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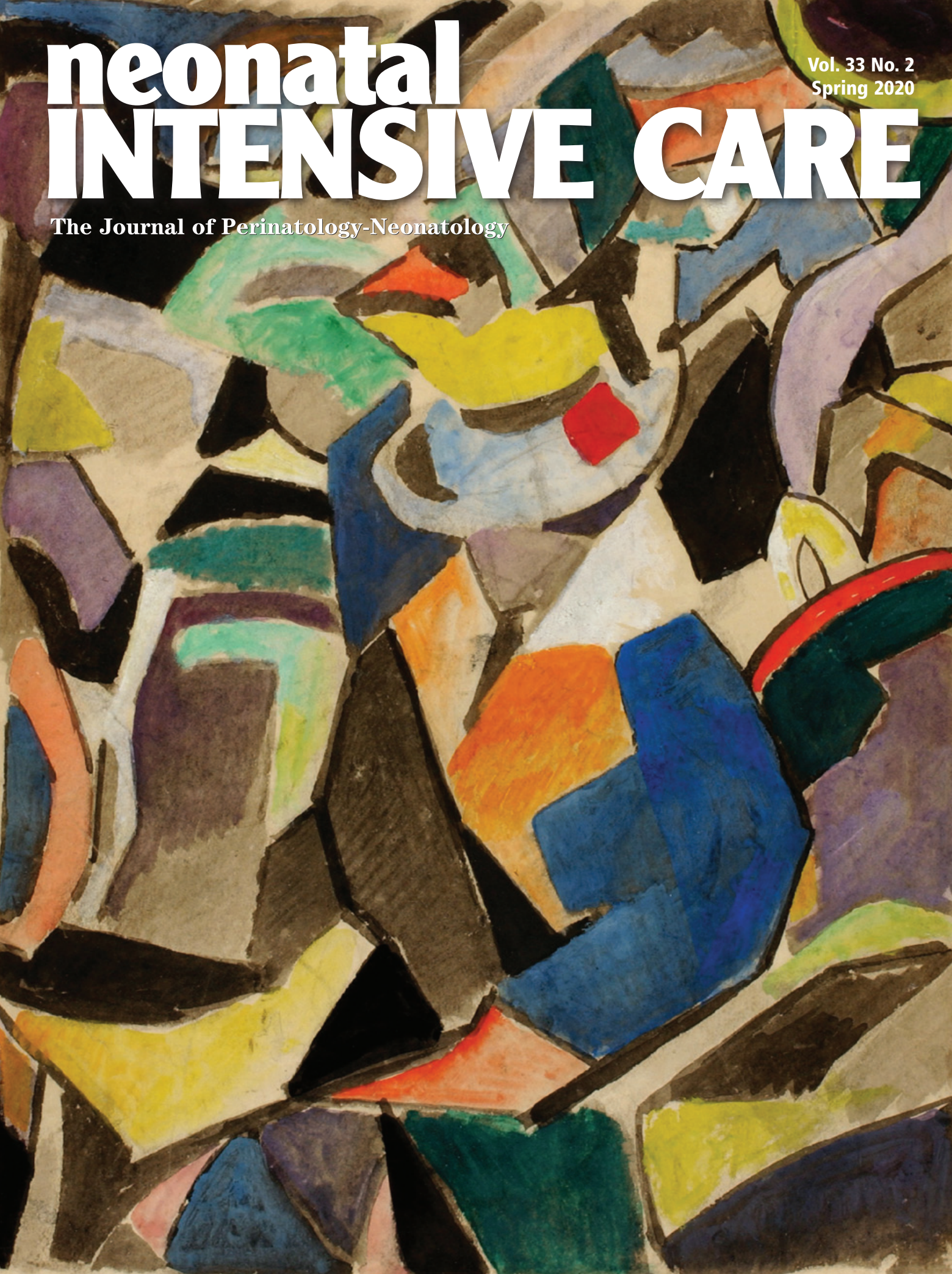

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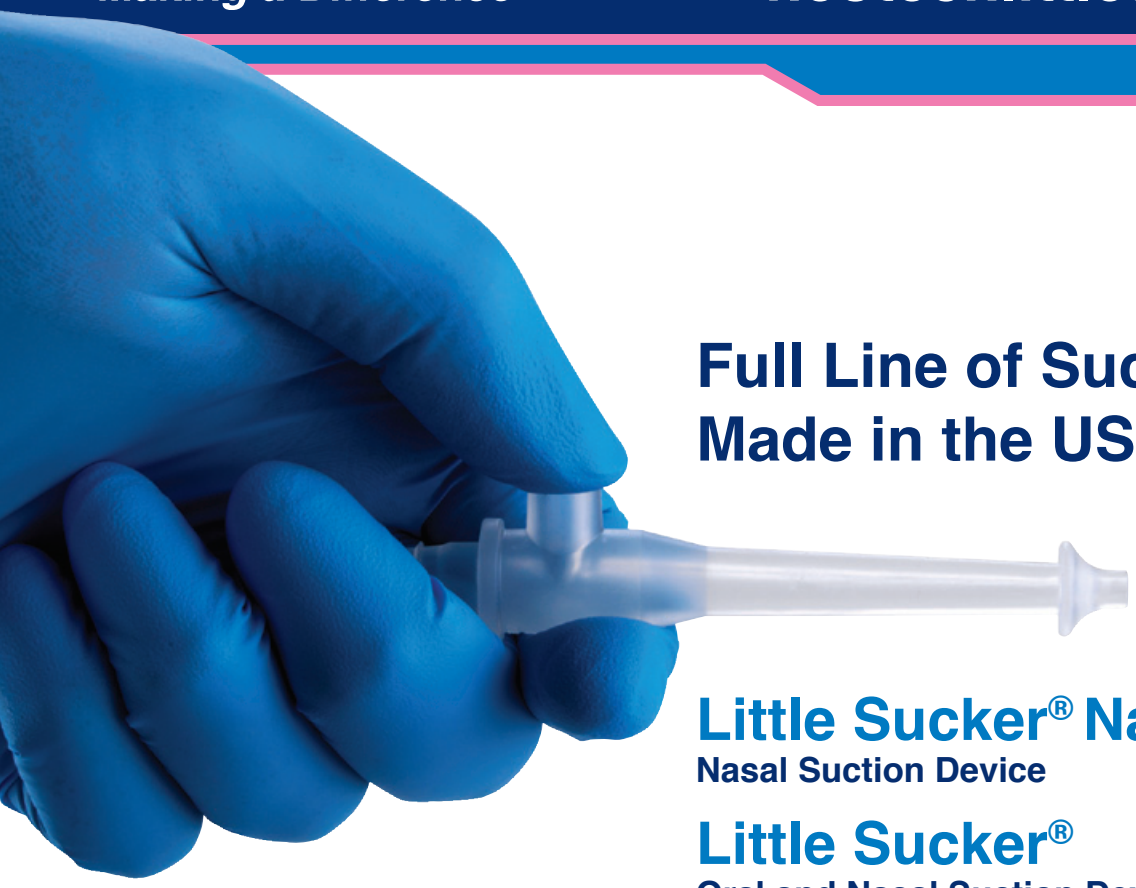

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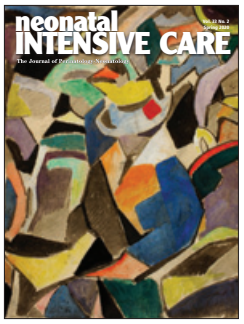

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Few Perinatally Exposed Infants Receive Recommended Hep C Testing

Fewer than a quarter of infants exposed perinatally to hepatitis C virus (HCV) undergo testing for the virus, according to a database study. "Hepatitis C virus infections are increasing in the United States as a likely complication of the opioid crisis," Dr Stephen W Patrick of Vanderbilt University Medical Center, in Nashville, said by email. "Our findings suggest that there is a need to improve public health systems that ensure infants exposed to hepatitis C are tested for seroconversion. For infants who are not appropriately tested and followed, there is a risk they will acquire the virus leading to liver failure." National guidelines say infants exposed to HCV should be tested with an HCV antibody at 18 months of age or with an HCV RNA PCR starting at 1 to 2 months. Published studies indicate that testing rates actually range from 16% to 68%. Patrick's team used linked databases to investigate HCV testing rates among more than 4,000 infants exposed to HCV who were enrolled in the Tennessee Medicaid program from 2005 through 2014 and followed until they were 2 years old. The prevalence of infants exposed to HCV increased each year, from 5.1 per 1,000 live births in 2005 to 22.7 per 1,000 live births in 2014 ($P<0.001$), with rates rising most sharply for white mothers. Overall, 23% of infants exposed to HCV underwent any HCV testing in the first 24 months of life, and only 18% satisfied the definition for adequate testing, the researchers report in Pediatrics. Factors associated with adequate HCV testing included white race, urban residents, maternal tobacco use, maternal HIV co-infection, lower birth weight, small for gestational age, NICU admission, and more well-child checks. After accounting for other factors, African American infants exposed to HCV had 68% lower odds of undergoing HCV testing than white infants, a significant difference. "Unfortunately," the authors note, "there are currently no recommended medical interventions to lower the risk of vertical transmission during pregnancy. Of infants who acquire HCV, 20% will have an acute resolving infection, 50% will develop a chronic asymptomatic infection, and 30% will develop a chronic active infection." "Physicians should be aware that hepatitis C infections among pregnant women are rising and exposed infants are seldom tested for seroconversion," Patrick said. "Primary-care physicians caring for infants should be aware that hepatitis C-exposed infants should be tested within the first two years of life." "In addition," he said, "because testing for hepatitis C virus in pregnancy is not universal, providers caring for infants should be aware of risk factors that are associated of hepatitis C infection, including opioid exposure."

Newborn Transfer May Not Reflect True Rate of Complications

Neonatal transfer was the factor most often associated with unexpected, severe complications at birth, particularly at hospitals that had the highest rates of complications, according to a cross-sectional study. "Transfers were more likely to be necessary when infants were born in hospitals with lower levels of neonatal care," Mark A Clapp, MD, MPH, of Massachusetts General Hospital in Boston, and colleagues write. "Thus, if this metric is to be used in its current form, it would appear that accreditors, regulatory bodies, and payers should consider adjusting for or stratifying by a hospital's level of neonatal care to avoid disincentivizing against appropriate transfers." The Joint Commission recently included unexpected complications in term newborns as a marker of quality of obstetric care, but it does not currently recommend any risk adjustment for the metric. The authors aimed to learn which factors regarding patients and hospitals were associated with such complications. Severe, unexpected newborn complications include death, seizure, use of assisted ventilation for at least 6 hours, transfer to another facility, or a 5-minute Apgar score of 3 or less. "This measure

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Cover: Abstract. Smithsonian American Art Museum and its Renwick Gallery. Carl Newman, born Philadelphia, PA 1858-died Abington, PA 1932.

has been proposed to serve as a balancing measure to maternal metrics, such as the rate of nulliparous, term, singleton, vertex-presenting cesarean deliveries," the authors explain. The study's findings "highlight the challenges in developing obstetric quality metrics," David B Nelson, MD, and Catherine Y Spong, MD, of the University of Texas Southwestern Medical Center in Dallas, write in an invited commentary. Valid indicators "should reflect not just an adverse event but also an event that could occur less often with improvements in clinical care" without leading to "unintended adverse consequences," they continue. "Unexpected newborn complication rates — measured in part by neonatal transfers — fail both of these principles," Nelson and Spong explain. "It is intuitive that lower-level neonatal care facilities would have higher rates of neonatal transfer" and are therefore inadvertently penalized, given how "neonatal transfers dominate the composite," they write. For their study, the researchers used county-level birth certificate data from the National Center for Health Statistics and included all live-born, term, singleton newborns weighing at least 2500 grams who were born from January 2015 to December 2017 in US counties that had exactly one obstetric hospital (to ensure that all births in the county were attributed only to that hospital). After excluding deliveries outside of obstetric facilities, the total sample included 1,754,852 births from 576 hospitals. All of the hospitals performed at least 300 deliveries a year. Hospital data came from the 2015 American Hospital Association annual survey and primarily provided the number of hospitals with obstetric-only beds and neonatal intensive care units (NICUs).

Sleeping difficulties are normal in babies

New parents struggling for babies to sleep through the night may not be doing anything wrong, according to new research that suggests that many apparent sleep problems are really part of the normal development of the baby. For example, the study found that 6-month-old babies still take 20 minutes, on average, to fall asleep. And at the age of 2, young children still wake up an average of once each night. The study also found that many variations are normal, said lead author Dr Juulia Paavonen of the Helsinki University Hospital in Finland. "We now know that the individual differences are very large and that the patterns related to falling asleep, waking up, staying awake at night and sleeping rhythms often develop at different rates," Paavonen said by email. Parents often worry about how well babies sleep because constant nighttime awakenings can disturb everyone in the home and feed concerns that babies are not developing normally. In particular, for first-time parents, irregular sleep may seem a sure sign that babies are sick, injured or hungry. For the study, the researchers surveyed the parents of almost 5,700 children about how well babies slept during their first two years of life to get an idea of what types of sleep problems the parents worried about, and what could be a reason for Concern instead of just an exhausting part of normalcy. Overall, about 40% of parents were worried about babies' sleep when children were 8 months old, the study found. Children's sleep gradually became more stable and consistent over time, researchers report in Sleep Medicine. Babies and young children generally slept between nine and 10 hours at night, but the amount of daytime sleep decreased from approximately five hours in total for babies to approximately two hours for young children. As daytime naps decreased from two to one, on average, and children slept less hours in total during the day, they also reduced their total sleep time to approximately 12 hours by the time they completed their second birthday. However, it is not so common for babies to take more than 40 minutes to fall asleep or have night wakings of an hour or more at the age of 8 months, the study found. It is also unusual for babies to be awake for more than 45 minutes at a time at night at 12 months, or for more than half an hour at 18 months. These may be circumstances in which it makes sense for parents to consult with a pediatrician to see if there is anything unusual that makes it difficult for babies to sleep, the study team concludes.

Racial Disparities Persist in Preterm Birth Risk

College education and high socioeconomic status do not erase US racial disparities in birth outcomes, according to a new analysis of all US live births from 2015-2017. Very early preterm birth — birth before 28 weeks gestational age — was five times more likely to occur in non-Hispanic black women of high socioeconomic status as similarly situated white women, even after statistical adjustment for a host of potentially confounding factors. Being of non-Hispanic black race was the single strongest predictor of preterm birth (PTB) at less than 28 weeks' gestation. The adjusted odds ratio (aOR) of 4.99 surpassed an interpregnancy interval under 1 year (aOR, 4.47), chronic hypertension (aOR, 2.84), and prior history of preterm birth (aOR, 2.81). "Even among college-educated women with private insurance who are not receiving (Women, Infants, and Children support), racial disparities in prematurity persist. These results suggest that factors other than sociodemographics are important in the underlying pathogenesis of PTB and in etiologies of racial disparities," wrote Jasmine Johnson, MD, and her coauthors in the abstract accompanying the presentation at the meeting sponsored by the Society for Maternal-Fetal Medicine. The analysis that Dr Johnson and her coinvestigators used, she explained during her plenary session presentation, still found significantly elevated risks for preterm birth for non-Hispanic black women after accounting for marital status, prior history of preterm birth, tobacco use, an inter-pregnancy interval of fewer than 12 months, and carrying a male fetus. "Birth certificates do not inform the lived experiences of one's self-identified race, and how that experience – or possibly just one's identification with a particular racial group – may positively or negatively affect their clinical risk of preterm birth," said Dr Johnson. "In this study, as in others, race is a social construct. It's a surrogate for social and societal racism that disproportionately affects birth outcomes of women of color." Using non-Hispanic white (NHW) women as a reference, women who described themselves as non-Hispanic black (NHB) had increased odds of preterm birth at 34 and 37 weeks gestation as well. Women identifying as both NHB and NHW had numerically elevated odds for preterm birth at all time points as well, but the odds at 37 weeks didn't reach statistical significance. The results were based on a retrospective population-based study of a cohort drawn from the National Vital Statistics birth certificate data of all live births in the United States between 2015 and 2017, explained Dr Johnson, a maternal-fetal medicine fellow at the University of North Carolina, Chapel Hill. Drawing from a nationally representative sample and having a population-level design drawn were strengths of the study, she said. Women with singleton pregnancies without anomalies who identified as NHB, NHW, or as both NHB and NHW were included if they also had high socioeconomic status. Including women who identify as both black and white was another strength of the study, Dr Johnson added. She explained that, for the purposes of the study, high socioeconomic status was defined as having 16 or more years of education and private insurance, and not receiving WIC benefits. In addition to the primary outcome measure of preterm birth at fewer than 37 weeks gestation,

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secondary outcomes included preterm birth at fewer than 34 and fewer than 28 weeks' gestation, as well as low birthweight (LBW) and very low birthweight (VLBW). About 11.8 million live births occurred during the study period, and 11.3 million of those were singleton pregnancies without fetal anomaly. After excluding women who did not meet the racial self-identification or socioeconomic status inclusion criteria, the investigators arrived at the final study population of 2,170,688 individuals. Of those, 2,017,470, or 92.9%, were non-Hispanic white, while 144,612, or 6.7%, were non-Hispanic black. The remaining 8,604 participants, or 0.4%, identified their race as non-Hispanic black and non-Hispanic white.

Increased Preterm Deliveries in Pregnant Women Hospitalized for Flu

Among findings in pregnant women hospitalized for influenza in high-income countries is a substantially higher prevalence of preterm deliveries, according to an international group of researchers. Dr Fatimah Dawood of the Centers for Disease Control and Prevention, Atlanta, Georgia, and colleagues note that pregnant women are hospitalized for flu more often than their nonpregnant peers and the general population. But data on outcomes are largely limited to pandemics. To investigate, the team examined 2010-2016 health records from Australia, Canada, Israel and the United States. They identified more than 18,000 pregnant women hospitalized for acute respiratory infection or febrile illness (ARFI) and influenza-associated ARFI. Of 18,048 ARFI-coded hospitalizations, 1,064 (6%) included RT-PCR testing for influenza viruses within three days of admission. Influenza vaccination uptake was low (16%) in the tested patients, but this varied from 6% in Australia to 50% in the US. Overall, 614 women (58%) were influenza-positive. Most of this group (67%) were in the third trimester, and 20% had underlying conditions. The majority of the influenza-positive group (82%) were still pregnant at the end of the hospital stay. Of the 110 hospitalizations that resulted in deliveries during the stay, 101 (92%) were singleton gestation deliveries of live births with available outcome data. Up to 34% of these were preterm deliveries. This proportion, say the investigators, is "substantially higher than the estimated baseline preterm birth prevalence of 9% among the general population of pregnant women in high-income countries." There were no maternal deaths, although 5% of hospitalizations required intensive care. Summing up, Dr Dawood said, "We found that the majority of pregnant women who were hospitalized with fever or respiratory illness during six influenza seasons were previously healthy and had not received the current season's influenza vaccine." "Multiple studies," she added, "have demonstrated that influenza vaccination during pregnancy provides protection against influenza to both mothers and their young infants during the first few months of life, and influenza vaccines are recommended for pregnant women in any trimester of pregnancy. Our study highlights the need for ongoing efforts to improve influenza vaccine uptake among pregnant women."

Microbiome and Gut-Brain Axis in Premature Infants Focus of Conference

The International Conference on Human Milk Science and Innovation (ICHMSI) will host its first European regional conference in Barcelona, Spain, 7-8 February 2020, in partnership with the European Foundation for the Care of Newborn Infants (EFCNI). Chaired by professors Angelika Berger, MD, from the Medical University of Vienna and William D Rhine, MD, of Stanford University School of Medicine, ICHMSI hosts the latest scientific research on human milk and its current and potential clinical applications. The ICHMSI is the premier forum for thought leaders and medical experts in human milk science and research. This year's conference will explore the microbiome's influence on the gut-brain axis in premature infants, featuring scientists and researchers from across Europe. Recent research on the microbiome points to the direct connection between gut health and the brain of premature infants and a correlation between human milk nutrition and a healthy infant microbiome. Clinicians from Europe, Japan and the US will share medical advances and recent microbiome revelations that are bolstering the survival and critical development of extremely premature infants worldwide. They will also discuss advanced feeding protocols to achieve healthy growth using human milk nutrition. "It is an honor to co-chair the International Conference on Human Milk Science and Innovation during its European debut," Dr Berger said. "The conference will unite clinicians from all throughout the world to explore the full potential of human milk science in our smallest neonates." Dr Rhine added, "The leadership and support of EFCNI and Dr Berger extends the global reach of this year's conference, attracting a new subset of European clinicians. Bringing the conference to Europe for the first time will open the channels for greater insight into the various European clinical practices regarding human milk." This year's event will also feature the presentation of the third recipient of the Ruth A Lawrence Investigator Award for Research in Human Milk Science. The winner receives a $10,000 USD award and will have the opportunity to present their research to attendees during the next ICHMSI conference. Established in 2016 in honor of Ruth A Lawrence, MD, a pioneer in the field of human lactation and breastmilk, the award supports original research in human milk science and breastfeeding medicine. The European Foundation for the Care of Newborn Infants (EFCNI) is the first pan-European organization and network to represent the interests of preterm and newborn infants and their families. It gathers together parents, health care experts from different disciplines and scientists with the common goal of improving the long-term health of preterm and newborn children by ensuring the best possible prevention, treatment, care and support. For more information, visit www.efcni.org.

Erythropoietin Fails to Stem Death, Neurodevelopmental Problems in Extreme Preemies

The hope that giving high-dose erythropoietin to extremely preterm infants would prevent death and neurodevelopment impairment appears to have dimmed. A new study of 941 infants born at 24 to just under 28 weeks of estimated gestation has shown no benefit to the treatment in that primary composite endpoint. The combined rates of death or severe impairment were identical by age 2—26%—regardless of whether the newborn received the drug or placebo. "I was disappointed in the results as we hoped it would provide a benefit to our target population," chief author Dr Sandra Juul, who heads the division of neonatology at the University of Washington in Seattle, said. Doctors are looking for better ways to treat extremely preterm infants, because despite better survival, about 40% of babies born before 28 weeks still have major impairments such as deafness, blindness, cerebral palsy or intellectual disability. The researchers focused on erythropoietin because of its importance in fetal brain development. Four earlier phase 2 trials, included in a 2017 meta-analysis, collectively suggested significant improvement if erythropoietin is used. About 7% of hospitals that treat extremely preterm infants already give

erythropoietin to the majority of such babies, according to a 2019 study in the American Journal of Perinatology. But the new study showed no benefit of erythropoietin when given within 24 hours after birth to 32 weeks of postmenstrual age. Thirty US hospitals participated in the study. When the researchers looked at individual outcomes when the children were 22 to 26 months postmenstrual age, they also saw no benefit for erythropoietin therapy. Death occurred in 13% of the babies who got the drug compared with 11% given placebo. Rates of sepsis, retinopathy of prematurity, necrotizing enterocolitis, intracranial hemorrhage and bronchopulmonary dysplasia were also not significantly different between the two groups. Eighty-eight percent in the erythropoietin group were discharged alive versus 90% in the control group. Median time to discharge was 101 days with the drug and 102 days with placebo. But the drug therapy didn't produce troublesome side effects.

Low-Dose Aspirin a Simple and Safe Way to Prevent Preterm Birth

For pregnant women in low- and middle-income countries, low-dose aspirin in early pregnancy provides a safe, effective and inexpensive way to protect against preterm birth, results of the ASPIRIN trial confirm. The importance of this study is that it "reframes the use of aspirin in pregnancy as not just a preventive measure for preeclampsia for which it is often recommended, but also for the prevention of preterm birth," lead author Dr Matthew K Hoffman of Christiana Care Health System, in Newark, Delaware, said. The ASPIRIN study included nearly 12,000 women pregnant for the first time with a single baby in India, Pakistan, Zambia, Democratic Republic of the Congo, Guatemala or Kenya. By random assignment, about half took aspirin (81 mg/daily) and half took placebo starting in the first trimester. Women were included in the study only if they maintained a pregnancy for more than 20 weeks. As reported in The Lancet, women taking aspirin were 11% less likely to deliver before 37 weeks' gestation than were women taking placebo (P=0.012). In addition, aspirin cut the risk of early preterm birth before 34 weeks by 25% (P=0.039) and perinatal death by 14% (P=0.048). Importantly, Dr Hoffman said, there was no increase in serious adverse events in mothers or infants in the low-dose aspirin arm compared with the placebo arm. The ASPIRIN study results are in line with previous meta-analyses that showed similar reductions in preterm birth and perinatal mortality. "Because of the large sample size, this trial was able to show these benefits definitively in a diverse group of women from various low- and middle-income countries. The low cost and proven tolerability of aspirin in this population suggests that our aspirin regimen can be readily and safely adopted across a range of clinical sites globally," the researchers write in their paper.

Infant Deaths, Poor Conditions at Indian Hospital Spark Uproar

In a dimly lit shanty in northwestern India, Padma Rawal sobs inconsolably as she recalls losing her 5-month-old infant, and recounts the hospital ordeal she endured last month. Her infant, Tejash, is one of more than a 100 children who have died at a government hospital in Kota in the state of Rajasthan since early December. Infant deaths are common in India, but the spike in fatalities at a state-run institution and evidence of poor hygiene, broken equipment and staff shortages has made headlines and triggered a row between the two main political parties. District data in fact shows the infant mortality rate at the JK Lon Hospital in Kota has improved to 5.69% with 963 deaths in 2019 down from 6.11% in 2018, when 1,005 deaths were reported. But details from affected families and two preliminary investigations have

emerged, embarrassing the regional government and local health authorities. Padma said there were three or four infants in each bed when she was there in late December. "Why are you crying? Your child is going to die anyway," Padma recalled one doctor telling her, as she sat weeping beside her husband, Sanjay, and daughters—Kanika, 6, and Purvi, 4. The parents of nine children who either died or were being treated at the hospital all described staff shortages, poor sanitary conditions and a lack of basic provisions such as blankets despite very cold weather. Rajasthan Health Minister Raghu Sharma tweeted that most of the infants who died had low birth weights and were in critical condition. He vowed "strict action" would be taken against any officials found guilty of negligence. At least 112 children have died at the hospital since the start of December, even as authorities scrambled to bring in additional staff and equipment amid public outcry. Around three quarters of the recent deaths occurred in JK Lon's neo-natal intensive care unit (NICU), which treats babies up to a month old, said an official directly aware of the matter. Hospital officials said infant mortality rates may appear high, partly because it handles many referral cases and is a hospital of last resort. It is the only one with an NICU in a 200 km radius. A preliminary probe into the deaths at JK Lon found that of 533 pieces of equipment in its pediatrics section, 320 were out of order, including defibrillators and ventilators. JK Lon's medical superintendent, Suresh Dulara, who took additional charge of the centre in late December, said that the hospital had started repairing equipment. A separate probe by the National Commission for Protection of Child Rights, a government agency, found that infrastructure and sanitation was "pathetic." "Pigs were found roaming inside the campus of the hospital," it said. The deaths and surrounding furor set off a row between India's two main political parties. The Congress party, which sits in opposition nationally, won Rajasthan state in December 2018 elections. It pointed to the higher overall death rate at the hospital under Prime Minister Narendra Modi's ruling Bharatiya Janata Party (BJP), which ran Rajasthan previously. The BJP hit back, saying appropriate funding has been assigned to the state under the National Health Mission and urged the state to request further financial support. Modi's government has raised expenditure on healthcare recently and set a target to take the annual health spending to 2.5% of GDP by 2025. It was 1.4% in 2017-18. Latest government data show a decrease in infant mortality nationwide to 33 per 1000 live births in 2017 from 53 in 2008.

Decolonizing Parents Cuts NICU Staph Transmission Risk

Treating colonized parents of neonates hospitalized in the neonatal intensive care unit (NICU) may reduce the risk of parents spreading StaphylococcuS aureus to the infants, a recent study has shown. "Treating parents of neonates in the NICU with intranasal mupirocin and 2% chlorhexidine-impregnated cloths compared with placebo reduced the risk of a neonate acquiring S aureus colonization with strains that were the same as S aureus strains identified from the parent(s) at time of study enrollment," write Aaron M. Milstone, MD, MHS, from Johns Hopkins University, Baltimore, Maryland, and colleagues. "In this trial, more than half of neonates who acquired S aureus had the same strain as their parent(s)." According to the authors, neonates have an immature microbiome at the time of their admission to the NICU and rarely are already colonized by S aureus. Instead, they become colonized in the NICU after exposure to the organism from colonized or infected people and contaminated objects in the environment. StaphylococcuS aureus remains a common cause of outbreaks and healthcare-associated infections in NICUs and can seriously impact affected infants, with long-term sequelae such as poor neurodevelopmental and growth outcomes.

Although infection prevention strategies in NICUs typically center on healthcare workers and the physical environment as reservoirs for exposure of infants to S aureus, parents may also serve as an important reservoir for transmission of the bacterium. With this in mind, Milstone and colleagues conducted their double-blinded, randomized controlled trial across two tertiary care NICUs to investigate whether treating parents would reduce the risk of their infants becoming colonized with S aureus. The Treating Parents to Reduce Neonatal Transmission of StaphylococcuS aureus (TREAT PARENTS) trial enrolled 236 infants. It included infants who had not had a previous culture positive for S aureus, had at least a 5-day NICU stay, were no more than 7 days old if admitted to the NICU from an outside location, and had at least one parent who tested positive for S aureus at screening. The study's primary endpoint was infants' acquisition within 90 days of the same S aureus strain that their parent had. Secondary outcomes included infants' acquisition of any strain of S aureus and neonatal S aureus infections. Parents in the study received 5 days of treatment. They were randomly assigned to intranasal mupirocin and topical bathing with 2% chlorhexidine-impregnated cloths (n = 117) or placebo treatment with petrolatum intranasal ointment and nonmedicated soap cloths (n = 119). Of the 236 enrolled infants, 208 (55% male; 76% singleton births; mean birthweight 1985 grams; 76% vaginal births) were included in the analytic sample, although 18 of these were lost to follow-up.

Nihon Kohden Introduces Revolutionary Ventilator Designed for Lung Protection

Nihon Kohden, a US market leader in precision medical products and services, announced the launch of its new NKV-550 series ventilator system that offers a full suite of respiratory therapy applications and is capable of performing any respiratory function necessary in a critical care setting for patients of all ages—from neonate through adult. The NKV-550, which will be introduced for the first time at the annual American Association for Respiratory Care Congress 2019 in New Orleans, is a revolutionary ventilator that features an integrated touchscreen, intuitive interface and advanced, onscreen treatment support. The NKV-550 was developed to seamlessly transition between invasive ventilation, noninvasive ventilation and high-flow oxygen therapy, allowing clinicians to effortlessly respond to a patient's respiratory support needs without having to change machines. "Every product we bring to market is designed to simplify workflow for clinicians and benefit patients," said Yasuhiro Yoshitake, president and CEO of Nihon Kohden America. "We saw a tremendous need in the respiratory market for a comprehensive ventilator that could respond to any patient situation while also providing the same ease and control of modern smartphone technology." The NKV-550 is the first and only ventilator to offer Protective Control, a remote monitoring system that allows respiratory therapists and clinicians to check on a patient and adjust therapy while safely behind an isolation window or control room window. When dealing with a communicable disease or a patient in isolation, the feature protects both the clinician and the patient because respiratory therapists and clinicians will not lose precious minutes donning protective gowns, gloves and masks before responding to the needs of an infectious patient, a potential hazard many healthcare workers face. The NKV-550 was created based on the lung protective approach to ventilation and features the

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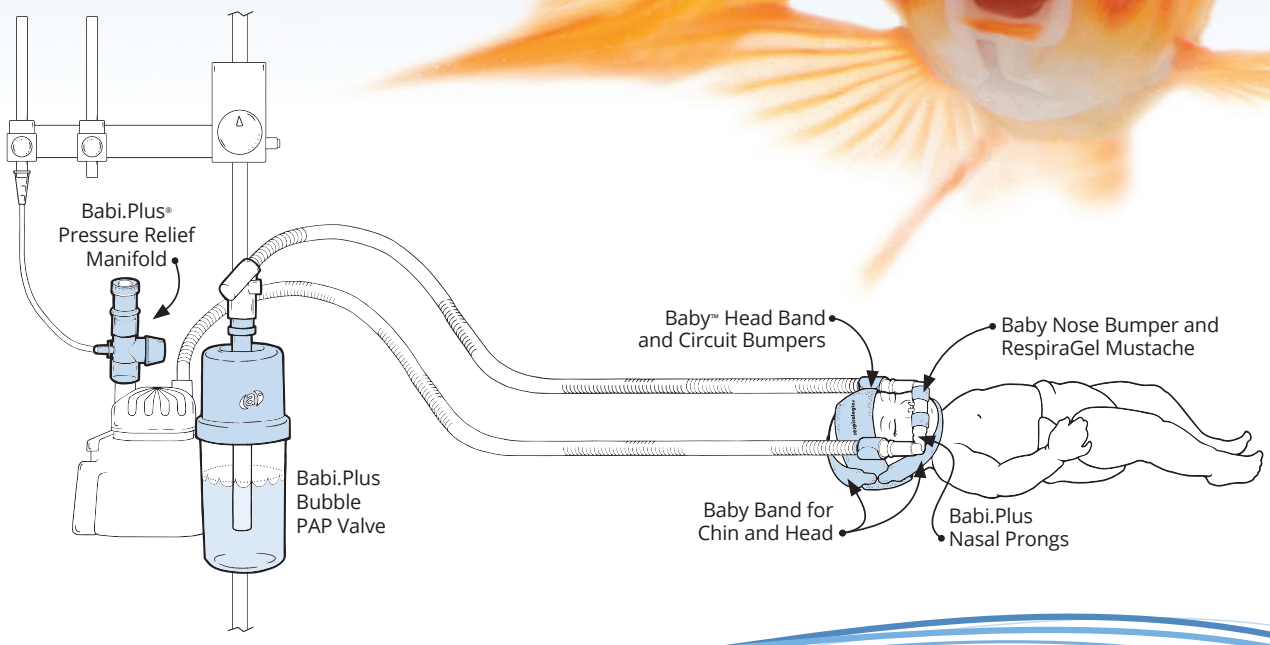

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USDTL Test Helps Identify Newborns Exposed to Fentanyl Abuse

Over the last few decades, United States Drug Testing Laboratories, Inc. (USDTL), has been quietly making a huge impact on the lives of some of the most vulnerable Neonatal Intensive Care Unit (NICU) patients, newborns exposed to substances of abuse during gestation. Today USDTL announced that they are the first laboratory in the world to commercially offer newborn fentanyl testing in both meconium and umbilical cord tissue specimens. Fentanyl, defined by the Center of Disease Control (cdc.org), is a synthetic opioid that is extremely addictive. Like other opioids, abuse during pregnancy can cause newborns to go into dangerous withdrawal known as Neonatal Abstinence Syndrome (NAS) and/or have other devastating physical abnormalities. Fentanyl is a powerful, inexpensive drug that is being cut into illicit substances and its presence is increasing throughout the country.

"Traditionally, fentanyl was mainly accessible via prescribed patches and intravenously, so testing for it was generally reserved for people that had specific access to it. Now, the distribution of fentantyl is booming through illicit drug trade communities in volumes that are difficult to estimate. Unfortunately, testing for fentanyl as part of a detection or exposure protocol is becoming the new normal. We are grateful to be able to develop and offer these tests to answer the call of so many hospital partners that are trying to get on top of this epidemic," said Joseph Jones, Chief Operating Officer at USDTL. Meconium and umbilical cord tissue are both considered advanced long-term drug testing specimens because both start capturing substances in the newborn's system up to approximately 20-weeks before birth. For comparison, newborn urine drug testing has a typical lookback window up to approximately 2-3 days before birth. This longer window of detection from advanced specimens makes it possible to get a better picture of what is going on with the newborn. "Adapting our tactics — from a population health standpoint — and being able to test for more prevalently abused drugs in the industry is crucial. The landscape continues to change and as a community we have to be prepared to keep up with the trends," said Douglas Lewis, President and Founder of USDTL.

Twins, triplets have higher risk of medical mix-ups in neonatal ICUs

Doctors are much more likely to make mistakes ordering medicines or treatments for babies in the ICU when these infants are twins or triplets than when they are they singletons, a US study suggests. So-called wrong patient orders have long been a bigger risk in the neonatal intensive care unit (NICU) than in general pediatrics wards, and these mix-ups are more common when newborns haven't yet been named or have a name very similar to another hospitalized baby, researchers note. But research to date hasn't offered a clear picture of whether siblings in multiple births are more likely to be subject to wrong patient orders. For the current study, researchers examined data on 10,819 infants treated at six NICUs run by two healthcare systems in New York City between 2012 and 2015. Most of these babies, 85.5%, were singleton births; 14.5% were multiples like twins or triplets. Multiples in the NICU were 75% more likely to have wrong patient orders than singletons. "The current study is the first to demonstrate that multiple births have a significantly greater risk of order errors than singleton births, and that the excess risk is attributable to errors between siblings receiving care in the NICU at the same time," said Dr Jason Adelman, lead author of the study and chief patient safety officer at NewYork-Presbyterian Hospital/Columbia University Irving Medical Center in New York City. "These results were remarkably consistent across two large health systems, suggesting a more widespread rather than an isolated problem," Adelman said by email. To assess wrong patient orders, researchers focused on how often clinicians entered requests for medicine or treatments or tests in electronic medical records — and then retracted the request within 10 minutes and placed an identical request for a different NICU patient. This so-called retract and reorder (RAR) process suggests that clinicians noticed an error and went into the records to fix it, the study team notes. Overall, there were 66 RAR events for every 100,000 orders made for multiples, compared with 41.7 RAR events for every 100,000 orders made for singletons, the study found.

Smallest surviving baby boy ever born saved by doctors using NAVA technology

The smallest surviving baby boy believed to ever born has survived despite weighing only 258 grams at birth after 24 weeks and five days of gestation. Dr Ryo Itoshima, one of the doctors behind this miraculous recovery, says the Getinge innovation Neurally Adjusted Ventilatory Assist (NAVA) played a crucial role in the lung development. After months in the neonatal intensive care unit (NICU) at Nagano Children's Hospital in Japan, little Ryusuke Sekino has finally been able to move home together with his parents. He is believed to be the smallest baby boy ever born to leave a hospital safely. It was in October last year that his mother Toshiko gave birth to him via an emergency C-section. Neonatologist Ryo Itoshima was on duty that night. "I got really worried when the obstetrician told me that the estimated body weight of the baby was less than 300 grams. Two duty doctors work in our NICU every night, but that specific night three more doctors came in to support," he recalls. The baby spent his first months in the NICU on different mechanical ventilation modes HFOV, invasive NAVA and the longest treatment, two and half months, was with the Getinge innovation, NAVA. NAVA is a ventilation mode where the patient's own respiratory drive controls timing and assist delivered by the ventilator. It uses the diaphragm activity to deliver assist adapted to the patient's effort. In this specific case Non-invasive NAVA (NIV-NAVA) was used, which is a synchronized non-invasive ventilation mode, independent of leakages, allowing a better trigger and synchrony as well as a gentler application of nasal masks or prongs. "The baby's lung condition, BPD, was not good even after extubation — so we used NIV-NAVA after extubation for a long time, more than two months. This is the final step in liberating a patient from mechanical ventilation," explains Dr Ryo Itoshima. "NIV-NAVA supported the baby's own respiration well and helped his weight gain and lungs to develop, especially after extubation. Without NIV-NAVA, the baby would surely have needed

reintubation and the lung damage would be much worse." At three months old, Ryusuke finally put on weight day by day and his lung conditions started getting better. In April, at six months old, he was ready to go home with his parents. By this time, he had increased his weight thirteen fold, up to 3374 grams. "We are very happy that we could help them, they now stand safely at home at the starting line of his life. It is truly my favorite moment at work; when a baby leaves our hospital healthy and the parents are smiling. Little Ryusuke got to me, I almost feel like I have one more son of my own." says Dr Ryo Itoshima.

Masimo and MS Westfalia GmbH (MSW) Expand Partnership

Masimo and MS Westfalia GmbH (MSW) announced that MSW will integrate additional Masimo measurement technologies into MSW's plug-and-play hybrid Jenny platform, to help clinicians assess brain function, oxygenation, ventilation, and resuscitation status. After launching the Jenny modular point-of-care monitoring device with integrated Masimo noninvasive, continuous rainbow SET measurements (including total hemoglobin, SpHb) and Masimo sidestream and mainstream NomoLine capnography, MSW plans to add Masimo Next Generation SedLine Brain Function Monitoring, O3 Regional Oximetry, and Oxygen Reserve Index (ORi) to Jenny. By doing so, MSW will make the platform an even more versatile and comprehensive monitoring solution, suitable for use in a variety of care areas, including the ICU and the OR, as well as in EMS and military settings. The three additional technologies, currently available directly from Masimo on the Root Patient Monitoring and Connectivity Platform, are:

- Next Generation SedLine Brain Function Monitoring, which assists clinicians in monitoring the state of the brain under anesthesia, with bilateral data acquisition and processing of EEG signals and an enhanced Patient State Index (PSi).
- O3 Regional Oximetry, which may help clinicians monitor cerebral oxygenation in situations in which pulse oximetry alone may not be fully indicative of the oxygen in the brain.
- ORi, the first noninvasive and continuous parameter to provide insight into the oxygen reserve of patients receiving supplemental oxygen.

Eugen Kagan, CEO of MSW, said, "Our company's mission is to save lives and improve quality of life for our patients. For more than 25 years, our goal has been to develop products that assist healthcare providers in the hospital and pre-hospital markets by helping to improve patient outcomes and increase patient satisfaction and workflow efficiency — while lowering the cost of healthcare. We accomplish this by developing revolutionary approaches to new product development and by partnering with best-in-class partners like Masimo so we may meet the needs of a constantly changing healthcare landscape. The expanded technology partnership between MSW and Masimo allows us to offer our customers the most innovative technologies, helping them overcome many of the daily challenges they face in healthcare delivery." Joe Kiani, Founder and CEO of Masimo, said, "It's great to see MSW's commitment to incorporating our full suite of noninvasive, continuous measurements into their all-in-one modular Jenny platform. We are happy to be able to help MSW accomplish its wonderful mission." ORi has obtained CE marking and is not available in the US.

Thyroid Function Test Abnormalities Linked to Preterm Birth

Thyroid function test abnormalities in pregnancy, including those at subclinical levels, are linked to a higher risk of preterm birth, according to a new meta-analysis. However, there is no evidence, as yet, to indicate that treatment improves outcomes. "Among pregnant women without overt thyroid disease, subclinical hypothyroidism, isolated hypothyroxinemia, and thyroid peroxidase (TPO)-antibody positivity were significantly associated with higher risk of preterm birth," the authors write. Noting that recent large clinical trials have failed to show benefit from routine screening and thyroid hormone treatment for the abnormalities, the authors of an accompanying editorial propose a shift in focus. "It is time to trust the findings of the major clinical trials, move past consideration of screening for and treatment of mild thyroid testing abnormalities detected during pregnancy, and focus instead on determining their physiological context," write Anne R Cappola, MD, ScM, University of Pennsylvania, Pittsburgh, and Brian Casey, MD, University of Alabama at Birmingham, in their editorial. David S. Cooper, MD, professor of medicine and radiology, Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins University School of Medicine, Baltimore, Maryland, who was not involved in the study, agrees that research could turn to causative factors. "As the authors point out, future research could be focused on why preterm delivery is associated with subclinical hypothyroidism and/or TPO antibody positivity, since it may not be low thyroid hormone levels that are primarily responsible," he said. "Whether additional randomized controlled trials of thyroid hormone therapy, which are very difficult to do and very expensive, will be forthcoming is uncertain," he added. Preterm birth is the leading direct cause of morbidity and mortality in children under the age of 5 years, and overt hypothyroidism is a well-known risk factor, hence the concern about the less certain role of milder or isolated thyroid abnormalities is warranted. To take a closer look, the Consortium on Thyroid and Pregnancy — Study Group on Preterm Birth analyzed 19 published and unpublished prospective study cohorts involving 47,045 pregnant women, who were a mean age of 29 years and had a median gestational age at blood sampling of 12.9 weeks. Importantly, investigators from each cohort provided individual participant data, making the analysis the largest of its kind to date, allowing for a rigorous analysis and the ability to standardize definitions of thyroid function test abnormalities. "Previous studies have used widely differing definitions of thyroid function test abnormalities, and by gathering the individual participant data, we were able to homogenize these definitions to those currently used," first author Tim IM Korevaar, MD, PhD, Academic Center for Thyroid Diseases, Erasmus Medical Center, Rotterdam, the Netherlands, said.

Weight-loss surgery between pregnancies tied to better outcomes

Obese women who have weight-loss surgery between pregnancies may be less likely to experience complications like high blood pressure and preterm births in their second pregnancy, a recent study suggests. Researchers examined hospital records from 2002 to 2014 for more than 1.6 million women 15 to 45 years old in New South Wales, Australia. The study focused on 326 women who had bariatric surgery between their first and second pregnancies and 461,917 women who had two pregnancies without a weight-loss operation in between. The study found that for obese women who had the surgery between pregnancies, the risk of complications dropped markedly from the first pregnancy to the second, although it didn't reach the level seen in the general population of women. "The odds of adverse pregnancy outcomes among women who have bariatric surgery do not decrease to the level observed in

the general birthing population; however, there was substantial improvement," lead study author Dr I Ibiebele of Royal North Shore Hospital in New South Wales and colleagues write. "Although body mass index (BMI) was not directly assessed in this study, bariatric surgery performed for the management of obesity, in accordance with current clinical criteria, is likely to result in improved pregnancy outcomes in women who have a subsequent pregnancy," Ibiebele and colleagues write. During the study period, there was a 13-fold increase in hospitalizations for women having bariatric surgery for the first time, the analysis found. Compared with women in the general population, those who had bariatric surgery had higher rates of high blood pressure, diabetes and preterm deliveries overall. But women who had bariatric surgery between their first and second pregnancies were 61% less likely to experience high blood pressure, 37% less likely to have infants that were large for their gestational age, 63% less likely to have a preemie and 36% less likely to have their baby sent to the neonatal intensive care unit (NICU) than in their first pregnancies. Women who had surgery and those in the general population were around the same age when they had their first pregnancy. But the women who had bariatric surgery waited an average of two years longer to have their second child, the study found.

EXECUTIVE PROFILE

Astarte Medical

Describe your product(s) and its unique features.
NICUtrition by Astarte Medical is a real-time clinical decision support tool to more effectively implement a hospital's own enteral feeding protocol and promote compliance to overcome the challenges of manual standardization, understand protocol adherence or lack thereof, and gather useful insights from feeding data. The platform analyzes preterm infant feeding and developmental milestones while in the NICU for the benefit of neonatologist, nurses, dieticians and department heads. Optimizing nutrition management in the NICU, particularly through successful progression of parenteral to enteral to oral feeding of preterm infants, remains a major challenge for clinicians. Clinical practice groups have developed feeding guidelines in an attempt to provide evidence-based care with less variability, which is known to improve outcomes and shorten length of stay, but there's no practical way to know whether clinicians are adhering to these guidelines. Studies have shown that implementing a standardized feeding strategy can accelerate the attainment of enteral and oral feeding milestones with a demonstrated reduction in central line days and parenteral nutrition, as well as reduced duration of ventilation days. With the ability to integrate through FHIR standards or Epic's AppOrchard, implementation is much simpler than custom integration projects or EMR reports with manual review. NICUtrition provides real time analytics which allows clinical teams to track milestones and metrics over time and observe the correlating patient outcomes.

Tell us about the latest advances in the area your product serves.
Nutrition, with direct impact on growth and cognitive outcomes, has become increasingly complex with a growing catalog of available dietary options. Optimization of human milk fortification, mainly through individualization and the quality of the fortifiers, are getting increased attention as recent studies suggest that it's not only growth *per se*, but the quality of growth that matters. Human milk fortifiers are used for targeted fortification of breast milk to provide preterm infants with the extra protein, calcium, phosphorus, and even salt, needed to build strong bones and healthy organs. However, these requirements are variable depending on the clinical condition and characteristics of each infant either present at birth or evolving during NICU stay. Therefore, human milk fortification needs to be adapted to the specific needs of each infant at each feed. Because there are so many variables and these infants are changing on a daily basis, it's difficult for any one person to keep up with all the data. A clinical decision support solution, like NICUtrition, enables neonatologists and dieticians with the tools they need to plan macronutrients between parenteral and enteral feeds to track daily and cumulative nutritional deficits by infant and across the unit.

Discuss your R&D process, including clinical user input.
NICUtrition was developed in consultation with the top thought leaders in neonatal nutrition. William W. Hay, Jr., MD, is a thought leader in preterm infant nutrition and highly respected neonatologist with more than 40 years of clinical neonatology and neonatal research experience. Dr. Hay serves as the company's Chief Medical Officer. He is widely published, with his research and scholarship appearing in more than 400 articles and books. Nicholas Embleton, MD, is a neonatologist and chair of the UK Neonatal Nutrition Network and is a member of our Scientific Advisory Board. Dr. Embleton has published over 100 peer-reviewed publications and book chapters. Katherine Gregory, RN, PhD, a NICU nurse by background, provided unique insights integrating her clinical experience with translational research focused on preterm infant gut health and nutrition. Dr. Gregory is Associate Chief Nursing Officer, Women and Newborn Health, at Brigham and Women's Hospital and is the company's Scientific Co-founder. Because feeding is a time-intensive activity primarily for the nurses, we also facilitated user focus groups with over 30 NICU nurses. The ability to design software that not only addresses the key needs of our users but also captures their daily priorities and mindset was imperative.

What new technology do you see as having the greatest impact on your area of expertise?
In order to truly harness the power and impact of precision nutrition for preterm infants, we need to consider how the microbial community in our gut is shaped by nutritional factors and how that community then shapes growth and development. Astarte Medical has the largest dataset of microbiome sequence data and corresponding clinical data to develop the first vital sign and monitoring system for the gut. This new, patent pending technology called MAGI, the Microbiome And Growth Indicator, is a digital diagnostic that leverages machine learning to provide real-time quantification of gut health. With the ability to stratify infants, MAGI will enable better stewardship of antibiotics, optimized nutrition, and acceleration of microbial interventions, such as pre and probiotics. With the addition of MAGI to our NICUtrition platform, we will have a comprehensive clinical decision support solution for optimal feeding, nutrition and gut health in the NICU.

A Case Study in Evaluating the Clinical Utility of Early Warning Systems: HeRO

William E King, MS

Background

HeRO was proven to improve all-cause mortality by 22%,[1] and mortality after infection by 40%,[2] in the largest randomized controlled trial among premature infants, and after eight years of commercialization, HeRO monitoring has been adopted in 50 NICUs throughout the world, having monitored approximately 100,000 babies and saving the lives of a number likely in excess of 500.

Nevertheless, metrics describing the predictive performance of the HeRO Score may not have been adequately described.

No case better illustrates the difficulties in assessing the performance of HeRO than the slide in Figure 1, reprinted (including the caption) from a previous report.[3]

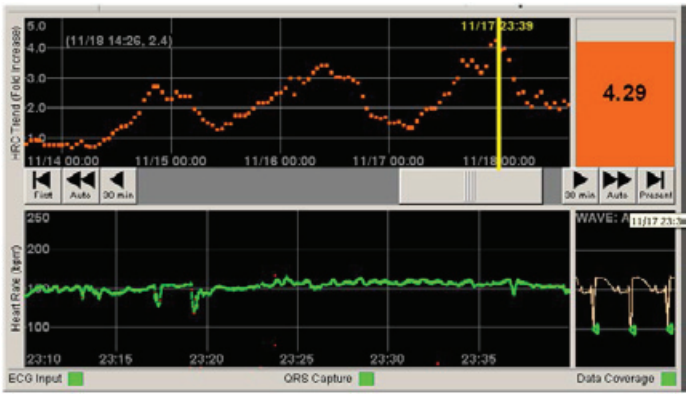

Figure 1. "In this case, the HeRO score acutely spiked from about 1 to progressively higher scores over a 4-day period. At the time indicated by the yellow line, the HeRO score was 4.29, and the associated 30-minute electrocardiogram shows decreased beat-to-beat variability with several superimposed decelerations. At that time, the patient had clinical signs of sepsis and a positive blood culture… Acute increases in HeRO score in the days prior to clinical deterioration may represent opportunities for earlier diagnosis and treatment, leading to better outcomes."

From a clinical standpoint, the HeRO trend in Figure 1 represents the potential for a major improvement in patient care. For three days prior to the diagnosis, the patient's HeRO Score was spiking. Evidence from the RCT would indicate that had this patient been randomized to the HeRO treated group and his or her HeRO Score had been displayed, the diagnosis might have been made at the first or second spike—*days earlier*—rather than during the third spike.[4] The literature is clear that earlier administration of antibiotics is more effective—even a single hour's delay is measurable in mortality.[5,6,7,8] It is this scenario, playing out time after time among the roughly 1500 patients randomized to HeRO-display, that led to the mortality improvement demonstrated in the RCT.

William E King is CEO of Medical Predictive Science Corporation.

Sensitivity, Specificity, and ROC

This was a clear clinical victory for HeRO monitoring, but how is it quantified statistically? Many clinicians are trained to evaluate a potential test based on sensitivity and specificity. The first problem is that the test, the HeRO Score, isn't binary, it's continuous. Every increment in HeRO Score adds risk to the patient—a score of 4.2 is worse than 4.1. But to calculate sensitivity and specificity, a single threshold must be chosen. Since around 10% of HeRO Scores are >2.0, representing at least double the predicted risk, this analysis will utilize that score as the threshold.

There is also a slightly more difficult problem: choosing a time window. Sensitivity and specificity have traditionally been used to measure a single-point-in-time test against the "gold standard" (or "reference standard") condition. HeRO is not a single-point-in-time test—HeRO is updated every hour continuously. But to calculate sensitivity and specificity, a time window, prior to the diagnosis, must be chosen. This decision is as crucial as the HeRO Score threshold because an elevated HeRO Score prior to the chosen time window will be evaluated as a False Positive, whereas inside the time window the same condition will be evaluated as a True Positive. Equally, a low HeRO Score prior to the time window is a True Negative, whereas inside the time window it is a False Negative.

Traditionally, our group has chosen the time window of 24 or 48 hours prior to the diagnosis, but the problem is obvious from Figure 2: under this scenario, the first and second spikes are False Positives. In fact, if we calculate based on the HeRO threshold of 2.0, and a 24-hour window, the points on the graph above yield a sensitivity and specificity of *merely 57% and 58%*, respectively. Yet if we expand our time window to 48 or 72 hours, the troughs in HeRO become False Negatives, and the sensitivity and specificity are not improved.

When the patient status is not clearly "sick" or "well," the analysis should ignore the associated data. During the time period commencing with the positive blood, urine, or CSF culture to 10 days following that culture, the patient status is

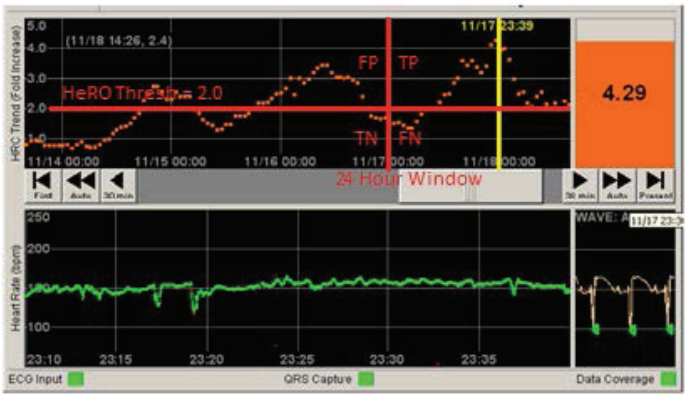

Figure 2. Thresholds defining True Positives, True Negatives, False Positives, and False Negatives, required to calculate Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value, imposed on the slide from Fig 1. Based on the data in this figure, Sensitivity and Specificity are 57% and 58%, respectively.

ambiguous: the patient is likely receiving therapy and recovering. He or she may still be symptomatic or they may have recovered quickly. For the purposes of analysis, these data clearly cannot be labeled as "sick", but neither can they be labeled "well". It is best to ignore the data in this time window from the analysis dataset.

In fact, if we apply these definitions (48-hour window in advance of *Positive* Blood, Urine, or CSF Culture, HeRO threshold of 2.0) to all 1500 VLBW control patients in the RCT, we get a Sensitivity of 44.7% and a Specificity of 86.5%. Sweeping the HeRO threshold over all possible values (0.0 to 7.0) allows us to calculate the Sensitivity and Specificity at each threshold, which yields the area under the curve of the ROC of 0.740.

Our group has reported using these sorts of definitions, despite the clear over-penalization visible in Figures 1 and 2.[9,10,11,12,13,14,15,16] But there are reasonable techniques to minimize these over-penalizations that paint a different picture of the model performance.

Optimizing the Test and Reference Standard

Penalizing the model for "spikes", ie peaks and troughs, can be avoided. Rather than analyze each individual hourly HeRO Score as a separate predictor, we will consolidate all of the HeRO Scores from a 24-hour period into a single number: the maximum HeRO Score. This makes clinical sense: clinicians tend to act based on the highest score over a reasonable period of time, and certainly 24 hours fits within the cyclical rhythm of NICU operation.

By the same token as ignoring data after the diagnosis, we will change the way we deal with the data days in advance of the culture. As seen in Figures 1 and 2, in many cases the HeRO Score will be elevated for days in advance of the culture. But in other cases, it will rise only the day before. From a clinical standpoint, both are acceptable—they both offer the opportunity for earlier diagnosis. How can we reward the model in both cases without penalizing it either?

Since HeRO Scores were statistically significantly different between HeRO-display and control patients in the RCT for at least 7 days prior to culture,[2] there is significant justification to choose a 10-day window *before* (in addition to after) the culture to be ignored from the analysis. So, only the data in the day prior to the day of the culture will be analyzed as "sick" (or more correctly, "about-to-become-sick"), and only data that is at least 10 days removed (either before or after) from a culture will be "well".

The effect of these two changes (analyzing only the highest HeRO Score in a 24-hour period, and ignoring the ambiguous data from well before the culture) has dramatic impact on our metrics of model performance, and the ROC rises from 0.740 to 0.761.

Many techniques have been described to deal with an imperfect reference standard.[17] Consider changing the definition of "sick" from *positive* culture to *any* culture. Certainly, the implications of clinical sepsis among neonates are debatable and beyond the scope of this report.[18] But there is no denying that the presence of a culture (of any result) is a very good surrogate for the clinician's belief at that point in time that the patient might be sick. In fact, our group found that the *presence* of laboratory tests is a better predictor of impending infection than the *results* of those laboratory tests. How can this be? The *presence* of laboratory tests is a surrogate for clinician intuition that the patient is sick, and it turns out that clinician intuition, based on a consideration of the full condition of the patient, is better than the results of the labs at predicting infection. Similarly, the presence of a culture—even a negative one—indicates that clinicians were suspicious of infection at that point in time.

Choosing the definition of "about-to-become-sick" as the presence of *any* culture in the next day, while choosing the definition of "well" as the absence of *any* culture within ±10 days further improves the ROC from 0.761 to 0.789.

This leads us to the approach that we propose as the most appropriate way to examine HeRO's efficacy as a predictor of infection. We choose "about-to-become-sick" patients as those who will have a *positive* culture drawn in the next day, while "well" patients will be those who are not within ±10 days of *any* culture. While it is clear that the patients labeled as sick or well are highly likely to be so, these definitions eliminate the messy middle ground—those patients whose status could be argued one way or another—from the analysis. Applying these definitions to the dataset, ROC improves from 0.789 to 0.821.

Forward looking metrics

But in the context of a continuous early warning system like HeRO, what do sensitivity, specificity, and ROC *actually mean*? In this context, Sensitivity is the probability that the HeRO Score will be above the threshold in the time window we have defined *prior to* the patient's diagnosis. In other words, it looks back in time, once it is already known that the patient is sick. Equally, specificity looks back from points in time where it is known that the patient was healthy.

Is this relevant from a clinical standpoint? It has been stated that "both sensitivity and specificity…are of no practical use when it comes to helping the clinician estimate the probability of disease in individual patients."[19] The point of an early warning system is to tell the clinician, *right now*, what is likely to happen to this patient *in the future*. Indeed, clinicians are prone to a failure of logic known as confusion of the inverse,[20] best illustrated by the scenario described as follows:[21]

"An example of this with regard to sensitivity, consciously chosen in a form that makes the problem clear, would be

Table 1. Summary of metrics of model performance for various types of analysis. Sensitivity, Specificity, PPV, NPV, and Risk Ratio all calculated at a HeRO threshold of 2.0. Dataset consists of the ~1500 VLBW patients randomized to HeRO non-display in the RCT.

Analysis of	Def'n of Sick	Def'n of Well	Sens	Spec	ROC	PPV	NPV	Risk Ratio
Each hourly HeRO Score	Pos Cx within 48 hrs	More than 10 days since Pos Cx	44.7%	86.5%	0.740	9.6%	98.0%	5x
Maximum daily HeRO Score	Pos Cx in the *next* day (up to 48 hrs)	More than ±10 days from Pos Cx	61.0%	79.8%	0.761	4.5%	99.2%	6x
Maximum daily HeRO Score	Any Cx in the *next* day (up to 48 hrs)	More than ±10 days from Any Cx	54.4%	89.0%	0.789	35.0%	94.7%	7x
Maximum daily HeRO Score	Pos Cx in the *next* day (up to 48 hrs)	More than ±10 days from Any Cx	61.0%	89.0%	0.821	12.1%	98.9%	11x

converting the logical proposition *This animal is a dog; therefore it is likely to have four legs* into the illogical proposition *This animal has four legs; therefore it is likely to be a dog.*"

Positive Predictive Value and Negative Predictive Value better address this *clinical problem* of identifying infection, because they both look *forward*. If a patient has a high HeRO Score, the Positive Predictive Value is the probability that he or she will be diagnosed with infection in the subsequent time period. Conversely, Negative Predictive Value starts with a low HeRO Score and represents the probability that the patient will remain healthy over the subsequent time period.

Indeed, it is Sensitivity that is inversely confused by clinicians with PPV (and Specificity with NPV). While Sensitivity, Specificity, and Area Under the Curve (AUC) of the Receiver-Operator Characteristic (ROC) Curve derived from them have their places, Positive and Negative Predictive Values better capture the importance of information provided to the practicing clinician who must make *forward looking* decisions.

But PPV and NPV are biased by a very important factor: the incidence rate of the event in the population. Is a PPV of 10% good? It depends upon the incidence rate. If 8% of patients have the condition, a 10% PPV isn't changing the picture very much. If 1% of the patients have the condition, a 10% PPV indicates that the patient is at 10x risk, and in the case of late onset neonatal sepsis, that would likely push clinicians toward labs, at the least.

When assessing late onset neonatal sepsis, this becomes problematic. When looking at all patients in a NICU, the incidence rate of late onset sepsis might be 2-5%; whereas looking at only VLBW patients, it might be 10-25%; and when looking at ELBW patients, it might be 20-50%.

This problem of incidence rates is even further exacerbated by the definition of sick—what to do (again) about clinical sepsis? Is it appropriate to penalize an early warning system that is elevated prior to a patient who deteriorates, gets sick, but doesn't grow a culture not because there were no bacteria in their blood, but because clinicians failed to draw enough blood *to determine* that there were bacteria in the patient's blood? Is that a True Positive or a False Positive? Whichever is chosen, the incidence rate is altered drastically. In the numerator, there are about 4x as many blood, urine, or CSF cultures as there are positive cultures in this dataset. In the denominator, over one third of patient days are within ±10 days of any culture. When cases are *positive* cultures and controls are ±10 days removed of *positive* culture, the incidence rate is 1.5%; when cases are *any* cultures and controls are ±10 days removed of *any* culture, the incidence rate is 9.8%; finally, when cases are *positive* cultures and controls are ±10 days removed of *any* culture, the incidence rate is 2.4%.

Both of these decisions, patient population and definition of infection, dramatically affect the incidence rate, and thereby the PPV and NPV, rendering both of those values nearly useless for the purpose of comparing model performance. Risk Ratio, however, is the PPV / (1-NPV), and the beauty there is that the incidence rate applies equally to both the numerator and denominator, cancelling itself out. We propose Risk Ratio as the best single metric of performance of an early warning system because it is forward looking *and* robust to changes in incidence rate caused by differing patient populations and definitions of "sick".

Table 1 summarizes the effect of each of the techniques described above on each of the metrics of model performance.

Discussion

Myriad clinical scoring systems, early warning systems, or rapid response systems have been described and implemented, and while some have been successful,[22] most large multicenter randomized controlled trials fail to show benefit;[23,24] and fewer than 15% of ICUs use severity scoring systems.[25] The difference in effect on outcome lies in the difference between *accuracy* and *actionability*. Though this report has spent considerable time describing the accuracy of HeRO to predict infection, many researchers have described models with higher ROC areas for predicting other clinical events that have failed to improve outcomes, whereas HeRO was proven to reduce all-cause in-hospital mortality, mortality after infection, and mortality measured at neurodevelopmental follow up assessments at 18 months. But a model will only improve outcomes if it improves the *actions* taken by clinicians. While something like the APACHE score may have better metrics of performance, it has proven to be simply a regurgitation of what the clinician already knows and is acting upon. HeRO, throughout its development process, was designed to provide *new information*, and we intentionally chose to not utilize demographic and laboratory information *despite the fact that they improved the ROC Area* and other metrics of performance. As opposed to repeating back to the clinicians something that they already know, we distilled HeRO down to new information that *changes clinical actions*. It may be that compromising accuracy for the sake of actionability is the key that led to the improvement in mortality. To quote Amelia Earhart, "The most difficult thing is the decision to act."

This report has been focused on esoteric statistics: ROC areas, predictiveness curves, risk ratios, etc.; but it will finish with this

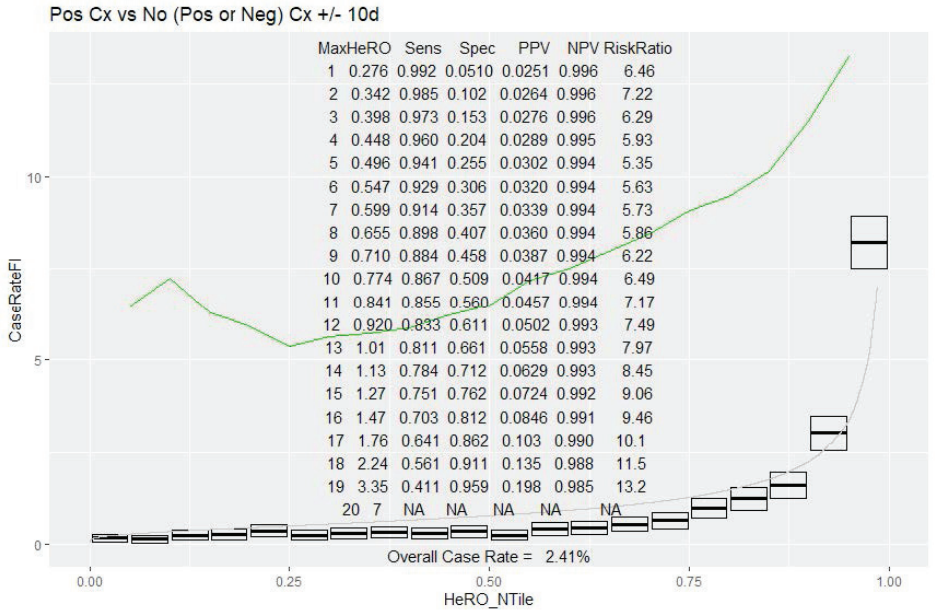

Figure 3. Predictiveness curve comparing highest HeRO Score in a 24-hour period with incidence of positive blood culture in the subsequent 24-hour period as cases, while excluding data within ±10 days of any culture from controls. The smooth gray line represents the HeRO score, i.e. the predicted risk of the event. The thick black lines represent the observed risk for patients in the ventile (20 equisized groups), with the box representing the 95% confidence intervals. The overlapping of the black boxes over the gray line indicates that the model is well calibrated, even in spite of the inherent bias caused by choosing the highest HeRO score in any 24-hour period. Finally, the green line, although plotted on the same scale, represents the Risk Ratio at the given threshold (e.g. patients above the 18th ventile, or 90th percentile of HeRO Score, are 11.5x more likely to have a positive blood culture in the subsequent 24-hour period than those below the 90th percentile).

final thought: these metrics of performance are what we use to *extrapolate* the impact of a test onto patient outcomes, because it is expensive and time consuming to conduct randomized controlled trials to actually find out. But, do we really care that 0.80 and 0.90 distinguish ROC areas that are "acceptable" from "excellent" from "outstanding",[26] whatever those terms signify? In the context of neonatal infection, do we know what sensitivity is required to improve the timing of antibiotic administration, or what negative predictive value is required to improve antibiotic stewardship? The point is that the performance metrics of HeRO are immaterial because *we ran the RCT*. HeRO monitoring yields *actionable* information that changes clinician behavior, resulting in reduced mortality, reduced length of stay, and improved targeting of antibiotics. The rest are simply the means.

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Impacts of Mother's Own Milk and Donor Milk on the Developing Neonatal Gut Microbiome

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The newborn gut microbiome is affected by many factors and infants born preterm are at risk for developing dysbiosis, an upset and imbalance in homeostasis of the needed combination of bacteria, acid components, and human milk oligosaccharides. Commensal bacteria, or good and helpful bacteria, contribute greatly to the needed gut microbiome which will help to establish adaptation from the protective intrauterine environment of the fetus to the harsh, pathogen laden world of the newly born baby.[1] Colonization of the infant gut begins at birth and a timely and appropriate exposure and acquisition is important to establish the needed immune response.[1]

How the microbiome develops

Development of the fetal gut microbiota begins in the third trimester of fetal development. What was once thought to be a sterile environment is now known to have amniotic trophic factors which are swallowed by the fetus helping to grow and build the intestinal tract and prepare for extrauterine life. This fluid serves to prepare the baby for breast milk feedings which are very similar in nature to the amniotic fluid and differ from mom to mom. Amniotic fluid begins the establishment of a microbiome and immunity. Mother's colostrum and breast milk, along with necessary symbiotic interactions, will continue the process [3].

Further development of the needed microbiome will continue following delivery. In the term and preterm infant, many factors can affect the normal progression of colonization. Birth mode, vaginal or caesarean section, gestational age, maternal steroid and antibiotic use, infant exposure to antibiotics, and feeding choice all impact this microbiome development.[4,5,6] Infant ingestion of maternal vaginal and colonic bacteria begins an initial colonization of the infant gut. A study by Ferretti, et al, researched 25 mother infant pairs over a four month period following delivery. Swabs were obtained from moms and babies and bacterial colonization compared. Bacteria from all sites in the mother were quickly shown in the infant's oral and fecal samples. Some bacterial strains, were found only transitionally, and not at the later collection date. These early colonizing bacteria are thought to be the pioneers. These pioneer bacteria are needed only to serve as catalysts, triggering reactions between bacteria and epithelial tissues, causing immune modulating. Over four months, the infant microbiota differ from maternal, suggesting that an early seeding of maternal bacteria occurs from these sites, but only begins the necessary reactions needed to mature the final components [3].

Infants born prematurely or by caesarean section are noted to have a disruption in the normal colonization process. Bacteria and microbiota from alternate sources become the inoculators of initial seeding. High concentrations of bacteria can come from maternal skin, hospital, and neonatal intensive care unit (NICU) sources causing a disproportionate balance and dysbiosis of the infant gut [7]. This dysbiosis is associated with multiple problems in both preterm and term infants. Preterm infants have a higher incidence of necrotizing enterocolitis (NEC), early sepsis. Inflammatory responses due to dysbiosis can increase the incidence of retinopathy of prematurity and chronic lung disease. Later onset of diseases such as asthma and allergies, inflammatory bowel disease, and celiac disease are among a few of the chronic conditions affected by or potentially triggered by early dysbiosis.[8,9,10,39] Colonizing bacteria are considered so important to the emerging infant gut, they are described as an "ancillary organ". The microbiota consists of 100 times more bacterial genes than human genes in the body. The microbiota is more metabolically active than the human liver and is responsible for the adjustment to a pathogen heavy extrauterine life, normal intestinal function, and advancement to an active immune status. As such, this growing "ancillary organ" is responsible as the catalyst for healthy adaptation. The lack of an intact and balanced microbiome causes upregulation of inflammatory processes and increased incidence of infant, childhood, and adult diseases.[2]

HMOs

Continuing and emerging information regarding the infant intestinal microbiome pieces together answers to decades old questions surrounding preterm diseases and response. NEC rates and severity has been decreasing with greater understanding of human milk and infant feeding.[39] Human milk oligosaccharides (HMOs) and their role in the infant microbiome is a point of ongoing study and research. Long and short chain fatty acids are better understood and research involves their place in this puzzle of what creates and affects the microbiome and how we can best support the growth and health of the tiny babies we serve.

Human milk is a living food full of nutritional components as well as protective properties which play a key role in immune and gut protection during a critical period of development.

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Among the many known benefits of human milk are unique, immunological components including: secretory immunoglobulin A (SIgA), lactoferrin, and human milk oligosaccharides.[11,12] HMOs in human milk are complexly designed and highly specific; more so than those found in any other milk. With approximately 200 identified structures, researchers currently know that HMOs work synergistically to provide a perfect balance, interacting together.[1] The infant gut microbiome is rapidly established in the weeks following delivery. Many factors can affect the microbiome of the infant including: mode of birth, antibiotic use, gestational age, mother to infant transfer, and nutrition.[13,3,39] Obesity, diet, and genetics, can alter the HMO composition thus affecting infant outcomes.[14,1,40] Secretor status of mothers is also known to be a genetic factor in the microbiome of human milk. Mothers are described as secretors or non-secretors of an HMO molecule (FUT2) which affects the structure of HMOs in their milk. FUT2 has been positively correlated with an increase in Bifidobacterium, a positive commensal bacteria, and increased milk microbiota. FUT2 status can alter the number and composition of HMOs present in the milk affecting the profile of commensal and harmful pathogenic bacteria in the infant gut.[15,16] This status is associated with genetic makeup and blood type, but has also been noted to vary by geological location.[1] While genetics and secretor status are unable to be changed, supplementation of infants without the positive benefits of this preferred profile of HMOs is an area of discussion.[17]

Some HMOs are known as prebiotics, assisting in the development of a healthy commensal, or good bacteria, profile in the infant gut. While research continues on the complex interactions of HMOs, there are some key understandings. HMOs are readily available in breastmilk. As these HMOs are consumed and reach the colon of the infant, they remain intact, serving as substrates for healthy bacteria such as Bifidobacterium, known to be a key player in the downregulation of inflammatory responses. These beneficial bacteria are thought to influence epithelial cell development, cell proliferation, and differentiation, inhibiting negative bacterial growth. Consistent exposure to large quantities of HMOs is thought to trigger normal gut development posing the question of whether infants who receive formula and/or parenteral nutrition experience the opposite.[18]

Human milk consumption also influences the incidence of bacterial, viral, and yeast caused infections. HMOs play a role in this prevention by preventing pathogen adhesion to healthy intestinal mucosa. Pathogens must adhere to the host to begin duplication and the infectious process. Some HMOs resemble the surface of pathogens or the mucosa, and act as a decoy for pathogens to "stick" to, blocking attachment of the bacteria, virus, or fungi, preventing infection. Deadly pathogens attach to these specific HMOs which are not digested. These HMOs continue through the intestinal tract, pathogens connected, and are excreted from the body in the feces. The potentially infectious pathogens are successfully "escorted" out of the infant and into the diaper.[1]

A small portion of HMOs are actually digested and absorbed into the circulation of an infant, traveling to all body systems and directly interacting with the infant, serving as signal modulators. By directly interacting with immune cells, responses to stimuli can be altered. HMOs have been shown to inhibit inflammatory responses to E. Coli invasion. The mucosa-associated lymphoid tissue system (MALT) consists of many systems of concentrated and responsive lymphoid tissue. The BALT (bronchial-associated lymphoid tissue) and NALT (nasal-associated lymphoid tissue) play an important part in the activation of infant immune responses and are triggered by exposure to HMOs in mother's human milk microbiota. Epithelial tissue in the hypopharynx and bronchial pathways, can be positively stimulated when exposed to HMOs in colostrum and early transitional milk. The GALT (gastrointestinal-associated lymphoid tissue) is also triggered when exposed to the milk flora. Oral administration of colostrum to preterm infants and those babies who are not receiving oral feedings is proving beneficial in the prevention of ventilator associated pneumonias and other respiratory infections. Peyer's Patches in the intestine, also part of the GALT system, are upregulated when exposed to human milk resulting in protection for the intestinal lining.[11,21,22,12] Dendrites present in the intestinal lumen interact with commensal bacteria stimulating a release of cytokines assisting T-helper cells. This reaction, beginning with exposure to healthy commensal bacteria contained in the milk microbiota, is necessary to convert the newborn from an intrauterine bias to these cells which protected them from intrauterine rejection.[19,2] Now in the extrauterine world, a switch is needed to begin a shift from passive to active immunity, thus protecting the infant. Effective colonization with HMOs and commensal bacteria is needed for this shift.[20] Negative cytokine responses resulting in inflammation are decreased in the presence of healthy amounts of HMOs. Lymphoid immune cells interact directly with HMOs and cytokines to begin an immune response cascade. This cascade includes signaling of T and B cells lymphocytes and immune globulin A, which circulate throughout the body setting up a "high alert" readiness, and immune and anti-inflammatory responses.[23,11,12,21]

While healthy acquisition of a normal infant microbiome including a balanced and diverse combination of HMOs and commensal bacteria is developing in the healthy, exclusively breast fed babies, premature infants are in need of more than this milk made for term infants. Babies born early have a less diverse gut microbiome including higher levels of pathologic bacteria and fewer colonies of commensal bacteria such as prebiotics Bifidobacterium and Bacteroides. An irregular balance known as dysbiosis is associated with a higher incidence of NEC and infant sepsis.[10] Higher levels of inflammation associated with a less diverse HMO presence and fewer commensal bacteria are tied to increases in retinopathy of prematurity, chronic lung disease, and neuro-cognitive impairment. Considered protective, human milk exposure also reduces the incidence of life-long issues such as inflammatory bowel disease, type II diabetes, auto-immune problems, allergies and asthma, cardiac disease and obesity. A balanced HMO presence, supporting the colonization of the premature infant gut with healthy commensal bacteria is needed to promote proper gut microbiome, support the progression of trophic feedings, and to protect against NEC.[10]

Fatty acid effect on microbiome

Multiple studies suggest that fatty acids influence the composition of the HMOs and gut flora. Composition of fatty acids differs significantly between human milk, preterm, and term formulas which can affect the composition of HMOs available to enrich the growing gut environment.[24,1] Maternal diet, especially during pregnancy, and consumption of fish oil and linoleic acid positively affect the maternal gut pattern. These bacteria may be transmitted to mother's milk via the entero-mammary pathway which provides a route for maternal gut flora to enter the milk. Positive correlations between consumed PUFAs (polyunsaturated fatty acids) and milk

Bifidobacterium levels have been established.[25] The CHILD study (Canadian Healthy Infant Longitudinal Development) studied the composition of fatty acids, HMOs, and microbiota in mother's milk. Fatty acid composition was found to influence the microbiota of the milk. Transfer of lipids from the infant's oral cavity to the maternal breast during retrograde milk flow while breastfeeding is a possible means of bacterial deposit in the breast to colonize milk.[24] Various fatty acids are known to influence the milk microbiota both positively and negatively, making this information valuable to understanding their impact on commensal bacteria and pathogens.[26] Acid composition can promote positive microbiota profiles by providing antibacterial properties and/or prebiotic purposes by altering bacterial function and strength.[27]

Mom/MOM is Best

Human milk is definitely shown to be best in establishing a healthy gut profile for both term and preterm infants. A more diverse profile is noted in human milk that is mom's own milk (MOM).[9,10,28] The gut flora of the preterm infant differs vastly from that of its term counterpart. The preterm infant, being born early, does not benefit from the third trimester to prepare its intestinal tract for extrauterine life. The intrauterine gut is not precolonized with exposure to amniotic fluid and immune modulations have not occurred. Enteral feedings may be delayed. Mother may not produce colostrum and transitional milk due to the effects of early preterm delivery, hypertension, or illness. These alterations to the normal progression of colonization, can contribute to a higher incidence of NEC, neonatal sepsis, and other morbidities commonly seen in the NICU.[39] Human milk can be a path to recovery and normalization for these preterm babies.[14]

Donor human milk (DHM) has become the preferred alternative in the absence of MOM. Benefits of an exclusive human milk diet are well known, but how the microbiome is affected is an area of concentration. Holder pasteurization, used by donor milk banks to remove bacterial and viral pathogens, can also reduce bioactive and cellular components such as immunoglobulins and lactoferrin.[29] Oligosaccharides and PUFAs are retained.[30]

Multiple studies are now available to guide and support the decision to augment MOM with DHM in reference to the development of the neonatal gut microbiome. With the need for good seeding of the neonatal intestine and positive development of the intestinal flora already established, DHM can now be set as a partner to MOM in achieving this need. Choice of feeding greatly impacts early development of the preterm gut microbiome.[9,10,28] Infant fecal samples offer insight into bacterial flora in the early neonatal period. Infants receiving high levels of mom's own milk compared to infants receiving partial MOM and mostly donor milk show differences in quantities and richness of the flora, yet are similar in microbiota composition. A study by Cong, et al, showed that the microbiome of infants receiving a minimum of 70% of mom's own milk favored a diverse array of bacteria which grew over increasing time. Infants fed DHM exclusively or 70% DHM did demonstrate a profile similar to those infants receiving MOM, but the diversity and growth over time lacks.[9] Pasteurized DHM can provide an HMO profile similar to MOM, but because of multiple donor pooling, the HMOs present are more homogenous and not as diversified.[31,1] Infants fed MOM demonstrate a greater diversity from birth, as well as a consistent and gradual climb in the needed flora compared to formula fed infants. The gut microbiota noticed in preterm infants fed MOM were similar, despite mode of birth or gestational age, suggesting that mother's own milk can counter the possible negative effects of caesarean or preterm birth. DHM supplementation was partially successful in promoting a microbiome similar to the MOM group. While DHM is favored over formula for promoting the crucial neonatal gut flora and reducing incidence of other neonatal morbidities, infants receiving their mother's personalized milk receive extra benefits. The flora of infants receiving formula differ significantly.[10] Infants fed formula or receiving parenteral nutrition are not receiving the abundant HMOs available in MOM or DHM[1]. While differences are noted in total colonies, the similarity of MOM to DHM was documented while stark differences are noted in formula fed babies. The richness and continued colonization of infants fed MOM as compared to DHM continued over the ensuing months. Both MOM and DHM enrich the microbiota and create an environment conducive to promoting the cellular modulation and down regulation of inflammatory processes needed to protect preterm infants. DHM is a preferred alternative to formula, but MOM is most effective in building an early, favorable and growing neonatal gut profile.[9,10] Emphasis on the urgent need to track, counsel, and assess mother's pumping on a daily basis should be affirmed through ongoing staff education and collaboration with lactation services.

HMOs in donor milk are not significantly affected by pasteurization, but their ability to influence the active growing microbiome may be diminished due to the lack of live bacteria necessary to interact and grow the flora.[32]. This is a significant observation to note as a higher level of MOM in the preterm infant diet is associated with a more diverse and rich composition. MOM provides a unique diet specifically tailored to the current gestation of baby, provides antibodies, and mimics the intrauterine exposure received prior to birth. DHM is most often pumped by mothers who have delivered term infants and are pumping at different times in the post gestation period. While DHM is proving a similar (to MOM) composition in bacterial flora, MOM is better personalized to the needs of the preterm infant.[28] A study by Cacho and associates demonstrated the ability to restore the living microbiota of DHM by adding MOM to the mix. Even small amounts of mother's milk added to DHM and incubated over four hours, successfully restored the live bacterial count. Best outcomes were noted at 10% and 30% MOM to DHM.[33] Restoration shows great promise in the future, but also supports the thought that MOM provides the best option. Support of early pumping, especially in the preterm infant, is of great importance to promote the overall best outcomes for the infants we care for.

Fatty acid functions were found to be enriched in both MOM and DHM. Timing of DHM pumping is a factor in the use of MOM versus DHM. Preterm milk provided by an infant's own mother is matched to the baby's needs.[34] Preterm colostrums, higher in SIgA and antibodies is usually pumped for approximately 7-14 days post-delivery while term colostrum begins to transition within 2 to 3 days. Mother's own milk is better suited to the current stage of the infant which may play a big part in the differences between the two. MOM is also custom suited for the infant as the entero-mammary pathway is responsible for recognizing potential pathogens experienced by the infant and creating specific antibodies to potentially reduce the incidence of sepsis. Skin to skin and early breastfeeding of any kind are critical to support this function.[35]

Supporting Breastfeeding and Providing Mom's Own Milk

With the understanding that we need to promote as much human milk as possible, that donor human milk is good, but that mother's milk is best, it's easy to see that neonatal nurses and staff need to be educated and prepared on how to support breast pumping and feeding. The astute care giver will monitor milk production, pumping logs, ask mom daily about her pumping and output, and work with lactation support to intervene quickly. NICU staff are the most frequently seen people involved in mother's care once she is discharged home. Continued surveillance by these staff people can ensure quick identification of milk volume or pumping problems. Early and often skin to skin care is essential to begin the mother-baby bond and physical communication between mom and baby. Skin to skin provides a cross talk between mother and baby's microbiome. Mother is exposed to baby's bacteria via the skin and respiratory systems and begins to produce specific antibodies to help baby with extrauterine adaptation. Mother's gut microbiome begins to seed baby with pioneer bacteria ready to interact and create the emerging neonatal microbiota.[28,34,35]

Early suckling at mother's breast will provide infant oral bacteria to interact with the breast providing an exchange to mom's breast tissue and seeding of her milk microbiota via retrograde milk flow while nursing. Even preterm infants who are not gestationally prepared to drink at the breast can spend time on a pumped breast with small amounts of milk available. Baby will be able to stimulate mom, get small amounts of milk, and provide this bacterial exchange.[24]

Technology plays a huge part in initiating and maintaining milk supply, volume, and availability, especially in pump dependent moms. When baby is too weak to go to breast frequently, is ill or premature and taken to the NICU, or unable to successfully latch due to congenital anomalies or other issues, the breast pump becomes the baby. Once baby is delivered, mom goes through three stages of milk production, initiation, building volume, and maintenance of volume. Each stage of production must be successful for the next to develop well.[36] The research-based Symphony PLUS® breast pump with Initiation Technology™, mimics irregular newborn sucking, and has been shown to decrease the time to lactogenesis in pumping mothers by an average of more than 24 hours. This unique pumping program makes a big difference in the initiation of milk production. This significant increase in mother's own milk, especially in the first week of life, influences neonatal outcomes.[37] Each person caring for mom and baby must understand the needs of mom and her pumping or breastfeeding. Staff education and practice need to begin the standardization of practice. A solid process of pumping in labor and delivery within 1 hour of birth, if mom is stable, is an evidence-based process that leads to early initiation of milk production.[38]

Nurses must be open to the idea of promoting "breastfeeding" in the smallest of babies in many stages. Skin to skin care should be considered the early preterm infant's first exposure to breastfeeding. Helping mom to effectively pump and store her milk must be considered a priority. Obtaining even small amounts of early colostrum and MOM must be considered as important as monitoring blood pressure, titrating vasopressors, and managing airways. The proof is always in the smallest of things and with the emerging information regarding the importance of establishing the infant microbiome, providing MOM is no small matter. If we as a caring, nurturing, and evidence-based body of care can provide this support, we will be able to impact not only the apparent needs, but the smaller details that change an infant's entire outcome.

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Impact of a Tracheostomy on Pediatric Development: Consideration for Interventions

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Critical Early Development

Critical development of anatomy, physiology, swallowing, mobility, and other skills begin in utero and continue from birth through childhood. Immediately after birth, speech, language, and cognition are added to the many areas of development that a child is quickly undergoing. It is well documented that primary speech and language development occurs from birth to age three and during this same timeframe, infants and toddlers are making vast changes in gross and fine motor development.[1] These skills continue to develop throughout childhood but at a slower pace than initially seen in infancy and early childhood (birth to age three years).[1] When this process is complicated by medical conditions requiring a tracheostomy, the manner in which the systems interact for development are compromised even further.

Impact of a Tracheostomy on Development

Pediatric tracheostomy placement is occurring with greater incidence due to the advancements in medical interventions and the increased survival rate of infants who are premature and those with congenital abnormalities. Long term tracheostomy placement has been associated with delayed acquisition of language and social development.[2-4] Additionally, long term tracheostomy may impact parent-child bonding and the ability of the child's family to know their wants and needs due to the communication impairment.[5]

A tracheostomy in a developing infant or toddler can impact speech and language development, fine and gross motor development, and oral-motor sensory awareness. When a tracheostomy is placed, the patient transitions from having a typical respiratory system with end expiratory pressure (pressure remaining in the lungs after expiration) to an open system, with a loss of pressures. The human body functions with a pressurized system and this system impacts coughing, speech, swallowing, trunk support, and postural stability, among others.[6] In infants and toddlers, this is particularly important as the gross motor development of trunk control for sitting, crawling, standing, and walking has a direct correlation with self-feeding and advancement of oral intake.[6] Because of these potentially negative effects on crucial development, it is imperative to provide the pediatric population with a closed system that normalizes the physiologic factors that impact their development.

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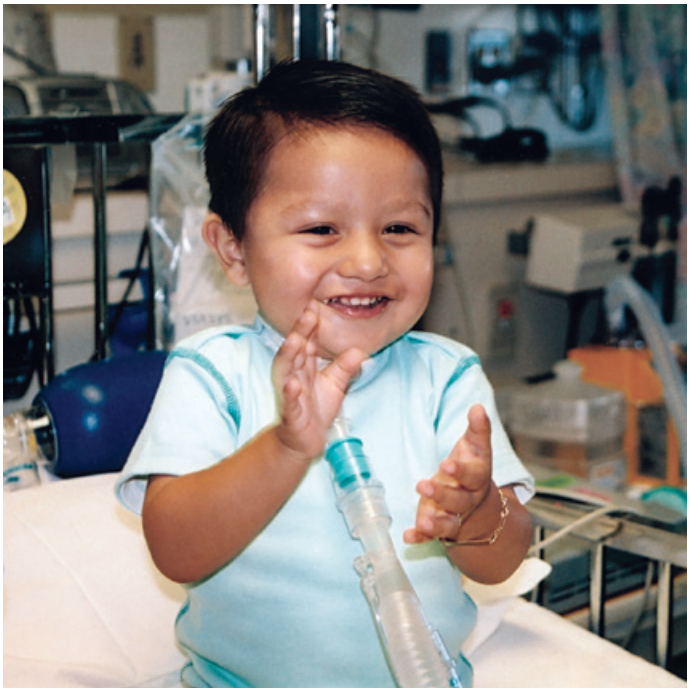
Impact from Restoring Typical Pressures

A primary means for closing the system, in a pediatric patient with a tracheostomy, is to use a bias-closed position, no-leak valve. When a patient has a tracheostomy, airflow is directed in and out through the tracheostomy tube and bypasses the upper airway. Using the Passy Muir® Valve allows a patient to breathe in through the tracheostomy tube and out through the upper airway (mouth and nose). The Valve works by closing at the end of inspiration, which redirects 100% of airflow upwards through the vocal cords and upper airway. Research has shown that this redirection of airflow assists with improving secretion management, increasing sensory awareness, improving swallowing, and restoring natural physiologic PEEP (positive end expiratory pressure), among other benefits.[7]

Assessment and usage of a Valve is important for the normalization of the social and language development of these children and to be a first step towards decannulation. Due to the limited volitional participation of infants and young children, the clinical assessment for pediatric use of a Valve presents with specific challenges that are unlike those observed in the adult population. The primary consideration during assessment is that the patient has a patent airway, meaning the patient can exhale around the tracheostomy tube. Having a qualified team, familiar with airway management, is a key component of successful Valve use.



The participation of infants, toddlers, and young children in the assessment process is more difficult than with adults because of their limited ability to follow commands and volitionally vocalize. Therefore, additional methods such as transtracheal pressure measurements, may be used to assess airway patency.[8] With research indicating that the age of tracheostomy and decannulation may have an impact on speech and language development, it is imperative that speech-language pathologists have a grasp of both normal development and the delays that may occur with disruptions in development. Providing access to vocalizations at as early an age as possible and providing a speech and language enriched environment may assist with promoting more typical language development and decreasing the negative impact of a tracheostomy. In addition to speech and language development, research from the adult population suggests benefits for improved secretion management, cough, psychosocial development, and improved swallowing.[7]

Not only is speech and language development a potential concern, the respiratory system and intrathoracic and intra-abdominal pressures also are diminished by having an open system.[9] With the redirection of airflow, the patient is no longer using the upper respiratory airway—airflow does not go through the upper airway and glottis (vocal cords). Use of the upper airway and glottis typically provides restrictions that allow for control of exhalation and assists with controlling expiratory lung volumes.[10] This loss of pressure may impact gross motor function for mobility and postural stability. The loss of lung volumes and pressures also may negatively affect swallowing.[11-13]

Use of the Valve during physical therapy helps restore the pressure support in the trunk, allowing for natural increases in intrathoracic pressure (ITP) and intra-abdominal pressures (IAP) in response to increased postural demands. With an open tracheostomy tube and therefore, an open system, thoracic pressures cannot be increased or sustained as airflow passes through the tracheostomy tube and bypasses the upper airway. This difficulty would be observed when a patient needs to crawl, sit, push, or stand up. The typical means of gross motor movement for mobility is to engage the glottis (vocal cords) to restrict the expiratory lung volume in order to stabilize the chest and upper body.[10] Placing a Passy Muir Valve on the tracheostomy tube closes the system and restores a patient's ability to use the upper airway to control expiratory flow and improve ITP and IAP.

Consider that with infants and young children, a tracheostomy also could limit or diminish gross motor development. During infancy and early development, children are progressing through the stages of head control, trunk control, sitting, reaching, standing, and walking. Without good ITP and ITA, these functions could be significantly impacted and even delayed. A vicious cycle may begin as fine motor skills related to feeding, self-feeding and other levels of function are directly linked to gross motor development. These delays and limitations can be mitigated by using a Passy Muir Valve to return the young child to a more normalized use of the upper airway with control of volumes and improved trunk control and postural stability.

The negative impact on pressures, such as subglottic pressure, and the diminished stimulation of sensory receptors may affect feeding and swallowing, to include oral-motor sensation. Henningfeld, Lang, and Goday (2019) reported that g-tube feeding and delayed feeding skills were associated with tracheostomy. They also hypothesized that children with tracheostomies would have more feeding issues than their age-matched peers without tracheostomy.[14] During review, they found that a history of ventilator-dependence, cuffed tracheostomy tube, and speaking valve use during inpatient care were inconsistently associated with later feeding and nutrition evaluations, with an implication that speaking valve use has the potential to decrease later issues with feeding.

Essential Need: Assessment and Intervention Plan

With the wide range of developmental skills which may be impacted by a tracheostomy, it is essential for clinicians to have an assessment plan that incorporates the use of a Valve and then a treatment intervention plan that includes both Valve use and activities for speech and language development, gross motor development, and feeding skills. General activities that may be used with children who have a tracheostomy to assist with improving upper airway use, sensory awareness, and speech and language development include enriching the speech and language environment, training use of the upper airway through interactive tasks, and providing infants and children with access to a more typical aerodigestive system through use of a Valve. Research also has shown that feeding and swallowing improve feeding and swallowing. Therefore, increasing function through use of the Valve and providing oral stimulation and access to oral intake provides an opportunity to improve oral nutrition. The impact of a tracheostomy and links between gross motor and language development have been discussed in the literature. It is important to provide a closed system which assists with restoring more normal thoracic and abdominal pressures impacting gross motor movements and even swallowing. While a tracheostomy may cause an open system in an otherwise closed environment, restoring more typical function through use of the Valve not only closes the system, restoring pressures, but ends the vicious cycle that begins with a tracheostomy.

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Automated Closed-Loop Oxygen Control: A Review

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Overview

Physiologic Closed Loop Oxygen Control (PCLC) has been used since the late 1970's, including a non-invasive closed loop control solution described in 1979.[1] There have been numerous studies with results supporting the feasibility of clinical use of automated closed loop oxygen control.[2-8] The fundamental functions of Proportional-Integral-Derivative (PID) or fine control—fast stepwise closed loop control algorithms has been described.[3-7,9] Of these, the 2016 review by Fathabadi et al., provides a comprehensive technical overview, suggested future directions, and safety considerations of neonatal automated oxygen control algorithms.[9] Additional discussion describes how these systems can be integrated into the oxygen blenders of portable ventilation systems.[10] To date, PCLC algorithms have been used clinically in oxygen tents,[1,11,12] mechanical ventilators,[13-16] nasal continuous airway pressure and high flow nasal cannula.[7,17-20] The concept of PCLC has been present for some time as previously alluded. Significant effort in developing ideal settings and testing of these algorithms exists in four published validation accounts in dogs,[21] pigs,[10] sheep,[22] and lambs.[23]

Both scientific and clinical discussion has centered around the use of algorithms in closed loop control systems in maintaining SpO_2 at studied physiologic targets deemed acceptable specifically in the preterm infant population.[24-28] The closed loop controllers monitor arterial blood oxygen saturation (SaO_2) most commonly via the use of pulse oximetry (SpO_2) in real-time. As the SpO_2 values fluctuate above or below a set point or range, a central processor computes the necessary adjustment in the fraction of inspired oxygen (FiO_2) that is being delivered. The intention is that a PCLC can react faster than a human caregiver to apply oxygen when needed, but also minimize potential overshoot, and therefore limit oxygen exposure to which the patient is subjected over time, particularly incidences above the specified target range.[1,8,14,29-31] For all the aforementioned benefits of PCLC, including the provision of clinical flexibility, the attendant clinical management and standard of care towards the patient should still remain unchanged, as ultimate responsibility for the patient is in the clinicians.

Optimal Oxygen Target Level in Neonates

As oxygen control is relevant to both neonatal and adult patient populations, it is also prudent to mention that contention exists in literature on which SpO_2 target ranges to use, especially for the case of preterm infants, where oxygen saturations can affect mortality and retinopathy of prematurity.[26,32,33] Defining and establishing an optimal neonatal oxygen target is important, though clinically challenging. Based on the NeOProM meta-analysis study of some of the largest randomized controlled trials, including SUPPORT, Benefits of Oxygen Saturation Targeting II (BOOST II), and the Canadian Oxygen Trial (COT), the European Consensus Guidelines recommended an oxygen saturation target of between 90% and 94%, with suggested alarms limits of 89-95%.[34]

Currently, after much evaluation of suggested oxygen target ranges in neonates, both the American Academy of Pediatrics (AAP) and European Union on Oxygen Saturation Standards (EUOSS) have evolved in a similar fashion with smaller variation making suggested target ranges narrower based on available information from the literature. The SpO_2 upper alarm limit recommended to be 95% by both bodies, however there is some variation on lower alarm limits. The EUOSS has suggested 89% as the lower SpO_2 alarm limit, while the AAP has not committed to a lower target number due to both practical and clinical factors.[35]

Physiology/Pathophysiology

Premature infants are patients that often require careful oxygen supplementation, targeting a specific range of blood oxygen saturation. There is a clinical challenge of managing a delicate balance of avoiding both hypoxemia and hyperoxemia until their lungs are sufficiently developed to maintain appropriate physiological oxygenation without support. Oxygen lability yields to a critical state in premature infants where saturation and oxygen exposure need to be addressed to help prevent iatrogenic contribution to the development of diseases such as retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) as a result of hyperoxia, as well as necrotizing enterocolitis (NEC), increased risk of mortality, and long term neurological effects secondary consequences to prolonged hypoxia. Physiological mechanisms that typically respond to hypoxia (e.g., control of ventilation and circulation) in term newborns are not fully developed in many premature infants. The difficulty lies in not only the infant's lack of autoregulatory mechanism control of hypoxia, but also physiological protection against iatrogenically induced hyperoxia.[36]

Clinical Challenges in Management

The oxygenation challenge for clinicians in management of

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preterm infants is what is essentially a negative therapeutic index; optimal oxygenation and elimination of hypoxia, whilst preventing consequences of hyperoxia. Supplemental oxygen use in neonates has been a common practice since 1940. PCLC is one tool that helps clinicians address minimization of hypoxic and hyperoxic concerns in premature infants. As such, automated control of oxygen, using PCLC react faster than a human caregiver to apply appropriate oxygen when necessary, minimizing overcorrection, and limiting oxygen exposure.[29,30]

Challenges Related to Maintaining Infants' Oxygen Levels Within Target Saturation Range in Non-PCLC Attempts

Many factors may affect adherence to target oxygen goals in a neonatal clinical setting. Several interventions might improve compliance, such as decreasing nursing workload, increasing training and awareness of the target saturation range, as well as establishing titration protocols. In a prospective observational study of preterm infants receiving supplemental oxygen and CPAP, continuous oxygen monitoring over 24 hours showed that infants were in the target SpO_2 range only 31% of the time.[13] In a systematic review of 16 studies involving 2935 nurses and 574 infants investigating adherence to target oxygen levels in preterm infants, the authors concluded that compliance in targeting oxygen in preterm infants is low, especially in maintaining SpO_2 below the upper limit.[26] One retrospective observational study linked nurse-patient assignment data with continuous oxygen saturation data and determined the proportion of the time oxygen saturation was within target range. The authors concluded that fewer patients per nurse may be associated with improved rates of meeting oxygen saturation goals in premature newborns.[37] The presence of policy-specific saturation limits is associated with a reduction in the influence of individual nurse opinion on target saturation.[38] Another study showed that narrow oxygen saturation alarms led to increased alarm incidence, which then resulted in alarm fatigue and its associated negative consequences.

Goals of Supplemental Oxygen in Neonates

The primary goal of oxygen supplementation in neonates is to support their metabolic needs while avoiding the adverse effects of hypoxia and hyperoxia. Hypoxia occurs when tissue oxygenation is insufficient, is associated with increased morbidity and mortality in neonates. In a recent meta-analysis, the NeOProM collaboration group concluded that a lower SpO_2 range was associated with a higher risk of death and necrotizing enterocolitis.[27] The same group also confirmed that lower SpO_2 leads to a greater risk of patent ductus arteriosus requiring surgical ligation, as well as a higher rate of mortality at postmenstrual age of 36 weeks and at hospital discharge with the lower SpO_2 group. In addition to NeOProM, a post-hoc analysis of the Canadian Oxygen Trial (COT) demonstrated that prolonged hypoxemic episodes lasting at least 1 minute during the first two to three months after birth were associated with late mortality or neurodevelopmental impairment at 18 months.[39] Similarly, a subgroup analysis of the Surfactant Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT) found that mortality in the lower SpO_2 group was greater for small for gestational age SGA infants.[40]

In the opposite direction to hypoxia, hyperoxia is also associated with adverse effects in neonates, including BPD, due to oxygen toxicity to the lungs, and ROP, the result of excessive tissue oxygen resulting in reactive oxygen species that damage retinal blood vessels in premature infants. Published in 2000, the Supplemental Therapeutic Oxygen for Pre-threshold Retinopathy of Prematurity (STOP-ROP) trial showed a higher SpO_2 target in preterm neonates was associated with a greater risk of BPD and longer durations of hospitalization than those assigned to the lower SpO_2 target.[41] Furthermore, when compared to a high SpO_2 target, a lower SpO_2 target group was associated with fewer incidents of ROP requiring treatment.[24]

PCLC Clinical Evidence

Published closed loop oxygen control clinical trials in neonates agree that clinically relevant oxygenation performance is at least as good with automated control as with conventional manual control. It is reported that in automated control there was a marked improvement for time spent in target SpO_2 range, less time spent below designated range, lower overall oxygen exposure, and reduced FiO_2 manual adjustments. The device used for most of the recent clinical trials in neonates is Avea-$CLiO_2$ (CareFusion; Yorba Linda, CA, USA). In a non-peer reviewed article Wilinska and Wasco document their use of $CLiO_2$ "routinely for about 1 year and have found it to be very effective in a broad range of patients."[42] These authors published a more recent paper introducing their registry, which at publication was at 121 infants from 5 units, which showed no reports of the device not working and a perception of improved care. The authors state that the data will be analyzed and published when the registry reaches 1,000 infants.[43]

Claure and colleagues, who developed the $CLiO_2$ algorithm, conducted a pilot clinical trial with this system in 2009.[44] The study involved sixteen infants with frequent hypoxemia episodes and compared maintenance of SpO_2 within the intended target range during one 4-hour period of manual adjustment and one 4-hour period of automatic adjustment. This randomized study was conducted using the Avea infant ventilator with automated FiO_2 adjustment function built in. The authors concluded that "automated FiO_2 adjustment improved maintenance of SpO_2 within the intended range with less exposure to supplemental O_2" and that further randomized trials are needed to detect clinical outcome effects. A subsequent additional study conducted the largest randomized controlled trial to date at the time, enrolling thirty-two infants.[45] This study involved two consecutive 24-hour periods, one with FiO_2 adjusted manually and the other by the $CLiO_2$ system. Again, improved maintenance of SpO_2 in the intended range while reducing integrated oxygen exposure was demonstrated. Staff effort was also noticeably reduced compared to manual adjustment.

In 2014 and 2015, three additional trials, all using the Avea-$CLiO_2$ system, were published.[16,46,47] These studies were in agreement that SpO_2 performance under automated control is at least as good as with manual control, with additional benefits of decreased both hyperoxia and hypoxia. Similarly, Hallenberger et al in the CLAC study, demonstrated that another neonatal-focused algorithm improved both time in target range (61.45 vs 71.2%; $p < 0.001$) and reduced time below range assisting to avoid hypoxia, with added benefit of reduced workload related to manual adjustments. This study was implemented with mechanical ventilation and nCPAP using a three-hour run-in phase followed by two consecutive 24-hour periods of a randomized combination manual/automated. In contrast to comparing improvement in only a single target SpO_2 range, another study in neonates (n=50 noninvasive support and n=30 mechanical ventilation) determined the efficacy and safety of

the $CLiO_2$ system in both a lower (89-93%) and a higher (91-95%) range. The study was implemented with consecutive 24-hour study arms of a randomized combination manual/automated, with a second stage of randomization for the lower and higher SpO_2 target ranges. Consistent with the previous studies, this study showed that automated FiO_2 improves the time in target range regardless of the lower (62% vs 54%; $p < 0.001$) or higher (62% vs 58%; $p < 0.001$) SpO_2 ranges, further noting a greater improvement in the lower SpO_2 target range, and reduced manual FiO_2 adjustments. Secondary analyses of the study highlighted reduced time in target range, independent of target range, with only a reduction in hyperoxemia for the lower (89-93%) target range.[48]

Two proportional-integral-derivative (PID) algorithm for automated control of FiO_2 in neonates trials came to press being treated with (1) the $CLiO_2$ system in mechanical and noninvasive ventilation,[49] and (2) a novel algorithm in nCPAP or HFNC.[7] In the recent $CLiO_2$ system the algorithm was implemented as a standard of care and the authors performed a retrospective analysis of manual and automated control with a 90-95% target range. It was demonstrated that over 9 months, automated control improved the time in target SpO_2 range (48.4% vs 61.9%; $p < 0.01$) and decreased the time below and above target range, thereby significantly reducing the patient hyperoxemia but not hypoxemia exposure.[49] A similar study duration was used in a separate trial for four hours and the time spent within the target saturation range was significantly greater for automated control compared to manual (81% vs 56%; $p < 0.001$).[30] Additionally, these studies showed that the infants spent less time receiving extreme high and low FiO_2 concentrations with a virtual elimination of prolonged episodes of hypoxia and hyperoxia.

In 2019, the latest neonatal randomized controlled crossover study, compared routine manual care to two 'versions' of a closed-loop automated control (CLAC) algorithm — fast and slow responding oxygen titration.[50] The slow response algorithm was studied in 2014, wherein neonatal patients on automated control exhibited greater time in target range.[51] $CLAC_{fast}$ and $CLAC_{slow}$ were conducted in NICUs neonates were randomized for 8 hours each in three FiO_2 modes: (1) routine manual care, (2) $CLAC_{fast}$, and (3) $CLAC_{slow}$. Comparison of time in target range showed: (1) the two automated modes were non-inferior to each other (Mean±SD [95%CI]: $CLAC_{fast}$ 68%±11% [65% to 71%] vs $CLAC_{slow}$ 65%±11% [61% to 68%]), $p<0.001$), and (2) the $CLAC_{fast}$ was superior to routine manual control ($CLAC_{fast}$ 68%±11% [65% to 71%] vs Manual 58%±11% [55% to 62%], $p<0.001$).[50]

Prior PCLCs, providing automated control of oxygen have been solely designed, developed and implemented as a primary use in pressure-based respiratory support systems. A novel PCLC, Oxygen Assist Module (OAM; currently a CE-marked product), is the first PID PCLC with the sole aim to be implemented with high velocity nasal insufflation (HVNI), a form of NIV shown to augment breathing through a nasal cannula patient interface. In 2018 Reynolds, et al completed a randomized clinical trial designed to provide clinical validation for the OAM (Vapotherm, Exeter, NH, USA) used in conjunction with the Vapotherm Precision Flow device for titrating oxygen to neonates requiring non-invasive respiratory support. Data analyzed from 30 preterm infants were included in the results of the OAM (denoted as $IntellO_2$ at the time of the study) clinical trial. Time in target range is denoted by SpO_2 target range designated at 90-95% (or considered 90-100% if FiO_2=21%). The time in the target SpO_2 range (median) was achieved significantly more in the automated vs manual control (80% vs 49%; $p < 0.0001$). The OAM recorded data every 1 second on multiple patient parameters, of which SpO_2 was included. The automated control provided significantly less SpO_2 variation (0.03 vs 0.06; $p < 0.00001$) as demonstrated in the coefficient of variance calculation. The mean FiO_2 for the 30 patient data sets analyzed was significantly different between automated vs control (0.34 vs 0.29; $p < 0.0001$). The most common FiO_2 in the automated arm was at 0.21 (air) vs 0.30 for manual control. In addition, during OAM automated control, the patients were significantly less likely to be hypoxic and hyperoxic. Further, the OAM's automated control reduced the duration of these hypoxic and hyperoxic episodes as well.[8]

Conclusion

Clinical evidence to date has shown the performance and safety of automated closed-loop oxygen control in treating premature infants. Automated oxygen control has been shown to maintain target SpO_2 and decrease hypoxia and hyperoxia in premature infants. Along with targeting SpO_2 goals, automated control offers clinical flexibility in accommodating patient needs through more specific control of oxygen targets and alarms. Automated oxygen control can assist care givers in maintaining preterm infants in recommended specified targeted oxygen saturation ranges as reported by SpO_2 and help optimize care giver time to tend to other needs these fragile patients may have. Automated oxygen control is available in Europe, therefore the question remains: does the benefit outweigh the risk of not implementing these automated oxygen control systems worldwide so long as the same level of care and supervision remains in place for these challenging neonates? Additional data on long term outcomes can be gathered through a registry and compared to historical controls.

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Diaper Dermatitis and Fecal pH: The Role of the Infant Gut Microbiome

Media Esser, PhD, NNP-BC, APNP, CWN and Tracy Shafizadeh, PhD

Introduction

Diaper dermatitis (DD) is a common occurrence in the NICU, with an estimated 29% of infants in the Neonatal Intensive Care Unit (NICU) affected during their hospitalization.[1,2] The function of the skin plays a role in the development of DD among infants, along with internal factors such as fecal pH and the composition of the infant gut microbiome. The prevalence of DD among infants in the NICU is variable in the literature. The lack of consistent management methods, inconsistent assessment tools, and variability due to the subjective nature of assessment lead to a lack of reliability among published studies.[3] Additionally, DD may be associated with the care complexity of the infant during their hospitalization. Factors such as time to full feeds, type of feeds, stooling frequency, antibiotic usage, and characteristics of severity of illness have been described in DD literature related to assessment and management.[4] Emerging data suggest that DD may be an early indicator of gut dysbiosis, or an overgrowth of pathogenic bacteria in the infant gastrointestinal (GI) system. Gut dysbiosis has been linked to many negative health outcomes in preterm infants, including increased risk of late onset sepsis, necrotizing enterocolitis, and diminished growth.[5,6,7] Recognition of DD as a symptom of this condition provides early and effective intervention during the window of immune development during the first few months of life.

Underlying Factors of Diaper Dermatitis

Diaper dermatitis is an inflammatory skin condition that occurs as a result of overhydration and the interaction of stool enzymes and the condition of the skin.[8] In addition to exposure of skin to urine and feces, pH plays a key role in the development of DD. Infant skin has a higher pH initially and continues to mature over the course of weeks to months depending on the prematurity of the infant at birth.[9] Hoeger, et. al. described a significant change in skin pH among non-hospitalized infants between 30 to 90 days of age.[10] The non-hospitalized infant is fed without complication in comparison to the infant in the NICU that has additional implications for the change in skin pH.

Additionally, prolonged exposure of the perianal region to urine and feces leads to a more alkaline skin pH, increasing the risk for diaper rash.[11,12]

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Fecal pH also plays a significant role in the development of diaper dermatitis, in that fecal enzymes, which are activated at elevated pH, have a direct irritant effect on the skin. Indeed, human breastmilk contains specific carbohydrates, called human milk oligosaccharides (HMO), which promote the growth of *Bifidobacterium longum* subsp. *infantis (B. infantis*) in the infant gut. *B. infantis* is an infant-adapted gut bacterium that efficiently converts HMO from human milk into acidic byproducts, lactate and acetate, creating a fecal pH of ~5.0.[13] In the absence of *B. infantis*, the production of these acidic byproducts is limited, causing fecal pH to rise to ~6.0 or higher. Unfortunately, due to modern medical practices in the US over the past century, most infants no longer maintain appreciable levels of *B. infantis* in their gut microbiome during infancy, and recent studies show that most infants in the US today have an elevated fecal pH.[14]

Prevention of Diaper Dermatitis

Currently, prevention is the key to decreasing DD among infants. Preventative methods in the literature promote the use of emollients and barrier products. The maintenance of skin integrity with topical administration of emollients and other DD products may provide mitigation of symptoms, but lack complete elimination. Additional approaches to promoting skin health from an internal perspective can be more intuitive to the elimination of DD. Proper nutrition is essential to the normal function of body systems demonstrating the importance of GI health. Infants in the NICU are often fed small amounts initially with extended length of time until full enteral feeds are established. Premature infants require the fortification of human milk with nutritional additives to promote adequate nutrition.[15] The addition of fortification, such as human milk fortifier in liquid form, can contribute to changes in pH of the GI system that may contribute to DD.[16] In addition to prioritizing a human milk diet, the infant gut microbiome should be considered in this fragile population. As mentioned, the presence of *B. infantis* in the infant converts HMOs in human milk to acidic end products, lowering fecal pH to the skin-protective range.

Safe and effective colonization of *B. infantis* in the infant GI system has now been demonstrated through feeding the probiotic strain *B. infantis* EVC001 to term, breastfed infants.[14,17,18] Furthermore, infants in this study who received *B. infantis* EVC001 had a significant reduction in the number of loose, watery stools per day compared to controls, along with a reduction in average fecal pH (5.97 to 5.15).[17] In addition to the significantly lower in pH and improvement in stool consistency,

infants who received *B. infantis* EVC001 also showed an 80% reduction in GI pathogens associated with autoimmune and allergic conditions later in life. Based on this growing body of evidence, LabCorp national diagnostic lab has recently updated the infant stool pH reference range to pH 4.5-5.5, corresponding to the observed benefits within this range.

Conclusion

Skin care for the vulnerable infant in the NICU should be based on a holistic examination of the NICU environment. This examination should include optimization of extrinsic and intrinsic modalities to promote skin health among this fragile population. Restoration of the infant gut microbiome with *B. infantis* EVC001, and subsequent reduction in both frequency and pH of the stool, may be an effective way to address the underlying gut dysbiosis and manage the biochemical factors that precede the onset of DD, rather than waiting to treat the skin topically once signs and symptoms have been identified.

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