under general anesthesia between April 2016 and December 2017. All subjects had antepartum hemorrhage and were candidates for blood transfusion. During the procedure, all patients were monitored as per hospital standards, and in addition, with Masimo SpHb. All blood samples (Lab Hb) were analyzed using the same Coulter laboratory analyzer to avoid variance induced by the use of multiple devices. Lab Hb and SpHb values were recorded before induction of anesthesia (baseline), before transfusion, and after transfusion. Blood transfusion was carried out when Lab Hb decreased by more

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than 20% from baseline. The researchers found significant positive correlations between SpHb and invasive Hb at the three points of comparison: baseline (r = 0.946), pre-transfusion (r = 0.902), and post-transfusion (r = 0.698). Differences at those times were insignificant: p = 0.196, p = 0.092, and p = 0.570, respectively. Using Bland-Altman analysis, they found low bias and moderate limits of agreement: 0.348 g/dL (-0.584 and 1.280) at baseline measurement, 0.314 g/dL (-0.561 and 1.188) at pre-transfusion, and 0.348 g/dL (-0.584 and 1.280) at post-transfusion. The investigators concluded, "Continuous SpHb Masimo Pulse CO-Oximetry shows an appropriate clinically reliable Hb calculation in comparison to Invasive Hb even in patients undergoing CS with low hemoglobin. Further studies are needed on larger sample size with multicenter collaboration. Furthermore, we recommend the assessment of this technique on patients with common morbidities, such as high cholesterol, high blood pressure, and diabetes." The researchers also noted that "SpHb evaluation has the potential for additional benefits, including patient comfort, increased safety, and decreased complexity for healthcare staff, who are not exposed to the risks of needle-stick injury and bloodspill contamination." SpHb is not intended to replace laboratory blood testing. Clinical decisions regarding red blood cell transfusions should be based on the clinician's judgment considering, among other factors, patient condition, continuous SpHb monitoring, and laboratory diagnostic tests using blood samples.

Study Looks at Biomarkers During Pregnancy

A discovery by Stanford School of Medicine researchers of biomarkers in the blood and urine of women who later develop a dangerous complication of pregnancy could lead to a low-cost test to predict the condition. The findings, which were published online Dec. 9 in *Patterns*, lay the groundwork for predicting preeclampsia — one of the top three causes of maternal death worldwide — months before a pregnant woman shows symptoms. Predictive testing would enable better pregnancy monitoring and the development of more effective treatments. Preeclampsia is characterized by high blood pressure late in pregnancy. It affects 3% to 5% of pregnancies in the United States and up to 8% of pregnancies worldwide, and it can lead to eclampsia, an obstetric emergency linked to seizures, strokes, permanent organ damage and death. At present, preeclampsia can be diagnosed only in the second half of pregnancy, and the sole treatment is to deliver the baby, putting infants at risk from premature birth. "The advantage of predicting early in pregnancy who will get preeclampsia is that we could follow moms more closely for early symptoms," said the study's co-lead author, Ivana Marić, PhD, a senior research scientist in pediatrics at Stanford Medicine. In addition, taking low-dose aspirin starting early in pregnancy may lower preeclampsia rates in women at risk for the condition, but pinpointing who could benefit has been challenging, Marić said. "There is really a need to identify those pregnancies to prevent tragic outcomes for mothers, and preterm births for babies, which can be very dangerous." Marić shares lead authorship of the study with Kévin Contrepois, PhD, former scientific director of the Stanford Medicine Metabolic Health Center. The study's senior authors are Nima Aghaeepour, PhD, associate professor of pediatrics and of anesthesiology, perioperative and pain medicine; Brice Gaudilliere, MD, PhD, associate professor of anesthesiology, perioperative and pain medicine; and David Stevenson, MD, professor of pediatrics and director of the Stanford Prematurity Research Center, which supported the research. "When you reduce preeclampsia, you also likely reduce preterm birth," Stevenson said. "It's a double whammy of good impacts." To figure out which biological signals could provide an early warning system for preeclampsia, the Stanford Medicine research team collected biological samples from pregnant women who did and did not develop preeclampsia. They conducted highly detailed analyses of all the samples, measuring changes in as many biological signals as possible, then zeroing in on a small set of the most useful predictive signals. "We used a number of cutting-edge technologies on Stanford University's campus to analyze preeclampsia at an unprecedented level of biological detail," Aghaeepour said. "We learned that a urine test fairly early on during pregnancy has a strong statistical power for predicting preeclampsia." The research team collected biological samples at two or three points in pregnancy (early, mid and late) in 49 women, of whom 29 developed preeclampsia during their pregnancies and 20 did not. The participants were selected from a larger cohort of women who had donated biological samples for pregnancy research at Stanford Medicine. For each time point, the participants gave blood, urine and vaginal swab samples. The samples were used to measure six types of biological signals: all cell-free RNA in blood plasma, a measure of which genes are active; all proteins in plasma; all metabolic products in plasma; all metabolic products in urine; all fat-like molecules in plasma; and all microbes/bacteria in vaginal swabs. The scientists also conducted measurements of all immune cells in plasma in a subset of 19 of the participants. Using the resulting thousands of measurements, as well as information about which participants developed preeclampsia and when in pregnancy each sample was collected, the scientists used machine learning to determine which biological signals best predicted who progressed to preeclampsia. They aimed to identify a small set of signals detectable in the first 16 weeks of pregnancy that could form the basis for a simple, low-cost diagnostic test feasible to use in low-, middle- and high-income countries. To estimate the accuracy of the machine learning models, the women were divided into two cohorts, a discovery cohort and a validation cohort. The researchers initially constructed the models with data from the discovery cohort, then confirmed the results by testing their performance on data from women in the validation cohort. A prediction model using a set of nine urine metabolites was highly accurate, the researchers found. These urine markers, in samples collected before week 16 of pregnancy, strongly predicted who later developed preeclampsia. The performance of the test was measured by a statistical standard used in machine learning known as area under the curve. An AUC of 1 for a test with two possible outcomes indicates perfect prediction, whereas an AUC of 0.5 indicates no predictive value, the same as the results obtained from a coin toss. For the urine markers, the AUC was 0.88 in the discovery cohort and 0.83 in the validation cohort, indicating high prediction capability. Measuring the same set of urine metabolites in samples collected throughout pregnancy produced similar predictive power, with an AUC of 0.89 in the discovery cohort and 0.87 in the validation cohort. The researchers confirmed that their model had stronger predictive power than using only clinical features linked to a pregnant woman's preeclampsia risk, such as chronic hypertension, high body mass index and carrying twins.

Medication Approved for Neonatal Seizures

Sun Pharmaceutical Industries Limited announced that the US Food and Drug Administration (US FDA) has approved SEZABY (phenobarbital sodium powder for injection) for the treatment of neonatal seizures. With this approval, SEZABY becomes the first and only product specifically indicated in

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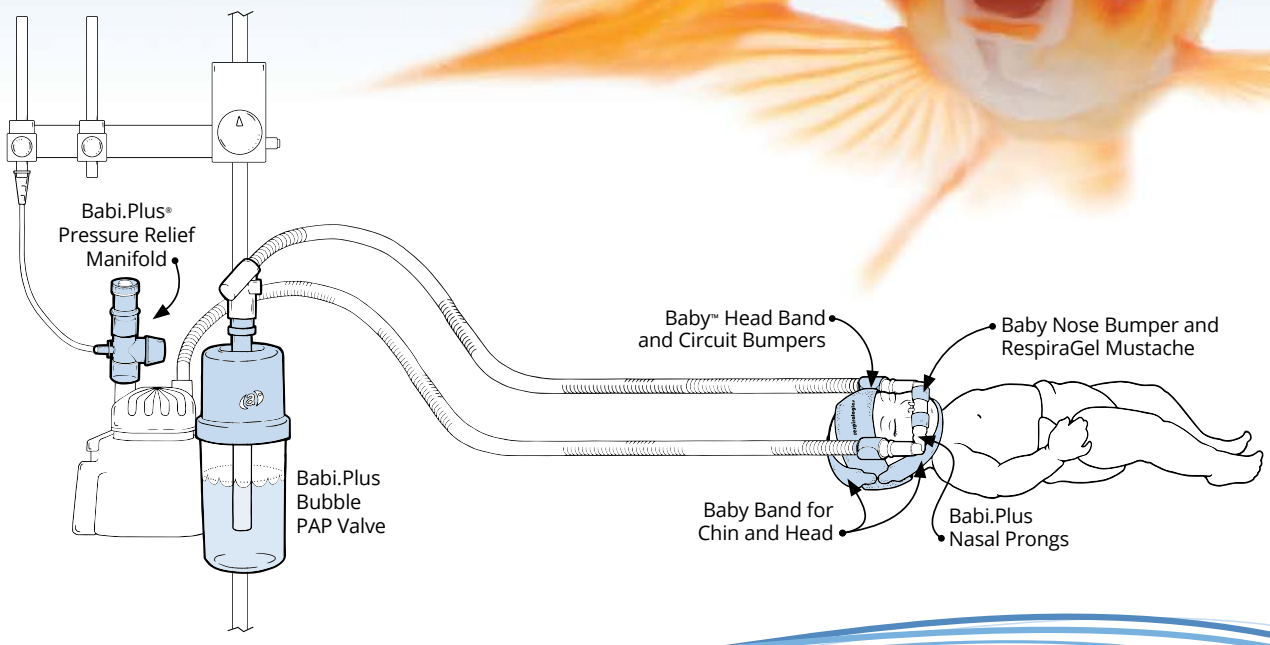

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the US for the treatment of neonatal seizures in term and preterm infants. SEZABY is expected to be available in the US in Q4FY23. SEZABY is a benzyl alcohol-free and propylene glycol-free formulation of phenobarbital sodium powder for injection. It was granted orphan drug designation by the US FDA for the treatment of neonatal seizures. SEZABY was recently licensed by SPARC to Sun Pharma. Under the terms of the license agreement, SPARC is eligible to receive a milestone payment on approval of SEZABY by the US FDA. "SEZABY is an exciting addition to our growing portfolio of specialty branded products in the US," said Abhay Gandhi, CEO North America, Sun Pharma. "As the first and only product specifically indicated to treat seizures in term and preterm infants, SEZABY has the potential to make a difference in the lives of patients and their families." "For years, physicians have had limited treatment options to manage neonates with seizures. SPARC is proud to have developed benzyl alcohol-free and propylene glycol-free phenobarbital sodium powder for injection as the first treatment option now approved by the US FDA," said Anil Raghavan, CEO, SPARC. SEZABY was approved based on the results of NEOLEV2, a phase 2 study that levetiracetam compared to phenobarbital in the first-line treatment of neonatal seizures evaluated.

New Lung Treatment for Neonates

Beyond Air, Inc., a clinical-stage medical device and biopharmaceutical company focused on developing inhaled nitric oxide (NO) for the treatment of patients with respiratory conditions, including serious lung infections and pulmonary hypertension, and, through its affiliate Beyond Cancer, ultra-high concentration nitric oxide (UNO) for the treatment of solid tumors, announced that the US Food and Drug Administration (FDA) has approved LungFit PH to treat term and near-term neonates with hypoxic respiratory failure (often referred to as persistent pulmonary hypertension of the newborn or PPHN) (prescription use only). LungFit PH is the initial device from the LungFit therapeutic platform of nitric oxide generators that use our patented Ionizer technology and is the first FDA-approved product for Beyond Air. Steve Lisi, Chairman and CEO of Beyond Air, commented, "The FDA approval of LungFit PH enables a new era of nitric oxide therapy and marks a pivotal event for Beyond Air as we officially enter the US market. As the first and only approved nitric oxide generator and delivery system, LungFit PH empowers healthcare providers to maximize the efficiency of a hospital when treating PPHN by moving beyond their reliance on traditional, inefficient delivery systems and the associated burdensome logistics and safety requirements." Lisi added, "I am immensely proud of the Beyond Air team for navigating a multitude of obstacles over the past five years, especially the last 27 months during the global pandemic, to bring this revolutionary device to market. The approval of LungFit PH validates our patented Ionizer technology and lays out a premarket approval model for our other LungFit platform devices, including LungFit PRO and LungFit GO. We believe that LungFit PH is just the first in a series of our medical devices that, if approved, will become available for treating a wide variety of respiratory diseases as we remain dedicated to our mission of harnessing the power of nitric oxide for all who can benefit from this transformational therapy." LungFit PH uses patented Ionizer technology to generate unlimited on-demand nitric oxide from ambient air and deliver it to a ventilator circuit, regardless of dose or flow. The device uses a compressor to drive room air through a plasma chamber where pulses of electrical discharge are created between two electrodes. The LungFit PH system uses power equivalent to a 60-watt lightbulb to ionize the nitrogen and oxygen molecules, forming nitric oxide with low levels of nitrogen dioxide (NO_2) created as a byproduct. The gas is then passed through a Smart Filter, which removes the toxic NO_2 from the internal circuit. For the treatment of PPHN, the novel LungFit PH system is designed to deliver a dosage of NO to the lungs that is consistent with the current standard of care for delivery of 20 ppm NO with a range of 0.5 ppm – 80 ppm (low concentration NO) for ventilated patients. Each Smart Filter will last 12 hours regardless of ventilator demands and replacing a filter takes just a few seconds. NO gas is a vasodilator approved in dozens of countries to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO) in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilator support and other appropriate agents. Low concentration inhaled NO therapy has been the standard-of-care for PPHN for over 20 years in the United States. PPHN is a lethal condition and secondary to failure of normal circulatory transition at birth. It is a syndrome characterized by elevated pulmonary vascular resistance (PVR) that causes labile hypoxemia due to decreased pulmonary blood flow and right-to-left shunting of blood. Its incidence has been reported as 1.9 per 1,000 live births (0.4-6.8/1,000 live births) with a mortality rate ranging between 4-33%. This syndrome complicates the course of about 10% of infants with respiratory failure and remains a source of considerable morbidity and mortality. The Beyond Air commercial team will be actively working with select hospitals beginning this month to make LungFit PH available to them with a broader US hospital launch expected in the first half of 2023.

Twins Born From Embryos Frozen 30 Years Ago

Twin babies have been born to an Oregon couple from embryos frozen more than 30 years ago. It is believed to be a new record for the longest-frozen embryos ever to result in a successful live birth. They were stored at around -196C (-323F) in liquid nitrogen on 22 April 1992. Rachel Ridgeway, a mother of four from Oregon, gave birth to the twins on 31 October. The father, Philip Ridgeway, said it was "mind-boggling". Lydia Ann and Timothy Ronald Ridgeway likely set a new record, according to the National Embryo Donation Center (NEDC), a private faith-based organisation that says it has helped birth more than 1,200 infants from donated embryos. NEDC's previous record-holder, Molly Gibson, was born in 2020 from an embryo that had been frozen for nearly 27 years. "The decision... to adopt these embryos should reassure patients who wonder if anyone would be willing to adopt the embryos that they created 5, 10, 20 years ago," said Dr John David Gordon, who performed the embryo transfer. "That answer is a resounding yes!" The twin embryos had been created for an anonymous married couple using IVF. The man was in his 50s and reportedly relied on a 34-year-old egg donor. They were kept in storage at a fertility lab on the US west coast until 2007 when the couple donated them to the NEDC in Knoxville, Tennessee for another couple to use them instead.

The Truth About Stillbirths

A study has found that nearly one in four US stillbirths may be preventable. For pregnancies that last 37 weeks or more, that research shows, the figure jumps to nearly half. Thousands more babies could potentially be delivered safely every year. But federal agencies have not prioritized critical stillbirth-focused studies that could lead to fewer deaths. Nearly two decades ago, both the CDC and the National Institutes of Health launched key stillbirth tracking and research studies, but the agencies ended those projects within about a decade. The CDC never analyzed some of the data that was collected. Unlike with SIDS, a leading cause of infant death, federal officials have failed to launch a national campaign to reduce the risk of stillbirth or adequately raise awareness about it. Placental exams and autopsies, which can sometimes explain why stillbirths happened, are underutilized, in part because parents are not counseled on their benefits. Federal agencies, state health departments, hospitals and doctors have also done a poor job of educating expectant parents about stillbirth or diligently counseling on fetal movement, despite research showing that patients who have had a stillbirth are more likely to have experienced abnormal fetal movements, including decreased activity. Neither the CDC nor the NIH have consistently promoted guidance telling those who are pregnant to be aware of their babies' movement in the womb as a way to possibly reduce their risk of stillbirth. The American College of Obstetricians and Gynecologists, the nation's leading obstetrics organization, has been slow to update its own guidance to doctors on managing a stillbirth. In 2009, ACOG issued a set of guidelines that included a single paragraph regarding fetal movement. Those guidelines weren't significantly updated for another 11 years. Perhaps it's no surprise that federal goals for reducing stillbirths keep moving in the wrong direction. In 2005, the US stillbirth rate was 6.2 per 1,000 live births. The US Department of Health and Human Services, in an effort to eliminate health disparities and establish a target that was "better than the best racial or ethnic group rate," set a goal of reducing it to 4.1 for 2010. When that wasn't met, federal officials changed their approach and set what they called more "science-

based" and "realistic" goals, raising the 2020 target to 5.6. The US still fell short. The 2030 goal of 5.7 was so attainable that it was met before the decade started. The 2020 rate, the most current according to the CDC, is 5.74.

Study Finds Improved Neurodevelopmental Outcomes for Extremely Premature Infants

Prolacta Bioscience, the world's leading hospital provider of 100% human milk-based nutritional products for critically ill, premature infants, announced today the publication of a journal article that showed improved long-term neurodevelopmental outcomes in extremely premature infants who received Prolacta›s 100% human milk-based fortifiers as part of an Exclusive Human Milk Diet (Prolacta›s EHMD), compared with infants fed a cow milk-based diet in the neonatal intensive care unit (NICU). Published in the *Journal of Perinatology*, the retrospective, multicenter cohort study, "Neurodevelopmental Outcomes of Extremely Preterm Infants Fed an Exclusive Human Milk-Based Diet Versus a Mixed Human Milk + Bovine Milk-Based Diet: a Multi-Center Study," examined data from 252 premature infants with a birth weight of less than or equal to 1,250 grams. Researchers assessed the infants› development using the Bayley Scales of Infant Development III (BSID-III), the standard measure of infants› neurological development. They found that infants fed Prolacta›s EHMD in the neonatal intensive care unit (NICU) had significantly higher BSID-III cognitive scores and a trend toward improved language scores at a corrected age of 18 to 22 months. "This long-term outcome study demonstrated promising post-discharge cognitive scores for preterm infants fed an EHMD," said lead author Amy B. Hair, MD, of the Section of Neonatology, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas. "This data is further evidence that human milk nutrition and fortification are both imperative for long-term brain development in infants born prematurely." After adjusting for birth weight, gender, and the presence of necrotizing enterocolitis (NEC) — a serious and often life-threatening intestinal disease that affects neurological development — preterm infants who received Prolacta's EHMD, compared with those fed a cow milk-based diet (CMD), had: significantly higher BSID-III cognitive scores (96.5 ± 15.1 vs 89.6 ± 14.1; $P = 0.001$); improved language scores, with a difference that approached significance (85.5 ± 15.0 vs 82.2 ± 14.1; adjusted $P = 0.09$). «Infants without NEC also had higher BSID-III scores if they received an EHMD vs a cow milk-based diet,» noted Hair. «This suggests additional mechanisms involved aside from NEC prevention.» Nutritional management of extremely low birth weight (ELBW) infants in their first days and weeks of life has potentially long-term implications. During this crucial time, rapid growth and development of vital organs, including the brain and lungs, occurs. Furthermore, early fortification — within the very first days of life — with 100% human milk-based fortifiers is safe and proven to help achieve healthy neonatal growth in the NICU. "Studies such as this one continue to show that human milk and human milk-based fortifiers are critical for these fragile infants," explained Melinda Elliott, MD, FAAP, chief medical officer at Prolacta, and a practicing neonatologist. "The findings of this neurodevelopment study are especially significant as they demonstrate that human milk-based nutrition helps to give preterm infants the best chance at a bright future."

Spirometer Tested on Freedivers

ndd Medical Technologies (ndd), a global leader and innovator of diagnostic devices for the early detection of COPD and other chronic lung diseases, announces the successful deployment of its EasyOne Air portable spirometer for testing lung function at the world's largest freediving competition, Vertical Blue. In a true test of the EasyOne Air's capabilities in challenging field conditions, the benefits of the portable spirometer shone through, yielding accurate and consistent results in a sample of freedivers. Freediving is a form of underwater diving where participants plunge to depths as great as 100m, whilst holding their breath for periods of 3-4 minutes. The extreme nature of the sport puts freedivers at risk of lung barotrauma, pulmonary edema, and decompression sickness. The medical team at Vertical Blue wanted to ensure the safety of freedivers at the competition, and set about testing the participants' lung function to find trends and establish 'normal' values in this extreme diving population. As part of a long-term initiative, the medical team also aimed to demonstrate that the activity can be safe, and to identify any associated risks. Thanks to the EasyOne Air's unique ultrasonic flow measurement technology, highly accurate and consistent spirometry measurements were readily taken in the field, eliminating the need for cumbersome equipment associated with traditional spirometry methods. With instant results and no calibration or maintenance necessary, the team at Vertical blue were delighted with the device's performance, as Jamie Juliano RN, CFRN and co-owner of Freedive Medicine LLC, commented: "Freediving presents unique challenges for our medical team: Freediving often operates in austere locations where medical equipment is sparce. The EasyOne Air helped us to research and evaluate pulmonary-related risks and proved to be an invaluable tool during the competition. Having ndd by our side will aid in continued evaluation of the unique pulmonary situations Freedivers face when participating in this sport." EasyOne Air is designed to deliver accurate results immediately. With unique technology, premium precision components, and extensive quality control standards, high-quality spirometry results are always guaranteed.

Kit is First to Receive Marketing Authorization by US FDA for SMA Screening in Newborns

PerkinElmer Inc., a global leader committed to innovating for a healthier world, today announced that the US Food and Drug Administration (FDA) has authorized the marketing of the EONIS SCID-SMA assay kit for *in vitro* diagnostic (IVD) use by certified laboratories for the simultaneous detection of spinal muscular atrophy (SMA) and severe combined immunodeficiency (SCID) in newborns. This is the first FDA authorized assay for SMA screening in newborns in the United States and is part of the Company's broader EONIS Platform. SMA is a leading genetic cause of infant death and is characterized by muscle weakness and atrophy resulting from progressive degeneration and loss of the lower motor neurons in the spinal cord and the brain stem nuclei. SCID, which is a group of rare inherited disorders characterized by the absence of both humoral and cellular immunity, can also lead to life-threatening health complications if untreated. Early detection and intervention are critical for newborns affected by either condition. "For nearly three decades, PerkinElmer has delivered innovative solutions to laboratories and clinicians worldwide that help diagnose newborns with rare diseases and inherited disorders," said Petra Furu, general manager of reproductive health at PerkinElmer. "This authorization is a major milestone for newborn screening in the United States. Labs across the country will be able to access technologies that detect SMA and SCID, and provide them the confidence that every test meets regulatory, manufacturing and accreditation requirements."

The EONIS Platform is a robust, flexible system that utilizes real-time PCR technology to screen for both SMA and SCID using a single dried blood spot sample, combining DNA extraction and multiplexing. When combined with PerkinElmer's JANUS liquid handler, PerkinElmer's workflow allows for maximum automation and efficiency, and can be configured to a laboratory's individual requirements and throughput. Other components of the platform include the EONIS DNA Extraction kit and EONIS Analysis Software. The EONIS Platform is already CE-IVD marked for use by certified laboratories in countries that accept the CE mark.

New Vaccine Protects Babies

An experimental vaccine from Pfizer Inc. significantly reduced the risk of infants developing severe cases of a respiratory virus that kills hundreds of children each year, according to the company. Among mothers who received the vaccine for the respiratory syncytial virus, their infants had an 81.8% lower risk of developing severe lower respiratory tract infections requiring medical attention within three months of birth than infants whose mothers received a placebo, Pfizer said. Within the first six months of life, the risk was reduced by 69.4%, according to the company, which reported the results in a press release and said it intends to submit them for publication in a peer-reviewed scientific journal. The shot didn't reduce the risk of nonsevere cases by a statistically significant amount in the study, however, though the company said the study's results were sufficient to ask health regulators by the end of this year to approve the vaccine. "This is a major breakthrough after decades of lack of success," said William Gruber, Pfizer senior vice president of vaccine clinical research and development. If approved, Pfizer's RSV shot could be the first to go on sale for a common virus that usually causes a mild cold in healthy people but can be dangerous and even fatal in the very old and young, especially babies under one year. There is no currently approved RSV vaccine. The virus results in 58,000 hospitalizations annually of children under five years, and 100 to 500 deaths each year. Doctors have reported unusually high numbers of RSV infections in children this year, filling up hospital beds ahead of the normally busier winter season.

Immediate Skin-to-Skin Contact With Infant Improves Outcomes for Mother and Infant

Continuous skin-to-skin contact starting immediately after delivery even before the baby has been stabilised can reduce mortality by 25 per cent in infants with a very low birth weight. This according to a study in low- and middle-income countries coordinated by the WHO on the initiative of researchers at Karolinska Institutet published in The New England Journal of Medicine. Continuous skin-to-skin contact between infant and mother, or "Kangaroo Mother Care" (KMC), is one of the most effective ways to prevent infant mortality globally. The current recommendation from the World Health Organization (WHO) is that skin-to-skin contact should commence as soon as a low weight baby is sufficiently stable, which for those weighing under 2 kg at birth normally takes several days.

Connected: Preterm Infant Program Makes Progress

Martha Welch, MD, spent the better part of three decades in private practice treating children with emotional, behavioral, and developmental disorders before accepting a job on the faculty of Columbia University in New York City in 1997. She took the position, she said, with a mission: to find evidence to support

Continued on page 18…

SPOTLIGHT ON OXIMETRY

Nonin

Tell us about your oximetry products

You can count on Nonin. For more than 35 years, Nonin Medical has designed and manufactured noninvasive patient monitoring devices that deliver actionable measurements across a diverse range of patients and challenging conditions.

Nonin's oximetry products range from fingertips to tabletops, and wrist-worn oximeters to OEM oximetry solutions. We also offer a wide range of reusable and disposable sensors designed for different patient sizes, including neonates. Measurement parameters include SpO2, COHb, MetHb, and pulse rate.

Discuss your company's R&D efforts relevant to oximetry

A: Nonin is a proud pioneer in pulse oximetry. We introduced the first portable handheld oximeter in 1990, as well as the first fingertip pulse oximeter in 1995. This commitment to innovation continues to this day as we work to bring fresh ideas to market.

How have your products proven to be cost-effective?

Nonin offers competitive warranty periods on our devices and will attempt to repair devices covered under warranty. Additionally, our patient monitoring devices may indicate early warning signs of dangerous patient conditions, such as carbon monoxide poisoning or hypoxia. Early detection of these conditions may help avoid costly complications from more severe symptoms.

What kind of training and user-support programs do you have in place?

Nonin Academy is Nonin's exclusive educational platform providing easy access to on-demand presentations, interactive workshops, and clinical articles for Nonin partners. Additionally, Nonin's Customer Advocacy team works tirelessly to support customers with creative problem solving and cheerful attitudes. Furthermore, support resources — such as the Instructions for Use — are hosted online for easy access.

Nellcor

Tell us about your oximetry products

For more than 40 years, clinicians have trusted the Nellcor™ brand to provide fast, accurate and consistent pulse oximetry performance across the wide range of patient needs, from neonates to adults. Count on Nellcor pulse oximetry to help, with SpO2 measurements that are tied to true arterial oxygen saturation and cardiac-induced pulse — putting you closer to your patients.

Nellcor pulse oximetry with OxiMax™ technology meets six key challenges in neonatal monitoring.

Speed to Post

Seconds count in neonatal care decisions.[1] Don't lose them waiting for an accurate vital signs reading. Nellcor pulse oximetry has been shown to post on average up to 12 seconds faster than Masimo.[3]

Accurate Pulse Rates
Inaccurate pulse rate readings may guide clinicians to inappropriate or unnecessary interventions.[4] Nellcor pulse oximetry showed no clinically significant difference from ECG reference.[3,4]

Motion
Neonate motion can cause irregular venous blood flow that affects accurate monitoring.[4] Nellcor pulse oximetry was the first motion tolerant technology to comply with ISO 80601-2-61.2011.6

Low Saturation
Saturation rates as low as 66% in the first minutes of life may make neonates difficult to assess.[4,7] Nellcor pulse oximetry has demonstrated best-in-class accuracy at saturation rates as low as 60%.‡

Skin Sensitivity
Monitoring may be unavoidable, even though attaching a sensor may pose a risk to the fragile skin of a newborn.[9] Nellcor non-adhesive sensors use the patients' own skin moisture to secure sensor, while comparable in accuracy to adhesive sensors.[10]

Nuisance Alarms
Alarm fatigue can negatively impact your workflow and your ability to provide the best possible care. Nellcor SatSeconds alarm management may reduce alarms in neonates by 40 percent.[11,12]

Discuss your company's R&D efforts relevant to oximetry.
Being a leading manufacturer and brand in pulse oximetry, we continue to make technical improvements, as seen with the recently released Nellcor OxySoft™ neonatal adult SpO2 sensor.

Our Nellcor OxySoft SpO2 sensor is the first pulse oximetry sensor to use a silicone adhesive to protect fragile skin and improve repositionability. We designed the Nellcor OxySoft™ SpO2 sensor to perform better in low perfusion and thick tissue, stay on longer, and be repositioned without pulling on or damaging fragile skin. With brighter LEDs, a new silicone adhesive and a lower profile, it's a lighter touch on your patients—allowing you more time to connect.

How has your product proven to be cost effective?
We deliver ongoing value to our customers in many ways—complimentary education, training, peer-to-peer events, US-based technical support, and more.

A dedicated clinical product support team
Some companies may provide initial product training but charge for ongoing education—requiring more of your budget. We offer clinical education support with field-based product specialists at no extra charge. Our clinical field team of experienced clinicians includes many former nurses and respiratory therapists—who can directly relate to your daily challenges. They'll work with you to tailor education and training programs. Because they are located throughout the U.S., they can respond and assist you in different areas including:
- Alarm management tools and settings to help reduce nuisance alarms
- Proper sensor placement and application
- Knowledge of specialty sensors and their uses
- Effective and accurate monitoring in difficult patient situations such as motion and poor perfusion
- New or updated industry guidelines

US-based Nellcor pulse oximetry technical help
Our goal is to make technical support as easy and efficient as possible. Our US-based technical service support center has been around since the inception of our Nellcor pulse oximetry more than 40 years ago.

When you need help, we're here for you by phone at 1-800-Nellcor or online. Reach out to us and learn more about Nellcor pulse oximetry product support.

Online Nellcor pulse oximetry support resources
Customer support resources are in one location to help save you time. The Nellcor pulse oximetry support website offers:
- FAQs and links to educational courses
- Product manuals
- Sensor application guides and hang tags
- Hardware user guides
- Add-on software

Nellcor pulse oximetry offers a five-year warranty
We believe in protecting your investment from the start. That's why Nellcor pulse oximetry monitors have a five-year warranty. Other manufacturers typically offer one year.

More value for Nellcor pulse oximetry customers
Delivering excellent patient care depends on a lot of things, including efficient workflows, timely information, and flexibility. Our investments in technology, services, and partnerships are designed around these priorities:
- **Nellcor pulse oximetry analytics tool.** Data insights can enhance your research, clinical studies, and education. This complimentary tool, which you can download, allows you to transfer patient data from your Nellcor pulse oximetry monitors to a computer. Then you can view and analyze data for one or more patients, as well as customize data displays, graphs, and reports. The data insights can help you make even more informed patient care decisions, like identifying who may need a sleep study or home oxygen support.
- **Alarm analysis program.** By analyzing the frequency of device alarms under your current settings, we can work with you to optimize alarm settings. That helps to create better focus without missing any clinically significant alarms. This program may considerably reduce your alarms. If you are interested in participating in an alarm analysis, please contact your Nellcor pulse oximetry representative.
- **Nellcor SatSeconds alarm management.** Controlled through monitor settings, Nellcor SatSeconds alarm management is engineered for simple workflow integration. It differentiates between serious hypoxemia and minor transient events—so you can have peace of mind when responding to alarms for patients most in need.
- **OEM solutions.** We integrate our pulse oximetry technology into most multiparameter monitors (MPM)—allowing many hospitals to have Nellcor pulse oximetry technology no matter which MPM provider is used. Ultimately, this is a way for more clinician and patient needs to be met. Partnerships with other companies ensure your flexibility and ability to use accurate, consistent pulse oximetry monitoring. You'll receive the same Nellcor pulse oximetry training that every customer receives. OEM partner solutions are backed by a global team of clinical, engineering, and

marketing professionals, ensuring advanced technology and collaboration with people you know and trust.

What type of training and user support programs do you have in place?

Our clinical education and training programs are designed to help you provide innovative solutions and improve patient care. We are committed to delivering targeted educational solutions aimed at helping you achieve procedural and clinical proficiency. Stay on track with training courses, downloads, and other educational materials that fit your needs and equip you with the tools to succeed.

Build your knowledge and skills with free learning opportunities. Our professional and clinical education (PACE) program includes:

- Online Education (Accredited) Online Education (Non-Accredited)
- Peer-to-Peer Events
- Educational Grants
- MedEd Learning Experience podcast

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Improving Lives, One Breath at a Time

"You'll never experience anything as beautiful as caring for a baby who needs that one chance. A baby that looks so fragile. To send that baby home 2-3 months later and follow their development, it's overwhelming. They are beautiful, brilliant, and right on track."

Filled with vibrant people, culture, and natural wonders, the country of Tanzania is stunning. It is comprised of a diverse population of more than 59 million people with over 120 ethnic groups, various religious beliefs, and unique customs.[1] But for those living in the shadow of the majestic, snow-capped Mount Kilimanjaro—the tallest mountain in Africa—life can be grueling and often heartbreaking when it comes to bearing children.

Much of the population of Tanzania has limited access to neonatal intensive care units (NICUs) which could provide initial resuscitation and stabilization for newborns. The frequency of infant loss is high, with many mothers experiencing the heartbreak of multiple losses.

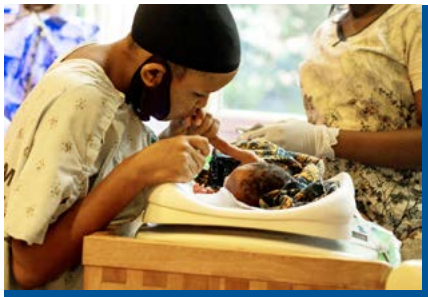
Premature infants face health challenges such as breathing problems, jaundice, growth and feeding difficulties, neonatal sepsis, and birth asphyxia that they struggle to overcome from day one. **Babies with extreme prematurity or critical illness rarely survive in Tanzania.**

Nonin in the NICU

The NICU at the Arusha Lutheran Medical Center (ALMC), located in northern Tanzania, sees preterm infants and neonatal patients fighting for life from area hospitals—some born as early as 24 weeks gestation. Providing a full range of advanced newborn support, the NICU has been able to achieve a survival rate of more than 92%.[6] A remarkable 73% of babies born weighing less than 1,000 grams (2.2 lbs.) survive thanks to low-tech respiratory support, thermoregulation, and proper nutrition.

These efforts are assisted by Nonin Medical's noninvasive monitoring solutions, which help the medical team accurately monitor each baby's oxygen saturation. The positive outcomes represent the highest level of neonatal care available in Tanzania and among the most advanced in East Africa.

As the Director of the NICU, Dr. Stephen Swanson continues to work toward improving outcomes both at ALMC and nationally for Tanzania. He attributes this success to many factors, including education and training of nurses **along with the ability to monitor his patients with Nonin's tabletop and fingertip pulse oximeters.** "I can't overstate how much Nonin's technology has helped us."



A gasp for air followed by the telltale cry, just moments after entering the world—a newborn baby will take their first breath. For preterm infants, the struggle to catch their breath with immature lungs and learning to establish the rhythmic cadence of breathing is more than developing a new skill. It's a battle.

Dr. Swanson and his team use Nonin's Avant® 9700 tabletop pulse oximeters and flexible 6000CN sensors that wrap around the infant's foot, providing actionable data. Nonin's proprietary PureSAT® technology works across diverse skin pigmentations,[8] which is especially critical for the safety of these precious patients.

> Children in sub-Saharan Africa are 15 times more likely to die before age 5 than children in high-income countries.[2]

The team at Nonin stays in contact with and provides ongoing service for the overseas NICU, and Dr. Swanson shares his successes with the Minnesota team. He says, "It is your pulse oximetry monitoring technology that alerts us to a baby's changing conditions. It's an everyday event to have 15 or 20 babies in our unit and **Nonin monitors—along with our own clinical observations—help to save lives."**

Submitted by nonin.com

"The ability to put a sick baby on a monitor, then act on reliable measurements and intervene before it's too late — it's one of the things that contributes to our survival rate."

"I can't overstate how much Nonin's technology has helped us."

– Dr. Stephen Swanson
NICU Director at ALMC

92%
Survival Rate

In 2021, the NICU cared for 340 babies with a 92% survival rate for these high-risk patients; remarkably, their rate is considerably higher than many other hospitals across the country.

Their smallest survivor was born at a tenuous 25 weeks of gestation and only 1.3lbs (612 grams).

ALMC finds a way to gather the resources they need and are proud to say that no baby is ever turned away because of family finances. The NICU receives a steady stream of doctors and government officials who are interested in the types of interventions and methods that are working to improve perinatal care.

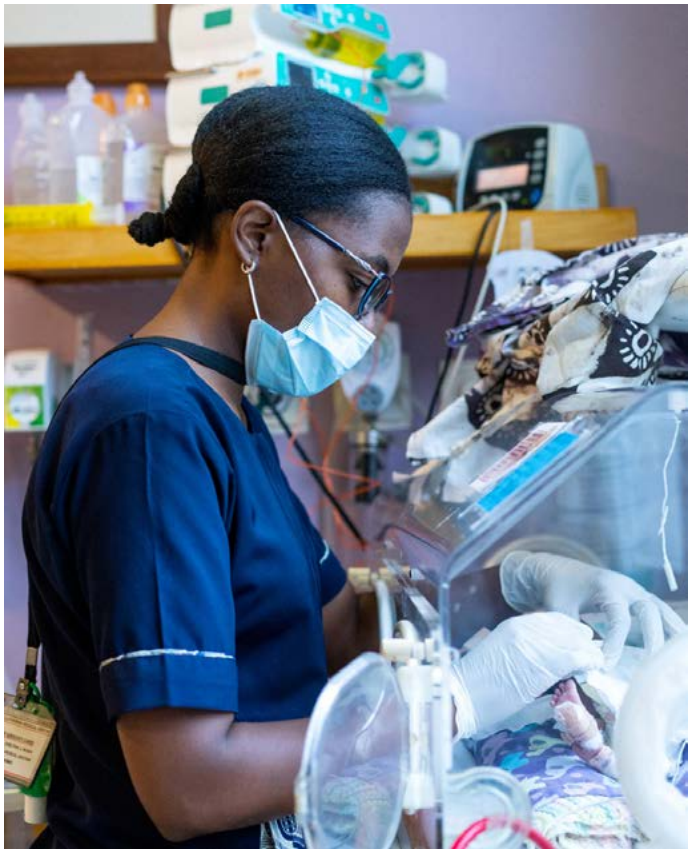
Their smallest survivor was born at a tenuous 25 weeks of gestation and only 1.3lbs (612 grams).

The reward for their determination and efforts is being able to send a baby home.

Dr. Stephen Swanson is an MD, DTM&H, FAAP, American Board Certified in Pediatrics, Infectious Diseases, Tropical Diseases, ALMC Consultant Pediatrician, and Medical Director, NICU. Dr. Swanson works as a pediatric and infectious disease physician and serves in the care of children at Arusha Lutheran Medical Center and Selian Lutheran Hospital in Tanzania. He is developing one of the most

The Realities of Giving Birth in Tanzania

- Neonatal diseases are the #1 cause of death in Tanzania, even above ailments such as HIV/AIDS and malaria.[3]
- The infant mortality rate for Tanzania in 2022 is 35.6 deaths per 1,000 live births.[4]
- Preterm births account for 11.1% of the world's live births, with 60% of them in South Asia and sub-Saharan Africa. In the poorest countries, on average, 12% of babies are born too soon, compared to 9% in higher-income countries.[5]



innovative, low-technology Neonatal Intesive Care Units in Tanzania.

Nonin Medical has developed reliable technologies and manufactured durable noninvasive patient monitoring devices for healthcare professionals and consumers since 1989. Nonin pulse oximeters, cerebral and tissue oximeters, sensors, and software deliver dependable performance day after day—even in challenging environments. With a longstanding commitment to health equity, Nonin is committed to ensuring the accuracy and consistency of its pulse oximetry readings for all patients, inclusive of their skin pigmentation, age, gender, condition, or location in the world, backed by clinical studies and real-world use.

Arusha Lutheran Medical Centre (ALMC) is one of Arusha's newest zone referral hospitals. Located in the center of downtown Arusha, ALMC offers general and specialty care in many areas. The ALMC NICU provides a full range of newborn support, including overhead warmers; temperature-regulated, humidified incubators; phototherapy lights and fiber optic blankets for treating neonatal jaundice; and respiratory support. Arusha Lutheran Medical Centre's NICU annual budget is less than the cost of treating a single baby in an American NICU for three weeks. Most of this NICU care is provided for free or heavily subsidized rates.

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The Neotech Bridge Breastfeeding Assistance System

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Kate Spivak, inventor, PA-C, IBCLC.

Neotech Products LLC recently acquired the Bridge Breastfeeding Assistance System from Laally. Inventor Kate Spivak and her husband, Max, will remain essential members of the product team.

Tell us about your background.
Professionally, I'm a Physician Assistant and an International Board Certified Lactation Consultant.

I've spent most of my medical career in pediatric care, including primary care, neurology, and cardiology. For the last decade, I've also been helping families resolve breastfeeding issues as an IBCLC.

Personally, my family immigrated from Russia in 1998. I grew up and went to school in Brooklyn. Since meeting my husband, Max, we have lived in upstate New York, New Jersey, and now Pennsylvania.

We have two wonderful children, Allison and Matthew. Matthew was the first baby to ever try the Bridge.

What is the Bridge and how does it work?
The Bridge is an easy-to-use, breastfeeding assistance system that helps babies latch to the breast and helps promote milk production. It can be used in most circumstances in which a bottle would traditionally be used, e.g., slow weight gain, pain with latch, delay in milk production, jaundice, bottle preference, etc.

The Bridge consists of a silicone nipple cover with a built-in channel, which attaches to a syringe that can hold breastmilk or formula. When moms encounter supply or latch issues, the Bridge provides a surface for the baby to latch to and a steady supply of milk or formula to keep the baby feeding continuously. This helps the baby to breastfeed and increase mom's natural milk supply.

What drove you to invent the Bridge?
A lack of solutions for the most common issues I was seeing in practice was my main driving force. I consistently saw babies who were being supplemented with a bottle due to low supply and issues with latch. Conventional methods and tips rarely produced any results clinically.

If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

Theoretically, the solution was simple: keep the baby at the breast as much as possible. Realistically, there was no efficient way to do that until the Bridge was created.

What are some of the benefits of the Bridge?
The Bridge takes advantage of the body's natural response to breastfeeding—more stimulation equals more milk. The more the baby stays on the breast, the more milk is created by the body in response. The Bridge allows you to supplement while breastfeeding at the same time. This encourages the natural hormonal feedback mechanism that encourages milk production.

From the parents' standpoint, the Bridge is like no other because it can be used by the parent without help. It's intuitive and does not require an extra set of hands.

The Bridge also provides a surface for the baby to latch on to if the baby is having an issue with latching to the breast.

The Bridge uses a syringe for supplementation, which is key because it gives the parent control over how much supplement the baby gets, the rate, and the timing of supplementation. All these factors help maximize breast emptying and minimize supplementation.

What are some of the challenges you've experienced with competitive products?
There have been no challenges with competitive products because the Bridge is the first of its kind. The bigger issue is the change of behavior that has to happen for people to start using the product.

Think of the iPad in 2010. It was a completely novel idea that people didn't know they needed until it was created. The Bridge is the same. I believe one day it will be the primary answer to supplementation for mothers who want to breastfeed. It will replace the bottle.

Why should hospitals be using the Bridge?
Hospitals are often the first places where babies are exposed to bottle feeding. Hospitals should use the Bridge to help support mothers in the initial stages of breastfeeding if supplementation has been recommended.

It's the ultimate answer for all reasons that the baby could potentially need a supplement (e.g., hypoglycemia-low sugar,

jaundice, weight loss, etc.) without actually interrupting the breastfeeding process.

Describe the journey leading to the Neotech Products acquisition.
As with most startups, our journey was filled with ups and downs. We faced issues that seemed to have no answers and we learned new skills that we never thought we'd need.

Thankfully, the journey was filled with inspiring feedback from families who were able to succeed in their breastfeeding journey because of the Bridge. That's what kept us going.

One of the most successful and inspiring entrepreneurs we encountered, Jules Sherman, suggested we reach out to Neotech because of their similar mentality of primarily helping babies. The rest is history.

Why was Neotech the right company for you?
It was clear from the very first meeting that Neotech was the perfect partner. They understood the product without us having to explain its value. It was more of a brainstorming session about how we can bring it to the people who need it rather than an "elevator pitch." Neotech's family values, reach, and baby-first mission are what makes them the "right company."

How will you be involved moving forward?
I look forward to working with Neotech as the number one supporter of the Bridge. I will continue to serve as an educator, mentor, and ambassador.

We revolutionized the at-breast supplementation method over the last few years and we are excited to see what the next chapter will bring in the hands of Neotech.

We feel like parents who sends their kid off to college (involved, helpful parents). We'll be ready to jump in if the Bridge or Neotech need our help, but we would also like for it to find its place in the world with the support and ideas of its new owner.

News…continued from page 11
what she'd observed in her practice—that parents could, by making stronger emotional connections, change the trajectory of development for preemie infants. With that understanding, Welch created Family Nurture Intervention (FNI), which has been shown to improve the development of premature babies. "We saw that no matter what happened to the baby, no matter how avoidant the baby might be, we're able to overcome this with emotional expression," said Welch, who is now a professor of psychiatry at Columbia University Medical Center. Over the course of the intervention, families work with a specialist who helps bring mother and baby together—both physically and emotionally—until both are calm, which can initially take several hours and over time, minutes. FNI appears to help families—especially mothers—re-establish an emotional connection often interrupted by their babies' stressful and uncertain stay in a neonatal intensive care unit (NICU). In turn, both the infant and maternal nervous systems become better regulated, according to researchers. Babies born preterm can face a range of short-term and long-term challenges such as breathing problems due to an underdeveloped respiratory system, an increased risk of infection from an underdeveloped immune system, and learning difficulties, according to the Mayo Clinic. Many aspects of FNI are not new: The neonatal intensive care unit has long incorporated activities such as scent cloth exchanges, talking to the baby, and skin-to-skin contact. But the approach Welch and her colleagues advocate emphasizes building a bond between the mother and the infant. Mounting evidence shows that FNI can improve a wide range of outcomes for premature babies. In a 2021 study, for example, Welch's group showed that FNI was associated with lower heart rates among preemies in the NICU. A 2016 study linked the intervention to reduced depression and anxiety symptoms in mothers of preterm infants. And a 2015 randomized controlled trial showed FNI improved development and behavioral outcomes in infants up to 18 months. A new study published in *Science Translational Medicine*, showed that the intervention led to a greater likelihood that babies had improved cognitive development later on, narrowing the developmental gap between healthy, full-term babies.

FDA Panel Recommends Withdrawal of Makena for Preterm Birth
A federal advisory panel recommended the United States withdraw from the market an injection given to women at risk for giving birth prematurely. Many of its members argued this step is needed to allow further testing to see if this drug actually works. The Food and Drug Administration has been seeking to pull the approval of hydroxyprogesterone caproate (17P) injection (Makena, Covis) since 2020, after the drug failed to show a benefit in the PROLONG study. This study was meant as a confirmatory trial for the accelerated approval the FDA granted Makena in 2011 based on promising results from an earlier small study, known as the Meis trial. The manufacturer, Covis, contends that the flaws in the PROLONG study made Makena appear ineffective. The FDA asked its Obstetrics, Reproductive and Urologic Drugs Advisory Committee to review the evidence gathered to date on Makena at a hearing that ran from Oct. 17 to Oct. 19. At the conclusion, the FDA asked the committee to vote on whether the agency should allow Makena to remain on the market while an appropriate confirmatory study is designed and conducted.

The vote was 14-1 against this plan. There needs to be another

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Mountain View Hospital Delivers Family-Centered Care, with Healthy Outcomes and Happy Nurses, Through Innovative NICU Design

Anduin Anderle, RN

In the U.S., one in 10 babies are born prematurely, but in many areas of the country, families struggle to access the maternity and neonatal care they need. Each year, approximately 150,000 babies are born to moms living in communities where there can be difficulties obtaining high-quality healthcare before, during and after pregnancy.[1]

At the same time, the nursing shortage continues to impact healthcare delivery throughout the U.S. A 2021 American Association of Critical-Care Nurses (AACN) survey found only 14% of registered nurses were very satisfied in their current positions, and more than two-thirds (67%) intend to leave their current nursing positions within three years.[2]

Mountain View Hospital (MVH), a physician-owned hospital located in Idaho Falls, Idaho, has established a new Level III neonatal intensive care unit (NICU) to better serve families in its community. The innovative NICU design keeps families of premature babies together, while creating a work environment where clinical staff feel valued and supported in caring for their tiny patients.

Meeting the community need for neonatal care

In the state of Idaho, where Mountain View Hospital (MVH) is located, the pre-term birth rate is 8.5% and infant mortality rate is 4.4%, according to the 2021 March of Dimes Report Card.[3] MVH's original NICU, built 20 years ago, could only care for babies born at 35 weeks' gestational age or older.

Babies born earlier than 35 weeks and/or with conditions that exceeded MVH's Level II NICU, needed to be sent to another facility for care, which sometimes meant temporarily separating them from their mothers.

"It was clear that the community needed more places to care for these sick babies and expanding to a Level III NICU let us be able to keep families together," said Brandi Klingler, BSN, RN, MVH NICU Manager.

MVH's goal was to create a Level III NICU that simultaneously met the needs of babies, families and staff. The hospital teamed with Dräger on an integrated contemporary design with innovative neonatal equipment to enable the NICU to achieve its care objectives.

"Mountain View wanted to do more than create a NICU. We wanted to create the best NICU in the area, so we shot for the moon. We worked hard to develop a facility that could help deliver parents peace of mind," said Jake Maughan, RRT-NPS, MVH's NICU Clinical Project Manager.

Focused on family centered care

Design priority number one for MVH was to keep families together.

"We believe keeping parents closely involved with their child's care not only helps their peace of mind, but it has also been shown to reduce stress for babies and improve their short- and long-term health outcomes," said Klingler.

In MVH's new Level III NICU, each of the 14 care rooms is designed to provide a private space and nurturing environment in which neonates can thrive and be with their parents. Parents have 24/7 access to the new NICU.

One of the rooms is large enough to host twins or sicker babies, complete with a queen-size Murphy bed so parents can sleep comfortably.

"We wanted families to have their own space to be with their baby. Our NICU was set up to always allow mom and the dad or whatever support person the neonate needs to be at their bedside," said Brandi Watt, RN, NICU Registered Nurse. "There is also enough room for our team to provide high quality care with the family in the room."

Technology driven for optimal outcomes

Standardizing on advanced neonatal technology was essential for the new NICU.

"Most of our neonates' problems are respiratory-driven," Watt commented. "So, we knew if we could provide amazing respiratory care, we were going to have good outcomes along the way."

The NICU team chose the Babylog VN500 ventilator featuring lung-protective technologies including volume guarantee, which stabilizes mean delivered volumes to prevent lung injury and can reduce the total duration of ventilation.

Anduin Anderle, RN, serves as Marketing Manager for Neonatal Care & Thermoregulation, North American region, for Dräger, an international leader in the fields of medical and safety technology.

They have also implemented the Babyleo TN500 IncuWarmer, which provides a neuro-supportive environment to help reduce toxic stimuli that neonates are usually protected from in utero. This feedback supports developmental care initiatives to reduce harmful stimuli that can negatively impact neonate development, family stress levels, and staff well-being.

"We have everything we need to take care of the sickest infants here," said Klingler.

"I'm really looking forward to being able to do more for these babies," said Kendall Hanson, RN, MVH NICU Registered Nurse. "It was hard when we would get a baby that we couldn't keep because we didn't have the equipment we needed. I'm excited to be able to care for more of these babies and keep them with their families."

Designed for staff satisfaction and seamless care delivery

MVH's NICU, with what Watt refers to as "top-of-the-line in respiratory care" equipment, supports high nursing satisfaction and the ability to both retain and recruit new staff members.

"Recruiting excellent nurses is one thing we have been focusing on – and our state-of-the-art equipment really is a selling point," said Klingler. "I think it shows we are invested in taking good care of these babies, and a lot of nurses really want to be a part of that."

MVH considered not just the diagnostic and therapeutic technology, but also how the overall look and feel of the NICU could help support a happy and healthy work environment.

Because medical caregivers spend long hours in the NICU, it is essential that the environment mimic circadian rhythms and reduce toxic stimuli such as unnecessary alarms. In MVH's new NICU, light and sound levels in all care rooms are continually monitored. MVH chose to fill the walls with restful outdoor scenes from the local area for parents and staff to enjoy. Every space optimizes workflow, adheres to infection prevention practices, and provides privacy.

In addition, the ergonomic GeminaDUO wall-mounted supply system improves NICU workflow by placing critical connections and components within easy reach of caregivers. This head wall system was configured to create a dedicated family space, while lighting options provide high-quality light sources for examination and allow caregivers to safely navigate their workspace when the overhead lights are dimmed.

"Whether it is air, oxygen, suction or plug in cords, [GeminaDUO], the way it is made and how you can just plug things on either side of it, frees that up and makes more space," said Maughan. "It is more user-friendly, and I can see that producing better outcomes."

"Having an edge with equipment is definitely a good thing," Maughan added. "We hope people who want to take care of babies like we do will see that advantage and want to come here because of it."

"We like it all," said Watt. "From the environmental comfort our technology provides for families and infants to the easy-to-use monitoring systems for nurses."

Healthy babies, happy families, satisfied clinicians

The MVH NICU team is now able to care for up to 14 neonates as young as 25 weeks gestational age, keeping families together within a dedicated environment that is pleasant for babies, family and staff members.

Advanced technologies, improved workflow with easy patient access, and ample room for point-of-care equipment help nurses and other clinicians provide high levels of care efficiently and safely.

MVH's Ned Hillyard, Ph.D., Chief Clinical Operations/Compliance Officer, offers this advice to other hospitals on NICU design:

"Quality and patient outcomes should always be at the forefront. The patient must be the centric focus."

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study as a "tiebreaker" to determine which of the previous Makena trials was correct, said FDA panelist Michael K. Lindsay, MD, MPH, who is also director of the division of maternal-fetal medicine for Grady and Emory University Hospital Midtown, Atlanta. "I think there needs to be another trial," Lindsay said. "If you can do the trial without the medication being FDA approved, then I am supportive of that." Members of the FDA panel noted the difficulties that would ensue if Covis attempted further study of Makena with the drug still approved, including difficulties in recruiting patients. Indeed, there were delays in recruiting patients for the PROLONG trial in part because Makena was perceived as the standard of care for pregnant women who had a prior spontaneous preterm birth. That led to efforts to enroll patients outside of the United States, particularly in Eastern European countries. Panelist Cassandra E. Henderson, MD, of the New York-based Garden OB/GYN practice, was the dissenter in the 14-1 vote.

Withdrawing the approval of Makena may lead to increased use of pharmacy-compounded versions of this medicine, as women look for options to try to extend their pregnancies, she said. "They may seek it in other ways and get something that we don't have any control over, and we don't know what the fetus may be exposed to," Henderson said. Henderson also said there should be greater discussion with patients about questions of potential "intergenerational risk" because of fetal exposure to the medicine. Covis could add a registry similar to the University of Chicago's DES Program to its research program for Makena, she said.

Sentec and PyrAmes Form Partnership to Bring Noninvasive Care to Critically Ill Infants

Sentec and PyrAmes have established a commercial partnership to bring Boppli, PyrAmes' first-of-its-kind continuous noninvasive blood pressure device, to neonatal intensive care teams throughout the United States. Boppli has received Breakthrough Device Designation from the US Food & Drug Administration (FDA) and will be available after FDA 510(k) clearance, which is anticipated in the first half of 2023. "We are excited to join forces with Sentec to commercialize our Boppli product," said Xina Quan, PhD, Co-Founder and CEO of PyrAmes. "This important step enables us to bring our breakthrough technology to market and transform patient care. We believe Sentec is an ideal partner for us in the NICU, given our companies' shared mission and focus on noninvasive technologies to enable better healthcare delivery." In the neonatal intensive care unit (NICU) today, a baby's blood pressure is either monitored continuously through an invasive arterial catheter or intermittently through cuff measurements. Both techniques present certain clinical challenges. The Boppli platform offers a new solution to overcome those challenges. "Blood pressures can be difficult to obtain with a cuff, especially in our tiny neonatal patients where the cuffs are too big which impacts accuracy. Arterial lines are the alternative, but any invasive line increases the risk of infection, so we are always trying to remove them earlier if we can. A non-invasive option that provides continuous, accurate measurements would be an important step forward so we can keep a close eye on our babies without causing them pain or overstimulation," said Lamia Soghier, MD, MEd, MBA, Medical Director and Quality & Safety Officer of the NICU at Children's National Hospital. Recent clinical research for neonates has highlighted the importance of neuroprotective care for premature infants, providing an optimal sensory

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Three-Part Series on Aerodigestive Changes and Considerations for the Neonate

Part Three: Use of the Passy-Muir® Valve and Swallowing for Neonates in the NICU

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

This article is the final segment of a three-part series addressing potential aerodigestive changes and considerations for preterm and sick-term infants in the neonatal intensive care unit (NICU). Because of the prevalence of aerodigestive challenges leading to feeding and swallowing difficulties is high for sick-term and preterm infants in the NICU, this series was provided to address some of the primary considerations for this patient population.[1,2] The first article addressed considerations related to extubation, high flow nasal cannula, and pre-feeding skills. The second article addressed feeding trials, protocols, and troubleshooting. Problem-solving critical decisions about developmental expectations and cautious opportunities to feed are essential to optimizing feeding outcomes after the NICU.[3] Some of the considerations for oral feeding trials, multidisciplinary approaches, and troubleshooting changes in breath sounds were discussed in the second segment. This final segment addresses considerations for neonates and infants with tracheostomies, including use of the Passy-Muir Valve (PMV®).

Q: Do infants with tracheostomy in the NICU need to tolerate a PMV before PO trials are started? Is a swallow study needed at some point?

A: If a PMV is an option based on etiology for tracheostomy and clinical status, my clinical experience suggests that establishing tolerance of a PMV before oral feeding trials are initiated in the NICU population is optimal. For both vented and non-vented neonates, the PMV appears clinically to improve swallowing integrity and swallowing physiology under fluoroscopy. However, a definitive relationship between swallow function and use of a one-way valve has not yet been established in the literature, especially for neonates.[3]

The neonate's co-morbidities and the reason for the tracheostomy are the starting point for our differential. Was the tracheostomy placed due to need for long-term ventilation, or were there any airway pathologies? Might they preclude tolerance of a PMV? When was the last time ENT saw the infant to assess airway integrity?

Most tracheostomies in patients in the NICU are performed in cases of chronic respiratory failure requiring prolonged mechanical ventilation or upper airway obstruction related to structural airway abnormalities.[4] Chronic lung disease (CLD) is most often the underlying cause for prolonged mechanical ventilation, with extremely low birthweight and multiple failed extubations predicting the need for tracheostomy in neonates.[5] Structural airway abnormalities in the neonate may include subglottic stenosis, Pierre Robin sequence, tracheomalacia, vocal fold paralysis, or craniofacial syndromes.

Neonates requiring tracheostomy often have other issues and multiple co-morbidities (gross and fine motor delays; altered postural control; sensory, oral-motor, and neurologic deficits; or gastrointestinal issues) that need to be considered regarding readiness to feed. If co-morbidities do not preclude a PMV trial, there is discussion with the team, especially the RT, about readiness, benefits for that neonate, and a timeline.

The neonatal swallow is highly pressure and sensory driven. This is especially critical for those neonates trached in the delivery room, who are chronically vent dependent from birth, and who then have no previous motor learning about swallowing with a normal aerodigestive system. With an open tracheostomy tube, pressures within the aerodigestive system (subglottic positive pressure, negative esophageal pressure, and intra-oral pressures) are altered. Restoration of these pressures via a PMV allows exhaled air to pass into the upper airway and may improve bolus control along the entire swallow pathway for the neonate. Intraoral airflow facilitated by the PMV may increase awareness; therefore, management of oral secretions, as well as restoring taste and smell, may help "guide" the neonatal swallow.

Initiating PMV Trials

My goal in the NICU is to initiate PMV trials following our NICU protocol, which considers etiology for tracheostomy placement and clinical status, and then problem-solve with the RT. We work closely with ENT and Pulmonology to problem-solve those infants who are not progressing as we would expect. In our NICU, our criteria include post-initial tracheostomy change by at least seven days or greater, medically stable, awake and engaged, patent upper airway, reasonably able to manage oral secretions, trach collar or HME, or typically the following lower ventilator

Ms Shaker is the Senior Clinician for Feeding and Swallowing in the NICU/Pediatrics at Advent Health for Children in Orlando, Florida. She is a recognized expert in swallowing and feeding across all pediatric settings and teaches both nationally and internationally to physicians, nurses, and therapists. With almost 45 years' experience, Ms Shaker has been a part of large level III and IV NICUs since 1985. A Board-Certified Specialist in Swallowing and Swallowing Disorders, Ms Shaker's passion is infant-guided feeding and family-centered care. She is the author of several articles on NICU intervention and co-author of The Early Feeding Skills Assessment Tool for NICU Infants. She can be reached through her website: www.Shaker4SwallowingandFeeding.com.

Use of the PMV 007 in-line with mechanical ventilation for an infant.

settings: Fraction of Inspired Oxygen (FiO2) ≤50%, PEEP ≤10, and PIP < 40 cmH_2O.

In our NICU, the ENT typically places a Bivona Flextend TTS (Tight to the Shaft) tracheostomy tube; the cuff rests tight to the shaft of the tube, with the profile of an uncuffed tube. Our ENTs tell us that this allows for a variety of airway management needs. The TTS cuff can be inflated with water to help seal the trachea for a ventilated neonate if needed, but in our NICU even with ventilated neonates, the cuff is typically deflated. If cuff inflation is required, it is unlikely that the neonate would be tolerating the required lower ventilator settings for PMV trials. If the neonate was tolerating the lower ventilator settings, the RT would suction and deflate the cuff very, very slowly to help the infant adjust to the change and suction post cuff deflation.

When readiness is then established, the RT and therapist proceed with a PMV trial, using the PMV®007 (Aqua color™) in-line with the vent and the PMV®2001 (Purple color™) for non-vent dependent neonates. It is important to start with a secure, swaddled, developmentally supportive position; offering a pacifier or the infant's own hands to mouth; and rhythmical vestibular and tactile input to optimize state regulation and provide a positive experience. Visual engagement and a familiar voice from the parent and the therapist often help to calm and reassure the infant. This step may take several sessions, depending on that neonate's unique history, co-morbidities, and age. Neuroprotection and infant-guided progression are essential along the way. The newness of restored airflow into the upper airway may be an unfamiliar and, at times, somewhat frightening sensation for the neonate. If the infant senses secretions and coughs for the first time, that event may surprise the infant; reassurance is often successful. Short daily trials to gain comfort with sensed secretions and airflow into the upper airway are offered and progressed in terms of frequency and length based on the infant's communication and tolerance.

Then, if co-morbidities and readiness safely allow, and with the PMV donned, we begin with offering pacifier dips. Once pacifier dips are tolerated, this is followed by cautious experiences with limited, brief therapeutic oral feeding trials with interventions (developmentally supportive positioning, single sips via a slow flow nipple, co-regulated pacing, and resting). Once the neonate has some careful infant-guided experience with swallowing nutritively with the therapist, we then objectify swallowing physiology in radiology, due to the high risk for silent aspiration in the neonatal population.[6] I carefully plan the study to allow imaging both with the PMV donned and doffed, gathering data and providing insights for the medical team and nursing staff related to observed benefits of the PMV. This process is always tailored for each neonate through collaborative team problem-solving.

Once an instrumental assessment is complete, then therapeutic interventions and options for oral feeding are determined and appropriate goals are addressed. When considering some of the more prevalent challenges faced in the NICU as it pertains to feeding considerations and tracheostomies, this series of discussions provided an overview of protocol and therapeutic interventions. While we still have much to learn as it relates to working with the pediatric population, especially the medically complex and fragile infants with tracheostomies, clinicians who are using the PMV with this population continue to inform our practice with their clinical experience and research. The more that we address the needs early in the patient's care, the better chance the patient has to feed, manage secretions, and communicate. Understanding the physiology and pathophysiology of respiration and swallowing are critical to providing best practices. Being informed about normal infant anatomy and potential upper airway obstruction which may impact airway patency are key to successful Valve placement. Providing access to the upper airway will enhance overall care and progress of the patient. If a facility has established a team, policies and procedures, and a best practice guideline, then managing this special patient population will be possible when using a PMV during mechanical ventilation, PO, and communication. 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.

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environment for babies who should otherwise still be in utero. Everything from sound and light levels to the frequency of painful or stimulating procedures (such as blood draws, cuff measurements, suctioning, or even diapering) can impact proper neurological development. More and more, NICUs are creating quality care bundles with the goal of systematically providing neuroprotective care and improving neurological outcomes for their patients. Sentec's flagship transcutaneous CO_2 monitoring technology has been adopted by top NICUs around the world looking to keep a close eye on their patients' respiratory status while limiting painful and invasive blood draws. The exclusive distribution partnership between PyrAmes and Sentec will allow Sentec customers to be among the first NICUs to adopt the Boppli solution. "We are humbled and enthusiastic about offering our healthcare customers yet another option for noninvasive monitoring that advances their goals of providing less invasive, more neuroprotective care in this critical and vulnerable patient population," said Bob Cormier, President of Sentec North America. "We are confident that our partnership with PyrAmes will provide value to our companies, our customers, and most importantly, to patients.

Donation Helps Significantly Expand Capacity for Sickle Cell Disease Screening in Ghana

PerkinElmer Inc., a global leader committed to innovating for a healthier world, today announced the Company has donated to Ghana's Health Services' initiative to increase the country's screening of newborns for sickle cell disease (SCD) from its current 4 percent of all babies born in the country to 50 percent by 2030. PerkinElmer's contribution of easy-to-use, scalable laboratory solutions enables Noguchi Memorial Institute for Medical Research, University of Ghana to be a Center of Excellence and National Training Center for SCD newborn screening with the ability to build screening capacity for an additional 50,000 babies annually. The PerkinElmer-provided Migele™ Gel Electrophoresis Systems will support Ghana's need for reliable, fast, and cost-efficient SCD screening. With the government's desire to enact a country-wide screening program, the PerkinElmer solution's flexible and scalable design can meet growing high-capacity requirements as screening coverage and sample volumes increase. "PerkinElmer is committed to helping the government of Ghana develop sustainable end to end solutions that focus on screening and diagnosis, in addition to comprehensive care for SCD," said Marika Kase, business director, reproductive health at PerkinElmer. "We would like to congratulate Ghana Health Services and the Sickle Cell Foundation for the milestones gained so far, in advancing the diagnosis and care of patients with the disease in the country. We hope that this donation will facilitate development of Ghana's SCD screening program and will therefore improve the lives of children in the region." As part of its commitment to the Sub-Saharan African region, PerkinElmer, together with the Novartis Africa Sickle Cell Disease program, is aiming to expand advocacy efforts to educate patients, caregivers and communities about the importance of newborn screening and early intervention with hydroxyurea (HU) and other SCD treatments.

Study Finds Vat Pasteurization Retains Molecular Structure of Naturally Occurring Bioactive Proteins in Human Donor Milk

Prolacta Bioscience, the world's leading hospital provider of 100% human milk-based nutritional products for critically ill,
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Importance of Connectedness to Attachment for NICU Parents

Nicole Nyberg MSN, APRN, NNP-BC

Introduction

Admission into the Neonatal Intensive Care Unit (NICU) has a significant impact on the infant, parents, and the entire family unit. Through the lived experiences of NICU families, we have learned that parents face a range of emotions, including stress, anxiety, grief, guilt, feelings of helplessness, and depressive symptoms that often lead to post-traumatic stress disorder. The experience can be traumatic, cause psychosocial distress, affect parent-child bonding, and negatively affect both short-term and long-term developmental outcomes for the infant (Lean et al., 2018). Recent literature has focused on identifying the specific aspects of the NICU experience that parents find stressful, so family-based interventions can be directed specifically to amend parental distress.

The Impacts a NICU Admission Have on Parent-Child Attachment

Once an infant is whisked away to the NICU, even if the admission was anticipated, all of the parent's idealistic moments have instantly been replaced by a traumatizing experience. The initial crucial moments of parent-child bonding, skin-to-skin care, and nursing have been stripped from them, and their instinctual parental obligations are taken from them just as their baby was taken to the NICU.

The NICU environment is unfamiliar. In the NICU, new parents cannot perform the much-anticipated parenting activities such as holding, bathing, nurturing, feeding, comforting, or diaper changing. Parents experience a loss of control due to the care team members and policies dictating their ability to interact with their infant, resulting in parental role alteration (Sabnis et al., 2019; Woodward et al., 2014). The alteration in parental role becomes even more amplified when parents feel like guests as they walk through the intimidating NICU hallways to "visit" their baby. Parents report their perceived loss of parental role, the physical separation, and the feelings of helplessness in their inability to protect their infant from painful procedures as the most stressful aspects of their NICU experience (Woodward et al., 2014).

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Unfortunately, the perceived parental role alteration can negatively influence parent-infant attachment, which impacts the overall health and well-being of the infant and parent. For children, bonding with a parent is fundamental for appropriate growth and development. If parents feel incompetent, unprepared, uneducated, and unable to care for their infant, it will impact their ability to bond with and learn their infant's developmental cues. Promoting a secure attachment between parents and infants has many long-term benefits; studies have shown that securely attached children have increased social competence, enhanced emotion regulation skills, and greater independence (Gibson et al., 2020).

Family-Integrated Care

The high-intensity NICU environment, coupled with the forced separation between an infant and parent, is also very traumatic for parents and will interrupt the attachment process. Unfortunately, parent-child bonding will not only be affected during the NICU experience but in the months and years to follow. To help mitigate the parent's feelings of powerlessness which commonly interfere with parental engagement and attachment, a personalized, family-integrated approach that fosters empowerment and actively involves parents in decision-making should be instituted.

Recently, due to the forced separation of parents and their infants in the NICU during the COVID-19 pandemic, as part of the "New Existence," there has been a focus on shifting the paradigm away from the system-and-provider-centric paradigm to one that focuses on the experiences and outcomes of patients

(Beryl Institute, 2022). According to the Beryl Institute Family Experience Workgroup (2022), caregivers should be designated as "essential care partners" at healthcare facilities, not "visitors" but key members of the care team who play a critical role in patient outcomes. According to the Consensus Statement released by NANN, AWHONN, and NPI in 2021, the purpose of family-centered care and neonatal intensive parenting units (NIPU) is to transform typical NICU care into a family-integrated model in which parents are ultimately involved in all aspects of care while in the NICU and are valued as respected members of the care team. By accepting parents as essential members of the care team, they will embrace their role as integral care partners, empowering them to stay engaged and ultimately promoting parent-child bonding.

Additionally, integrating trauma-informed care with family-centered care into all aspects of care for the NICU infant and family can not only alleviate but positively transform some of the trauma they have endured. Many hospitals have started to become more aware and recognize the emotionally traumatic impacts of having a child with a serious medical issue. Within trauma-informed care, a cultural transformation takes shape as a caring collective of energized, empowered, and engaged professionals become more connected with NICU families (Caring Essentials).

Properly identifying interventions that effectively promote attachment in NICU families may foster advantageous short- and long-term developmental health outcomes and promote maternal and paternal well-being (Kim et al., 2020). The provision of focused, family-integrated care in the neonatal environment enhances parent-infant attachment and often includes skin-to-skin care, psychotherapeutic interventions, baby diaries, and the use of photos and videophones to allow parents to see their infant when they cannot be physically near them (Kerr et al., 2017).

Parents may be physically separated from their infant in the NICU due to the need for a higher level of care for the infant, geographic distance from their home, or additional responsibilities at work or to care for other children at home. Therefore, care team members in the NICU must purposefully engage families to bridge the separation gap because family caregivers are critical to positive and successful patient outcomes. The involuntary separation between the infant and parents due to restrictive visitation policies during the COVID-19 pandemic challenged NICUs even further to find more creative ways to promote an environment of family-integrated care; to help parents feel connected to their infant despite the limited physical interactions.

Supportive Tools to Promote Connectedness

Connectedness, defined as the state of being joined or linked, is crucial to parent-infant attachment. Despite parents being physically separated from their child, supportive tools are now available to ensure that parents remain involved in all aspects of care, ultimately enhancing their connection to their infant. The advances in technology, with the use of webcams and/or the ability to virtually communicate updates with parents, have not only helped to minimize stress and anxiety for parents, but they foster feelings of connection, collaboration, closeness, calmness, love, and attachment. Once these fundamental building blocks are established, it catalyzes the process of attachment between parents and infants. According to Kilcullen et al. (2022),

parents have reported that the ability to see their infant via the webcam enhanced their ability to bond with their infant, and they experienced "feelings of love" and that they could "build a connection when they were not there."

Additionally, there are platforms that allow the NICU care team members to communicate and connect on a personal level with the family via messages or by sharing a video or photograph. By sharing patient-specific, memorable moments with caregivers (moving into an open crib, taking a full bottle, or sharing a therapy session), the NICU care team members can efficiently communicate with families in a secure and meaningful way. Once a care team member captures a special moment or milestone (such as an image, video, or text message), it can be shared with the parent through a HIPAA-compliant apps like AngelEye Health's CameraSystem and PatientConnect solutions.

The parents receive a push notification to notify them that they have a new message, image, or video to view, and the messages can be translated into the parent's native language. The NICU clinicians can also provide clinical updates, introductions, and offer virtual updates during rounds to foster collaboration and ensure that the parents continue to feel like active care partners even when they cannot be physically present. There is evidence to suggest that NICU family satisfaction scores improve when personalized information is provided to families (Gibson et al., 2020). As one parent reported, "I felt seen and acknowledged and it felt like I was receiving messages from my baby."

Parents genuinely appreciate when NICU care team members share photos, videos, and memorable milestones of their baby. NICU care team members foster a more personalized, family-integrated approach by sharing information that spotlights the small victories throughout each shift. This enhances the connectedness between the parents and infant and strengthens the relationship between the parents and NICU clinicians. Developing a trusting relationship with NICU clinicians is difficult for parents to achieve but necessary for parental well-being. As NICU nurses are often the lifeline between the parents and their infant in the NICU, their consistent presence, coupled with holistic, personalized care supported with regular communication, fosters a more trusting relationship with the parents. Critical care patients and their families have identified a lack of information/knowledge as a key factor that influences their experience of critical care (Garner et al., 2020).

Most importantly, parents reported that the care team's messages helped them feel more connected to their child, minimized their anxiety and "provided reassurance" and "peace of mind." For NICU parents, it is not the quantity of information provided, but the degree of empathy it is delivered with that reduces parental stress and allows for successful parent-infant attachment. With the implementation of empathetic, caring communication, even via messaging, parents feel valued and therefore know how much the NICU care team values their child. As one mother reported, "It made me feel happy to see the nurses taking great care of my baby and treating him like he was special and cute." The personalized approach from the care team strengthens the connection, collaboration, and team dynamics ensuring that the parents feel like essential members of the care team.

Communication from the NICU care team provides the parents comfort and reassurance and assists them with the transition into parenting at home. Virtual education and training can also be provided and customized for parents throughout their NICU stay and in preparation for discharge. With the ability for care team members to send patient-specific images and videos, they can offer parents anticipatory guidance and help them troubleshoot potential questions. NICU care team members can send videos showing parents how to prepare and mix their infant's home feeding plan, the best way to secure their oxygen tubing, or how to troubleshoot a pulse oximeter that is not reading well. Parents may also have access to the videos or images to reference beyond discharge. With the support and coordination of care, the virtual updates and education provided throughout the NICU stay keeps the parents engaged and minimizes their stress as discharge approaches. Promoting parental involvement equips parents to confidently care for their infant, bridging the common gap in knowledge between the NICU and home.

Additionally, members of the NICU care team report that the ability to send personalized, virtual updates is "easy and fun" and the "best gift we could give them [parents] during their separation." Once parents receive the virtual updates, it minimizes phone calls, ultimately decreasing interruptions in nursing workflow. A mother reported that "it was nice to see the updates and messages on my son's progress, and it was enough where I didn't have to call for an update." By consistently sharing information, parents stay updated, informed, and in active collaboration with the care team despite when they are not physically present. The NICU care team members recognize the importance of personalized messages; as one nurse stated, "I think parents really appreciate the updates, and it's a nice way to help them feel more connected." Sending the parents a clear picture enhances the bond between care team members and parents and has "impacted families tremendously because they feel more connected."

It has been widely accepted in research that NICU parents experience stress, fear, anxiety, parental role alteration, trauma, and depressive symptoms once their infant has been admitted to the NICU. To help mitigate the adverse effects and promote parent-infant attachment, family-integrated care interventions that support, engage, empower, and educate NICU parents throughout the NICU experience must be implemented. Using supportive tools to bridge the gap when parents cannot physically be present with their infant leads to better patient satisfaction scores and improved outcomes. Keeping parents involved and updated virtually helps form positive relationships between the care teams and parents, demonstrating the importance of their contribution as crucial care team members.

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Air Way Obstructive Mucous Casts in an Extremely Preterm Infant with Severe Fetal Inflammatory Syndrome

Koravangattu Sankaran and Xiaolan Zhang

Abstract

Conservative obstetric management strategy following preterm premature rupture of fetal membranes and loss of amniotic fluid in the absence of active fetal infection but with concomitant severe fetal inflammation and severe oligohydramnios can result in birth of an infant with dry lung syndrome, presence of sticky upper and mid airway mucous casts causing obstruction of air ways, lung collapse with or without pulmonary hypoplasia. In such a scenario the case room resuscitation calls for swift diagnostic assessment and, quick timely management strategy in order to save and preserve intact life. We present such a case of a male infant weighing 690 gms, born with severe respiratory distress to a 37 year old primigravida at 23 weeks and two days gestational age and with a history of preterm premature rupture of membranes started at 21 weeks and 2 days.

Introduction

The conservative obstetric management of preterm premature rupture of membranes may result in birth of infants with neonatal sepsis, dry lung syndrome, pulmonary hypoplasia, acute respiratory distress and fetal inflammatory syndrome.[1,2,3] The maternal prophylactic antibiotic treatment may also create a situation where the fetus shows evidence for fetal inflammation without infection.[4] In such a scenario it is possible in some pregnacies to have a birth of a neonate through oligohydramnios with dry lung, mucous plugging and lung collapse.[5] Certainly these infants will have acute respiratory distress at birth creating an enormous challenge to the attending physician. Here in we present such a case.

Case Report

A male infant was born to a 37 year old primigravida at 23 weeks and two days gestation. Both parents were healthy, educated at postgraduate level. Mother reported normal periods had early ultrasound and normal antenatal screening tests for fetal anomalies and inborn errors of metabolism. The pregnancy was complicated by mild hypertension and rupture of membranes at 21 weeks and 2 days (PPROM). Her temperature was normal. Obstetric examination confirmed rupture of membranes and loss of amniotic fluid (AF). Fetus was active with normal heart rate and variability. She was in hospital for 4 days for observation and was treated with prophylactic antibiotics. I (first author) saw her on consultation discussed resuscitation guidelines, pros and cons on survival including oligohydramnios, lung growth and fetal infection. They were reminded that the membranes were fetal origin and the barrier was broken. Parents elected for full resuscitation if the infants condition was reasonable at birth. She returned to the hospital few days later at night with labor pains and uterine contractions. I was the supervising neonatologist that night.

A live male infant with was born by spontaneous vaginal delivery with a birth weight of 690 gms. The APGAR scores were 3 at 1 min 4 at 5 min and 6 at 10 minutes respectively. Bag mask with intermittent positive pressure ventilation with high (10 to 12 cm) positive end expiratory pressure did not result in any appreciable clinical improvement. Endotracheal (ET) intubation with 2.5 ET tube and bagging also showed no improvement. During the procedure of intubation I noticed a mucous strand at the glottis. Realizing this, it was our thought that the lack of air entry may have been due to partial air way obstruction. After removal of ET tube on direct visualization a fairly long stringy mucous cast was pulled out using a McGill forceps. Reintubation and bagging with 100% oxygen showed some improvement in color.

Encouraged by this action the trachea was flushed out using half strength surfactant at 0.5 ml aliquots instilled, bagged and suctioned out through ET tube until the clinical condition showed remarkable improvement. The material suctioned out was yellowish and mucousy at first. A sample was sent for culture. Once the infant was thought to be stable a full dose of Surfactant mixed with 125 microgram of budoniside was administered. Placenta was sent to pathology. Both parents were present and observed the entire resuscitation process. After a brief moment of skin to skin contact with mother the baby was transferred to Neonatal Intensive Care Unit (NICU) and placed on high frequency oscillatory ventilation (HFOV)

In NICU after further stabilization, routine canulations, cultures and blood work the infant was placed on our NICU tiny baby protocol for ongoing care as we have one of the best intact survival statistics in Canada (Canadian Neonatal Network annual report). Blood and tracheal aspirate cultures returned negative. Placental pathology was negative for chorioamnionitis. The only abnormal blood test was very high white blood cell count (44,000) which returned to normal range in 10 days. Tracheal budoniside was repeated in 0.5 ml surfactant was repeated for 3 more doses at weekly interval. The progress of the baby was fairly unremarkable and was able to be discharged home at 39

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weeks and 5 days post conceptional age with a discharge weight of 2.6 Kg. At follow up contact several month later for permission of publication mother reported excellent growth and appropriate development.

Discussion

We believe swift diagnostic assessment, quick case room resuscitation and management of this infant was unique and interesting. To our knowledge and after a limited literature search we failed to reveal a similar case publication. The antenatal consultation and advanced and proactive discussion with our resuscitation team certainly helped in the seamless and up-to-date management of this case. Fetal inflammation without fetal infection along with rapid turn over of white blood cells and subsequent release of cytokines and chemokines concomitant with oligohydramnios can accelerate the production and deposition of mucous and cell debris in fetal lung facilitating the formation of tracheal plugs and obstruction. The same process in the traheobronchial tree and terminal airways can induce inflammatory storm in the lung laying foundation for later development of bronchopulmonary dysplasia (BPD). Mitigation of this process was the intent of the treatment with budoniside. We have previously observed occurrence of severe BPD, pulmonary hypertension and lung infection in such infants.[6] The neonatal outcomes long and short term has not been very good following prolonged rupture of membranes in general.[7,8] Fortunately our case did very well both long and short term. PPROM and chronic loss of AF can also induce pulmonary hypoplasia. However we believe pulmonary hypoplasia did not occur in this case as the PPROM was of relatively short duration and amniotic fluid balance was not broken in an adverse matter. Certainly the smooth progress and ability to wean off oxygen fairly rapidly was in support of this assumption. The idea of using dilute surfactant solution was in fact an adaptation of similar process we have been accustomed to, in the case room management of meconium aspiration syndrome Surfactant is a biological soap. We all know that soap can be used to break down particular matters and makes it easy to be suctioned out. In this case certainly, it helped us to break down mucous and cell debris in the upper and mid air ways and enabled to be suctioned out as frothy aspirate. The unrecovered surfactant solution went down the airways to help in the lung inflation and air exchange. Quick thinking, awareness of mucous plugs and anticipatory management in case room resuscitation process can save lives of preterm infants.

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Parents of this infant specially requested to keep the identities private. So the consent is kept in my file, Dr Sankaran was responsible for the care of the infant, Dr Zhang was a visiting fellow did literature search a d reviewed the manuscript.

Arm Adduction and Movement of Peripherally Inserted Central Catheters in Neonates

Faiza Javed, MD, Estephaine Rivero, MD, Shabih Manzar, MD

Peripherally inserted central catheters (PICC) are needed to facilitate secure long-term central intravascular access in premature infants.[1] PICC inserted through the lower limbs has a low risk of complication compared to the upper limbs.[2] In practice, it is often noted that the PICC tip moves with the arm position. For that reason, providers prefer an X-ray with the arm next to the chest (adducted position) to see the tip of the PICC. This article highlights the importance of knowing the difference between the effect of arm adduction on the movement of the PICC tip inserted through the cephalic vein and the basilic vein.

Interestingly, with adduction on the arm, the PICC inserted through the cephalic vein moves outwards while it moves inwards when the basilic vein is used.[3] Figure 1 demonstrates the inward movement of the PICC tip when the arm is adducted (a basilic vein was used to insert the PICC).

Figure 2 explains the difference between the cephalic and basilic vein PICC. Adduction of the arm (movement towards the chest wall) pulls on PICC inserted through the cephalic vein while pushing it into the basilic vein.

In summary, it is crucial to appreciate the expected migration of PICC when the upper arm is used and to know the outward-inward movement difference between the cephalic and basilic vein PICC lines.

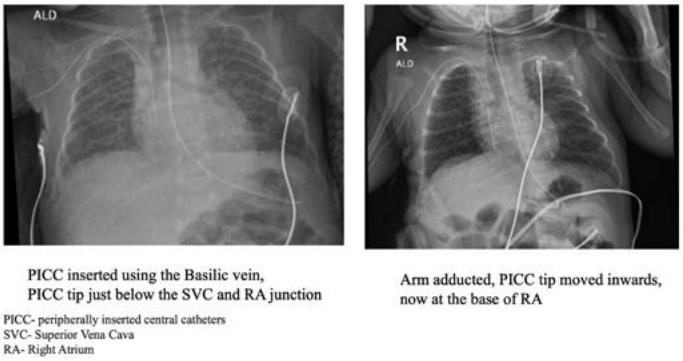

Figure 1. X-rays showing the movement in Peripherally Inserted Central Catheters (PICC tip) with the adduction of the arm.

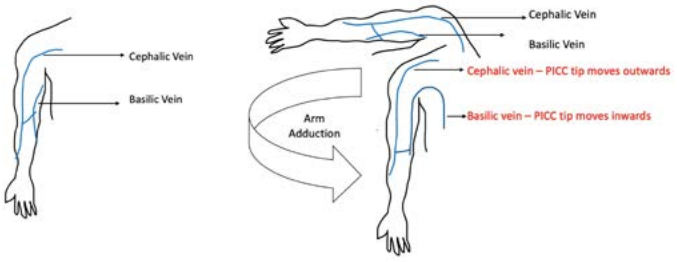

Figure 2. Diagram showing the anatomy and the effect of arm adduction on the movement of PICC.

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Congenital Central Hypoventilation Syndrome in the Neonate: A Historical Literature Review and Recommendations

Dawn Headrick, BSRC, RRT, RRT-NPS and Christopher Russian, PhD, RRT, RRT-NPS, RPSGT, FAARC

Introduction

Congenital central hypoventilation syndrome of the neonate (CCHS) has long been considered a disorder of respiratory control. The first case was reported in 1962 by John Severinghaus and Robert A. Mitchel in *Ondine's Curse: Failure of Respiratory Center Automaticity While Awake*.[1] In 1970 Mellins et al. in the publication, *Failure of Automatic Control of Ventilation (Ondine's Curse)*,[2] first described patients with CCHS as having disordered respiratory control and autonomic regulation. Subsequent reports focused more on it being a disorder of ventilatory control. It has further been distinguished as a disorder of autonomic regulation.[3] In 2003, it was discovered that CCHS was a result of a mutation on the PHOX2B gene.[3] The PHOX2B genotype is used to guide physicians in the assessment and anticipatory management of individuals diagnosed with CCHS.[3] The primary purposes of this paper are 1) to review the pertinent literature related to diagnosis and treatment of congenital central hypoventilation syndrome in the neonate, 2) to increase awareness of the genotype identified as the marker for congenital central hypoventilation syndrome, and 3) to understand the multiorgan complications associated with CCHS.

History

Congenital central hypoventilation syndrome (CCHS) is known colloquially as Ondine's curse.[4] In 1999 the American Thoracic Society issued a statement on CCHS estimating only 160-180 cases worldwide.[3] However, due to the advent of a simple polymerase chain reaction test to definitively diagnose CCHS in 2003, more than 1000 cases worldwide have been confirmed.[3] In 90% of isolated cases, CCHS is identified as autosomal dominant, in which only one copy of the altered gene causes symptoms.[4]

Definition

CCHS is defined by the frequency, duration, and severity of hypoventilation while awake or asleep. Hypoventilation during sleep in children is defined as a PCO2 >50 mmHg during >25% of total sleep time.[5]

Signs and Symptoms

The hallmark sign of CCHS is alveolar hypoventilation.[6] Patients with CCHS demonstrate alveolar hypoventilation with diminutive tidal volumes and monotonous respiratory rates during sleep, and in severe cases, also during wakefulness.[7] In addition, they have a diminished sensitivity of CO_2 receptors in the medulla.[4] Initial symptoms are usually observed in the neonatal period, with the first case being reported in 1970.[8] Newborns will present with apnea, cyanosis, hypoxemia, hypoventilation, and/or persistent respiratory failure with the inability to wean off ventilatory support.[9] The most distinguishing symptom is shallow breathing while asleep.[4] However, they usually do not exhibit signs of respiratory distress when challenged with hypercarbia or hypoxia.[6]

Diagnostic Testing

CCHS is commonly mistaken for many treatable diseases.[4] CCHS is diagnosed when cardiac disease, neuromuscular disease, or an identifiable brainstem lesion is ruled out.[4] Electrical activity of the diaphragm (EAdi) can be measured to assess the neural respiratory drive and respiratory control.[10] However, the diagnosis is confirmed by testing for mutations on the PHOX2B gene.[6]

Diagnostic Testing Literature

In *Congenital Central Hypoventilation Syndrome and Sudden Infant Death Syndrome: Disorders of Autonomic Regulation*, Rand, et al.[6] reported that in 2003 Amiel et al.,[11] Sasaki et al.,[12] and Weese-Mayer et al.,[13] analyzed the genes responsible for maintenance or function of the ANS (autonomic nervous system) and published the findings in their respective journals.[11,12,13] This led to the discovery of PHOX2B as the gene which defines the diagnosis of CCHS. Amiel et al. described heterozygous mutations resulting in expansion of the PHOX2B finding for CCHS.[11] Patients could display PARMs (polyalanine repeat expansion mutations) or non-PARMs. It was further identified that the greater the PARM length, the more severe the respiratory and autonomic dysfunction. In 2013, CCHS was highlighted within the category of respiratory and autonomic disorders of infancy, childhood, and adulthood (RADICA). The genetic basis for CCHS was identified as mutations of the paired-like homeobox gene, (PHOX2B). Identification of the PHOX2B genotype-CCHS phenotype relationship has opened research avenues to help reduce the burden this disease imposes. It was further noted that up to 25% of the cases of CCHS are inherited mutations from an infected parent. A small note was made about the use of MRI testing on the structures of the brain which control breathing. However, results were inconclusive due to the small size of the cohort used.[11]

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In *Dysregulation of Locus Coeruleus Development in Congenital Central Hypoventilation Syndrome*, Nobuta, et al.[14] used a transgenic mouse model by which they were able to identify CCHS gene mutations early in the embryonic stage. It was noted that disruption of the locus coeruleus (LC) nonadrenergic neuron development may be a common feature allowing early detection of CCHS.

In *The Genetics of Congenital Central Hypoventilation Syndrome: Clinical Implications*, Bishara, et al.[15] introduced three testing methods for establishing CCHS and its severity: 1) PHOX2B targeted mutation analysis (screening and fragment length analysis), 2) PHOX2B sequencing test, and 3) deletion/duplication analysis.[15]

In *Monitoring Diaphragm Electrical Activity and the Detection of Congenital Central Hypoventilation Syndrome in a Newborn*, Szczapa, et al.[10] describes a single case study performed on a 4560-g female born via cesarean section at 38 weeks gestation. The patient's neural respiratory drive and respiratory control were measured using a NAVA catheter. This catheter has sensors which can detect the electrical activity of the diaphragm (EAdi). Testing was prompted due to respiratory insufficiency and an older sibling suffering from cerebral palsy. The patient was observed to display hallmark signs of CCHS while asleep. Further testing was done, and the patient was found to have the genetic marker of PHOX2B.

In *Rare Cause of Neonatal Apnea from Congenital Central Hypoventilation Syndrome*, Tovichien, et al.[8] determined the diagnosis of CCHS in neonates can be made in the absence of hypercapnic ventilatory response. Further molecular testing for the PHOX2B gene confirms the diagnosis.

Summary

With the discovery of the PHOX2B gene being linked directly to CCHS, physicians are now able to definitively diagnose and set up an early treatment plan for those born with or displaying symptoms of CCHS. In 2018 studies were published by Bishara, et al. in *The Genetics of Congenital Central Hypoventilation Syndrome: Clinical Implications*, which established testing methods to confirm the severity of CCHS.

Treatment Modalities Literature

In *A Case of Congenital Hypoventilation Syndrome with a Novel Mutation of the PHOX2B Gene Presenting as Central Sleep Apnea*, Amimoto, et al.[7] reports a 5-month-old, having been diagnosed via polysomnography (PSG) with sleep apnea, underwent further testing and was revealed to have CCHS. Positive pressure ventilation via a tracheostomy tube is recommended during the first few years of life. However, the parents refused, and the patient was placed on non-invasive positive pressure ventilation (NIPPV). Pressures were titrated during PSG to achieve optimal alveolar ventilation.

In *Congenital Hypoventilation Syndrome: Diagnostic and Management Challenges*, Kasi, et al.[6] reiterated all patients diagnosed with CCHS will require ventilatory support for life, at least during sleep. Positive pressure ventilation (PPV) via tracheostomy is the preferred method during infancy and childhood. Older children and adults may qualify for non-invasive positive pressure ventilation (NIPPV) via a nasal mask, nasal prongs, or face mask. Diaphragm pacing (DP), which uses the patient's own diaphragm as the respiratory pump, was introduced as an alternative to those patients who do not require full-time ventilator support.

Kasi, et al. noted adult CCHS patients with 20/25 PARM genotype also display cardiac arrythmias. Although this is usually considered a milder mutation, the adult onset cardiac arrythmias most often require a pacemaker.

Challenges to managing CCHS, in adults, were noted to include avoiding alcohol and illicit substances due to their ability to depress the respiratory response. Pregnancy may also decrease ventilation due to the increasing size of the uterus. Adequate ventilation and oxygenation should be closely monitored in this group, especially if utilizing DP.

In *Congenital Hypoventilation Syndrome: An Overview of Etiopathogenesis, Associated Pathologies, Clinical Presentation, and Management*, Zaidi, et al.[4] introduced intelligent volume-assured pressure support (iVAPS) ventilation as a non-invasive positive pressure ventilation (NIPPV) mode which modulates to assure constant alveolar ventilation. Researchers have also been trialing the use of NAVA during NIPPV, which might be beneficial on young children who would usually be supported via a tracheostomy. If this approach is successful in keeping the alveolar ventilation consistent, a tracheostomy may no longer be needed in young children.

Zaidi, et al. reported the use of pharmacological agents, such as progestin, has shown to have a therapeutic effect by inducing respiratory neuroplasticity and activating chemosensitive neural circuits.[4] In vitro experiments are also being conducted in hopes of localizing and recovering the activity lost with the PHOX2B gene mutation.

In *Guidelines for Diagnosis and Management of Congenital Central Hypoventilation Syndrome*, Trang, et al.[5] reported that patients with CCHS demonstrate a decreased respiratory rate and reduced tidal volumes. Management of this requires ventilatory support. Table 1 highlights important features of ventilatory management.

There are four types of ventilatory support available: positive pressure through a tracheostomy, positive pressure through a

Table 1. Keys to CCHS Ventilatory Management[‡]

Ventilation Requirements During Sleep
• Respiratory assessment, both spontaneous and assisted ventilation, while asleep and awake.
• Trained caregivers monitoring of patients.
• Home ventilators recommended.
• All ventilations parameters are set and adjusted by professionals on a regular basis.
• All safety guidelines are followed during ventilation including back-up rates and alarms.
• All ventilated patients monitored with oximetry and capnography.
• Target pCO2 35-45 mmHg and SpO2>95%
• Tracheostomy is the most common method of ventilation in neonates and young children.
• Uncuffed cannulas recommended.
• Supplemental humidification recommended.
• Mask ventilation is preferred for older children. But still requires close monitoring.
• Follow up with maxillofacial and dental specialists recommended.
• Phrenic nerve pacing allows greater mobility for those patients who require 24 hr ventilatory support.

[‡]Results adapted from Trang et al.[5]

Table 2. CCHS Ventilatory Support: Benefits v. Risks§

	Benefits	Risks
Non-Invasive Mask Ventilation	· Non-invasive · Avoids tracheostomy · Easy to handle equipment · Short training time · Portable · Allows for speech development	· Airway not secure · Leak could cause to be ineffective · Limited interfaces in pediatrics · Potential pressure sores · Hard to use for >18 hrs. · Potential for aspiration
Tracheostomy	· Airway is secure · Allows for prolonged mechanical ventilation · Provides effective ventilation, even during infections · Ease of suctioning the airway · Prevents obstructive apneas	· Requires specialized training and care · Higher cost · Potential for phonation/speech delays · Complications: infections, decannulation, granulomas, tracheomalacia, etc.
Phrenic Nerve (Diaphragm) Pacing	· Freedom of mobility during ventilation · Creates a more physiologic type breathing · No mask related facial trauma · No risk of accidental decannulation	· Specialized surgical procedure · Potential to cause OSA · Pacer malfunctions · Airway is not secure · No alarms if pacer not working effectively · Use >12-16 hrs. per day is not recommended
Negative Pressure Ventilation	· Non-invasive · Avoids tracheostomy · Easy to handle equipment · Short training time · Patient could be device free during daytime · Much cheaper than a tracheostomy · No mask related facial trauma · No risk of accidental decannulation	· Less effective ventilation · Not portable · Can cause OSA · Airway is not secure · Most sleep supine · Possible skin irritations

§ Results adapted from Trang et al.[5]

mask, phrenic [diaphragmatic] pacing, and negative pressure ventilation. It was noted that newly designed home ventilators allow for mixed ventilation modes. Pressure control modes can be combined with minimum guaranteed tidal volume or minute ventilation,[5] which addresses the decreased respiratory rate and reduced tidal volumes. Such advancement allows for greater freedom during activities of daily living. However, there are benefits and risks associated with each of these four types of ventilatory support. See Table 2 for a summary.

Summary

Early diagnosis through testing for the PHOB2X gene is the key to long term management. Due to the absence of hypercapnic response, a tracheostomy with PPV has become the standard of care, especially in the neonate. Once a person is old enough to maintain a more regulated sleep/wake cycle, NIV and diaphragm pacing has shown to be successful.

Multiorgan Complications Literature

In *The Genetics of Congenital Central Hypoventilation Syndrome: Clinical Implications*, Bishara, et al.[15] expands on the ANS dysfunction associated with CCHS. Patients diagnosed with CCHS may also have one or more of the following multiorgan complications.

- Hirschsprung's disease (HSCR) occurs in 20% of patients. It typically presents in the neonatal period, equally affecting males and females.
- Sinus pauses of >3 seconds requiring a pacemaker are seen in children with 20/27 PARM. CCHS patients with 20/25 PARM and NPARMs should be monitored for arrythmias as they get

Table 3. CCHS Organ Systems Evaluation Recommendations¥

System	Frequency	Tests/Procedures
Pulmonary	· <3 yrs of age: every 6 months · >3 yrs of age: annually	· Comprehensive test during sleep and awake: pulse oximetry, capnography, polysomnography, cardiorespiratory
Cardiovascular	· Annually	· Blood pressure · Echocardiogram · Cardiac monitor >72 hrs
Gastrointestinal	· Initial diagnosis · Subsequently if symptomatic	· Barium enema · Rectal biopsy
Neurodevelopment	· <3 yrs of age: every 6 months · >3 yrs of age: annually	· Neurocognitive tests
Oncologic	· 0-6 yrs: every 3 months · 6-10 yrs: every 6 months · >10 yrs of age: oncologist recommendation	· Chest x-ray · Abdominal ultrasound · Urine catecholamines
Ophthalmologic	· Annually	· Comprehensive ocular exam

¥ Results adapted from Kasi, et al.[9]

older.
- Tumors of neural crest origin may occur. There is an increased risk of developing neuroblastoma tumors of the sympathetic nervous system.
- Ophthalmologic complications may occur. Pupillary abnormalities were more frequent in patients with 20/26 and 20/27 PARMs.[15]

In *Congenital Central Hypoventilation Syndrome: Optimizing Care with a Multidisciplinary Approach*, Kasi, et al.[9] informs that clinical features of CCHS can evolve over time, affecting many organ systems. These areas include pulmonary, cardiovascular, gastrointestinal, neurodevelopmental, oncologic, and ophthalmologic. Coordination of care among these disciplines can be challenging. Table 3 shows the recommended areas of evaluation and frequency. In *Guidelines for Diagnosis and Management of Congenital Central Hypoventilation Syndrome*, Trang, et al.[5] further iterates that there is no curative treatment for CCHS. Management includes assisted ventilation and multi-disciplinary care.

Summary

CCHS not only affects the pulmonary system but has been shown to have long term effects on many other organs. It is necessary to monitor and test these areas regularly.

Controversies

As of date of drafting this literature review, no controversies in method of diagnosing CCHS or the need for monitoring of multi-organ systems throughout the patient's lifetime were disclosed. However, the management and ventilatory support recommendations published in the 2010 ATS Statement[5] was updated in 2020. These include, but not limited to:

- The use of new modalities allows for a more stable CO_2, as opposed to gold standard use of tracheostomy.
- Reassessing the airway every 3-6 months in children with a tracheostomy for the first 2 years, as opposed to every 12-24 months.
- Pressure control ventilation remains to be the recommended mode but with additional back-up rates or minimum inspiratory capacities when available.
- Mask ventilation may be considered in infants and young children with close monitoring, as opposed to prior recommendations of not being used on children under 6-8 years of age.

Recommendations

The pertinent literature was reviewed as it relates to definition, testing procedures to produce definitive diagnosis, and current treatment options. Due to space and time constraints, reporting literature findings on research into the different genotypes and how they manifest in multiorgan systems, was deliberately avoided. The current review and subsequent recommendations are believed to be relevant and useful to the respiratory care practitioner and educator.

In the presence of alveolar hypoventilation, the diagnosis of CCHS is confirmed by testing for mutations on the PHOX2B gene.[6] Once diagnosed, maintaining constant alveolar ventilation is imperative for cognitive and physical maturation.

CCHS is inherited in an autosomal dominant manner. Therefore, deliveries should be performed at a tertiary care center equipped for intubation and mechanical ventilation. Prenatal testing of the fetus is recommended when traits are known or suspected by one of the parents.[6]

If diagnosed when an infant or very young child (<3 years of age), a tracheostomy is recommended in conjunction with positive pressure ventilation. Infants and young children do not have established wake/sleep routines and run the risk of hypoxic neurologic insults. As a child becomes older and into adulthood, they may become candidates for non-invasive ventilation via mask or "biphasic cuirass ventilation" (BCV),[16] or through diaphragm (phrenic nerve) pacing.

There is currently no cure or pharmacological adjunct for CCHS. Some form of supportive ventilation will be required throughout their life. It was also noted that due to the range of severity of CCHS, multiorgan testing should be performed as recommended.

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News…continued from page 24

premature infants, announced the publication of a journal article that compares the effects of various manufacturing methods on bioactive proteins in donor human milk. The naturally occurring bioactive proteins in human milk play a vital role in infant nutrition. In addition to providing key nutrients like amino acids, calcium, and phosphorus, bioactive proteins also protect against bacterial and viral infections and contain anti-inflammatory properties. The peer-reviewed article, which focuses on structural and functional changes of bioactive proteins, found that the molecular structure of bioactive proteins in donor human milk that had been vat pasteurized most closely resembled those in raw milk controls, compared with other human milk processing methods, including ultra-high-temperature (UHT) sterilization and retort sterilization. Authored by Ningjian Liang, PhD; David C Dallas, PhD; and colleagues at Oregon State University and the University of California, Davis, "Structural and Functional Changes of Bioactive Proteins in Donor Human Milk Treated by Vat-Pasteurization, Retort Sterilization, Ultra-High-Temperature Sterilization, Freeze-Thawing and Homogenization" was published in September in the peer-reviewed journal Frontiers in Nutrition. The study compared the effects on human milk when treated by commonly used processing methods. The researchers concluded that different bioactive proteins have different sensitivity to the treatments tested. Overall, vat pasteurization preserved more of the bioactive proteins than UHT sterilization or retort sterilization did. This was especially true of three bioactive proteins: immunoglobulins, lactoferrin, and caseins. Intake of human milk is especially critical for babies born prematurely, with mother's own milk (MOM) being the best feeding option. When an adequate amount of MOM is not available, the American Academy of Pediatrics recommends the use of donor human milk. Donor human milk must be processed to eliminate the possibility of pathogen contamination before being given to infants in the neonatal intensive care unit (NICU). Once the milk is processed and/or pasteurized to ensure safety, bioactivity is impacted. But prior to this study, the extent of those changes based on each processing method were unknown. "Currently, donor milk processors lack information about the extent to which different processing techniques degrade or preserve bioactive milk proteins. Our study addresses this critical research gap as we examined the extent to which various treatments can preserve bioactive proteins," wrote Liang, a postdoctoral researcher in the laboratory of David Dallas, an assistant professor in the College of Public Health and Human Sciences at Oregon State University. "This information will support milk processors in determining how to optimally process donor milk to preserve specific milk proteins." Liang et al. tested processed milk samples using the SDS-PAGE method, which separates proteins based on their molecular weight. They then tested the milk samples using the enzyme-linked immunoabsorbent assay (ELISA), a widely used laboratory technique that measures proteins and other substances. "The more we learn about the importance of bioactivity in human milk, the more important it is that we understand how processing affects the milk we rely on to provide optimal nutrition to our patients," said Melinda Elliott, chief medical officer of Prolacta and a practicing neonatologist. "This study reinforces that how human milk is processed matters. Prolacta's human milk-based products are vat pasteurized to preserve as much of the natural bioactivity of the milk as possible."

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Safe Discharge Planning for Neonates

Science-Based Algorithm for Personalized Jaundice Risk Assessment in the Context of the Revised 2022 AAP Guidelines

Gilbert Koch PhD, Judy Moore MSc, Sven Wellmann MD

Introduction

The vast majority of all newborn infants become visibly jaundiced and 8-10% of them requiring treatment.[1] Hospital stay of the mother and her neonate should be long enough to allow clear identification of any potential medical problems. Hence, decision to discharge home a neonate is based on the assessment of the risk of developing neonatal problems such as neonatal jaundice, which may not become apparent in the first few days of life. One major challenge facing clinicians is determining precisely those neonates who will develop jaundice in the days post-discharge. Despite clinical risk factor assessment and plotting of "current" bilirubin values on nomograms, some neonates are discharged although at risk of jaundice in the coming days and, thus, at risk of developing kernicterus. Studies have demonstrated that 35% of all readmissions in the first week of life are related to neonatal jaundice.[2]

Performing risk assessments of all neonates in a hospital facility is a manual and time-consuming task. With a shortage of healthcare providers, it is also becoming more challenging to perform thorough risk assessments or to provide follow-up appointments in a timely manner for assessment of neonates at risk of jaundice. Furthermore, human error is a risk in a traditional hospital workflow and may include inaccurately displaying a bilirubin value on a nomogram. A validated tool which automates the assessment procedure including plotting of bilirubin values and prediction of bilirubin progression into the future, not only saves valuable time and resources but also removes the risk of human error.[3]

In September 2022, the American Academy of Pediatrics (AAP) published revised clinical practice guidelines for management of hyperbilirubinemia in neonates.[4] These new guidelines provide valuable recommendations for (i) prevention of hyperbilirubinemia, (ii) assessment and monitoring for hyperbilirubinemia, (iii) treatment of hyperbilirubinemia, (iv) post-discharge follow-up, and (v) hospital policies and procedures.

We introduce here the validated online prediction tool NeoPrediX B.1, which (i) includes all new recommendations from the 2022 AAP guidelines, (ii) automatically documents bilirubin measurements, and (iii) predicts and shows personalized bilirubin progression up to 60 hours into the future. Utilizing such a science-based prediction tool enables caregivers to accurately assess bilirubin for each individual neonate prior to discharge from hospital. It supports caregivers in answering daily clinical questions such as:

- Can the neonate be safely discharged home?
- Is an additional bilirubin measurement necessary?
- Is the neonate at risk for clinically relevant hyperbilirubinemia?

The presented prediction tool can be integrated into electronic medical record systems provided by healthcare companies such as EPIC or Cerner, or can be used as a standalone online version.

Methods

The field of medicine is undergoing a fundamental change, transforming towards a modern, data-driven, patient-oriented approach. This paradigm shift also affects perinatal medicine as predictive science-based algorithms and artificial intelligence are applied to enhance and individualize maternal and perinatal care.[3]

NeoPrediX B.1 is an example of such a science-based mathematical algorithm that handles various input combinations of total serum bilirubin (TSB) and transcutaneous bilirubin (TcB) measurements to predict bilirubin progression up to 60 hours into the future. In a healthy human, production and elimination of bilirubin is in equilibrium. However, in neonates, this equilibrium is initially perturbed due to maturation,

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Figure 1. Screenshot of the NeoPrediX B.1 prediction tool visualizing measured bilirubin values and bilirubin progression into the future in the context of the revised 2022 AAP guidelines. The case study presents a neonate born 35+0 weeks of gestational age (GA) with a birth weight of 2500 grams and no hyperbilirubinemia neurotoxicity risk factors. The red crosses correspond to the actual bilirubin measurements taken at 58 and 80 hours of postnatal age. The solid blue line represents the predicted bilirubin progression for up to 60 hours after the last measurement, thus, up to 140 hours. In addition, the upper shaded blue area indicates a safety margin for the bilirubin prediction ranging from 0% (the predicted curve) up to +25% (safety margin) at 140 hours. The dashed magenta line shows the GA-dependent phototherapy threshold according to the 2022 AAP guidelines. The different colored areas below this line correspond to the different discharge recommendations from the 2022 AAP guidelines. Given this detailed information, we recognize that need for phototherapy treatment is low in this neonate, and the associated discharge recommendation from the 2022 AAP guidelines is to perform an additional bilirubin measurement in the next 1-2 days, as stated on the top of the figure in yellow. Consistent with the 2022 AAP guidelines the rate of increase (per hour) is also calculated and the distance of the last measurement to the phototherapy threshold is displayed. As indicated at the bottom of the figure, information can be turned on or off using the check boxes.

resulting in hyperbilirubinemia. This physiological principle is mathematically characterized with the help of differential equations based on the law of mass action and principles. The tool was developed and validated on various independent datasets obtained from different hospitals worldwide (Europe, USA, and Africa) utilizing thousands of TSB and TcB measurements. The prediction tool gained a broad understanding of possible bilirubin progressions by combining trained knowledge with bilirubin measurements from a new neonate. This combination allows accurate prediction of individual bilirubin progression utilizing either TSB or TcB measurements, or a mixture of both.

Results

To demonstrate the functionality and the provided information by the NeoPrediX B.1 prediction tool, a case study of a neonate born 35+0 weeks of gestation and weighing 2500 grams at birth is presented. In Figure 1 and its corresponding legend, the entire functionality of the prediction tool is explained, including visualization of measured bilirubin values and bilirubin progression into the future in the context of the revised 2022 AAP guidelines.

Conclusions

Combining actual bilirubin measurements with a science-based algorithm offers caregivers and parents risk assessment of jaundice and assurance of safe personalized medicine, optimizing monitoring and care of each individual neonate. It safely supports daily decisions of caregivers in the discharge planning process by avoiding unnecessary and unidentified hyperbilirubinemia and life-threatening kernicterus. We are convinced that similar tools predicting the dynamics of other biomarkers for an individual fetus or neonate will become an indispensable part of personalized maternal and perinatal care.

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Useful Respiratory Calculations in the NICU

Estephanie Rivero, MD, Faiza Javed, MD and Shabih Manzar, MD

Most neonatal intensive care unit (NICU) admissions consist of preterm infants. More than half of these infants require respiratory support in some form. We describe here a few quick calculations that assist with the respiratory management of these infants.

Respiratory Severity Score (RSS)[1]

RSS = Mean airway pressure (cmH_2O) × Fraction of supplemental oxygen (FiO_2 0.21–1.00). RSS could be used to predict the chances of successful extubation. It could be used in conjunction with the extubation calculator (http://extubation.net/).[1,2]

Pulmonary Acuity Score (PAS)

PAS score could help in assessing the severity of the respiratory disease. PAS score = (FiO_2) (support) + medication, where the support score is: 2.5 for the ventilator, 1.5 for continuous positive airway pressure, and 1 for NC. The medication score is 0.20 for systemic steroids, 0.10 for a diuretic or inhaled steroids, and 0.05 for methylxanthines or intermittent diuretics.[3,4]

Effective FiO_2 (E-FiO_2)

Based on weight and NC flow, obtain the factor, then look at that factor on the table to see the precalculated effective FiO_2 for the corresponding FiO_2.[5,6] E-FiO_2 helps in weaning the NC support.

BPD outcome/NIH calculator

Bronchopulmonary dysplasia (BPD) is common among extremely premature infants. The outcome calculator could help with making decisions on treating with steroids.

https://neonatal.rti.org/index.cfm

Author contribution

Dr Rivero, Dr Javed, and Dr Manzar conceptualized the study and wrote the draft.

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None

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Conversing with Patients and Parents

Leslie Altimier, DNP, MSN, RNC, NEA-BC

The auditory system begins structural development very early in the embryonic period and matures into an adult-like structure by the end of the second trimester (Best, et al., 2018; Moore & Linthicum, 2007). Hearing begins to develop at 25–26 weeks of gestational age, with the development of cochlear hair cells that process sounds. In utero, the fetal auditory system is functionally mature by 23–25 weeks which is demonstrated by having physiological effects in response to auditory stimulation (Harding, et al., 2019). At 26–28 weeks of gestational age, infants can demonstrate responsiveness to voice (Kisilevsky et al., 2009). Around 30 weeks of gestational age, active listening is developing and attunement to maternal voice occurs (Smith et al., 2007; Harding, et al., 2019). At this stage, infants are reflexive in their responses, becoming reactive to events and people, and as they become familiar with their environments, they become anticipatory (Coupe & Goldbart, 2016). These reactions become more differentiated as infants begin to perceive consistencies in their routines and develop specific preferences. When caregivers/parents interpret infant behaviors as meaningful, they are likely to act in ways that are nurturing and contingent (Tomassello &Todd, 1983; Tomassello and Ferrar, 1986).

In phonology and linguistics, a phoneme is a unit of sound that can distinguish one word from another in a particular language (Wikipedia.org; Best, et al., 2018). The differentiation of phonemes is possible by 35 weeks and the fetus can now discriminate voice and sustain auditory memory (Graven, 2000). The capacity for prenatal learning and language acquisition has also been suggested as early as 35 weeks of gestation (Guarini, et. al., 2016; Caskey, et al., 2011). Unfortunately, prematurely born infants (especially <28 weeks) develop their auditory system in the abnormal environment of the neonatal intensive care unit (NICU) (Maitre, et al., 2014). At a term-equivalent age, significant delays have been found in auditory brainstem responses of preterm infants reflecting atypical brainstem maturation (Stipdonk, et al., 2016). Even preterm infants with normal brain ultrasound scans experience this when exposed to a loud chaotic extrauterine NICU environment (Stipdonk, et al., 2016; Therien, et al., 2004).

Having a preterm infant is challenging for parents and families and there is an increased risk of psychological stress. Being separated from an infant and dealing with the disruption to family life can impact the development of parent–infant interactions and early bonding. Mother–preterm infant dyads can be at higher risk of relationship difficulties than mother–full-term dyads (Borghini, et al., 2006 & Forcada-Guex, et al., 2006; Harding, et al. 2019). In a study by Borghini, et al., (2006), only 20 and then 30% of mothers of preterm infants had secure attachment representations at 6 and 12 months, respectively, following the birth compared to 53 and 57% in a term comparison group. These early interactive experiences are important in the development of future communication skills.

Infants born very prematurely are cared for in the NICU at a time when they normally would be listening to and learning the rhythmic voice of their mother's speech while in utero (Moon & Fifer, 2000); therefore, speech and language development during early childhood in preterm infants is often delayed (Caskey, et al., 2011). In utero, the maternal voice is one of the most prominent stimuli during the development of the auditory system (Gerhardt & Abrams, 2000; Fifer & Moon, 1994; Caskey, et al., 2014). In contrast, infants born very prematurely and cared for in a modern NICU are exposed to language input for only a small percentage of the time with prolonged periods of silence rather than useful maternal language as the primary input and are exposed to excessive noxious noises from monitors and other equipment (Caskey, et al., 2011 & Rand & Lahav, 2014; Newman, 1981). Hearing and visual impairment, language delays, and sensory processing issues may occur because fetal sensory development has been interrupted by preterm birth and exposed to the unpredictable and altered early sensory input they receive in this relatively language-poor environment for the first months of their lives in the NICU (Altimier & White, 2020).

Early language experience is necessary for the normal development of speech and language processing (Benassi, et al., 2016; Vohr, et al., 1988). Studies in term children ages 2 months to 36 months have shown that the more parents talk to their children, the faster their vocabularies grow and the higher the children's IQ test scores are at age 3 (Vohr, et al., 1989; Casiro, et al., 1990). The rate of vocabulary growth and IQ scores are more strongly related to the number of words the parent says per hour to the child than to any other variable, including parents' education level and the socioeconomic status of the family (Vohr, et al., 1989). In addition, adult-child conversations are associated with healthy language development (Casiro, et al., 1991). These findings combined with the knowledge that language learning is likely occurring at early gestational ages make it crucial to better understand the language experience of very preterm infants in

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the NICU (Best, et al., 2018). This would provide evidence of the need for early, pre-discharge language interventions to prevent these delays (Caskey, et al., 2011).

A meta-analyses of studies of very preterm infants have found moderate-to-severe effects of school age on academic achievement, attention problems, behavioral problems, and executive functioning, as well as motor impairment (Aarnoudse-Moens, et al., 2009; de Kieviet, et al., 2009). In a cohort study of 7650 children, there was a decrease found in overall achievement, including mathematical abilities, social relationships, and emotional development by early school age, which all correlated with the level of prematurity (Quigley, et al., 2012; Milgrom, et al., 2013).

Most language studies are related to preterm language outcomes rather than language exposures (Best, et, al., 2018). Long-term studies on language outcomes in preterm infants reveal delays in various aspects of language development (Hart, et al., 1995; Gilkerson & Richards, 2007). Outcome studies of preterm infants show delayed receptive and expressive language processing, deficits in phonological short-term memory, lower IQs, and lower Bayley Mental Developmental Index scores at follow-up (Moore, & Linthicum, 2007; Graven, 2007; Maitre, et al., 2014; Stipdonk, 2016; Therien, et al., 2004; D'Souza, et al., 1981; Brown, et al, 1986). Factors contributing to these delays include perinatal insults (D'Souza, et al., 1981; Brown, et al, 1986; Janowsky & Nass, 1987); gestational age at birth (Jennische & Sedin,1999; Guarini, et al., 2016; Benassi, et al., 2016); low birth weight (Vohr, et al., 1988; Vohr, et al., 1989; Casiro, et al., 1990; Casiro, et al., 1991; Holwerda-Kuipers, 1987; Wright, et al., 1993); altered neurological pathways (Maitre, et al., 2014; Therien, et al., 2004); neonatal morbidities, disease processes, and severity of illness (Caskey, et al., 2011; Hubatch, et al., 1985; Brothwood, et al., 1986; Lindahl, 1988); sepsis and neurotoxicity from drugs (Caskey, et al., 2011; Fuchs, et al., 2016; Raymond, et al., 2017; Best et al., 2018); genetic and epigenetic factors including sociocultural influences (Wright, et al., 1983; Stevenson, et al., 1988); duration of hospitalization, hearing status, and adverse environmental exposures (Caskey, et al., 2011); developmental interactions (Montirosso, et al., 2016; Pineda, et al., 2014; Rand & Lahav, 2014; Lariviere, et al., 2011; Gabis, et al., 2015; Welch, et al., 2015; Smith, et al., 2012); and language exposure (Chow & Shellhaas, 2016; Caskey, et al., 2011; Caskey, et al., 2014).

Caskey, et al.'s (2011) study attempted to describe the language environment to which a preterm infant is exposed in the NICU. They hypothesized that (1) pre-term infants would produce vocalizations as early as 32 weeks gestation, and (2) preterm infants who were exposed to more adult language while in the NICU would respond with more vocalizations. To do this, they utilized a Language Environment Analysis (LENA) digital language processor (LENA Research Foundation, Boulder, CO) with software that uses speech-identification algorithms to provide word and vocalization counts for adult and child language and to characterize the sounds in the recording (Xu, et al., 2009). An adult word count is the number of words a child hears from an adult within a specific amount of time. Conversational turns are defined as vocal sounds from the infant followed by a response from an adult within 5 seconds or an adult word followed by a child vocalization within 5 seconds. Each time that happens, one turn is counted. A child's vocalization is counted when a child's speech of any length is surrounded by .300 milli-seconds of silence or other sounds that are not the child's speech. LENA software does not count crying or vegetative sounds, such as sounds from the respiratory or digestive systems (i.e., breath sounds or burping) in the infant vocalization counts but does include protophones such as squeals, growls, grunts, and "raspberries" (Caskey, et al., 2014; Ford, et al., 2008). The vocalizations made by preterm infants usually consist of very short vowel sounds and grunts. LENA software also categorizes the audio data in the recording environment into language, noise, silence, electronic noise, overlapping language, and uncertain segments. The LENA device has previously been shown to have a high degree of fidelity in coding compared with trained human transcribers.

Language data were collected in the NICU by using the LENA digital recording device that was placed in the pocket of a specially designed infant vest. The digital language processor recorded 16 hours, starting in the morning, of adult speech, child vocalizations, and background noise in the NICU at 32 and 36 weeks of gestational age. The audio recording was downloaded and analyzed using LENA software. The LENA device has previously been shown to have a high degree of fidelity in coding compared with trained human transcribers. The mean adult word counts, conversational turns, and child vocalizations for each of the recordings increased. There was a significant increase in the median total adult word counts from 1289 to 8255 ($P = .0001$), an increase in the median conversational turns from 15 to 36 ($P = .0009$), and an increase in the median child vocalization count from 77 to 153 ($P = .0003$) between the 32- and 36-week recordings (Caskey, et al., 2014).

Caskey et al., also compared mean hourly counts of adult and child vocalizations during parent visits with hourly counts when parents were not visiting. The hourly adult word counts increased by more than 380% at 32 weeks and by 220% at 36 weeks in the hours when a parent was visiting, and conversational turns increased by 520% at 32 weeks and by 160% at 36 weeks in the hours when a parent was visiting ($P < .0001$). Child vocalizations per hour were significantly increased at 32 weeks when a parent was visiting ($P = .0001$) and were increased by 36% but did not achieve significance at 36 weeks ($P = .08$). There were no differences in the analyses of adult word count, conversational turns, or child vocalizations if the infants with a history of language delay were excluded. This was the first study to break down the types of sounds to which preterm infants are exposed while being cared for in the NICU. It was also the first study to show that early exposure in the NICU of preterm infants to higher numbers of adult words positively correlated with cognitive and language outcomes after discharge (Caskey, et al., 2014). These data revealed the actual minimal language very preterm infants are exposed to during a critical time in their early development (Caskey, et al., 2011). Caskey, et al., (2014)

This is in contrast to a fetus of the same gestational age, which is in an environment where the maternal voice is again, the most prominent stimulus (Richards, et al., 1992). The increase in the percentage of time that infants are exposed to language between 32 and 36 weeks is partially explained by the fact that at 32 weeks, infants were often still in an incubator, where little language is audible unless it is directed into the hole of the incubator (Newnam, 1981). By 36 weeks, infants are often in an open crib and may be preparing for discharge, with parents visiting more often and holding infants for feeds which were more often given by mouth as opposed to by gavage tube. The increase in monitor noise at 36 weeks is also explained by the

move to an open crib because infants are then exposed to not only their own monitor noise but also those of nearby infants. (Caskey, et al., 2011).

Impacts of NICU Design

High-risk infants are both dependent on and vulnerable to the NICU environment. While dependent on the NICU for the maintenance of their physiologic functions during recovery from the insult of being born too soon, they are also vulnerable to all the stressors inherent in having fetal development occur outside the womb in the artificial environment of the NICU. As the preterm infant matures, the quality of the environment in which the infant resides plays a critical role in the trajectory of recovery, growth, and development (Altimier & Phillips, 2018).

There have been controversial opinions on which NICU design is best. Open-bed spaced units can be loud and overstimulating and block meaningful language exposure. Conversely, a single-family room (SFR) environment may be quieter but present a degree of social isolation and limited language exposure (Rand & Lahav, 2014). Low parental visitation and interactions also contribute to the sensory deprivation experienced by infants in neonatal units, suggesting that the sensorineural development of preterm infants is indeed affected by surrounding environmental exposures (Pineda, et al., 2014; Best, 2018). A number of studies have reported neonatal benefits for infants born preterm cared for in a single-family room (SFR) neonatal intensive care unit (NICU). Benefits reported include a reduction in mortality, sepsis, necrotizing enterocolitis (NEC), and duration of hospitalization; fewer apneas; more sustained high-grade lactation and their infants were more likely to be discharged on human milk (Gerhardt & Abrams, 2000; Fifer & Moon, 1994; Caskey, et al., 2011; Newman, 1982). This is important because human milk has been shown to be associated independently with improved neurodevelopmental outcomes (McMahon, et al., 2012; Nittrouer & Burton, 2005; Richardson, et al., 2001; Bayley, 2006; Hack, et al., 2005). 14,17,21-23

Research supports the concept that NICU design impacts outcomes. One systematic review collectively linked a range of aspects of the physical environment of the NICU to the well-being of patients, family comfort, and the caregiving process. Single-family rooms were deemed superior compared to open-bay units for patient care and parent satisfaction (Domanico, Davis, Coleman, & Davis, 2011). Others have demonstrated improved outcomes including increased privacy, increased parental involvement in patient care, improved noise control, improved sleep, decreased length of hospital stay, decreased rehospitalizations, reductions in costly hospital-acquired infections, and lower direct costs of care (Julian, Burnham, Sellenriek, & al., 2015; Ortenstrand, Westrup, Brostrom, & al., 2010; Sadatsafavi, Niknejad, Shepley, & Sadatsafavi, 2017a; Shahheidari & Homer, 2012; Stevens, Thompson, Helseth, Hsu, Khan, & Mun-son, 2014).

Parents typically prefer the intimacy of a single-family room and a quieter atmosphere with decreased noise levels (Altimier & White, 2020; Altimier & Phillips, 2022). Research shows that parental presence and holding in the NICU may promote healthy attachment and improve early neurobehavior in preterm infants and the SFR provides an environment that supports longer parental stays (Barton & White, 2016; Reynolds, Duncan, & Smith, 2013). High maternal involvement is associated with improved 18-month neurodevelopmental outcomes, especially in infants cared for in a SFR-NICU (B. Lester et al., 2016). In a study by Vohr, et al., (2017), infants cared for in SFR NICU's had higher Bayley III cognitive and language scores, higher rates of human milk provision at 1 and 4 weeks, and higher human milk volume at 4 weeks (B. Vohr et al., 2017).

A report of more mature infants born preterm (median gestations of 31-32 weeks) showed that mothers and infants within a SFR NICU have greater opportunities for family-centered care, privacy, one-on-one interaction, and skin-to-skin contact. Greater parent satisfaction has also been reported in more private environments (Briscoe, et al., 1988; Altimier & White, 2020). Several investigators have shown that improved family-centered care is associated with improved neonatal medical outcomes and more optimal neonatal neurobehavioral outcomes (Vohr, et al., 1988; Foster-Cohen, 2007; Sansavini, 2007). Maternal and paternal involvement reflects the NICU learning environment of the infant. Mothers living in poverty and who are more poorly educated have not only more barriers to visiting their infants in the NICU; but also have more disparities impacting long-term developmental outcomes (Luu, et al., 2009; van Noort-van Speck, et al., 2012; Krueger, 2010; McMahon, et al., 2012; Caskey, et al., 2014). Education level has been shown to be associated with higher adult word counts. One study previously found that for parents who earned at least a bachelor's degree, the mean daily adult word count was significantly higher (14,926) than the mean daily adult word count (12,024) for other parents (Caskey, et al., 2014).

It is known that early language experience is necessary for the normal development of speech and language processing, (Mayberry, et al., 2002; Nittrouer & Burton, 2005), 1995; and that there is an association between the amount parents talk to their children between birth and age 3 years and subsequent vocabulary growth and IQ scores at age 3 years (Hart & Risley, 1995; Gilkerson & Richards, 2009). When preterm infants are spoken to in the neonatal unit, they show better language and cognitive outcomes at 7 and 18 months (Caskey et al., 2014). Preterm infants also show better state regulation when hearing a familiar voice (Sajjadian et al., 2017). Early infant communication outcomes are even further improved if intonation (or Motherese) is used which also decreases infant stress (Gerken & Aslin, 2005; Kuhl, 2004; Harding, et al., 2019).

Neuroprotective Care

The time interval between 32 weeks and full-term is a period of critical brain development and may provide a window of opportunity for parents and caregivers to expose the infant to early language enrichment. Language exposure provided in the NICU from all caregivers may help to improve outcomes for these vulnerable infants. Since preterm infants are at risk of speech, language, and communication difficulties, providing parents with information about language development and strategies to promote communication are essential to integrate into neonatal care (Caskey, et al., 2014).

Learning the principles of neurodevelopment and understanding the meaning of preterm behavioral cues make it possible for NICU caregivers and parents to provide individualized developmentally appropriate, neuroprotective care to each infant. Partnering with families and restoring parent–infant attachment supports both the physiologic and emotional stability of infants and their parents (Altimier & Phillips, 2016).

Neuroprotective care should be delivered in the NICU not only by nurses, allied health, and medical staff (i.e., Neuroprotective Care) but also by parents (Altimier & Philips, 2016). The guiding Principles of Neuroprotective Care are outlined in Appendix A. The ideal method to improve long-term speech, language, and communication in preterm infants is to create a paradigm shift from nurses being the main caregivers to coaching parents to be significant caregivers. Some parent-training interventions begin during the infants' hospitalization and some within the first post-discharge year of life. One parent-training approach stems back to a landmark study (Rauh, et al., 1990; Achenbach, et al., 1990) of the Mother–Infant Transaction Program (MITP). The MITP's major focus was to sensitize parents to infant cues, in particular, those that signal "stimulus overload, distress, or readiness for interaction. The MITP begins during the babies' hospitalization in the NICU and extends after discharge. Milgrom, et al., (2013) followed Children's development longitudinally and found a difference of 10.6 IQ points favoring intervention infants at 9 years of age, but this group difference only began to emerge after 2 years of age (Milgrom, et al., 2013).

Reading and singing to a preterm infant is also important for future speech, language, and communication development. Specifically, vocal stimuli from caregivers can improve preterm infants' stability (i.e., heart rate, oxygen saturation, respiratory rate, and behavioral measures) with better feeding development (Saliba, et al., 2018). Mayne, et al., (2022) conducted a randomized trial to study the impact of a maternal-driven, infant-directed reading intervention on preterm infant language compared with matched controls. Infants born at 22–32 weeks in the NICU were gestationally stratified to a reading intervention (n = 33) or standard care (n = 34). At 32-, 34- and 36 weeks postmenstrual age, 16-h language recordings were obtained in the hospital utilizing the LENA system. By 36 weeks postmenstrual age, infants in the reading group had twice the number of conversational turns as infants receiving standard care, demonstrating that a maternal infant-directed reading curriculum in the hospital had a positive impact on interactive conversations by 36 weeks postmenstrual age (Mayne, et al., 2022).

Learning to develop an attachment to an infant through involvement in everyday care activities in the neonatal environment can support physical and emotional closeness for both the infant and parents which is an important precursor for developing early parent–infant interactions and communication (Evans et al., 2014; Flacking et al., 2012; Harding, et al., 2019).

Communication needs to have a higher profile in the management of infants in the NICU. Conversing with infants (and parents) in the NICU setting should not be an optional task. Everyday activities must include conversing. As healthcare professionals, would we ever enter an adult patient's room and initiate care without talking to the patient? Would we enter a toddler's room, ignore the parents staying with their child, and go about our care? Neonates deserve to have conversations as do their parents. I would argue that because neonatal brains are in a critical period of growth and development while in the NICU, healthcare professionals should be role models to parents by engaging in age-appropriate and appropriately timed conversations.

Appendix A; Guiding Principles of Neuroprotective Care (Altimier & Phillips, 2016)

a. All infants are in a critical period of brain growth and organization
   - Everything that happens in the NICU impacts brain development
   - Providing excellent, evidence-based care is always our goal
   - The way we provide our care, influences neurodevelopmental outcomes

b. Neuroprotective developmental care is relational
   - Treat every baby as a little human being who has their own unique identity
   - Talk in a "library voice" when near bedsides
   - Encourage "approach behavior" by approaching baby using a soft voice/whisper followed by gentle touch
   - Interact through verbal conversations, singing, and reading to baby
     - § Encourage "Conversation Turns" between mother and infant (words of a mother or vocalizations of an infant within 5 seconds of each other)
   - Do exams and procedures "with" the baby, not "to" the baby
   - Notice individual differences and preferences in each baby

c. Emotional connection with parents/families is essential for optimal outcomes
   - Parents are the most important caregivers for their baby in the long run
   - Involve parents, as much as possible as active members of the caregiving team
     - § Educate, coach, and mentor parents in becoming active participants in baby's care
     - § Encourage zero separation between parents and infant.
     - § Invited parents to participate in multidisciplinary rounds
     - § Encourage parents to tell us how they think their baby is doing (actively listen)
   - Support parent-infant attachment in every possible way while in the NICU
   - Provide psychosocial support for NICU parents as needed
   - Skin-to-skin contact is the most fundamental form of neuroprotective care
   - Skin-to-skin contact with the mother is the "natural habitat" for all newborns outside the womb
   - Encourage and facilitate skin-to-skin contact whenever possible, and for as long as possible

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HeRO Best Practices

An Implementation Guide to Maximize Clinical Benefit

William King

Overview

HeRO identifies abnormal neonatal heart rate patterns that are associated with cytokine expression and inflammation,[1,2,3] and has been used as an early warning system for infection, including sepsis.[4,5,6,7] In a 3,003-patient pragmatic randomized controlled trial, patients randomized to receive HeRO-monitoring in addition to standard monitoring experienced reduced all-cause mortality in the NICU [8] and at 18-22 months.[9] Among patients in the RCT with sepsis, those that received HeRO-monitoring additionally experienced improved neurodevelopmental outcomes at 18-22 months corrected age,[10] and reduced length of stay for survivors.[11] A recent analysis reported that the incremental cost-effectiveness ratio for HeRO was $34,720 per additional life saved in 2021 USD, and that NICUs implementing HeRO would be likely to improve top-line revenue and bottom-line profit, in addition to survival.[12]

The randomized controlled trial was pragmatic in nature, meaning that patients were randomized to have HeRO Scores turned on or off, and then outcomes were tracked, without any mandated interventions or clinical workflow. In essence, participating clinicians were left to their own to decide how to react to the HeRO Scores.

In keeping with the pragmatic design of the RCT, Medical Predictive Science Corporation has not in the past explicitly told HeRO users how they must implement HeRO monitoring, choosing instead to offer advice and share other users' protocols.

Now, with the experience of over 150,000 patients monitored by HeRO throughout the world, it is evident that the most important aspect of any HeRO installation is the clinician. Because like any Clinical Decision Support tool or Early Warning system, HeRO can only positively impact patient outcomes if it positively impacts clinical decision-making. And clinical decision-making can only be maximized, and hence the benefits to the patients maximized, if the clinical care team is fully and continually invested in HeRO.

Below, we lay out best practices we have observed in our customers to maximize the benefits of HeRO monitoring.

Protocol

We have surveyed our customers and found that while the protocols take many forms, the clinical workflow and decision cascade they describe are nearly universal. In all cases, HeRO is considered one of many indications of infection, yet in no cases does the HeRO Score displace the judgment of the clinician.

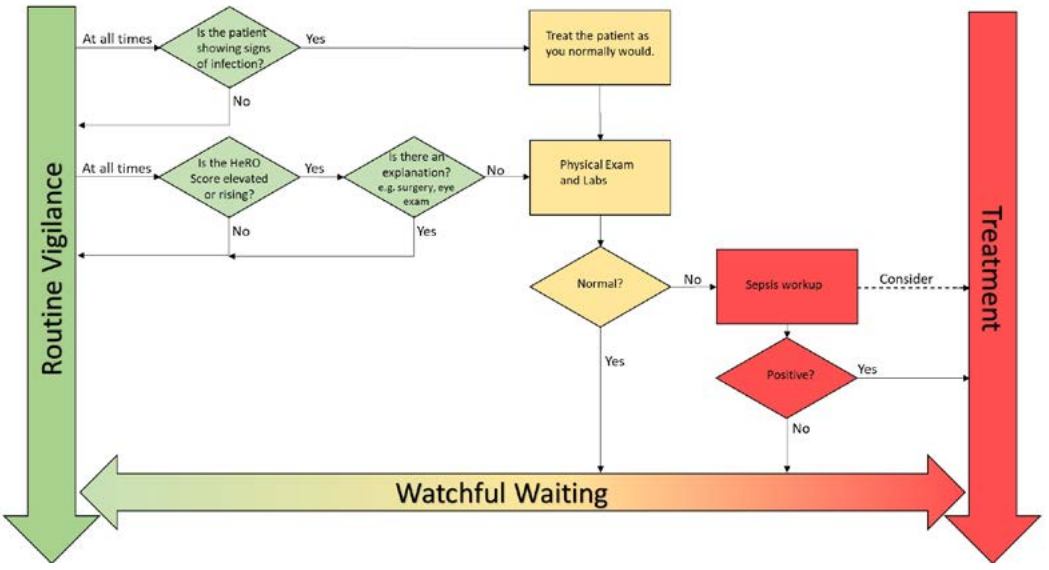

Figure 1. Typical HeRO Protocol.

In Figure 1, we show a typical HeRO protocol. In this example, clinicians are encouraged to treat a patient that is exhibiting signs and symptoms of infection as they normally would. This would typically lead to a physical exam and labs. If there are any abnormalities, then a sepsis workup with the possibility of immediate treatment depending upon the judgment of the clinicians.

Importantly, an elevated or rising HeRO Score, without a reasonable explanation (such as surgery, eye exam, or other known inflammatory process) leads to the same point in the cascade as when a patient is exhibiting signs of infection: perform a physical exam and obtain labs.

In essence, HeRO becomes another sign of infection that may initiate the diagnostic cascade. But in no case would HeRO displace clinical judgment, nor would treatment be initiated based solely on the HeRO score.

Another important point to note is that the choice of *which labs* is not mandated by this protocol, as we have found that NICUs in different geographies have different preferences. Where it has been studied**,** labs of all types have significantly higher predictive performance when coupled with an elevated HeRO Score. For example, Griffin et al found that model performance to predict infection was much higher when using *both* HeRO and labs than when using either alone,[14,15] Kurul and colleagues found that IL-6, PCT, and CRP were each significantly higher at the time of suspicion when prompted by an elevated HeRO Score in patients ultimately diagnosed with sepsis versus no sepsis (each $p<0.001$).[16] The same group recently published their protocol as part of a before/after study. They found that after implementing the HeRO monitoring protocol, morbidity (as measured by nSOFA scores) at the time of sepsis diagnosis was improved, there were no increase in blood cultures, and there were trends toward improved mortality ($p=0.13$) and decreased antibiotic usage per 1000 NICU days ($p=0.06$).[17]

A written protocol does not have to be exhaustive in every detail. But it serves as common ground for clinicians to all agree to utilize HeRO to inform clinical decision-making, while leaving latitude for the clinician to exercise their own best judgment.

Education

The second pillar of HeRO implementation is continuing education. When we bring a new site online with HeRO monitoring, we typically engage the staff through in-servicing. These are usually 15-20 minute sessions where we cover the development of the HeRO algorithm, the results of the randomized controlled trial, how to access the HeRO Score in the particular installation, troubleshooting, and the site's protocol. Clearly, this is a significant amount of material for a short session.

This, and the fact that there is near-continual staff turnover in a NICU, is why it is so important that the staff be encouraged to use our free on-line training at least annually, available to anyone (customer or not) at https://www.heroscore.com/mpsc-hero-training-courses/.

After successful completion of the appropriate training module, a staff-member can print or save a certificate that can be used to demonstrate proficiency.

This requirement for each staff member to complete on-line training can also be paired with a requirement to review the

Starting at the left, 5 days ago, the HeRO Score had risen from a baseline of 1 to 2 for several days, eventually reaching a peak greater than 5. At the time indicated by the yellow vertical line, the HeRO Score was 4.85 after a continuous rise for 24 hours. In the bottom part of the figure, the heart rate trace would not present as concerning to the unaided eye. The infant was diagnosed with *Klebsiella* septicemia (positive blood and urine cultures).

Figure 2. One slide from the HeRO Training.

	0400	0500	0600	0700
Basic Vitals				
Temp				
Temp Source				
T1 Site Continuous				
Bed Type			Radiant War...	
Bed Control Type				
HR	168	160	124	145
Resp	34	25	24	26
Cuff BP Mode				
CUFF BP (S/D)				
Cuff Mean				
Cuff Site				
SpO2	90	94	92	90
SpO2 Site			Right; Foot	
HeRO	2.4	2.4	2.4	2.8

Figure 3. Flowsheet

site's written protocol, which offers the chance for engagement, feedback, and continued refinement of best practices.

In addition to the free, on-line training, we also offer regularly scheduled webinars. Contact us at info@heroscore.com to find out the schedule or suggest a time that would work for your staff.

Finally, we offer on-site in-servicing for a nominal fee, which is an opportunity to cover the majority of staff members over a 2-3 day period. Again, contact us at www.heroscore.com, or by email at info@heroscore.com to schedule.

Documentation

Most of our customers chart the HeRO Score alongside, and at the same frequency, as other vital signs in their EMR. But we have seen that take several forms.

For some of our systems, such as HeRO solo, duet, and ES, the only option is to chart the HeRO Score manually in the EMR. While this guarantees staff engagement, it can be tedious and introduces an opportunity for human error in the data entry aspect of the task.

For customers that have HeRO Symphony, we include in the price of the product the ability to push HL7 messages to your EMR that include each hourly HeRO Score generated by the system. About half of our Symphony customers choose to automatically populate the patient record with this HeRO Score. While this limits human error in the data entry, it also removes the guarantee of engagement of the nurse.

For this reason, we believe the best practice is to choose to require the charting nurse to validate the HeRO Score, just as they are typically asked to do with other vital signs, before it becomes part of the permanent chart. We believe this offers the best balance between nurse engagement on the one hand, with minimizing tediousness and human error on the other.

Conclusion

The weight of evidence supporting HeRO monitoring among premature infants is overwhelming, but putting it into practice does not have to be. By following these simple best practices of developing a protocol, continually educating staff, and documenting the scores, HeRO users can be assured that they are maximizing the benefits of HeRO to the hospital and patients. We stand ready to offer our assistance every step along that path.

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Mr King studied signal processing and statistical pattern recognition, and has spent the last 24 years concentrating on predictive physiological monitoring for neonates. He has collaborated with academic researchers, developed and coded real-time algorithms to predict sepsis in neonates based on physiological monitoring data, managed the database of the largest randomized controlled trial of a medical device among premature infants, raised funding from investors, obtained FDA and other regulatory approvals, developed an FDA-compliant quality system, and met with customers throughout the world. He is currently Principal Investigator of an NIH-funded STTR grant to develop algorithms underpinning a growth and nutrition dashboard for premature infants.

News…continued from page 37

Increased Risks for Newborns of Women With Disabilities

Babies of women with disabilities have a greater chance of experiencing rare health complications and requiring intensive care — though many of the health issues are preventable, according to a new study. "There's good evidence that, especially for preterm birth and low-birth-weight babies, better access to prenatal care can make a big difference," says Hilary Brown, co-author of the paper and assistant professor in the department of health and society at the University of Toronto Scarborough. Published by the American Academy of Pediatrics, the study — one of the largest of its kind — found the greatest risks were in newborns of women with intellectual or developmental disabilities, and multiple disabilities. Researchers used data from the non-profit research institute ICES to look at all births in Ontario from 2003 to 2018. They compared the newborns of about 200,000 women diagnosed with a disability to the 1.5 million babies of women without disabilities. They also classified four types of disability in the mothers: physical; sensory; intellectual or developmental; and multiple disabilities. "Looking at different types of disabilities is important because when we think about making perinatal care more accessible, there's broad recommendations that can be made around physician training, but there's more specific recommendations we can make depending on the type of disability, such as making sure newborn intensive care units (NICUs) are physically accessible," says Brown, who holds a cross appointment at the Dalla Lana School of Public Health and is an adjunct scientist at ICES and the Women's College Research Institute at Women's College Hospital.

Early Protein Intake in Extremely Low Birthweight Infants – Striking the Right Balance with Human Milk

Erin Hamilton Spence, MD, IBCLC

Extremely low birthweight (ELBW) infants miss out on the critical and exponential growth and development normally occurring in utero. Early nutrition plays a crucial role in the successful transitions from in-utero to NICU life. The first few days after birth highlight a particularly vulnerable nutritional period for ELBW infants. Two very significant transitions take place. The *first transition* from the womb to ex-utero NICU life includes an extremely high risk for metabolic and fluid disturbances, including hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, and renal impairment. This period can last only a few hours for the more mature, larger infants, or two weeks or more for the smaller, less mature infants. In the NICU, we manage this transition initially with intravenous (IV) fluids and nutrients, while ultimately aiming for the goal of full enteral nutrition (EN). The *second transition* is achieved with feeding. Initiation and gradual advancement of human milk feeding (mother's own or donor milk), fortification, and continued advancement to "full" feeding replaces the need for parenteral nutrition (PN). Depending on the maturity, size, and degree of illness of the infant, this second shift to primarily EN may be accomplished in as little as a week or as long as a month.

During this brief period of two significant transitions, ELBW infant macronutrient intake guidelines are more concerned with presumed deficits and tolerance of each infant than any assumed growth goal. Significant weight loss in the first 3-5 days is expected for all ELBW infants. When coupled with signs of renal immaturity, this weight loss may be compensated for by increased total fluid goals. However, the ratios of macronutrient intake are not usually adjusted based on early weight loss.

Many different protein intake strategies have been employed to optimize outcomes in ELBW infants.[1] However, concern over the right dose of parenteral protein in the form of amino acids remains. By contrast, enteral protein goals seem clear. The American Academy of Pediatrics (AAP)[2] and The European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)[3] concur on their recommendations for *enteral* protein intake for stable ELBW infants: 3.5-4.5 g/kg per day. ESPGHAN highlights a minimum of 3.5-4 g/kg per day for infants meeting growth goals, and up to 4.5 g/kg per day for infants with suboptimal growth where energy and micronutrient needs are optimal. However, they differ in their recommendations for *parenteral* protein intake. AAP recommends 3.5-4 g/kg per day, while ESPGHAN recommends 2.5-3.5 g/kg per day. This lack of concurrence about both lower and upper recommended limits for parenteral protein intake add to confusion. This may be due in part to semantics about the components that make up the term "protein."[4]

Erin Hamilton Spence is the Director of Clinical Education and Professional Development, Prolacta Bioscience.

What is Meant by "Protein"?

Protein delivered via PN is comprised of free amino acids. These amino acids provide a stop-gap measure to prevent negative nitrogen balance and catabolism.[5] EN in the form of human milk, on the other hand, provides complex proteins as well as peptides and amino acids. These include non-nutritive bioactive components such as α-lactalbumin, sIgA, lactoferrin, lysozyme, VEGF, osteopontin,[6] leptin, and adiponectin.[7] It is possible this more complete and varied protein profile could enhance the capacity to achieve metabolic balance among ELBW infants.

The limitations of delivering "protein" via PN in the form of amino acid supplementation has been borne out in the clinical research setting. In a 2007 multicenter trial, Clark et al randomized preterm infants 23-29 weeks and 6 days of gestation to IV amino acid administration consisting of 1.0 g/kg per day and advanced by 0.5 g/kg per day to a maximum of 2.5 g/kg per day or to 1.5 g/kg per day and advanced by 1.0 g/kg per day to a maximum of 3.5 g/kg per day. The higher dose of amino acid supplementation not only failed to improve growth but also was associated with increased blood amino acid and urea nitrogen levels.[8]

More recently, in the ProVIDe trial, ELBW infants with a birthweight < 1000 g were randomized to receive a parenteral amino acid dose of 1 g/day or saline placebo in addition to standard nutrition for the first 5 days of life. The higher dose of amino acids failed to increase the number of infants who survived free from neurodisability at 2 years.[9] An earlier publication from this trial raised concern about worsened early metabolic disturbance when higher protein intake is not adequately balanced by improved phosphate delivery. Refeeding syndrome (RS), defined as serum phosphate < 1.4 mmol/L and total calcium > 2.8 mmol/L, occurred in 24% of infants overall and was higher in small for gestational age infants. In their prospective, randomized, multicenter controlled trial, RS was associated with a 3-fold increase in mortality. These findings suggest that excessive IV feeding of amino acids does not improve outcomes and may result in metabolic dysregulation.[10]

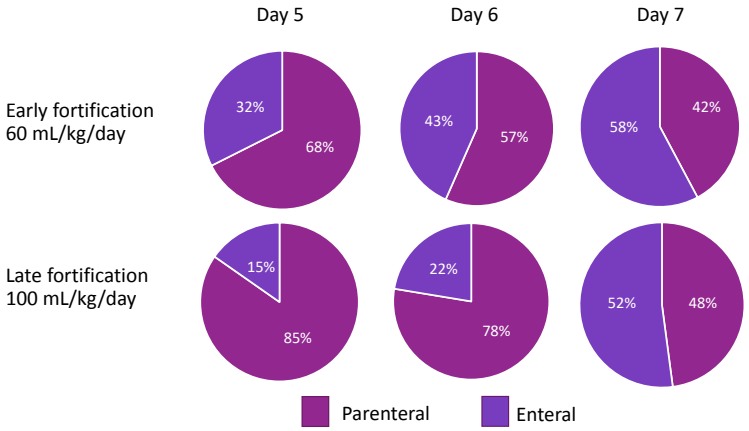

Figure 1. Transition Days from PN to EN: Early vs Late Fortification

What is Meant by "Full Feeds"?

To make clear communication even more difficult, the term "full feeds" can mean many things. Within an early NICU feeding guideline, at least two meanings emerge. Working from the first temporal goal of "full feeds," this is used to describe *the point in the transition from PN to EN at which parenteral protein intake is discontinued*. AAP recognizes this transition as "a critical period when total nutrient requirements may fluctuate as parenteral nutrition is weaned and enteral intake is insufficient," typically around total volume intake of 120 mL/kg per day.[2] Later within the same guideline, "full feeds" refers to *the point at which EN has reached the maximum pre-determined goal.* Depending on infant acuity, size, and gestational age, this will usually be somewhere near 160-170 mL/kg per day.[2] When both meanings are considered, this moment in time may span 2-5 days during a harrowing and prolonged NICU stay. While this may be a very small portion of a total NICU stay, the success of moving to "full feeds" and away from dependance on PN represents a significant milestone in extra-uterine life. Every ELBW who meets this goal will be more likely to avoid further compounding their burdens of prematurity.

Prioritizing EN via an Exclusive Human Milk Diet (EHMD)

Expediting the transition of ELBW infants from PN to EN results in reduced rates of RS.[11] In addition, there is evidence that ELBW infants who move more rapidly from PN to EN feeding have fewer comorbidities[12] and better outcomes.[1,13,14]

Until recently, fortification to improve early protein delivery at low feeding volumes had been avoided due to concerns about feeding intolerance (FI).[15] In current practice, the availability of a human milk-based fortifier (HMBF) can change our assumptions about goals for early nutrition. An EHMD with HMBF added to mother's own or donor milk improves early complete protein delivery. Use of an EHMD has been shown to facilitate transition from PN to EN by reducing the risk of FI[16,17] and necrotizing enterocolitis.[18-21] There is also a growing body of evidence that increasing human milk exposure during the first 2 weeks of life in ELBW infants improves structural connectivity network development in the brain.[22]

Ensuring Adequate Protein Intake with EN

In the short term, early fortification with a HMBF provides the advantage of a better quality and quantity of protein. Numerous studies have shown safety of early fortification with HMBF.[1,23] However, resistance to this practice exists due to debate about measurable outcomes.[15] In practice, more NICUs every year use a HMBF for early fortification, in contrast to the previous decades of standard late fortification employed when using cow milk-based fortifier. Why does this difference persist? Detailed attention to macronutrient intake during this time reveals an opportunity for improvement in NICU feeding guidelines. For example, within a standardized EHMD guideline, the ≤ 1000 g infant fortified with Prolacta's HMBF +6 early, at 60 mL/kg per day, vs late, at 100 mL/kg per day, can achieve enteral autonomy (aka discontinuation of PN) on the eighth day of feeding advancement, or 4 days after first fortification. One would not, therefore, expect an impact on "days to full feeds" due to early fortification. However, early fortification narrows the gap in total protein provision during days 5-9. Accumulated enteral protein intake with early fortification instead of late fortification amounts to an added 3.9 g/kg over 5 days (0.78 g/kg per day). This is a difference any neonatologist or NICU dietician should want to eliminate. While this may seem small, the increased portion of enteral protein allows for smaller doses of parenteral protein, while still achieving sufficient protein intake goals.

Early fortification with a HMBF shifts the balance away from PN to EN sooner, like an off-ramp instead of a giant-sized step. Each day fortification is delayed amounts to a near 50% difference in the enteral protein g/kg per day provided. In my example, early fortification on day 5 of an ELBW EHMD feeding guideline with volumes of 50-60 mL/kg per day amounts to enteral protein of 32.4% of total "protein" intake vs 15.3% with late fortification. On day 6, early fortification provides 43.4% of total "protein" intake vs 22.4% with late fortification. A detailed analysis of each day's macronutrient portions leads me to ask the question, why aren't more NICUs using early fortification?

Summary

Transition from PN to EN can be a vulnerable time for protein delivery. For any ELBW infant, the impact on total protein delivery can be large enough to matter. Decades of nutrition-focused research in neonatology have yet to incorporate a detailed understanding of optimal human milk feeding. Ideally, we could both recognize individual patient (and mother's and donor milk) variation within the framework of a standardized NICU feeding guideline. As we continue to learn more about human milk as the superior source for ELBW nutrition, I do hope this understanding will emerge. As of 2023, debate about exactly when to begin counting "growth" in ELBW infants and which growth standard is best rages on.[24-25] From both a short-term and long-term perspective, this seemingly small difference during this crucial window of vulnerability may be the key to "rely less on

the vascular system and more on the gastrointestinal tract as the preferred delivery route," as Dr. Martin suggests.[5]

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