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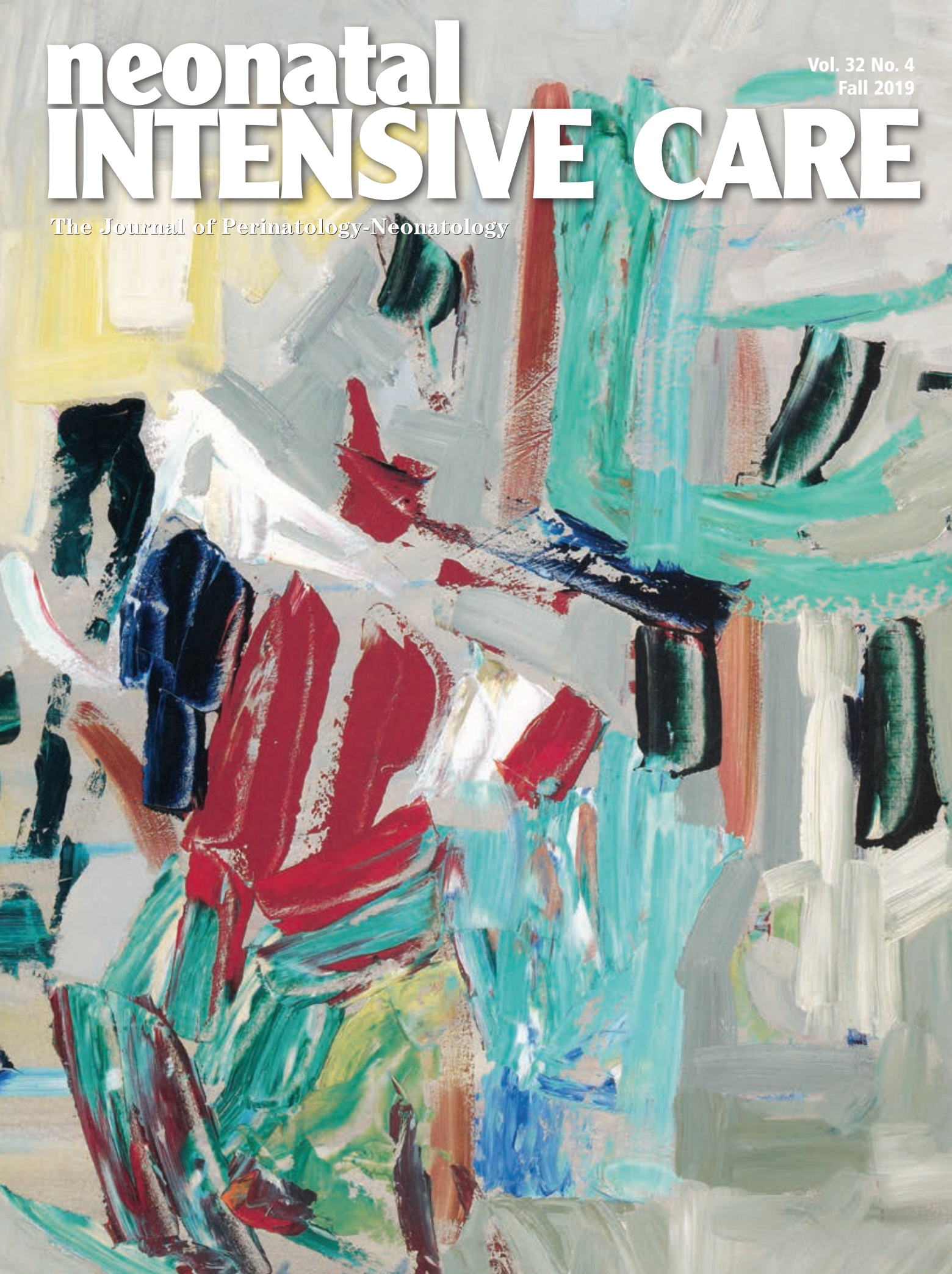

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Vol. 32 No. 4
Fall 2019

Table of Contents

DEPARTMENTS

ARTICLES

Editorial Advisory Board

News

☐ Fall 2019

New Product a Solution to Meet Updated Guidelines

Neotech Products is announced the release of their newest product, the NeoHeart ECG Pad. The NeoHeart ECG Pad was designed by a clinician as a solution to meet the new NRP guidelines for neonatal resuscitation by providing an all-in-one ECG pad that can be deployed in seconds, not minutes. "In a newborn resuscitation, time is everything! What I love about the new Neotech NeoHeart ECG Pad is that with one touch you can apply all 3 ECG leads securely and out of the way so that everyone can focus on stabilizing the infant and not the equipment," said Kathi Salley-Randall, MSN, RNC, CNS, NNP-BC. The NeoHeart ECG Pad features a 3-in-1 pre-wired electrode array and pre-measured sensor position for clinician ease of use. Its one-touch application makes it ideal for use in the delivery room. The NeoHeart ECG Pad was engineered for back application, allowing the chest to remain exposed. "As most of us know, it is extremely difficult to assess heart rate in the first critical minutes of a sick newborns life. Palpation and auscultation of heart rate in the delivery room are not accurate and more importantly take valuable time and hands away from more critical tasks. The new NeoHeart ECG Pad gives accurate heart rate readings in seconds (not minutes) so that we can quickly assess the newborn's needs and effectiveness of interventions without having to stop to check the heart rate manually," Salley-Randall said.

NeoConnect at Home OTC Reusable ENFit Syringe Line Unveiled

NeoMed is excited to unveil NeoConnect at Home, a reusable portfolio of ENFit syringes that do not require a physician's prescription. As a leading ENFit solution provider, NeoMed is dedicated to making it easier than ever for home patients to access the ENFit syringes they need. The NeoConnect at Home line of ENFit syringes is the first of its kind to be available over-the-counter (OTC) AND FDA 510(k) cleared for reuse. Ideal for patients in non-clinical and homecare settings, each syringe may be hand washed and reused up to 20 times by one user when cleaned per the cleaning instructions provided with the syringe. Reusability allows for a cost-effective and eco-friendly alternative to single use ENFit syringes. The syringe portfolio will be available in four convenient sizes (3 mL, 6 mL, 12 mL and 60 mL). Complete with a durable polypropylene plunger and silicone O-ring gasket, the syringes will feature clear barrels with easy-to-read black markings and will be offered in consumer-friendly case quantities. The product line will be available for purchase through retail and online stores, DME's and homecare companies in the fall of 2019. ENFit is the registered trademark of the Global Enteral Device Supplier Association (GEDSA) and is commonly used to identify ISO 80369-3 compliant connectors. ENFit connectors help reduce the risk of enteral tube feeding misconnections and improve patient safety. GEDSA encourages manufacturers to introduce enteral devices with ENFit connectors, and healthcare facilities to adopt feeding systems with ENFit connectors as soon as possible. "The development of our NeoConnect at Home line of OTC reusable ENFit syringes is a direct result of feedback from customers concerned about ENFit syringe access and availability. Not only have we made our syringes more accessible, we've added value by ensuring they can be reused. It is our hope that ENFit syringe OTC availability and reusability will make enteral feeding and medication delivery hassle-free and cost- effective," said Marc Waldman, Vice President of Business Development at NeoMed. "We are proud to be the first in the industry to offer reusable ENFit syringes that are available without a prescription. We believe that this innovation will improve ENFit device access and advance the worldwide adoption and implementation of safer enteral connectors," remarked NeoMed President Aaron Ingram.

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Oximetry Device Cleared by the FDA

Masimo announced that O3 Regional Oximetry has received FDA clearance for use on neonatal and infant patients (<10 kg). O3 may help clinicians monitor cerebral oxygenation in situations in which peripheral pulse oximetry alone may not be fully indicative of the oxygen in the brain. With this expansion of the O3 platform, the benefits of monitoring with O3 are now available to patients of all ages, from neonates to adults. O3, which uses near-infrared spectroscopy (NIRS) to monitor the regional hemoglobin oxygen saturation of blood (rSO2) on both sides of the brain, may be particularly helpful in providing insight into neonatal patient status because neonatal pathology is often brain-related. In neonates, O3 provides reliable measurement with a 3% ARMS trending accuracy specification. O3 sensors are available in three sizes, for adult (≥40 kg), pediatric (≥5 kg and <40 kg) and now infant and neonatal (<10 kg) patients. With its smaller size and flexible design, the neonatal sensor is designed to fit easily and comfortably on the delicate foreheads of tiny patients. O3 is available as a Masimo Open Connect (MOC-9) module for the Root Patient Monitoring and Connectivity Platform. Root is a powerful, expandable hub that integrates an array of technologies, devices, and systems to provide multimodal monitoring and connectivity solutions. Root's plug-and-play expansion capabilities allow clinicians to simultaneously monitor with O3 and other measurements, such as SET Measure-through Motion and Low Perfusion pulse oximetry, providing clinicians with expanded visibility of neonatal oxygenation status. Additional modalities available on Root include advanced rainbow noninvasive measurements such as total hemoglobin (SpHb), SedLine brain function monitoring (available for adult patients), NomoLine capnography, and more — all via an easy-to-interpret, customizable display. Using Root in combination with Masimo Patient SafetyNet or Iris Gateway, monitoring data from O3 can be automatically charted in electronic medical records (EMRs). Joe Kiani, Founder and CEO of Masimo, said, "From our inception, we have been committed to improving outcomes for the youngest and most fragile patients. Our foundational SET pulse oximetry was designed with neonates and infants in mind. These patients were not an afterthought. This focus has paid off for these young patients: SET pulse oximetry has helped clinicians reduce the incidence of severe retinopathy of prematurity (ROP) in neonates and improve critical congenital heart disease (CCHD) screening in newborns. O3 Regional Oximetry, with its ability to help clinicians accurately track cerebral oxygen saturation, will hopefully have a similar impact. We are happy to be able to bring O3's advanced capabilities and accuracy to the neonatal patient population."

Preemies and Early Arrivals Have Higher Risk of Heart Disease as Adults

Babies who are born too soon may be more likely to develop heart disease as adults than full-term infants, a new study suggests. Adults who were born before 37 weeks gestation were 53 percent more likely to develop heart disease than people who were full-term babies, researchers found. And people who'd been born just a little bit early — at 37 to 38 weeks gestation — were 19 percent more likely to develop heart disease. Pregnancy normally lasts about 40 weeks, and babies born after 37 weeks of gestation are considered full-term. Babies born prematurely — earlier than 37 weeks — often have difficulty breathing and digesting food in the weeks after birth. Preemies can also encounter longer-term challenges such as impaired vision, hearing and cognitive skills, as well as social and behavioral problems. Preterm birth has also been linked to an increased risk of high blood pressure and diabetes decades later. But research to date hasn't conclusively linked an early delivery to an increased risk of so-called ischemic heart disease, which happens with the arteries narrow and limit how much blood and oxygen reach the heart. For the current study, researchers examined data on more than 2.1 million babies born in Sweden between 1973 and 1994, following them through 2015 to see how many developed heart disease. Only 1,921 of these babies, or less than one percent, went on to be diagnosed with heart disease by ages 30 to 43. "Preterm birth interrupts the development of the cardiovascular system and other organs, leading to abnormal structure or function of blood vessels and other disorders such as diabetes that can lead to heart disease," said lead study author Dr Casey Crump of the Icahn School of Medicine at Mount Sinai in New York City. "Our findings were not explained by maternal factors that might contribute to both preterm birth and future heart disease, such as obesity, hypertension, diabetes, and smoking," Crump said by email. "In addition, we also compared persons born preterm with their siblings who were not, which suggested that the findings were not explained by other risk factors shared within families, but were more likely from direct effects of preterm birth." For every 100,000 babies born at full term each year, about 5.9 would develop heart disease as adults, researchers calculated. That compares to about 6.5 of every 100,000 babies born slightly early and 8.8 of every 100,000 preemies. One limitation of the study is that researchers lacked more detailed clinical data needed to verify the heart disease diagnoses, the study authors note. They also had too few extremely preterm babies to draw firm conclusions about the heart risks associated with delivery earlier than 34

weeks gestation. Another drawback is that the follow-up period was too brief to detect differences in heart disease rates later in adulthood, when the condition is more commonly diagnosed. Even so, the results suggest that adults born even a little bit early should take extra precautions to protect the heart, said Dr Thuy Mai Luu of the University of Montreal and CHU Sainte-Justine in Canada, who co-authored an editorial published with the report. "Some risk factors associated with cardiovascular diseases can be prevented through healthy lifestyle habits including a diet rich in fruits and vegetables, reduced sedentary time, regular physical activity and avoidance of primary and secondary smoke exposure," Luu said by email. "This is important to all, but maybe more so for children and adults born preterm," Luu added. "Given that it is hard to change behaviors, adopting a healthy lifestyle early in childhood is crucial; parents are central to this."

Childhood Asthma May Begin Before Birth

The risk for childhood wheeze is greatly reduced when babies collect the right bugs in their microbiome early in life, new research from two studies shows. "We've gone from the hygiene hypothesis to the microbial dysbiosis hypothesis," said Christine Cole Johnson, PhD, from the Henry Ford Health System in Detroit. "The microbes established in a baby's first months of life from the mother are important," she explained. The type of community that develops in a baby's gut and skin "affects not only asthma, but the whole immune system." "The answers aren't all in," she acknowledged, but evidence is mounting that we need more exposure to microbial diversity early in life. "We've seen that when a mother has a dog in the house, the cord blood lgE of the baby is lower, indicating that early exposure is a factor." Johnson presented new data on the interplay between maternal factors and infant gut microbiota and the effect that has on the risk for allergic asthma at the American Thoracic Society (ATS) 2019 International Conference in Dallas. She and her colleagues looked at fecal samples from infants — members of the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) — taken at 1 and 6 months. They used 16S V4 sequencing to see whether the bacterial taxa in the gut microbiota of those infants would predict who would have allergic asthma 10 years later. Gut bacterial diversification during infancy was slower in the now 10-year-old children with allergic asthma, and immature gut communities at 6 months increased the odds that a child would have allergic asthma at 10 years. Previous studies have shown that the risk for asthma is lower in children raised on farms and when a parent licks a pacifier to clean it. "We're the first group to show that very early microbial gut communities actually impact asthma outcome at the ages of 10 and 11," Johnson reported. In fact, the odds that a 10-year-old child will have allergic asthma are elevated if he or she was born by emergency cesarean, does not have a dog, is black, and has an immature gut bacterial community. In general, boys are more likely than girls to have asthma at a young age; however, boys often grow out of it but girls are less likely to. In the WHEALS cohort, a more mature bacterial community at 1 month and a more immature bacterial community at 6 months were associated with allergic asthma in both boys and girls.

More US Mothers Diagnosed With Depression at Childbirth

Growing numbers of new mothers are being diagnosed with depression before they leave the hospital with their newborns, according to a US study that suggests screening women at

childbirth could help get treatment for those who need it. From 2000 to 2015, the rate of depression diagnoses among women hospitalized for the delivery of a child rose seven-fold, from 4.1 cases per 1,000 patients to 28.7 per 1,000, the study found. The study wasn't designed to determine what caused the spike in diagnoses. It "could be the result of a true increase in cases of depression over the time period, better recognition of depression, or improved diagnoses after screening and assessment," said lead study author Sarah Haight, a researcher with the US Centers for Disease Control and Prevention in Atlanta. "Generally speaking, it's important for patients to know that depression — including perinatal and postpartum depression — is common and treatable," Haight said by email. "It's also important to know that it doesn't feel the same for everyone." During pregnancy and the postpartum period, depression affects about eight percent to 13 percent of mothers, Haight and colleagues note in Obstetrics & Gynecology, online May 9. Depression during pregnancy is tied to an increased risk of poor nutrition, alcohol and drug use, obstetric complications and preterm births. It can also affect children's mental and emotional health and motor development, the study team writes. By the end of the study, depression diagnosis rates were lowest in Hawaii and Nevada, at less than 14 cases for every 1,000 patients. Rates were highest in Vermont, Minnesota, Oregon, and Wisconsin, at more than 31 cases for every 1,000 patients.

Premature Birth Ups Risk of Kidney Disease Into Adulthood

Being born prematurely is associated with a significantly greater risk of developing chronic kidney disease (CKD) from childhood into mid-adulthood, a national cohort study in Sweden indicates. Even infants born between 37 and 38 weeks' gestation ("early" rather than premature) have a higher risk of developing CKD into mid-adulthood, although the risk is somewhat attenuated as gestational age increases, the study shows. "The third trimester of pregnancy is the most active period of fetal nephrogenesis, during which more than 60% of nephrons are formed," write Casey Crump, MD, PhD, Icahn School of Medicine at Mount Sinai, New York City, and colleagues. "Our findings underscore the importance of public health strategies to prevent preterm birth, including better access to preconception and prenatal care for high risk women, and reduction of nonmedically indicated deliveries before full term," they indicate. They also give advice for physicians on how to monitor patients born prematurely to try to reduce/limit their risk of developing kidney disease. The Swedish birth registry was used to identify 4,195,249 singleton live births that took place in Sweden between 1973 and 2014. "Overall, 4305 (0.1%) participants had a diagnosis of CKD," the researchers observe. "Preterm birth and extremely preterm birth (< 28 weeks) were associated with a nearly twofold and threefold risk of CKD, respectively, from birth into mid-adulthood [compared with full-term birth (P < .001)]," they add. Infants born between 37 and 38 weeks' gestational age were also 30% more likely to develop CKD into mid-adulthood compared with full-term birth infants (hazard ratio [HR], 1.30; P < .001). Indeed, across the entire age range from 0 to 43 years, gestational age at birth was inversely associated with risk of CDK at an adjusted HR of 0.92 for each additional week of gestation (P < .001), Crump and colleagues point out. "These associations were strongest in childhood," Crump notes. For example, the risk of developing CKD was highest for participants between the ages of 0 to 9 years, when it was over five times higher for preterm infants relative to their full-term counterparts. This association weakened as people got older but it was still significant for those between the ages of 10 and 19, when CKD risk was almost twice as high for those born preterm compared with those born at full term (HR, 1.97; P < .001). And for those between the ages of 20 and 43, risk of CKD was still about one third higher for those born preterm, compared with at-term, at an HR of 1.34, the investigators add. And among the 4305 participants who developed CKD over the study interval, over one third (34.2%) progressed to end-stage renal disease (ESRD). Again, across all age categories, the adjusted HR for ESRD was still twice as high for preterm infants compared with full-term infants (HR, 2.09; P < .001). For infants born early, the risk was still high (adjusted HR, 1.44; P < .001). The increased risk of CKD associated with preterm birth was evident in both males and females (P < .001 for both genders).

Microbiota in Reproductive Tract Linked to Preterm Birth

Certain bacteria in a woman's reproductive tract can contribute to early labor and can be a key predictor of premature birth, researchers have determined after a decade of studies into vaginal and cervical microbiota. "We're not claiming the vaginal microbiota is the reason for every single preterm birth that happens, but what we have found is that some microbes could be associated with a majorly elevated risk of preterm birth," said Jacques Ravel, PhD, from the University of Maryland School of Medicine in Baltimore. In their study of 2000 pregnant women, Ravel and his colleagues found that seven bacterial taxa, including Lactobacillus iners, significantly contribute to preterm birth — before 37 weeks of gestation. However, they also found that women whose vaginal microbiota contained high levels of the peptide beta-defensin 2 seem to be protected from spontaneous preterm birth, Ravel said. "Beta-defensin is among the panoply of our innate immune defense," he explained. It can compensate for the presence of microbes associated with an elevated risk for preterm birth. However, it is still unclear how potential clinical interventions could keep pregnancies from ending in early labor. "That is what we are looking at now," he reported. One of the first studies into the connection between microbiota in the reproductive tract and preterm birth was led by David Relman, MD, from Stanford University in California. Before that, researchers assumed that the microbiome was important for both maternal and fetal health, but were not clear on the role they played, Relman said. "It stood to reason that a disruption of some kind or some insufficiency or failure in the normal evolution of the microbiome during pregnancy could be a contributing factor in premature labor," he said. "But we were also mindful that there was already a lot of literature on premature birth around the world and we had a pretty good hunch that it was almost certainly a multifactorial problem, meaning genetics and a whole host of environmental factors — everything from stress to environmental pollution. And our research has proven that to be the case." Relman and his colleagues started by studying the microbiomes of pregnant women who lived near the Stanford campus and then branched out to a cohort in Birmingham, Alabama. They found that certain bacteria — especially Lactobacillus crispatus — appear to be an indicator that a woman will carry her pregnancy to term, but that L. iners do not offer the same protection.

New Birth-Weight Reference Is More Accurate

A new US reference for singleton-birth-weight percentiles uses obstetric estimates of gestation and thereby better identifies outliers, researchers report. "Given the concerns regarding the validity of previous birth-weight references based on maternal reports of last menstrual period, the need for an obstetric-

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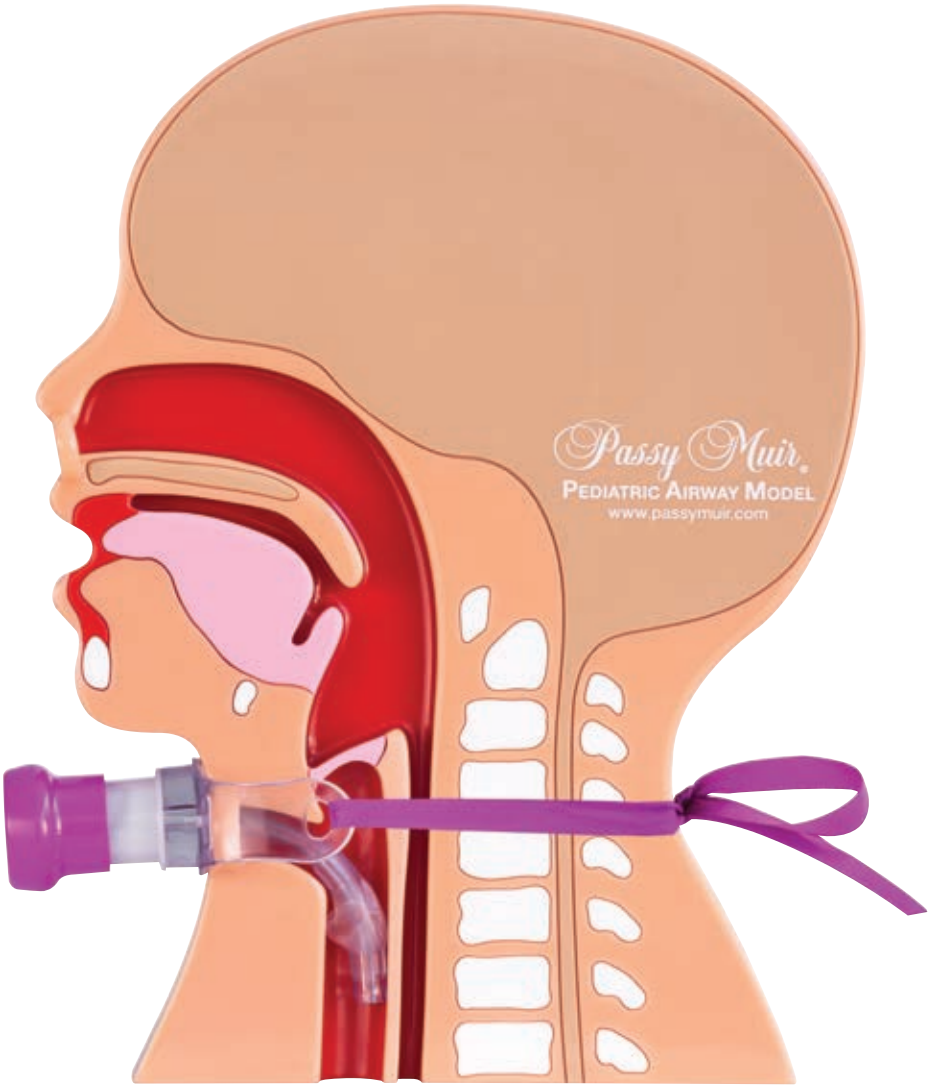

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estimate-based reference has become increasingly appreciated," said Dr Izzuddin M. Aris of Harvard Medical School, in Boston, and the National University of Singapore. "Thus, we hope that our new updated reference will allow clinicians (and researchers) to weigh its appropriateness against their specific needs," he said. Birth-weight-for-gestational-age is an important clinical indicator of perinatal morbidity, survival and long-term health outcomes in children and their mothers, Dr Aris and colleagues note in Pediatrics, online June 14. The team used data on more than 3.8 million live births from the 2017 U.S. natality files to create an updated birth-weight-for-gestational-age reference and used two smoothing techniques to develop percentile curves. The researchers also provide gestational age-specific cutpoints at the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles for male and female infants as well as for first-, second- and third-or-more-born infants. Cutpoints derived from these data identified 9.8% to 10.2% of births as <=10th percentile >=90th percentile and 2.6% to 3.3% of births as <=3rd percentile or >=97th percentile across preterm, term and post-term gestational-age categories. In contrast, cutpoints from US references based on data from 1999 to 2009 yielded a much larger variation in proportions of 2017 births at these thresholds, especially for preterm and post-term gestational-age categories. "We expect clinicians to be able to use the percentile thresholds from our updated reference to identify at-risk infants who may have had restricted or excessive fetal growth," Dr Aris said. "Researchers may also use this reference to derive continuous measures of birth size for studies examining predictors of fetal growth or associations of fetal growth with later health outcomes."

Parents Bring Newborns to ED for Many Non-Urgent Reasons

One of the hardest things about being a new parent is figuring out when babies are so sick they need to go to the emergency department and when worrisome signs or symptoms might actually be perfectly normal, doctors say. Anxious parents bring babies to the ED for all kinds of things that could go either way like conjunctivitis, concerns about how the stump from the cut umbilical cord looks, vomiting, strange looking stool, irregular breathing, and jerky or unusual body movements, Dr Zachary Drapkin of the University of Utah in Salt Lake City and colleagues note in a report in the American Journal of Emergency Medicine, online March 20. "Differences between potentially dangerous pathology and normal infant behavior can be subtle," Drapkin said by email. "It can be helpful if parents are counseled about what to expect over the first few days of life. Many of these issues could very effectively be addressed with improved access to primary care." Even for ED physicians, it can be challenging to distinguish normal infant signs, symptoms, and behaviors from potentially life-threatening conditions, Drapkin and colleagues point out. In their article, they address some common chief complaints of neonates and young infants presenting to the ED, and contrast reassuring neonatal and young infant signs and symptoms against those that need further workup and intervention. For example, babies with conjunctivitis (what parents may call goopy eyes) need to be seen in the ED when the cause is an infection, they note. Infection is more likely the culprit when there's lots of discharge and gunk. Normally, the umbilical stump left behind when the cord is cut at birth will turn black or brown and dry out before it falls off, typically within about one week. It can also have a foul smell like rotting fruit, the paper notes. But warmth, swelling, purulent discharge or a fever might indicate an infection that requires immediate medical attention. Nearly all babies spit up because their stomachs are so small, and this isn't necessarily a problem as long babies are urinating, feeding and growing normally. Unlike spit-up, projectile vomit may be caused by medical problems that could warrant a trip to the ER, the authors note. Infant stool, meanwhile, can be a greenish color for babies who are fed formula and more of a mustard color for breastfed infants, the doctors point out. Bloody or black stool after the newborn stage, however, might mean babies need to be checked for serious health problems like internal bleeding or bowel obstruction. Newborns can startle easily and have jittery movements in response to stimuli, and this is normal, they note. But jitteriness or jerky movements that continue over time and aren't in response to stimuli may mean there's a seizure problem or something else that requires an urgent checkup. Beyond the challenge of figuring out what infant health issues may be true emergencies, parents can also struggle to get same-day sick visits with pediatricians that could help them avoid a trip ED, said Dr Rajesh Daftary of the University of California San Francisco and Zuckerberg San Francisco General Hospital. "It's hard to estimate what number of emergency department visits by a newborn or infant could be averted with a same day visit, but it's certainly the majority," Daftary, who wasn't involved in the paper, said by email. "The challenge is trying to obtain these same day appointments." Nurse advice phone lines may help in some cases, but it can be hard for a clinician on the phone to make an assessment without directly examining a baby, Daftary added. "Urgent care clinics can be especially helpful if they are staffed by a physician or advanced practitioner (nurse practitioner, physician assistant) specializing in pediatric care," Daftary added. "Without that level of experience, an urgent care physician may opt to transfer a child to an emergency department where a more thorough assessment can be performed."

High BP Early in Pregnancy Linked to Birth Risks

High blood pressure during the first trimester of pregnancy, or an increase in blood pressure between the first and second trimesters, is linked to higher risk for gestational hypertension and preeclampsia, a study indicates. Both conditions heighten the risk for maternal stroke as well as for premature birth, stillbirth, and low birthweight. Preeclampsia also increases the mother's risk for life-threatening seizures, the authors write. "We compared the frequency of hypertensive disorders of pregnancy, including preeclampsia and gestational hypertension, among women based on ACC/AHA [American College of Cardiology/American Heart Association] blood pressure category at a first trimester study visit and blood pressure trajectory between study visits in the first and second trimesters," they explain. The findings by Alisse Hauspurg, MD, with the Magee-Womens Research Institute at University of Pittsburgh School of Medicine in Pennsylvania, and colleagues suggest that this study may identify otherwise "low-risk" women who may be at risk for a hypertensive disorder of pregnancy (HDP). In 2017, the ACC/AHA recategorized blood pressure levels and lowered the threshold for a diagnosis of chronic hypertension. Hauspurg and colleagues wanted to study the new guidelines' relevance for pregnant women. "Considering that the prevalence of pre-gestational hypertension has been projected to double in women newly-designated as having hypertension based on the new ACC/AHA guidelines, understanding risk in this group is particularly relevant for clinicians," the authors write. Among women who had elevated blood pressure in the first trimester (120/80 to 129/80 mmHg), 30.3% developed an HDP, which represents a

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42% higher risk than for women with normal blood pressure. Of women with stage 1 hypertension (130/80 to 130/89 mmHg), 37.8% developed an HDP, a risk 80% higher than that of women with normal blood pressure. Stage 1 hypertension was linked with more than 2.5 times the risk for preeclampsia with severe features (adjusted relative risk, 3.48; 95% confidence interval, 1.38 – 8.74). An increase in blood pressure between the first and second trimesters also raised the risk for a hypertensive disorder. Even for women whose blood pressure was normal during the first trimester, an increase in systolic blood pressure during in the second trimester raised the risk for a hypertensive disorder by 41% compared with women whose systolic pressure went down during that period. If the diastolic pressure went up, the risk was 23% higher compared with those whose diastolic pressure decreased during that time. The researchers used data from the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be cohort, a prospective observational study of women who had not previously given birth and who had single pregnancies at eight clinical sites between 2010 and 2014. The 8899 women who were included had no known history of prepregnancy hypertension or diabetes. The authors hope the study will spur further research in hypertension among pregnant women. "Further study to identify the efficacy of additional surveillance and potential risk-reducing interventions, such as low-dose aspirin, is needed in this population," they write.

MDA Convenes Panel of Experts

The Muscular Dystrophy Association (MDA) convened a panel of renowned experts in newborn screening (NBS), Pompe disease, spinal muscular atrophy (SMA), and Duchenne muscular dystrophy (DMD) to examine how the physician community can prepare for the expansion of NBS in neuromuscular diseases. In the review published today in JAMA Neurology, the authors discuss the challenges facing universal implementation of NBS, and the opportunities to prevent a lifetime of chronic disability and maximize the potential of newly available life-saving therapies through early diagnosis and the initiation of treatment before symptoms appear. The authors explain that in the US, decisions as to which diseases will be screened are made by the states, based on the US Department of Health and Human Services-endorsed Recommended Uniform Screening Panel (RUSP). Considerations for inclusion in the RUSP include evidence of a reliable screening test, approved effective treatment, and how early intervention can reduce morbidity. It may take years for RUSP-approved diseases to be adopted by all states, and each state's approach to adding new diseases to their NBS panel varies. "Newborn screening is one of the most important and impactful public health programs in the United States," said Dr Rodney Howell, chairman of the Board for the Muscular Dystrophy Association and professor of Pediatrics and chair emeritus of the Department of Pediatrics at the Miller School of Medicine at the University of Miami. "Since its inception, this program has saved and improved the lives of thousands of children. Its continued expansion to allow for screening for more neuromuscular conditions like Duchenne will benefit many more families by enabling them to receive the care their children need from day one." To attain the maximum benefits of NBS, careful follow up and continuity of care are essential, along with a well-defined path to communicating NBS results to affected families. "Once affected babies are identified via state newborn screening programs, MDA Care Centers at more than 150 top medical institutions across the US will play a key role in confirmatory diagnoses, treatment, and long-term follow up and care," says Lynn O'Connor Vos, president and CEO of the Muscular Dystrophy association (MDA). The paper concludes that the availability of advanced screening methods, the emergence of effective treatment, and the support of professional organizations may facilitate the expansion of NBS and that going forward, an increasing number of affected infants who are identified as newborns will be able to benefit from impactful, life-saving interventions.

Pressing Need for Extreme Preterm Infant Medical Care Leads to Crowdfunding Success

With its AmnioBed entering pre-clinical safety and device usability testing preceding clinical trials for FDA approval, Amnion Life recently launched an awareness and equity raising campaign. In the first six weeks, they have nearly reached the early goal of $200,000 of a $1 million unaccredited investor target, as part of a $5 million overall Series A funding round. Encouraged by the fundraising success, Amnion Life Founder and CEO Amir Fassihi, M.D. maintains the company's serious focus on developing better NICU solutions. There are an estimated 15 million annual premature births globally, with the number increasing more than 35 percent in the United States over the last 25 years. In 2016, the US Center for Disease Control and Prevention estimated there were 388,130 premature births, ranking the US as sixth in the world. "AmnioBed will offer improved thermoregulation, hydration, and skin protection, helping to reduce complications and save lives. Potentially improving the rate of weight gain and growth. Our solution may also significantly reduce direct costs of the NICU visit by decreasing complications associated with preterm birth while improving the infants' comfort," Fassihi said. AmnioBed solutions should provide a simulated fluid environment similar to the mother's womb; ideally recreating a more familiar environment for infants born before their due date. These premature infant amniotic bath incubators can comprise an incubating tank with synthetic or simulated amniotic fluid, heating element(s), temperature sensor(s), and/or thermostat(s) for regulation.

A Pea-Sized Device Is Approved to Close Holes in Hearts of Tiny Infants

A pea-sized device used to seal tiny but potentially deadly holes in the hearts of premature infants has been approved by US regulators, making it one of the smallest complex medical devices ever invented and cleared for sale. Abbott Laboratories' Amplatzer Piccolo Occluder is one of the first treatments to become available for a common congenital defect that can become dangerous for premature infants. The device can be used in babies weighing as little as two pounds in cases where a hole in the heart used to deliver oxygen-rich blood in the womb doesn't close after birth. The Piccolo is threaded into the heart using a catheter that runs through the femoral vein in the thigh. That avoids a taxing surgery for the undersized patients, who are often on ventilators, said Evan Zahn, director of the congenital heart program at Cedars-Sinai Smidt Heart Institute in Los Angeles. "We've never had anything like this, a device from a major medical manufacturer that was specifically designed with these tiny, really at risk, very fragile babies in mind," said Zahn, the lead investigator of the study that led to the device's approval by the US Food and Drug Administration. "We're talking about babies the size of the typical water bottle we all drink out of. They are incredibly frail, fragile and at risk for terrible morbidity and mortality." The Piccolo is not expected to be a major sales driver for the Abbott Park, Illinois-based company. Instead, it represents a significant technological advance as

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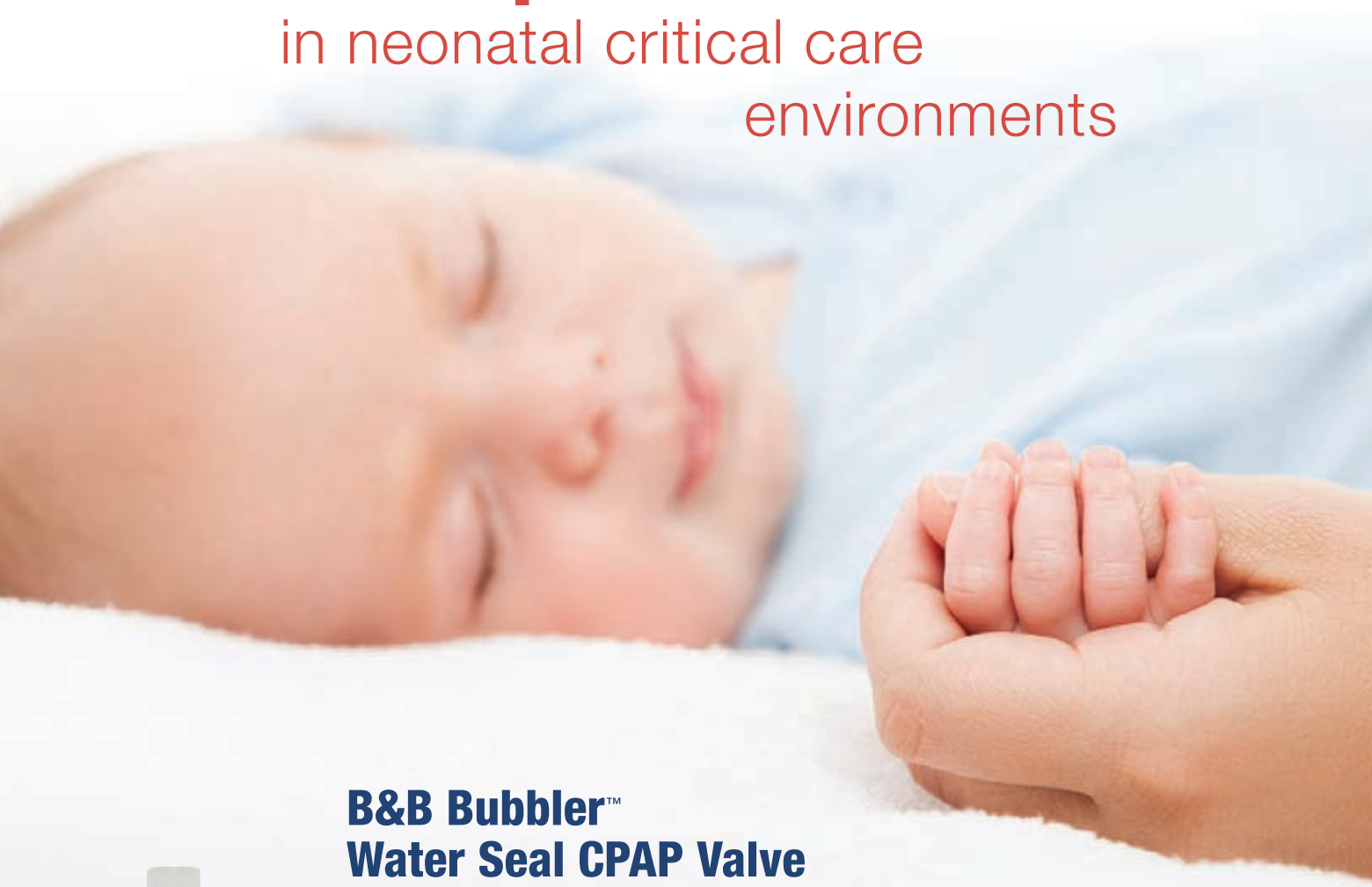

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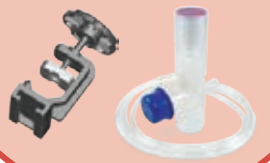

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medical-device manufacturers work to make their products ever smaller and easier to place in the body without taxing surgeries. Everyone is born with a small hole in their heart, a condition called patent ductus arteriosus. In the womb, the hole allows a fetus's blood to bypass the lungs and get oxygenated blood directly from the mother. Usually, the hole closes a few days after delivery. In some premature newborns, however, it never does, making breathing difficult and leading to a host of potential complications. They include developmental delays, damage to the brain and bowel because they aren't receiving the blood they need and injuries to the lungs that are flooded with fluid. For years doctors performed open-heart surgery to close the hole, a procedure now thought to do more harm than good to the smallest patients, Zahn said. Other treatments include medicine to ease the symptoms and encourage closure, though in most cases doctors, patients and families simply wait and hope the hole eventually seals.

Birth Rates at 30-year Low

The number of babies born in the US in 2018 fell to the lowest level in 32 years, according to a government report released. The numbers are part of a decades-long trend toward fewer and fewer babies being born each year — which means we're getting further away from the possibility of having enough children to replace ourselves, according to the report from the Centers for Disease Control and Prevention. "The major finding is that the fertility rates are reaching record lows," said the report's lead author, Brady Hamilton, a statistician and demographer at the CDC's National Center for Health Statistics. "There have been record lows in the teenage birth rate, which fell 7 percent compared to 2017." Hamilton and his colleagues found that the total number of births in 2018, at 3,788,235, was down 2 percent from 2017. The general fertility rate for 2018 was 59.0 births per 1,000 women aged 15 to 44, another record low for the U.S. For perspective, it's lower than in the years after the Great Depression. In 1936, for example, the general fertility rate was 75.6. More telling, perhaps, is the drop in the "total fertility rate," which also fell 2 percent compared to 2017 figures, to 1,728 births per 1,000 women of childbearing age. For the nation's population to reproduce itself at current numbers and remain stable, the total fertility rate would need to be at least 2,100 births per 1,000 women. So, essentially, for the population to remain stable, each woman needs to have at least two babies. At 2,000 there would be enough children to replace fathers and mothers. The extra 100 is to account for deaths.

Maternal Depression Can Impact Baby's Physical and Mental Health

Children with depressed mothers may end up with altered immune responses and at greater risk for psychological disorders, a new study suggests. Maternal depression may have a significant effect on the way children's brains work, the researchers write. "If you grow up with a clinically depressed mother, your body's stress response and immunity are (affected)," said study leader Ruth Feldman, the Simms-Mann professor of developmental neuroscience at the Interdisciplinary Center in Herzlia, Israel and an adjunct professor at the Yale Child Study Center in New Haven, Connecticut. "This is even if the family is of low-risk socioeconomic status, there are two parents and no issues of poverty or physical illness." That physical impact can lead to psychological issues, Feldman said. "This programming of the child's physiology to high stress reactivity charts a pathway to psychiatric vulnerability and symptoms," she explained. Feldman's team followed 125 newborn babies until they were 10 years old. When the infants were six months old, the mothers were asked to fill out questionnaires designed to look at levels of depression and anxiety. The researchers again touched base with the families when the children were six years old. When the children were 10, the researchers measured levels of the stress hormone cortisol and the immune marker secretory immunoglobulin in both mothers and children. The researchers also observed how the mothers and children interacted and noted whether the children displayed any symptoms of psychological distress, such as acting out or being socially withdrawn or anxious. Moms and their kids were also interviewed and diagnosed if they had any psychiatric disorders. Feldman and her colleagues determined that depressed moms had higher levels of cortisol and secretory immunoglobulin. Moreover, the depressed moms also displayed more negative parenting. "Depressed mothers are less engaged, less empathetic," Feldman said. They "show more negative and inconsistent (mood). They are more critical and hostile and are less sensitive to the child's non-verbal and verbal social communication." Children with depressed moms also had higher than normal levels of secretory immunoglobulin and were more likely to act out or to be anxious or withdrawn compared to children whose moms were not depressed. The study shows the impact a mom's depression can have on a growing child, said Dr Priya Gopalan, chief of psychiatry at the Magee-Womens Hospital and the Western Psychiatric Clinic of the University of Pittsburgh Medical Center, who was not involved in the study. That can include a heightening of the fight or flight response in children constantly exposed to a depressed parent, Gopalan said. The tuned-up fight or flight response in turn can lead to psychological problems in the children, she said. "This tells us … that we really need to get these moms treated," Gopalan said. "But we also don't want to shame our moms. They already feel guilt about what they are experiencing. "Studies like this give me more information to help me explain to depressed moms why it's good to get treated," Gopalan said. "Maybe moms will be more highly motivated to get treated if they think it will benefit their children." The new research "underscores the need to be aggressive at detecting and treating depression," said Dr Dorothy Sit, an associate professor of psychiatry and behavioral sciences at Northwestern University's Feinberg School of Medicine in Chicago. "The proper diagnosis and treatment is critical. With it we may be able to alter the pathway for mothers and their offspring."

Researchers Create First Longitudinal BMI Growth Curves for Preemies

Researchers have developed and validated longitudinal BMI growth curves for preterm infants using data from a large contemporary sample of infants in neonatal intensive care units (NICUs) in the US. In a paper, they note that longitudinal growth curves exist for weight and length in preterm babies but not for body mass index. "In preterm infants, the rate of weight growth is faster than length growth; thus, weight is often disproportionate to length at NICU discharge. To our knowledge, no longitudinal curves quantifying body proportionality have been published for preterm infants," write Dr M. Louise Lawson from Kennesaw State University, in Kennesaw, Georgia, and colleagues. The longitudinal BMI growth curves they developed are specific for sex, gestational age (GA) and BMI quintile at birth, and were derived from a racially-diverse cohort of more than 68,000 infants between 24 and 36 weeks GA. The curves apply only to preterm infants admitted to NICUs, because those infants born between 35 and 36 weeks GA and not admitted to

the NICU might have a different growth pattern, the researchers note. "Curves for all GAs, percentile groups, and both sexes revealed a postnadir linear increase in BMI over time, with the most premature infants showing the greatest increase," they point out. These BMI growth curves can be used in clinical practice to evaluate an infant's growth compared to his or her peers. Clinicians can compare the infant's calculated BMI with the curve for others with similar birth BMIs, they add. Tracking an infant's BMI growth across time can help gauge how the baby is developing relative to all percentile groups specific to the sex and GA, they explain. Summing up, Dr Lawson and colleagues note that preterm babies in the NICU are at increased risk for abnormal growth relative to healthy term babies. These BMI growth curves will provide clinicians with insight on how premature infants' body proportionality changes with age, the authors conclude. "It is our hope that together these curves will be used to identify and guide practice for infants growing disproportionately in weight relative to length, who currently are overlooked by growth assessment that is focused on size for age," they write.

Oxygen No Better Than Room Air for Fetal Resuscitation During Labor

Although oxygen supplementation is routinely administered for unfavorable fetal heart tracings, it is no better than room air for preventing fetal hypoxemia or acidemia, according to results from a randomized noninferiority trial. "I found it very interesting that substituting room air for oxygen did not impact umbilical cord gases," Dr Nandini Raghuraman from Washington University School of Medicine in St Louis, Missouri said. "We typically administer maternal oxygen supplementation in hopes of improving fetal status as interpreted by electronic fetal monitoring. Our results suggest that this may not be the case." More than 60% of women in labor receive supplemental oxygen to reverse perceived fetal hypoxemia, yet there is no proven benefit. Moreover, hyperoxygenation is associated with significant morbidity in infants, and the American Academy of Pediatrics recommends against initial neonatal resuscitation with oxygen. Dr Raghuraman and colleagues tested the hypothesis that room air for category II fetal heart tracings is noninferior to oxygen in improving fetal metabolic status as represented by umbilical artery lactate (a marker of metabolic acidosis and neonatal morbidity) in their randomized clinical trial of 114 women in labor at term (37 weeks' gestation or greater). Umbilical artery lactate did not differ significantly in the oxygen group (30.6 mg/dL) and the room air group (31.5 mg/dL). Results were similar in the subgroup of patients with recurrent late or recurrent variable fetal heart rate decelerations at the time of randomization. The groups did not differ in other umbilical artery gas components, including pH, base deficit, partial pressure of oxygen, and partial pressure of carbon dioxide.

Slow Weight Gain After Preterm Birth Tied to Elevated Retinopathy Risk

A postnatal weight-gain based model may be effective in identifying infants at risk of retinopathy of prematurity (ROP) according to data from a large retrospective study. This collaborative effort, Dr Gil Binenbaum said, "brings us one step closer to incorporating slow postnatal growth — an important predictor that we have known about for a while now — into our

Continued on page 54…

Prevalence Of Maternal Marijuana Use And Its Effects On Neonatal Growth And Breastfeeding In An Urban 'Babyfriendly' Hospital

Samantha Arevalo-Marcano, MD; Cihangir Buyukgoz, MD; Muhammad Zia, MD; Benamanahalli Rajegowda, MD

Introduction

Marijuana is the most commonly used and abused illicit drug in the United States. It is also a common drug used by women of childbearing age and pregnant women with a steady increase in recent years as evidenced from published reports[1,2,3] and our work shown in Figure 1. It is available as a natural product grown from a plant called "Cannabis sativa". Originally the plant was used for materials making ropes and clothes from its fiber. In 1900th century due to the influx of immigrants, marijuana was introduced and used as a recreational pot smoking. In 1971 during the war on drugs, FDA listed it as a category 1 restricted drug. Despite that, 33 states have approved its use for medicinal purposes since 1996 and 9 states along with Washington DC have legalized it for recreational use and many more states are following or considering the lead making it easily available illicit drug which can potentially do more harm than good. The CDC has reported a steady increase in marijuana use among children, adolescents including women of childbearing age, and pregnant women.[4,5] Tetrahydrocannabinol (THC) is an active ingredient in Marijuana which is available in varying concentration based on whether marijuana is smoking alone or used in combination with other addictive drugs like heroin, crack, cocaine, PCP, alcohol, or as an additive in food, or infused to liquids and assorted types of vapors. THC easily crosses the placenta at all stages of pregnancy and excreted in the breast milk in lactating mothers thereby exposing the developing fetus and the newborn infant with known and unknown risk factors.[6]

Objectives

Our institution is a level 3 perinatal center serving high-risk urban population. Majority being Hispanic and African American including a recent surge in other immigrant populations. Substance abuse among pregnant women was a major problem in the past and has been declining but marijuana use has been steadily increasing. At present, very little data are available including conflicting reports on its effects on the fetus and the newborn. The AAP and ACOG have warned women of child-bearing age and pregnant women to refrain from its use and avoid breastfeeding until more data are available. Our aim was to determine the prevalence of marijuana use among our pregnant population to evaluate the effects on the mother, the fetus, and the newborn.

Table 1. Maternal and Neonatal Variables

Cannabinoids Positive mothers	n=168
Maternal Age	
<20 years	27 (16.8%)
21-30 years	92 (55%)
31-36 years	49 (29%)
Ethnicity	
African American	93 (55.3%)
Hispanic	41 (24.4%)
Others	34 (20.2%)
Prenatal Care – No	76 (45.2%)
Psychiatric Problems	11 (6.5%)
Maternal Illness during pregnancy	11 (6.5%)
STD	20 (12%)
Group B Streptococcus carrier	26 (15.4%)
Cigarette Smoking	59 (35%)
Alcohol	9 (5.3%)
Neonatal Gender	
Male	90 (53.5%)
Female	78(46.5%)
Gestational Age	
Preterm (<37 weeks)	36 (21.4%)
Term	132(78.5%)
Birth weight average:	
Less than 2500grs	26%
More than 2500grs	74%
Extra mural delivery	5 (3%)

Material and Methods

The study was conducted from January 2007 through December 2016 over 9 year's period and was approved by Hospital IRB. Maternal and neonatal data was collected prospectively by the senior author on a daily basis which was further reviewed retrospectively by authors with collection of detailed data from the online electronic medical records. Mothers were evaluated by Obstetrician and Social Services and those who volunteered the information of Marijuana smoking occasionally or socially at least once during pregnancy or in the past or those with any risk factors identified in prenatal and intrapartum care underwent urine drug test after informed consent. The infants were automatically tested if the mother tested positive or there were high risk mother-infant criteria as assessed by Medical,

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Table 2. Maternal and Neonatal Urine Screen

THC and combination of drugs	Maternal +ve test n=168	Neonatal +ve test n=62
THC	142 (84.5%)	58 (93%)
THC+ Cocaine	17 (10%)	2 (3.2%)
THC+ Methadone	2 (1.1%)	0 (%)
THC+ Opiate	2 (1.1%)	1 (1.6%)
THC+ Multiple drugs	5 (3%)	1 (1.6%)

Nursing, and Social Service for evaluation of patient and family for child protection prior to discharge. Maternal characteristics included age, race, type of drug used, overall medical condition, and breastfeeding whereas Neonatal characteristics included gestational age, birth weight, head circumference, length, and the infant's overall medical condition. Statistical analysis done using sigma STAT 3.4 with P. values less than 0.05 considered at the level of significance.

Results

During the study period from January 2007 to December 2016, a total of 25,113 mothers were admitted who delivered live births. Out of these, 363 mothers had urine test positive for illicit drugs (hospital incidence of 1.5%). Amongst this group, 168 mothers tested positive for THC either alone or in combination with other illegal substances in the urine (an incidence of 45.6% of total drug use and 0.66% confirmed Marijuana use). Interestingly, only 58 of these 168 infants (34.5%) tested positive for marijuana (Table 2). The maternal characteristic features (Table 1) showed that 55% of mothers were between ages of 20-30 years, with predominant African American ancestry, and 53% of them with either inadequate or poor prenatal care. Gestational age at delivery was less than 37 weeks (21.5%). Maternal medical conditions (Table 1) included sexually transmitted diseases (Gonorrhea, Chlamydia, Herpes, Hepatitis C, Syphilis, HIV), GBS colonization, and Psychosocial problems. The neonatal characteristics included low birth weight less 2500 gms (26%) with gestational age less than 37 weeks (50%), head circumference range of 29.5-32.87 cm, and the length range of 44.5-51.5 cm. The weight, head circumference, and length are shown in the graph by comparing to standard medical values published for appropriate group (Graphs). Each showed a lag in all the categories to comparable groups which occur mostly after 35 weeks of gestation.

Discussion

Marijuana, although listed as a controlled substance by the FDA, it is legally available in the USA for medicinal use and even as recreational use by many states. Recent surge in legalizing Marijuana in many states with a public belief that it is safe to use but on the contrary the data are accumulating that it is harmful. Its use and abuse by women of child-bearing age,[7,8,9,10] women who are planning to get pregnant, who are pregnant and lactating women is of great concern since the end product of Marijuana (THC) and other metabolic toxins easily crosses the placenta at all stages of pregnancy and may have known and unknown effect on the developing fetus. In addition THC is also excreted in the breast milk of lactating mothers and continuation of the breastfeeding while using marijuana may result in accumulation of the drug in the newborn body fat resulting in high blood level which affects the developing brain of the newborns and the children as they grow. One study showed that 20% of pregnant women less than 20 years old were positive for Marijuana (THC) and also anticipated that this number may be doubled if routine screening is instituted instead of self-reporting. In our study we mostly depended on self-reporting but also used risks identified in the prenatal and intrapartum period to test urine for illegal substances. We have identified 168 mothers positive for THC or a combination of other substances (Table 2). Of these 84.5%

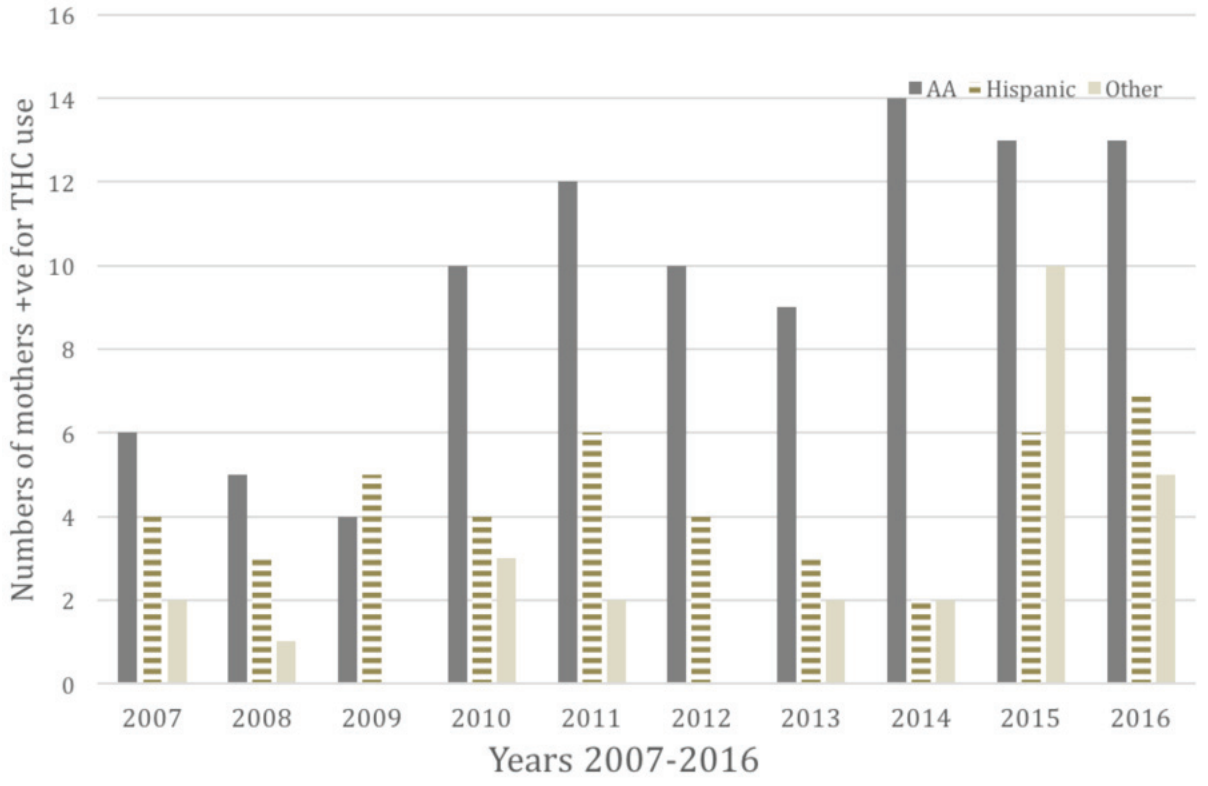

Figure 1. Yearly Pattern of THC Use of Races

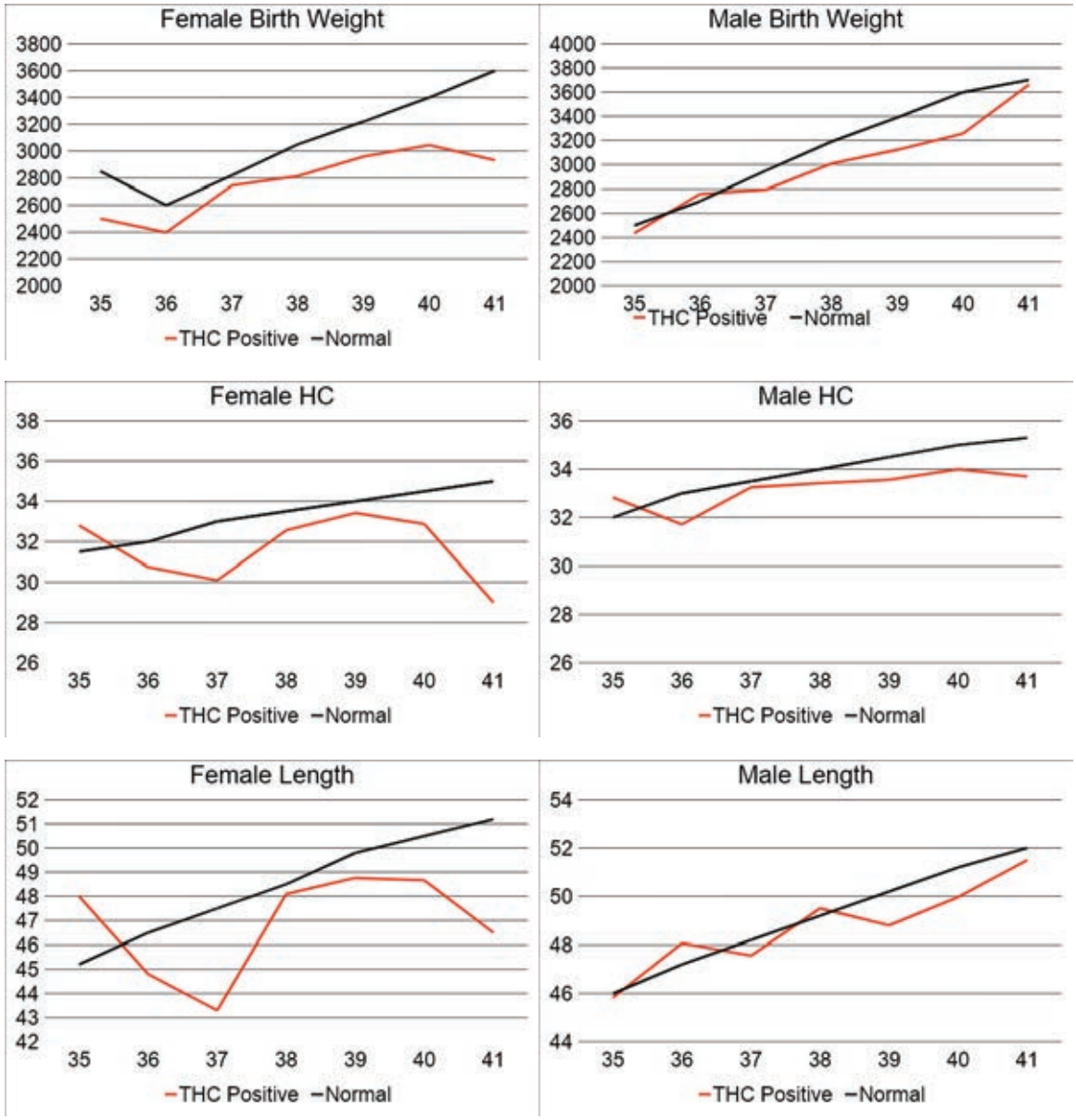

Figure 2. Birth weight, Head Circumference and Length

were positive for THC alone. Interestingly only one third of infants of mothers who tested positive for THC were positive on urine drug screen which indicates that most of our pregnant women were casual users with occasional smoker and showed no evidence of addiction to drug unless associated with multiple drug use. We did not see any women using prescribed or street opioid drugs which are epidemic in the Country. The incidence of Marijuana use was also low in our population, but its use is steadily increasing from year to year (Figure 1). The maternal characteristics as shown in the table noting predominantly African-American population with 55.3% of all drug use, sexually transmitted diseases with 34 % and psychosocial issues 7%. Most of the marijuana users received prenatal care though inconsistently, whereas associated multiple drug users were rather none or irregular prenatal visits. 5 of 168 mothers delivered extramural births. The gestational age less than 36 weeks was higher with 26%. The infant characteristics included birth weight, head circumference, and length which are shown in the graph. It has been reported that marijuana either alone or in combination with other drugs have adverse effects on the birth parameters with some neurobehavioral signs and symptoms manifested at birth.[7,8,9] In our study, there was a trend of all the birth parameters (weight, length, and head circumference) lag behind after 35 weeks gestation, although it is consistent with the published data. Our numbers were low for any evaluation and more data are required to make conclusions. 7% of our study population who were exclusively breastfeeding since it was encourage to breast feed given our hospital's designation as a Baby Friendly Hospital. Recently Bertrand et al[11,15] evaluated 50 women's breast milk who were on Marijuana and found that the THC was present in breast milk at varying levels up to 6 days after the last dose was used.[14] AAP caution all clinicians to advise mothers to abstain from Marijuana use while breastfeeding. Recently ACOG in its official committee opinion reports stated that women who are pregnant or are contemplating pregnancy should be encouraged to discontinue Marijuana use.[13] They also stated that in the absence of sufficient data, all women who are breastfeeding should discontinue Marijuana use. In our study, all the mothers were evaluated by Medical, Social and Nursing Service and most of the marijuana using mothers were cleared

to take the infant home with visiting nurse service, whereas large number of babies of multiple drug users (15 out of 26) were reported to Child Protection Service (ACS). There was only one infant who died (extremely immature less than 23 weeks gestation and less than 500 gms birth weight); the rest of the infants did not have any evidence of structural anomalies.

Conclusion

In conclusion, Marijuana is freely available, largely grown in the USA, and is likely used and abused by women of child bearing age. The data are limited but consistent that it may have some effect on the physical, psychological and developmental effect on the fetus and the newborn. Until further larger studies and more data are available, it is safe to follow the recommendation of AAP and ACOG to caution its use to pregnant and/or breastfeeding women. We have adapted these recommendations to counsel women on potential harmful effect of Marijuana use at our institution.

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Fentanyl Use in Less Than 1000 Grams Premature Infants

Shabih Manzar, MD and Nitin Walyat, MD

Use of opioids is now a national epidemic.[1] Its use in the neonatal intensive care unit (NICU) is further complicated by immaturity of neonatal neurodevelopment system, especially in preterm infants. When used in neonates, side effects include longer duration of mechanical ventilation, longer time to first meconium passage, and higher mean airway pressure levels.[2] Higher cumulative fentanyl dose in preterm infants correlated with a higher incidence of cerebellar injury and lower cerebellar diameter at term equivalent age.[3] Recently, Ancora et al[4] in a two year follow-up study on premature infants exposed to fentanyl, demonstrated a significant decrease in eye and hand coordination skills.

We took a quality initiative to look at the utilization of fentanyl in the high-risk population of extreme low birth weight (ELBW) premature infants in our level III NICU. The data were extracted electronically using the electronic health record software, EPIC Hyperspace, which we adopted in October 2018. All infants with birth weight less than 1000 grams, born between October 1, 2018 and May 30, 2019, were included in the audit. A computer search was generated and medical record numbers were obtained. Using the electronic health record software, EPIC Hyperspace, individual records of infants was accessed. Using the chart review tab, medications tab is accessed and then using filter 'fentanyl' was selected. The number of doses was recorded in numerical fashion. Total doses were counted (see Figure 1, case 4 is used in this example).

There were nineteen ELBW admitted during the audit period. The mean gestation age was $26^{3/7}$ (range $23^{0/7}$ to $28^{6/7}$) with the mean birth weight of 711 grams (range 345 to 970grams). Out of 19 infants, nine (47%) received no fentanyl at all. Twenty six percent (5 out of 19) received one dose while one infant received 3 doses, one received 6, one 18, one 38 and one 42 doses (Figure 2). A total of 112 doses were consumed in 8 months giving a figure of 14 per month.

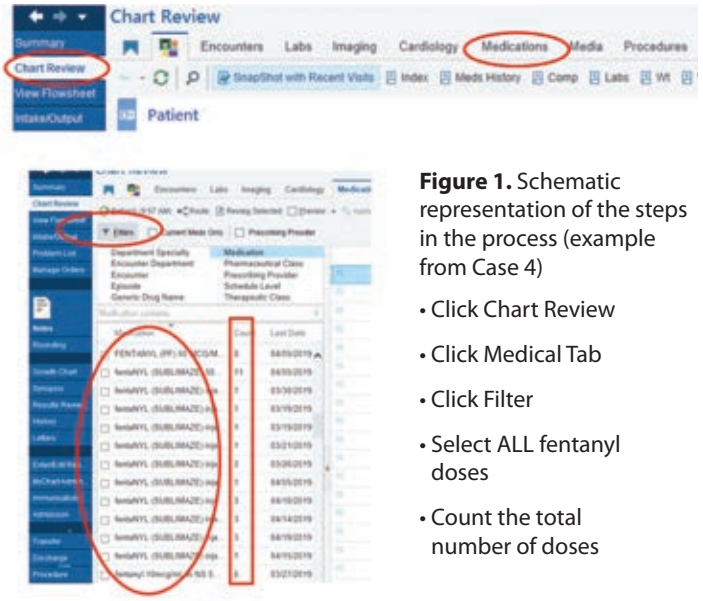

Figure 1. Schematic representation of the steps in the process (example from Case 4)

- Click Chart Review
- Click Medical Tab
- Click Filter
- Select ALL fentanyl doses
- Count the total number of doses

Discussion

Opioids are commonly used in neonates undergoing mechanical ventilation.[5,6] The use of analgesics is on the rise. Kumar et al[7] observed 9143 doses of parenteral analgesics with 19% use of fentanyl in their cohort of 2304 newborn infants. Similarly, Shah et al [8] studied a large cohort of infants born ≤28 weeks in the Canadian Neonatal Network and reported 7.6% of opioids use in NICUs. In our cohort, the majority of ELBW infants (73%) received only 0-1 dose, which was reassuring but the higher ranges use was alarming.

The limitation of our audit was the short time period due to non-availability of the EPIC software before October 2018. On detailed review of the cases with 18, 38 and 42 doses, it was noted, that these infants had prolonged ventilation and their Premature Infant Pain Profile (PIPP)[9] scores were greater than 12 requiring pharmacological intervention per our unit pain control policy (Appendix 1). We were able to collect base line data for our quality improvement project. The total use of fentanyl was 112 doses (ie 14 doses per month), to see a 20% change our target would be bring it down to 11 doses per month.

In addition to the issues with safety, adverse drug reaction and long term neurological problems with fentanyl, the other aspect is the cost. In a recent study Abushanab et al[10] reported high cost associated with the use of fentanyl in their NICU. We did not look at the cost involved with the use of fentanyl.

Basing on our preliminary data, we are planning a prospective QI project to look at fentanyl use and associated cost in our NICU. Our QI target would be to see a 20% reduction in fentanyl use in next 6 month of Plan-Do-Study-Act cycle.

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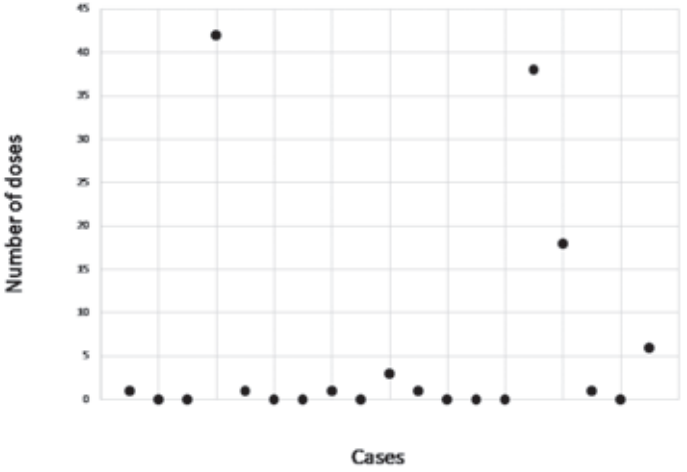

Figure 2. Fentanyl use in <1000 grams infants

In summary, based on our NICU audit, the fentanyl use in ELBW infants varies widely with most infants receiving 0-1 dose. Further investigation is needed to look at the fentanyl usage variability and associated cost in ELBW infants.

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Appendix: NICU Pain Management Procedure Protocol

What could happen if pain is left untreated?

1. Increase morbidity
2. Increase length of stay in the NICU
3. Exaggerated responses to pain later in life
4. Altered psychosocial effects – such as, hyperglycemia, increased oxygen consumption, decreased gut motility, increased heart rate and blood pressure
   (AWHONN Assessment and Management of Acute Pain in the Newborn; Anand, Hansen, & Hickey, 1990; Anand, 1993; Fletcher, 1987)

Pain Assessment

1. Include consideration of postmenstrual age or gestational and postnatal ages and neurobehavioral development, physiological changes associated with pain and stress, and physical indicators of pain.
2. Postmenstrual age includes gestation and chronological ages. PMA can be used if pre- (GA) and post- (CA) has same/similar effect on adaptation/response to pain.
3. For all patients, pain assessment is preformed and documented is performed by RN as soon as possible and definitely within eight hours of admission.
4. Premature Infant Pain Profile (PIPP) will be used to assess pain for all neonates in the NICU.
   Score ≤ 6 – minimal to no pain
   Score 7-11 – mild to moderate pain
   Score ≥ 12 – moderate to severe pain
   *Absolute scores should also be interpreted based on the neonate's pain response.
   a. PIPP score of ≥7 the physician should be notified and pain reassessed at least every 1-2 hours or more often by a RN.
   b. Post-operatively or post-procedurally pain should be assed every 15 minutes for 1 hour, then every hour for 5 hours. If warranted by the neonate's condition, assessment and scoring should continue every 1-2 hours.
   c. Once the neonate has minimal to no pain for a period of 6-8 hours, as indicated by a PIPP score of 6 or less, the RN will then reassess the neonate for pain at least once every 3-4 hours and as warranted by the neonate's condition.
   d. All reassessments and interventions are documented in the medical record. Documentation should also include interventions that improve and/or worsen pain.

Non-Pharmacologic Options

1. Non-Nutritive Sucking – using pacifier and/or sucrose 24%
2. Facilitated Tucking – holding infant's extremities close to the body in flexion/midline/containment
3. Swaddling – blanket wrapping extremities close to body, hands to mouth in flexion/midline/containment
4. Music – >31 week gestational age
5. Olfactory & Multisensorial Stimulation – massage (tactile) and breast milk or vanilla scent (olfactory)
6. Kangaroo Care & Maternal Touch – Infant with skin to skin contact with parent
7. Cluster Care – Group painful/over stimulating procedures together

Pharmacologic Options

1. Medications to preventive or minimize pain – Lidocaine 4% (LMX) cream
2. Mild to moderate pain – Acetaminophen PO, Ibuprofen PO (if > 6 months old), Morphine IV
3. Moderate to severe pain – Fentanyl IV, Morphine IV

Diaper Rash: An Early Indicator of Gut Dysbiosis

Tracy Shafizadeh, PhD

Diaper rash is a common occurrence during infancy, with an estimated 50% of all infants in a pediatrician's practice experiencing this condition at some point in their diaper-wearing years.[1] Although diaper rash itself is not usually harmful, emerging data now suggest that diaper rash may be an early indicator of gut dysbiosis, or an overgrowth of pathogenic bacteria in the infant gut. Gut dysbiosis has been linked to many autoimmune and allergic disorders later in life and recognizing diaper rash as symptom of this condition may allow for early and effective intervention during the window of immune development during the first few months of life.[2,3,4]

Current recommendations for preventing diaper rash usually include keeping skin dry and limiting prolonged exposure of skin to urine and feces.[5] However, a common misconception around the development of diaper rash includes the role of pH. Diaper rash is caused in large part by an elevation in skin pH, rather than a more acidic pH as commonly believed. In 1955, the average pH of the perianal skin in breastfed infants was reported to be between 5.3-5.5.[6] However, prolonged exposure of the perianal region to urine and feces leads to a more alkaline pH, increasing the risk for diaper rash.[7] Fecal pH also plays a significant role in the development of diaper rash, in that fecal enzymes, which are activated by elevated pH, have a direct irritant effect on the skin.[8]

Historically, breastfed infants were found to have an average fecal pH of ~5.0, and this was thought to explain the lower incidence of diaper rash in breastfed infants previously observed.[9] Indeed, human breastmilk contains specific carbohydrates, called human milk oligosaccharides (HMO), which promote the growth of lactic acid producing bacteria in the infant gut. Specifically, *Bifidobacterium longum* subsp. *infantis (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.[10] 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 stool pH.[11]

Safe and effective colonization of *B. infantis* in the infant gut has now been demonstrated through feeding the probiotic strain *B. infantis* EVC001 to term, breastfed infants.[11,12,13] Please see sentence restructure: 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 from 5.9 to 5.1.[12] A recent survey of consumers giving *B. infantis* EVC001 to their infants, marketed under the brand name Evivo®, showed that 70% of parents observed a reduction or resolution of diaper rash within one week of product use. In addition to the reduction in pH and improvement in stool consistency, infants who received *B. infantis* EVC001 also showed an 80% reduction in gut pathogens associated with autoimmune and allergic conditions later in life. Together, these results indicate that restoration of the infant gut microbiome with *B. infantis*, and subsequent reduction in both frequency and pH of the stool, may be an effective way to address the underlying gut dysbiosis as well as manage the biochemical factors that precede the onset of diaper rash, rather than waiting to treat the skin topically once diaper rash has occurred.

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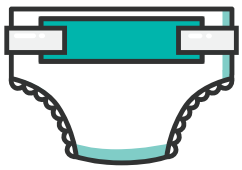

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The Next Generation in Hyperbilirubinemia Management: A Call for Accurate Point of Care Bilirubin Measuring Tools

Deepakshyam Krishnaraju, MSc, ME and Sivakumar Palaniswamy, MSc, BME

Background

Neonatal hyperbilirubinemia (newborn jaundice) is one of the most common physiological manifestations in newborns:[1-3] Hyperbilirubinemia presents itself in 60% of term neonates and in 80% of preterm neonates.[5-6] It is the primary reason for high readmission rates[4] due to its onset 2-3 days after birth, often after a neonate has been discharged from the newborn nursery. Although modest levels of hyperbilirubinemia are usually benign, reflecting the physiological maturation of the neonate's hepatic system, incorrect or delayed diagnosis could lead to bilirubin-induced neurological dysfunction (BIND). In some cases, it may lead to severe brain damage like cerebral palsy or kernicterus.[7-8] The clinical risk factors for BIND include prematurity, rapid rate of bilirubin rise (usually associated with isoimmune hemolysis), birth asphyxia, sepsis, hypoalbuminemia, and temperature instability.[29]

In the current healthcare environment which encourages a decreased hospital stay,[9] neonates face a greater risk of readmission for a number of reasons. Therefore, diagnostic assays for bilirubin should be adjusted in order to achieve accurate measures of bilirubin, reduce time to appropriate intervention, and prevent the development of chronic hyperbilirubinemia. An easily accessible, low cost, and accurate assay for bilirubin is essential for proper intervention to prevent the development of severe hyperbilirubinemia, especially with an increasing number of babies being discharged early. A system pairing efficient execution with well-defined quality metrics is the rationale for tackling the prevailing high readmissions due neonatal hyperbilirubinemia.

Inefficient Jaundice Management: Misaligned Priorities in the US Healthcare System

To better understand the need for an easily accessible, low cost, and accurate assay for bilirubin, it is important to first understand the root causes for higher readmission rates. Some of these causes (stemming from misaligned priorities in the current healthcare ethos) that trickle down resulting in inefficient jaundice management are discussed below:

Defensive Practice: The current US healthcare system faces a chronic misalignment of resources and priorities. The current medicolegal system has placed considerable pressure on practicing neonatologists and pediatricians, collectively leading to defensive testing practices. Physicians employ these conservative practices as lawsuits involving newborns sustaining peripartum neurologic injury can result in an average indemnity payment of $440,379, which may or may not be covered by malpractice insurance.[13] One survey of physicians practicing in "high-risk" fields such as obstetrics found that 93% practice defensively some of the time or frequently.[23]

Rising Administrative Costs: Healthcare in the United States is not focused on prevention, but on a reactive response to disease. Subsequently, this approach to care (and the associated administrative costs) has contributed to higher newborn mortality rates than most of the industrialized world.[11,12] For example, of the $2.9 trillion spent on healthcare in 2009, $765 billion was considered "waste"; this included categories defined as unnecessary services ($210 billion), excessive administrative costs ($190 billion), inefficiently delivered services ($130 billion) and fraud ($75 billion).[26] Furthermore, physician and ancillary service expenses continued to increase even when median inpatient admissions declined.[21] Although the US spends more on healthcare than any other nation in the world (18% of gross domestic product),[21,27] the newborn mortality rate in the US was higher than that of Cuba; the overall outcome and life expectancy in the US is ranked much lower than most developed nations.[10]

Ineffective Cost Savings Strategy: The cost of healthcare in the US per capita is the highest in the world.[28] This is a direct consequence of several misaligned priorities, as noted earlier. While much of the cost burden is created by chronic disease management in older demographics, costs related to neonatal care is also significant. The average length of stay for later preterm newborns is an average of 3.3 days at a cost of $7200, whereas younger preterm neonates have an average stay of 6.3 days at a cost of up to $202,700.[20] Overall, costs vary inversely with birth weight and gestational age. To survive in an environment with progressively lower reimbursement rates from both Medicare/Medicaid and private insurers, hospitals have started adopting cost containment strategies, resulting in a shorter than average length of stay for patients. For neonates, early discharge reduces the ability to effectively screen for hyperbilirubinemia. The burden of screening moves to the outpatient setting, which has much more variability in patterns of care and available services. These factors ultimately result in higher risk for readmissions due to hyperbilirubinemia.[14] Based on analysis of obstetrical records (which contained no clinical indication for late preterm delivery) it is suggested that patient and provider convenience are contributing to

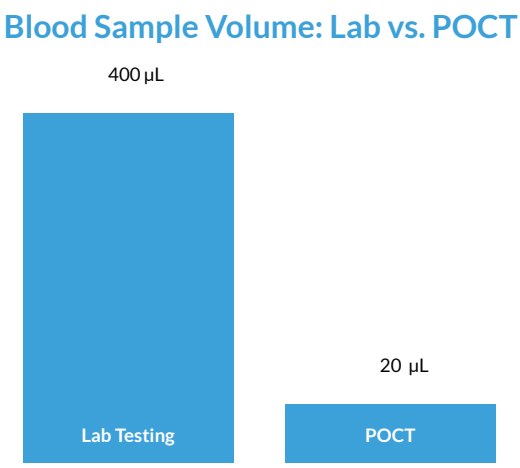

Figure 1. Blood Sample Volume — Lab-based testing vs POCT device

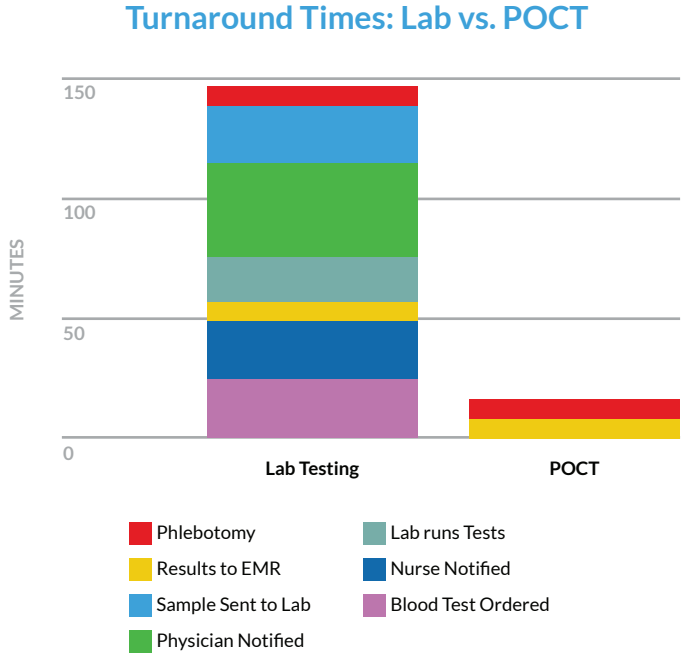

Figure 2. Time to Treatment — Lab-based testing vs POCT device

the increasing rate of late preterm delivery.[15] Late preterm deliveries make up a majority of preterm births and as such, face increased risk of complications.[16] Potentially avoidable preterm births accounted for 17% of late preterm birth (34-36 weeks of gestation) in one study;[17] another study suggested that unequal (higher) distribution of delivery occurs on Fridays among late preterm neonates.[18] Cost containment strategies implemented by healthcare facilities have been rendered ineffective by these trends, as the cost of care has increased with greater numbers of late preterm newborns admitted to special care nurseries or the NICU (neonatal intensive care unit).

Sectors of the healthcare community have now recognized that use of innovative technologies can be used to overcome barriers blocking access to care and improve care efficiency, while simultaneously reducing costs. Developments in healthcare IT and digital health are attempting to tackle avoidable admissions and readmissions, medical errors, defensive practice patterns, clinician and patient communication deficiencies, and bloated administrative services. Point of Care Testing (POCT) is one of several technological advances that have the potential to reduce operational inefficiencies and improve patient monitoring along with diagnostic accuracy. It can empower clinicians to quickly access critical laboratory values at the bedside, meaning time to diagnosis and appropriate treatments are minimized, and complications of delayed diagnosis are reduced. The subsequent downstream cost savings per patient cannot be understated.

Impact of Blood-based POCT on Hyperbilirubinemia Management in the NICU

Empowering Clinicians to Make More Confident Treatment Decisions: The emergence of clinical signs of hyperbilirubinemia depends on the rate of bilirubin rise, duration of hyperbilirubinemia, host susceptibility and presence of comorbidities.[30,31] As a result, the recommended methods for assessing hyperbilirubinemia include the measurement of total serum bilirubin (TSB) and/or transcutaneous bilirubin (TcB). These values, when plotted on a standardized hour-specific nomogram, can risk stratify a neonate and indicate need for treatment of hyperbilirubinemia. The premise of using this nomogram relies on bilirubin values being accurate.

The noninvasive nature and quick turnaround time of TcB have made it a good substitute for TSB in order to reduce the total amount of blood draws in neonates. However, the use cases for TcB are limited due to unreliable readings in the following scenarios: during phototherapy or exposure to sunlight because of the bleaching effect of light on the skin, confounding effects of skin melanin content among different ethnicities, and nonlinear deviation of TcB readings when bilirubin levels are greater than 15 mg/dL.[33] Therefore, tracking the efficacy of phototherapy continues to rely on total serum bilirubin levels. Since 1 in 10 neonates with jaundice achieve bilirubin levels >17 mg/dL,[32] TcB will likely underestimate bilirubin levels. It is common clinical practice that significantly elevated TcB levels are confirmed with serum testing. While TSB assays are accurate, they require up to 90 µL blood in currently available POCT systems and up to 0.4 mL in lab-based equipment per test. The TSB testing may need to be repeated every 4 to 12 hours depending upon the acuity of the newborn's condition. For those critically ill neonates in the NICU who require close monitoring of blood bilirubin levels, these blood draws are an immense burden. For a baby weighing 1 kg (2.2 lbs), the maximum blood draw limit per day is 2.5 mL, and 5 mL during a 30-day period;[35,36] any more could trigger the need for a transfusion. Current TSB assays can easily put neonates beyond the threshold for daily maximum blood draws.

An efficient POCT diagnostic device that requires minimal capillary sample blood volumes, similar to glucose meters in the neighborhood of 1 to 20 µL,[37] can empower clinicians to make quick treatment decisions with greater confidence. A follow-up test can be done straightaway when needed to double check the consistency of the results reported by a POCT diagnostic device. As a result, clinicians can still practice conservatively with minimal impact to the patient and at reduced cost to the healthcare facility.

More Efficient Patient Management: Patient encounter time can be classified into three categories: administrative time, diagnostic/care time and wait time.[33] Prolonged wait time can have implications on a patient's clinical status, especially in high acuity settings when there is a high probability of deterioration and requirement of additional procedures.[33,34]

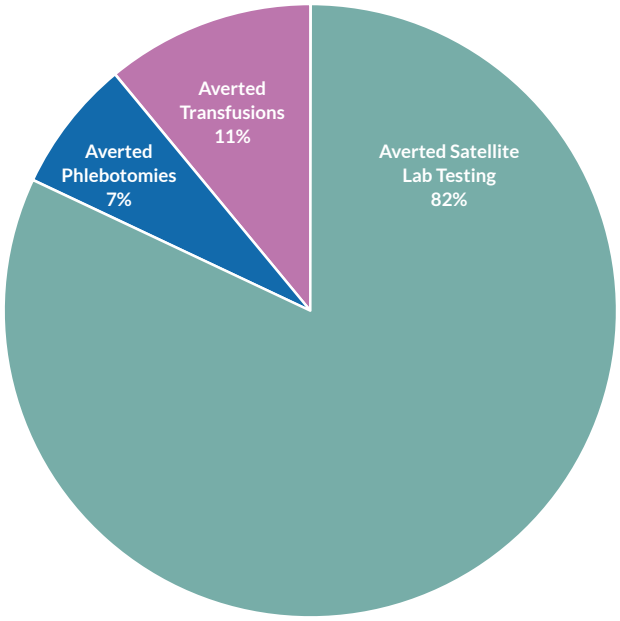

Figure 3. Percentages re ecting averted/saved costs using POCT technology25

A blood-based bilirubin POCT device, with a short TAT (turnaround time), can help reduce the waiting time between patient episodes. This means that clinicians can swiftly deploy evidence-based targeted interventions, such as phototherapy, before the need for an exchange transfusion, which involves considerable risks. Figure 2 shows a comparison between time to treatment using lab-based testing and a POCT system (135 mins vs. <15 mins). Additionally, these POCT devices increase patient satisfaction as the newborn and family do not have to wait for lab results performed in the central hospital lab (known to have wait times of approximately 2 hours) prior to discharge.

Decentralization of Blood Testing: A blood-based bilirubin POCT diagnostic device provides not only care efficiency to pediatricians and neonatologists, but also broadens the impact of visiting nurse services. According to guidelines published by the American Academy of Pediatrics,[29] every neonate discharged within 48 hours of life should have a follow up appointment 24-72 hours post-discharge. These checkups usually take place in a clinic where blood is drawn and sent to a testing facility. With the help of POCT devices, clinicians can determine bilirubin levels immediately rather than waiting for 24 hours, thereby identifying high risk cases without significant delay. This workflow particularly benefits resource-constrained settings where a patient's family must travel a significant distance to have pediatric-focused lab testing done.

Economic Impact of Blood-based Bilirubin POCT: Several factors influence the economic impact of POCT. These can be compared to the direct and indirect costs of routine laboratory analysis, with implications for economic impact on the quality and timeliness of care as mentioned above. The direct costs include the required staffing to run the tests, cost of reagents, equipment, and resources allocated to transport samples from clinical sites to affiliated laboratories. Indirect costs are associated with delays in time to results, diagnosis, and appropriate treatment, which in turn impact patient outcomes. Indirect costs are routinely much higher than direct costs.[24]

Healthcare facilities using POCT technology can leverage optimal cost savings by targeting indirect costs. Examples of this include reducing infant phlebotomy blood loss and blood transfusions, reducing preanalytical errors by decreasing blood sample exposure to manual manipulation, minimizing resource utilization, and decreasing time to diagnosis and appropriate treatment. This has been illustrated by a study[25] focusing on the effectiveness of neonatal point of care monitors on cost savings in the NICU. This single site study reported that compared to a specialized NICU satellite lab, which was already economically advantageous compared to a centralized lab, POCT may generate significant cost savings on critically ill infants weighing less than 1000 grams — the majority of the NICU demographic who require frequent measurement of bilirubin levels. The distribution of averted costs, which included phlebotomies, satellite blood testing, and transfusions is shown in Figure 3. It should be noted that most of the expense lies in the POCT equipment/rental cost which can be reduced with increased market availability and efficiently calibrated POCT units.

It can be argued that with broader use of POCT devices, an even greater impact will be felt in the outpatient setting. This technology is versatile enough to be used in outpatient clinics, in homes by visiting nurse services, and even in retail clinics. The impact on access and delivery of health care services is significant, especially for families with an at-risk newborn.

Conclusion

There is increasing pressure to reduce costs in the US healthcare system owing to the continual rise in hospital expenditures. This environment has resulted in facilities adopting aggressive cost containment strategies, with an emphasis on reducing length of stays and shifting diagnostic testing to the outpatient setting. As a result, this has strained the effective management of neonatal hyperbilirubinemia. Factors such as early discharge, variable access to pediatric ancillary services, and higher rates of premature birth have increased the risk for readmission of neonates for hyperbilirubinemia. In a high liability specialty like neonatology, this is very problematic and potentially costly. POCT technology has the potential to provide flexibility in diagnostic testing in a variety of clinical settings; however, there is a shortage of accurate POCT assays for bilirubin. These devices can positively impact the economic strain and scarcity of pediatric ancillary services in many facilities. Use of POCT technology can provide confidence to clinicians in their treatment decisions and facilitates the appropriate triage of patients. The immediate availability of accurate bilirubin values can create better efficiency in jaundice management by facilitating more timely intervention for neonates with jaundice — avoiding preventable complications from hyperbilirubinemia, eliminating unnecessary treatment costs, and reducing readmissions.

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Use of Initiation Technology to Proactively Reduce Risks of Delayed Lactogenesis and Sub-Optimal Lactation in Mothers of Term Infants

Jean Rucks Rhodes, PhD, CNM, IBCLC

Introduction

National efforts to promote breastfeeding have led to substantial gains in breastfeeding initiation rates, now at an all time high over 80%. However lactation duration rates continue to be less than optimal. The ability to initiate, build and maintain breast milk volumes sufficient to meet an infant's needs are dependent on complex interwoven factors. Hormonal shifts in the childbearing cycle drive pro-lactation breast changes during pregnancy and release barriers to lactogenesis after birth (also known as lactogenesis II or secretory activation). Post-birth hormonal changes are necessary but not sufficient for optimal milk production. Infant feeding behaviors have a critical role in determining lactation success, both related to timely onset of breast milk production within 72 hours and sufficient milk volumes to completely meet infant's needs.[1]

During the first few days of life, infant feeding behavior consists of short sucking bursts of varying intensities interspersed with long pauses. This early sucking behavior stimulates mothers' breasts for later milk production, indicating a unique synergy between mother and infant.[2-4] After the first two weeks, the key factor in maintaining breast milk production is frequent and sufficient removal of milk by breastfeeding or milk expression.[5,6] By that time, infants' sucking patterns have become two-phase to elicit milk ejection, then milk expression.

Many breastfeeding mothers are concerned they don't produce enough milk for their babies. Insufficient milk supply is a primary reason women give for discontinuing lactation, both in the early weeks and later months.[7,8] Historically, some of these concerns were attributed to delayed or insufficient breastfeeding, unrealistic maternal expectations of early milk production, and infant formula marketing encouraging the use of feeding supplements. In the last 10 years, nationwide breastfeeding advocacy programs within the federal government and by major health professional organizations have joined forces to promote comprehensive breastfeeding enhancement strategies, However, recent improvements in perinatal practices have not resolved the continued problem of sub-optimal lactation duration rates and mothers' continuing reports of "not having enough milk for my baby."

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Mothers who are unable to breastfeed

Mothers with hospitalized and/or preterm infants are at risk for delayed lactogenesis and suppressed lactation. They are more likely to have medical complications and operative deliveries and even if they did not plan to breastfeed, they are strongly encouraged to produce milk for their babies. These moms face several challenges, thus, numerous clinical protocols, best practices and national health policies specify strategies to support completely pumping mothers to provide milk for their babies.[1,9,10] Universally, lactation support of these mothers involves timely initiation of breast pumping.

Prevalent maternal risk factors for delayed lactogenesis/suboptimal lactation in mothers with term infants

Of the multiple maternal risk factors associated with delayed or suppressed lactation, primiparity, surgical delivery and BMI >27 are the most consistent and significant.[11-13] Trend lines show increases in all of these variables compared to 20 years ago. For example, the Department of Health and Human Services reports more than a third of U.S. births in 2015 were to first-time mothers. Additionally, U.S. cesarean section rates have been over 30% since 2005, and although declining slightly, they represent approximately one-third of all births.[14] Lastly, obesity is a national health crisis associated with multiple maternal/child morbidities. The following discussion briefly reviews these factors in relation to lactation outcomes.

Primiparity

A complete review of the literature on lactation risk factors exceeds the scope of this paper; however, discussion of several key findings will underscore the impact of selected variables. Of these, primiparity has one of the strongest associations with delayed lactogenesis (>72 hours postpartum), especially in primiparous women.[11-13,15] In a 2003 study of childbearing women, Dewey et al[12] reported 33% of first-time mothers experienced delayed lactogenesis compared to 8% of multiparas. Similarly, Nommsen-Rivers et al[13] found 44% of primiparas reported the onset of milk flow after 72 hours.

In these studies, multiple regression analyses reveal primiparity was the most significant risk factor for early milk production problems. Additionally, when lactogenesis was delayed, infants had a seven-fold risk of greater than 10% weight loss by day three leading to higher risks of dehydration, delayed meconium passage, higher bilirubin levels, greater infant readmission rates[12] and shorter duration of breastfeeding.[12,13]

Cesarean section

Several studies confirm unplanned surgical delivery is a significant risk factor for delayed lactogenesis and/or suboptimal breastfeeding.[11,12,16-18] Dewey et al[12] report a strong association between cesarean section and lactation delay: lactogenesis was delayed in 27% of women who had had scheduled cesareans and 56% of those with urgent cesareans. Likewise, Chapman and Perez-Escamilla found an 5.6 odds ratio (95% CI: 1.8-16.8) of delayed lactogenesis in women with unscheduled cesareans compared to a 1.4 odds ratio (95% CI: 0.5-4.4) in women with scheduled cesareans. High maternal cortisol levels, pain and elevated stress associated with operative delivery are believed to interfere with lactation initiation.

Maternal BMI and insulin resistance

Of all variables associated with delayed lactogenesis and suppressed lactation, perhaps the most studied is elevated maternal BMI. This astoundingly pervasive factor is highly correlated with premature delivery, operative delivery and glucose intolerance, all of which compound a mother's risk for lactation failure.

Without a doubt, the incidence of overweight and obesity in the US population is a national crisis that impacts all aspects of public health. At least half of childbearing women are overweight or obese before they become pregnant, with at least 50% gaining gain too much weight during pregnancy.[19]

According to Nommsen-Rivers,[20] Dewey et al,[12] and others,[21-26] there is a statistically significant, dose-response relationship between elevated maternal BMI, delayed onset of lactogenesis and/or shortened duration of lactation. In a recent systematic review by Garcia et al of 82 studies, obese women were found to have relative risks of breastfeeding initiation failure of 1.23 (95%CI, 1.03-1.47) and a delayed onset of lactogenesis (2.06 (95%CI, 1.18-3.61). As in other studies, these authors determined breastfeeding is jeopardized as BMI increases.

Furthermore, elevated BMI and obesity are known risk factors for glucose intolerance in pregnancy. Indeed, Riddle and Nommsen-Rivers[20,21] report any diabetes and/or insulin resistance in pregnancy is associated with a 2.6 fold risk of low milk supply within the first three months postpartum. Likewise, Matias et al report one-third of women with gestational diabetes has lactogenesis delay.

Collectively, documented risk factors for suboptimal milk production — primiparity, cesarean section, increased BMI and insulin resistance — present a daunting health care challenge for maternal-infant clinicians.

Solutions

Initiation technology

Traditionally, mothers most vulnerable for delayed lactogenesis or suppressed lactation were those who had to pump because their babies were premature or sick. Even with consistent standard breast pumping programs, average milk production in pump-dependent women was often lower than that of women breastfeeding healthy term infants. However, new breast pump initiation technology — designed to mimic normal newborn sucking patterns in the first few days of life — is able to mitigate this disparity.

The Symphony PLUS® breast pump with Initiation Technology™, which imitates irregular newborn sucking, decreases the time to lactogenesis in pumping mothers by an average of more than 24 hours.[3] When paired with a second pattern to maintain milk production once milk comes in, average milk levels exceed breast milk volumes of mothers using a standard pump pattern and approximate average milk volumes of breastfeeding mothers.[2-4]

Three clinical trials, referenced above, evaluate the effectiveness of Symphony PLUS with Initiation Technology varied in methodology and populations but had similar outcomes.

Although populations and methods were different, these studies yielded consistent and compelling results related to breastmilk production: pump-dependent mothers using Initiation Technology had:

- Onset of lactogenesis a day sooner than those using traditional pumping patterns
- Sustained milk production gains, producing ~65% more milk within the first two weeks.

If exposure to a pumping pattern that imitates normal newborn sucking behavior can positively influence lactation in women who can't breastfeed immediately and consistently after delivery (pump-dependent mothers), use of Initiation Technology might help other mothers who are breastfeeding but are at risk for delayed lactogenesis or suppressed lactation. First time mothers, those who have had cesarean sections, and/or those who have obesity or glucose intolerance might offset their risks by augmenting breastfeeding with breast stimulation designed to mimic a newborn infant's.

Timing of breast stimulation

Research related to timing of initial breast stimulation has focused on mothers of preterm infants. In 2012 Parker et al[27] conducted a randomized study of mothers of very low birth weight infants that suggested pumping within the first hour produces more milk than pumping one to six hours after delivery. Mothers who pumped within the first hour produced double the average daily milk volumes at one, three and six weeks. A later study by Parker and associates validated the importance of early breast stimulation.[28] Lastly, a 2017 abstract by Parker indicates NICU moms pumping within one-three hours of delivery the earliest onset of lactogenesis and were most likely to be lactating three to six weeks later.[29]

Closing Comments

Challenges

In many breastfeeding situations, interventions aren't started until a mother reports problems. By identifying mothers who at risk for suppressed milk production clinicians can intervene proactively. Many of these mothers may only need short-term assistance with breast pump Initiation Technology. Challenges to such interventions include timely introduction of breast pumping without interfering with new family development and the breastfeeding relationship. Additionally, thoughtful recommendations for breast pump use must consider mothers' risk factors, preferences, maternal physical condition and ability of the baby to adequately breastfeed.

Suboptimal breastfeeding continues to be a major public health challenge. While new evidence suggests several prominent

physical and demographic factors negatively influence lactation initiation and maintenance, little has been done to address these problems. **Risk factors included in the flow chart include:**

- Parity: Almost 40% of US births are to first-time mothers and up to 44% of these mothers are reported to have delay of lactogenesis (DOL).[13]
- Cesarean section: Approximately 1/3 of births are by C/S with a prevalence of DOL of 56% if the C/S is urgent.[12] Cesareans are often preceded by long, stressful labors and multiple medical interventions. In addition, multiparas having a primary C/S often have stressful adverse labor events.
- BMI: Elevated BMI, extremely common in childbearing women, is associated consistently DOL. In obese and very obese mothers, the prevalence of DOL is reported up to 58%.[25] Increased BMI is associated C/S and GDM.
- Insulin dependent gestational diabetes: Incidence of gestational diabetes (GDM) is ~23%[20] with 33% of these women having DOL.[24] The highest risk of suppressed lactation in women with GDM is in those with the most severe form, eg, those who are insulin dependent.[24] GDM as also associated with elevated BMI and C/S.

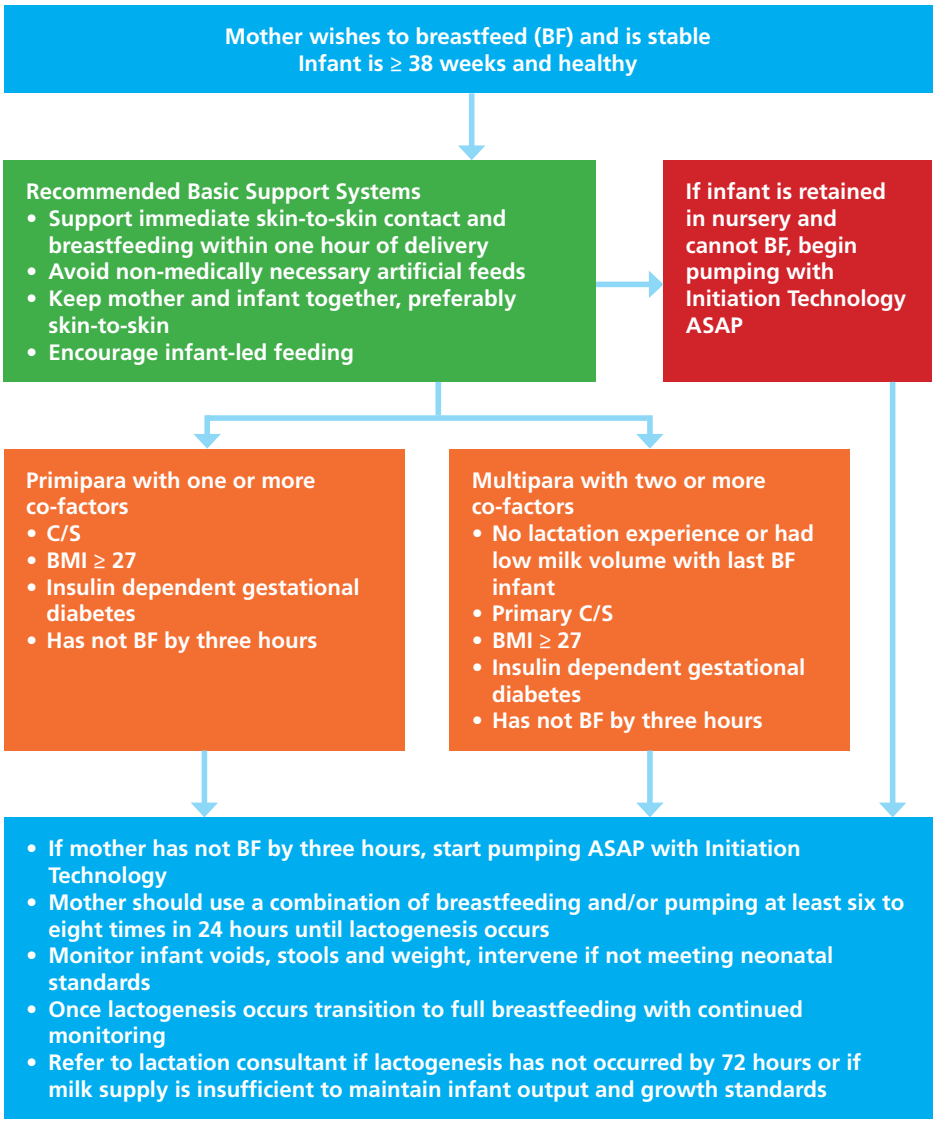
Additional notes

The goal of using Initiation Technology is to stimulate mothers' breasts with a sucking pattern proven to enhance milk production and its onset. In term mothers, the goal is to augment breastfeeding, not replace it. Early, consistent breast stimulation by infant and pump are, therefore, recommended for mothers who are highest risk. These interventions are proven safe and effective in women expressing milk for hospitalized infants.

Mothers with late preterm infants are well documented to have DOL and suppressed lactation due to infants' immature, less vigorous suck and reduced stamina. Any mother with a late preterm infant should augment breastfeeding as recommended by the flow chart for a primipara with ≥1 cofactor.

Mothers of infants who are unable to breastfeed due to infant immaturity, illness or medical observation should begin pumping with Initiation Technology within three hours of delivery, six to eight times in 24 hours. Further pumping decisions should be based on infant's ability to breastfeed. The following is a proposed flow chart to identify and support breastfeeding mothers who are at greatest risk.

Flow Chart for Use of Initiation Technology in Breastfeeding Mothers



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Maternal Fever, Fetal Tachycardia and Neonatal Depression

Shabih Manzar, MD

Abstract

A case of neonatal depression (ND) and severe acidosis (SA) is presented. In contrast to bradycardia associated ND and SA, the neonate had tachycardia at birth. The ND and SA observed were related to maternal fever and severe histological chorioamnionitis. The case presentation is followed by postulated mechanism and literature review.

Keywords: Chorioamnionitis, Fetal tachycardia, Neonatal resuscitation

Case

A male infant was delivered via vaginal delivery at $39^{3/7}$ weeks of gestation. Mother was a18- year-old G1P100. She had history of elevated blood pressures. Pregnancy medication included prenatal vitamins and no other medications. All her prenatal labs were negative including RPR, HIV and negative, hepatitis B, chlamydia and gonorrhea. Significant history revealed rupture of membrane of 19 hours prior to delivery, foul smelling amniotic fluid and fever with highest temperature of 102°F (38.9 °C). The cord blood gas showed severe acidemia (Table 1). Placental pathology showed no grossly visible lesions suggestive of infarct or neoplasia while histology showed stage 2, grade 2 chorioamnionitis.

Table 1. Cord gas results

	Cord Blood Arterial	Cord Blood Venous
pH	7.00	7.08
pCO2	50	39
pO2	26	36
HCO3	9.5	10.4
BASE DEFICIT	17.3	17.1
O2 Saturations	33.9	57.4

At delivery, the infant had no cry however the heart rate was good. Infant noted to have poor tone and poor respiratory effort. He was taken to warmer, dried, stimulated and bulb suctioned. He was then placed on continuous positive airway pressure (CPAP), oxygen saturations improved and infant was transported to neonatal intensive care unit (NICU). Apgar score was 5 and 8 at 1 and 5 minutes respectively. In the NICU the infant, while on CPAP, developed seizure and was placed on hypothermia therapy. Infant's physical examination was significant for tachycardia and abnormal muscle tone. Vital signs showed a temperature of 100.9 °F (38.3 °C) and heart rate of 191 beats per minute.

Discussion

As per the Neonatal Resuscitation Program (NRP) a rising heart rate is an indication of well being.[1] Fetal bradycardia and deceleration are well known to be associated with fetal acidemia,[2] however fetal tachycardia is not viewed as a risk factor for fetal acidemia and later neonatal depression. The exact mechanism of fetal tachycardia resulting in acidemia is unknown, however, it could be postulated that tachycardia increases the oxygen demand of the fetal heart leading to hypoxia. Persistent hypoxemia then generates lactic acid and causes shift in the buffer system resulting in acidemia. Tachycardia and cardiogenic shock resulted in acidosis has been reported earlier.[3]

Recently Toomey and Oppenheimer[1] showed an association between fetal tachycardia and acidemia. By using logistic regression model, they found tachycardia point estimate of 3.4 (95% CI 1.14-10.14). However, the association of degree of tachycardia with the severity of acidemia was not mentioned in the study. On careful observation of fetal heart rate (Figure 1), we noted a 20-25 minutes of significant tachycardia before birth that very well corresponded to the severe acidosis noted in the cord blood gas; pH of 7 with base deficit of minus 17.

The mechanism of fetal tachycardia secondary to maternal fever and chorioamnionitis could be explained with reference to the study by Romero et al.[5] A cytokine mediated fetal inflammatory response is initiated in response to chorioamnionitis. This response may have potential role in fetal hypoxia and acidemia reflected in the cord blood gas. This needs further investigation.

In conclusion, association of fetal tachycardia and significant acidosis, as seen in the case presented, highlights on the importance of monitoring fetal cardiac status during delivery. A high heart rate at birth could give a false sense of security in cases of maternal fever and chorioamnionitis and therefore should be viewed critically.

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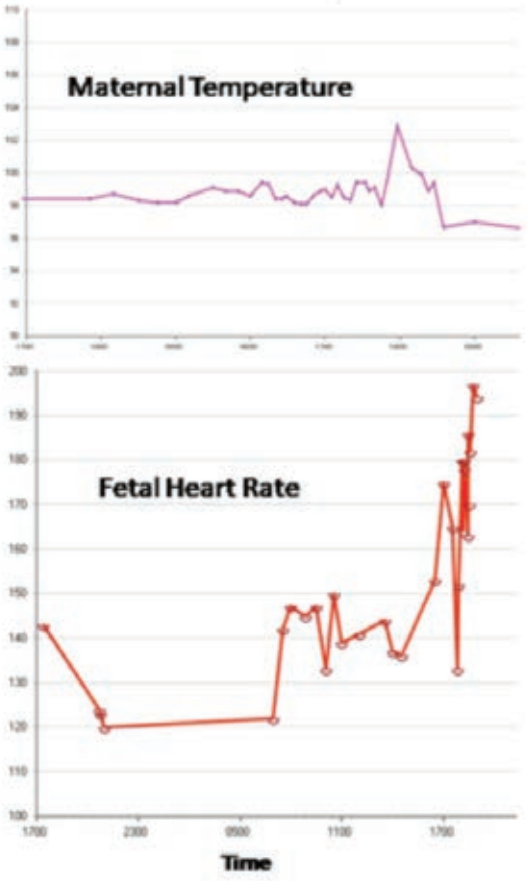
Figure 1. Association of Fetal Tachycardia with Maternal Fever



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Neonatal Skin and Wound Care: Preventing Skin Injury

Hy-Tape International, Inc.

Infants pose a major challenge for wound care professionals. Because neonatal skin is immature and thin compared with adult skin, it is more easily damaged and requires greater care.[1] This makes it critical that health care professionals follow specialized best practices when caring for neonatal wounds to minimize skin damage and ensure optimal outcomes for patients.[1,2]

Challenges of Neonatal Skin and Wound Care

Neonatal skin presents several unique challenges that make wound care more difficult. Skin has only fully developed at the 34th week of gestation, meaning that the skin of newborn infants is immature and much weaker than the skin of older children or adults. The dermis of neonatal infants may have less collagen and elastin fibers than that of an adult or older child, thus increasing the risk for edema, pressure injuries, and other tissue injuries.[1-3]

This problem is exacerbated in premature infants, whose skin may not be fully developed. In full-term infants, the outermost layer of the skin (stratum corneum) is between 10 and 20 layers thick; however, in premature infants, it may be less than two layers thick. This means that the skin is much more easily damaged, and critical functions, such as control of transepidermal water loss and prevention of absorption of toxic substances, may be compromised.[3]

Best Practices for Preventing Skin Injury

Identify At-Risk Patients

A wound care patient is inherently at greater risk of skin injury than a patient without a wound. Many skin injuries are caused by the application or removal of wound dressings or medical equipment. Neonates who are acutely ill are at an even greater risk. Infants born at less than 32 weeks are at extremely high risk for developing pressure injuries and other tissue injuries. It is essential that health care professionals take extra precautions with these at-risk individuals and regularly screen them for skin damage.

Identify Early Signs of Skin Damage

It is critical that health care professionals recognize when neonatal patients have early erythema because skin damage can progress much more quickly to pressure injuries or other more serious injuries when compared with adults. Reddening,

temperature differences, or pain can all be early signs that patients are at risk of skin damage. This can lead to partial- and full-thickness loss in the dermis and result in serious wounds. To prevent these issues, it is essential that health care professionals address skin damage early on.[3]

Regularly Cleanse and Reposition

Cleansing the wound area is important for preventing skin irritation and damage from wound effluent or incontinence. Dead tissue and foreign debris should be regularly debrided to prevent the growth of pathogenic organisms, and sterile saline solution should be used to cleanse the wound area. Wound areas that are subject to pressure or friction should also be positioned to prevent the formation of pressure ulcers.[2]

The Importance of Secure Wound Dressings and Gentle Adhesion

One of the most common causes of skin injury in neonates is medical adhesive. Weak neonatal skin can be irritated or damaged by harsh or excessively strong adhesives. This makes it critical that health care professionals use a gentle medical adhesive with infants. It is also important that the adhesive be secure and waterproof, to prevent incontinence or other foreign debris from reaching the wound area.[2]

Conclusion

Neonatal skin is immature and thin, is more easily damaged than adult skin, and requires special care to prevent skin injury. Injury prevention includes risk identification, monitoring for early signs of skin damage, regular cleansing

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and repositioning, and the use of an appropriate medical adhesive to secure dressings.

About the Company

Hy-Tape International offers high-quality adhesive tape and has served the market for over 70 years. Tapes are available in strips, patches, and kit rolls giving health care providers a wide range of options for securing dressings and devices. Free product samples are available at www.hytape.com or by calling 1-800-248-0201.

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Intrapulmonary Percussive Ventilation: An Overview

Morgan Meyers, BSRC, RRT, RRT-NPS, RCP and Joshua Gonzales, DHSc, RRT, RRT-NPS, RRT-SDS, RCP

Abstract

Intrapulmonary percussive ventilation (IPV) therapy is a safe and efficient options for patients requiring bronchial hygiene therapy, hyperinflation therapy, and patients receiving bronchodilation therapy. As a practitioner, it is important to understand the wide array of clinical applications IPV therapy can provide for patients ranging from neonatals to adults. Similarily, it is important to understand the benefits of using IPV therapy in conjunction with mechanical ventilation, ECMO, and chest percussion therapy. The purpose of this manuscript is to provide an overview for IPV therapy for clinical application to patients of all ages.

Key Words: intrapulmonary percussive ventilation, pulmonary clearance, lung recruitment, secretion mobilization

Introduction

Intrapulmonary percussive ventilation (IPV) was originally proposed by FM Bird in 1980s.[1] IPV delivers rapid, high flow, small tidal volume burst of gas into the airways to promote airway clearance, recruit areas of the lung, and improve pulmonary gas exchange.[2-4] These oscillations are created by a unique sliding venturi mechanism, the phasitron.[5] IPV can be superimposed on spontaneous breathing or mechanically ventilated patients via invasive and noninvasive interfaces.[2,6-8] When conventional therapies have failed, this modality is extremely effective for patients with chronic lung disease, neuromuscular impairment, neurological disorders, and postoperative patients.[2,4,9]

Indications, Contraindications, And Hazards

IPV is indicated for the mobilization of endobronchial secretions, bronchodilation, and atelectasis.[8,10-12] IPV provides many positive effects including lung recruitment, mechanical bronchodilation, improved functional residual capacity, improved breathing pattern, decreased work of breathing, and increases secretion mobilization.[10,11] This therapy would be beneficial for patients who are requiting increase oxygen or have atelectasis necessitating recruitment.[10] Finally, it can be used for patient who could benefit from clearing debris and mobilizing secretions.[10] This technique can be utilized in neonates, pediatrics, and adults in both acute care and long-term treatments. IPV can be applied via an artificial airway or natural airway in conjunction with a mask or mouthpiece. It is beneficial to use a mask for patients who cannot follow commands or lack the ability to create and efficient seal around the mouthpiece for the duration of the treatment.

IPV is contraindicated for the uses in the presence of untreated tension pneumothorax and for patients with pulmonary hemorrhage[7,10,13]There are some relative contraindications (Table 1) in which IPV may be ordered at the physicians discretion. Inherent risks associated with IPV include under/over ventilation, pneumothorax, under/over humidification, pneumomediastinum, pneumoperitoneum, and hemoptysis.[10] If any of these occur treatments should be discontinued.[10]

Table 1. Relative contraindications of IPV

Relative Contraindications	
Recent gross hemoptysis[7]	Pulmonary embolism[7]
Subcutaneous emphysema[7]	Acute spinal injury[7]
Esophageal surgery[7]	Recent spinal infusion[7]
Empyema[7]	Tuberculosis[7]
Pacemaker[7]	Bronchopleural fistula[7]
Increased intracrainial pressures (ICP)[7]	Acute cardiogenic pulmonary edema[7]

A limitation of IPV is that is must be administered to trained individuals.[1,8] In the event that IPV is used with an artificial airway a clinician must be present at all times.[10] IPV evokes secretion clearance and may necessitate suctioning.[10] Suctioning should be performed as necessary because patients cannot breathe through an obstructed airway and alveoli cannot be ventilated when transmitting airways are obstructed.[10] The IPV must be properly calibrated or the clinical efficacy of the device may be hindered.[10]

IPV is typically a safe, well-tolerated therapy with no serious complications but there are some relative complications (Table 2).

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Table 2. Relative complications associated with the use of IPV

Relative Complications	
Intercostal pain	Pharyngeal reflexes (nausea, vomiting)
Dry mouth	Conjunctivitis (from mask fit)
Increased temperature	Headache (hyperventilation)
Desaturations	Muscle cramps (hyperventilation)
Dyspnea	Dizziness (hyperventilation)

Patient Selection

IPV can be performed on patients ranging from neonatal to adult.[13] When conventional therapies have failed, this modality is extremely effective for patients with cystic fibrosis, neuromuscular impairment, and chronic obstructive pulmonary disease (COPD).[1,8,13] IPV has also been proven beneficial the management of patients with chronic lung disease, muscle weakness developed in the ICU, obese individuals, and postoperative patients.[2,4,13]

Patients with cystic fibrosis suffer from an increased amount of tenacious mucus in their airways and lungs.[14] This can lead to recurrent infection and inflammation.[14] IPV provides a more homogenous distribution of alveolar ventilation which helps to unstick mucus and propel it to the central airways to be expectorated.[15] Pseudomonas aeruginosa causes infections in immunodeficient patients such as those with cystic fibrosis. Pseudomonas aeruginosa is difficult to treat because it has become resistant to most conventional antibiotics.[16] Additionally the pathogen biofilm provides bacterial cells a safe environment to avoid antibiotics.[16] IPV can provide shear stress to the lungs which will disrupt biofilms, altering the behavior of pseudomonas aeruginosa thus improving lung function.[16]

Neuromuscular disease can affect all respiratory muscles leading to respiratory failure.[17] Respiratory failure is the most prevalent contributor to morbidity and mortality in patients with neuromuscular disease.[17] Patients with neuromuscular disease often suffer from dysphagia, cough inefficacy, and severe bronchial congestion which could contribute to respiratory infections.[1,2,8,17,18] This causes impaired airway clearance.[19] IPV has been shown to non-invasively manage refractory pleural effusions, reventilate ateletatic areas of the lung, and aid in secretion evacuation in neuromuscular patients.[1,8,18] Additionally IPV has helped to improved survival of children with neuromuscular weakness.[19]

Chest physiotherapy, including IPV, enhances sputum evacuation in Chronic Obstructive Pulmonary Disease (COPD) patients.[5] Not only can IPV improve oxygenation in COPD patient's, it can improve activities of daily living, perception of dyspnea, and lung function in patients with severe COPD[20,21] This method has been proven more effective that high frequency chest wall osculation in improving pulmonary function test linked to the small bronchial airways obstruction and respiratory muscle strength as well as a reduction of sputum inflammatory cells.[20]

IPV therapy can be a beneficial modality of airway clearance in chronic lung patients.[22] For example, Bronchiectasis is often treated with medication, oxygen, and pulmonary clearance therapy.[23] IPV can help to mobilize phlegm and improve the sensation of dyspnea.[23] IPV has been proven to be as effective as traditional chest physiotherapy while evoking less discomfort.[23] Additionally the likelihood of respiratory illness is reduced for patients using IPV resulting in less antibiotic, steroid, and bronchodilator use.[22] In turn IPV decreased hospitalizations to acute care facilities.[8,12,22]

Chest physiotherapy is often used prior to surgery and postoperatively to prevent pulmonary complications.[5] Postoperative pulmonary complications occur in 5-10% of all surgical patients.[24] Not only do these complications consume a considerable amount of healthcare resources but are also associated with higher morbidity and mortality[25-27] Postoperative pulmonary complications include atelectasis and pneumonia as a result of increased minute ventilation, respiratory rate, CO_2 production and oxygen consumption, and decreased tidal volume.[5,27] Additionally, cardiovascular surgery can effect gas exchange making it difficult to manage postoperative patients during mechanical ventilator and after extubation.[27] Following surgery, sedation and pain can cause decreased cough efforts resulting in retained secretions and atelectasis.[28] IPV can help recruit lung tissue while aiding in secretion mobilization, resulting in fewer pulmonary complications.[4,27,29,30]

IPV and ECMO

In severe cases where patients suffering from Acute Respiratory Distress Syndrome (ARDS) are not responding to conventional therapy Extracorporeal membrane oxygenation (ECMO) can be used as a life support system.[13,24] ECMO is uses for a variety of diagnosis in patients from infants to adults. IPV has been a safe and useful modality when utilized in conjunction with ECMO.[31] This combination resulted in an improvement in lung compliance facilitating quicker weaning of ECMO settings and eventually liberation from ECMO.[31,32] When combined with ECMO, IPV has shown to reduce ECMO times in patients with acute respiratory distress syndrome (ARDS).[13]

Infants with severe pertussis infection suffer from infection-associated bronchiole obstruction, making medical management difficult, even in the presence of ECMO.[32] IPV is a modality that can be used to decrease respiratory muscle loading.[24]

Patients awaiting lung transplant can decompensate substantiating the need from lung bypass with ECMO.[33] While ECMO can preserve the patient's life it cannot clean out the lungs or recruit the lungs.[33] IPV can provide positive pressure to open the lungs while the turbulent and shear forces help evacuate mucus.[33]

ECMO can be used following in-hospital cardiac arrest which advanced life support has been unsuccessful.[31] These patients can be left with diffuse edema and atelectasis in the lungs. IPV can be used to deliver medications, mobilize secretions, and recruit atelectatic regions of the lungs.[31,34]

IPV and End of Life Care

End-of-life practices are variable because physicians are not always accurate at predicting patient's length of survival.[35] The decision to enroll in palliative care does not mean that care will be discontinued, curative and restorative care can be delivered.[35] Respiratory secretions negatively impact palliative patients.[36] These patients are often weak and have difficulty clearing secretion. Currently there is no gold standard for treatment.[36]

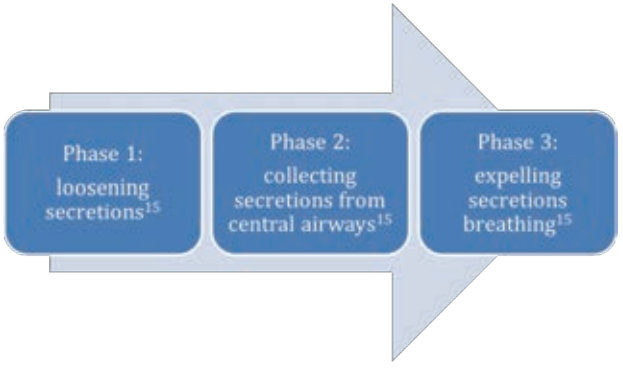
IPV was designated as one of the most promising treatments in palliative care for specific diseases.[36] Additionally IPV has been shown to help decrease the length of mechanical ventilation and ICU stay.[35] IPV can help to fulfill the goal of palliative care to prevent and relieve suffering of the patient while maintaining their quality of living during the terminal stages of their illness.[35]

For patients with end-stage lung disease lung transplantation is the only therapy that prolongs life and improves quality of life.[37] Donor availability is the main limiting factor, less than 25% of brain dead donors are considered for lung transplantation.[37] Making the decision to become an organ donor is an honorable task and has the potential to save many lives.[38] The process of organ procurement can take several hours, without proper care the organs will be lost. Donors must be managed with lung protective strategies including ventilator management, fluid balance, and pulmonary toilet in order to optimize lung function.[37] Due to neurologic injury donors are unable to clear secretions and are at risk for aspiration, substantiating the need for pulmonary clearance.[37] For patients who are failing conventional mechanical ventilation IPV may be utilized to improve ventilation and oxygenation.[38] IPV may be a safe and effective therapy to improve the number of organs available for transplantation.[37-39]

Mechanism of Action

The IPV is a pneumatic device, which delivers rapid, burst of air at rates of 80 to 400 cycles.[8,11-13,15,17,34,38,40,41] It can be driven by any 50-80psi gas source.[42] IPV delivers small pulsatile breaths by a piston mechanism, the Phasitron. The venturi effect entrains gas which is humidified by the nebulizer and pushes it through the Phasitron.[42,43] Each burst carries its own unique subtidal volume, adjusting to the patient's lungs.[3] The lower the compliance and higher the resistance, the less the sliding venturi will entrain.[3] Higher compliance and lower resistance allows for the venturi to entrain up to 4 times the ambient air to compensate for the low pressure.[3] The pulsatile flow generated from the Phasitron travels down the airways to the alveolar space where it quickly deceases into a gentle flow.[3] The pulsatile flow bathes the alveoli in oxygenated air while washing out CO2 and secretions.[3] The patient can inhale and exhale throughout the oscillating cycle. Medication may be nebulized during the duration of the treatment.[40] If no medication is indicated then saline or sterile water may be used.

IPV treats peripheral airway obstruction by mobilizing secretions, facilitating their removal.[2,4] IPV treatments consist of 3 phases:



Additionally IPV is efficient in treating disorders of ventilation by preventing and treating atelectasis.[2] IPV utilizes high frequency burst to deliver small tidal volumes of gases into the airways to mobilize and raise endobronchial secretions[13,15] These low tidal volume breaths have low pressure and high flow creating a positive transpulmonary pressure gradient.[13] The percussions recruit areas of the lung while carrying out CO2 and secretions with or without the patient's effort.[13]

The manufacture recommends a total treatment time of 20 minutes.[13] IPV can cause hyperventilation therefore the treatment time should be altered according to the patient population.[8,13] Although IPV can be used on the neonatal population it is important to proceed with caution. The IPV is efficient at blowing off CO_2, which may cause over ventilation in neonates, hindering their respiratory drive. Changes in CO2 levels, be it hypercapnia or hypocapnia, effects the cerebral blood flow of neonates, which can result in intraventricular hemorrhage.[44] Based off of this the IPV 2-C may be better suited for this population.

Devices

IPV-1C is a routine institutional IPV Flow Ventilator. The standard knobs for the IPV-1C are the master switch, operational pressure control, percussion, and manual inspiration (Figure 1.). The master switch turns the IPV on and off. The operating pressure (OP) is the pressure generated by the compressor.[13] Adjustments to the OP determine the flow rate feeding the Phasitron.13 Higher OP are useful for ventilation and recruitment whereas lower OP increase mobilization of secretions.[13] OP which hare too low will interrupt internal components of the IPV machine, substantiating the importance of maintain operational pressures between 20-40psi. The frequency is the number of percussion administered per minute.[13 8,11-13,15,34,38,40,41] The rate of percussions is highly dependent on the operational pressure and the pneumatic pressure delivered to the machine, creating a wide range of percussion rates. Higher frequencies generate a vibratory effect and facilitate secretion clearance. While lower frequencies imply greater recruitment and provide a greater ventilator effect.[13] For adults it is recommended to utilize 100 to 400 percussions per minute at an operating pressure of 40psi. Once the baseline OP and frequency have been established it may be beneficial to adjust the frequency to maximize the ventilator and vibratory effects of the IPV.13 Manual inspiration button delivers gas through the Phasitron.10 The longer the button is depressed the greater the tidal volume generated.[10] The Phasitron includes a reservoir to solution to maintain hydration of the airways while oxygenating.[45] Prescribed medications can be added to the reservoir.[34] If no medication is ordered normal saline or sterile water can be used.

IPV-2C is similar to the IPV-1C containing a master switch, operational pressure control, percussion, and manual inspiration but it provides additional premium features.[10] These additional features include inspiratory time, inspiratory flow, and demand continuous positive airway pressure (D-CPAP).[10] The inspiratory flow determines the peak inspiratory pressure (PIP) delivered to the patient.[10] The inspiratory flow should be increased to achieve chest wiggle in the apices down to the nipple line.[10] The inspiratory time selects the interval at which the pulsations are delivered.[10] This can be programed from 0.5 seconds to 25 seconds.[10] This will affect the inspiratory to expiratory (I/E) ratio for each percussion.[10] The I/E ratio will range from 1/1 to 1/3 ratio. The inspiratory time will remain 1 second, the expiratory time will be adjusted.[10]

Figure 1. Percussionaire IPV-1C: (A) percussion, (B) manual inspiration, (C) master switch, and (D) operational pressure control. Note: the IPV-2C had additional knobs and switches.

Altering the parameters of IPV has considerable effects on the efficiency of the treatment.[46] The parameters are interdependent, therefore a change in adjustment of one parameter will effect another parameter and in turn the patient. Parameters should be set according to the age, disease, and clinical condition of the patient.

Therapy can be delivered via mouthpiece, mask, or artificial airway.[7,10] When using a mouthpiece the patient should be seated upright position.[10] Most patients allow air to leak through their nose or around the mouthpiece with the percussions.[10] The patient should be instructed to make a tight seal around the mouthpiece with the lips while splinting the cheeks.[10] The patient may inhale and exhale normally with the pulsations.[10] The process is very similar for patients with an artificial airway for patients with an artificial airway but there is less concern for cheek fatigue.[10] If a patient cannot follow instructions it may be necessary to deliver the treatment with a mask.[10]

Clinical Goals

The purpose of IPV would be to mobilize secretions in the airways, which are congested as a result of secretion retention, edema, and bronchiolar spasm.[2–4] In turn this will create uniform alveolar ventilation for enhancing oxygen uptake and CO2 elimination.[2–4]

Table 3. Goals of IPV therapy

Goals of IPV Therapy
Facilitate long-term liberation from mechanical ventilation
Prevent intubation
Improve Ventilation/Perfusion Match
Improve Oxygenation
Improve recruitment of Lung
Decrease work of Breathing

IPV facilitates quicker extubation resulting in shorter length of mechanical ventilation.[35,47,48] With this it also produces long-term liberation from mechanical ventilation with lower rates of reintubation.[47] Additionally IPV is associated with shorter Intensive Care Unit (ICU) stays when compared to standard therapy.[47]

IPV can improve the delivery of albuterol into the lungs.[49] By using low levels of percussions and increasing the OP, albuterol delivered to the ling may increase up to two fold.[49] Decreasing the frequency of percussions increases tidal volumes and albuterol delivery is correlated with the tidal volume.[49] Peak pressures and airway resistance levels should be monitored closely when increasing the OP to insure patient safety.[49]

Parameters to Monitor

Many variables must be closely monitored during the use of IPV (Table 4). Not only is it important to monitor the IPV machine itself, but also the patient's clinical appearance. The patient should be assessed prior to the initiation of the treatment in order to establish baseline levels. Once the treatment is started the inspiratory flow should be started low and increased until there is sufficient chest wiggle from the apices to the nipples. Mobilization of secretions from lower regions of the lung upward toward the airway can cause obstruction of the trachea and main bronchi.[13] It may be necessary to suction the patient when chest wiggle is decreased or absent, when a mucus plug or secretions are suspected, if there is a decrease in SpO_2 or when there is an increase in CO_2 levels. Therefore it is important to follow IPV with suctioning.[13] The patient can be auscultated throughout the treatment. An equilibrium, in which oscillations are heard in all lung fields, will be achieved once the ideal pressure is reached. Upon palpation a vibratory effect should be felt throughout the chest wall surface.

Arterial blood gas (ABG) will provide accurate assessments of the impact of IPV on ventilation and oxygenation. As discussed before IPV has high frequency rate which can be extremely effective at the removal of CO_2.[50] In some cases this may cause over ventilation and effect the patients drive to breathe.

A chest X-ray should be performed routinely.

Table 4. Parameters to monitor during the use of IPV

Patient	
PaO2/FiO2	Blood pressure (systolic and diastolic)
PaCO2	Chest X-ray
SpO2	Mean arterial pressure (MAP)
Heart rate	Arterial blood gas (ABG)

IPV with Mechanical Ventilation

When intubated a patient's natural defense mechanisms are removed, putting the patient at greater for pulmonary complication.[51] Intubation causes impaired cough reflex and mucociliary escalator which can lead to pulmonary complications including ventilator-associated pneumonia (VAP) and atelectasis.[41] IPV is used facilitate the removal of secretions, reduce airway resistance, and to treat atelectasis in mechanically ventilated patients.[41,52] Patients using IPV have less occasions of pneumonia, improved oxygenation, and respiratory muscle performance.[41] Additionally mechanical ventilation prolongs the patients hospital admission, weaning process, and increases mortality.[41] IPV lower median number of hours of ventilator assistance.[47]

Various ventilators respond to IPV in different manners in regards to triggering, cycling-off, and PEEP.[43] In some ventilators IPV causes continuous autotriggering.[43] In other vents IPV has

caused intrinsic PEEP on top of the PEEP generated by the IPV device.[43] Based off of this it is extremely important for trained personnel to delivery therapy and monitor patients closely.[8]

IPV vs CPT

Prolonged bed rest and intubation can result in muscle weakness and wasting, increased secretions, and increased risk for atelectasis and pneumonia.[53] This is only heightened for individuals with tracheostomies.[53] Early intervention is important in respiratory care and is effective in avoiding complications and improving the prognosis of critically ill patients.[53] Traditionally this is treated with chest physiotherapy (CPT) but IPV has been shown to be a safe and feasible therapy to enhance the effects of CPT.[34,41,53,54] IPV will improve mucus clearance while promoting alveolar recruitment, reducing diaphragmatic work of breathing and energy expenditure of breathing.[47,53] Following treatments, IPV is associated with less dyspnea and discomfort.[47] In practice IPV has speeded improvement when compared with traditional CPT resulting in lower occurrence of pneumonia, improved muscle performance, and improved gas exchange.[53,54]

Conclusion

As a practitioner, it is important to understand the benefits and hazards of IPV therapy prior to the initiation of clinical practice. IPV therapy provides a safe and efficient way to mobilize secretions from the airways of patients of all ages when used appropriately. Additionally, IPV therapy is a viable option of therapy for patients suffering from atelectasis, experiencing an increase in airway resistance, and some difficult to extubate patients.

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Sepsis Prediction During Outbreaks At Neonatal Intensive Care Units Through Body Surface Screening For Gram-Negative Bacteria: Systematic Review And Meta-analysis

Thomas Harder*, Sebastian Haller, Tim Eckmanns and Juliane Seidel

Abstract

Objective: This systematic review focuses on the prognostic accuracy of neonatal body surface screening during outbreaks caused by Gram-negative bacteria for prediction of sepsis. In a previous systematic review we reported that only limited evidence of very low quality exists regarding the predictive value of this screening under routine conditions. We aimed to investigate whether this is different in outbreak settings.

Results: We identified five studies performed during outbreaks in three countries, comprising a total of 316 infants. All studies were at high risk of bias. In outbreak settings, pooled sensitivity of body surface screening to predict sepsis was 98% (95 CI 60 to 100%), while pooled specificity was 26% (95% CI 0.5 to 96%). Evidence quality was low for all outcomes. Extending a previously published systematic review, we show here that in contrast to routine settings sensitivity of body surface screening for sepsis prediction is very high, while specificity is still insufficient. Surface screening appears to be a useful component of bundles of interventions used during outbreaks, but the evidence base is still limited. PROSPERO Registration Number: CRD42016036664.

Keywords: Systematic review, Meta-analysis, Outbreaks, Prognostic accuracy, Gram-negative bacteria

Introduction

At neonatal intensive care units (NICUs), outbreaks caused by Gram-negative bacteria are an important public health problem. Management of such outbreaks includes the implementation of complex interventions, comprising isolation, hygiene measures and antimicrobial therapy. Body surface screening of newborns is often performed as part of this bundle of interventions.[1] However, the significance of screening within this bundle is unclear.

Recently, we published a systematic review showing that only limited evidence of very low quality exists regarding the sensitivity and specificity of these screening procedures for the prediction of sepsis in routine settings. Moreover, we observed that over all published studies, sensitivity was as low as 41%, while specificity was only 56%.[2] However, we did not include reports on outbreaks in this former systematic review, for the following reasons: Screening for colonization by Gram-negative bacteria is likely to perform differently during outbreaks of Gram-negative bacteria, compared to routine settings. During an outbreak, the increase of incidence influences positive as well as negative predictive values. Therefore, during the conduct of the project we decided to split the data base and to analyze outbreaks separately. In addition, we used this systematic review to address the issue of applying methods of evidence-based public health to outbreak reports as part of the piloting phase of the Project on a Framework for Rating Evidence in Public Health (PRECEPT).[3]

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Main text

Methods

The systematic review reported here builds upon a systematic review for which the protocol has been published in the International Prospective Register for Systematic Reviews (PROSPERO; registration no. CRD42016036664). It was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (see Additional file 1: Table S1 for the completed checklist).[4] For a detailed description of the methodology of the previous review, see.[2] In brief, electronic databases searched were MEDLINE and EMBASE. In addition, for the current review we additionally searched the Worldwide Database for Nosocomial Outbreaks (https://www.outbreak-datab ase.com) for additional publications, using an adapted search string (date of last search: 29 June 2018).

To be eligible, a study had to:

- Include infants up to an age of 12 months who are in a NICU (irrespective of gestational age and birth weight) AND.
- Report on an outbreak at a NICU caused by a Gram-negative bacteria species AND.
- Report the results of body surface screening for Gram-negative bacteria AND.
- Report on late-onset sepsis in these infants.

As in the previous review,[2] we did not make any restrictions regarding study design, language or publication status (published/unpublished). From the eligible studies, two independent reviewers (TH, JS) extracted study characteristics and assessed risk of bias, using standardized forms. In case of disagreement, a final decision was made by consensus.

Table 1 Characteristics of included studies

Study	Country	Study period	No. of participants (in final analysis)	Gestational age (weeks)	Birth weight (g)	Age at screening (days)
Hill et al. 1974 (I) [8]	USA	1972	31	28–38	1100–3380	3–90
Hill et al. 1974 (II) [8]	USA	1972	23	28–38	1100–3380	3–90
Parry et al. 1980 [9]	USA	1978	128	NR	NR	NR
Samuelsson et al. 2014 [1]	Sweden	2006–2011 (recurrent outbreaks)	38	25 (36 for controls)	725 (2570 for controls)	NR
Tsiatsiou et al. 2015 [10]	Greece	2011	96	26–40	800–4300	10–80

Study	Screening interval (s)	Screening location	Outbreak bacteria species/strain	Definition of sepsis	Control measures	Risk of bias
Hill et al. 1974 (I) [8]	Weekly	Rectal/respiratory	*Klebsiella pneumoniae* type 26	NR	Enhanced hand-washing; use of long-sleeved gowns; isolation	High
Hill et al. 1974 (II) [8]	Weekly	Rectal/respiratory	*Klebsiella pneumoniae* type 26	NR	Enhanced hand-washing; use of long-sleeved gowns; isolation	High
Parry et al. 1980 [9]	Daily	Nose/throat/umbilicus/rectum	*Citrobacter diversus*	NR	Closure of nursery; sterile cleaning; cohorting	High
Samuelsson et al. 2014 [1]	Weekly	Nose/throat/perineum/rectum	*Serratia marcescens*	Positive blood culture plus ≥ 2 additional criteria; or: negative blood culture plus ≥ 3 additional criteria[a]	Hand hygiene; cleaning; handling of venous catheters; distribution of patients in room; antibiotics	High
Tsiatsiou et al. 2015 [10]	Weekly	Perianal/stool	Carbapenem-resistant *Acinetobacter baumannii*	NR	Antimicrobial therapy; closure of department to new admissions	High

NR not reported

[a] Additional criteria: (1) leucocyte particle conc. $< 5 \times 10^9$/L or $> 20 \times 10^9$/L; (2) platelet particle conc. $< 100\ 10^9$/L; (3) C-reactive protein > 15 mg/L; (4) impaired respiratory function with respiratory rate > 70 breaths/min, grunting/gasping or increased ventilator support in ventilated infants that cannot be explained by other factors

Table 2 Measures of prognostic accuracy of included studies

Study	Sensitivity (%)	Specificity (%)	Prevalence of sepsis (%)	Positive predictive value for sepsis (%)	Negative predictive value for sepsis (%)
Hill et al. 1974 (I) [8]	92	0	39	37	0
Hill et al. 1974 (II) [8]	100	81	9	33	100
Parry et al. 1980 [9]	100	93	2	18	100
Samuelsson et al. 2014 [1]	100	0	26	26	–[a]
Tsiatsiou et al. 2015 [10]	100	93	8	57	100

[a] Cannot be calculated

As in the previous review,[2] for risk of bias assessment the QUADAS (Quality Assessment of Diagnostic Accuracy Studies)-2 tool[5] was used. Risk of bias was judged to be "high", "low" or "unclear". We used the methodology of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group to assess the quality of the evidence for each body of evidence (true positives, true negatives, false positives and false negatives).[6]

As reported earlier,[2] for quantitative data synthesis on prognostic accuracy, 2 × 2 tables were constructed to calculate sensitivity and specificity. Summary estimates using hierarchical summary receiver operating characteristics (HSROC) models and summary receiver operating characteristics (SROC) plots were constructed, accounting for the correlation between sensitivity and specificity.[7]

Results

A total of 3871 entries were identified in Medline and Embase. In addition, 227 potentially relevant outbreaks were identified in the Worldwide Database for Nosocomial Outbreaks. During the screening process, four studies[1,8-10] were found to be eligible. One study[8] comprised two separate studies; therefore we finally included five studies into the analysis (see Additional file 2: Figure S1). The characteristics of these studies are shown in Table 1.

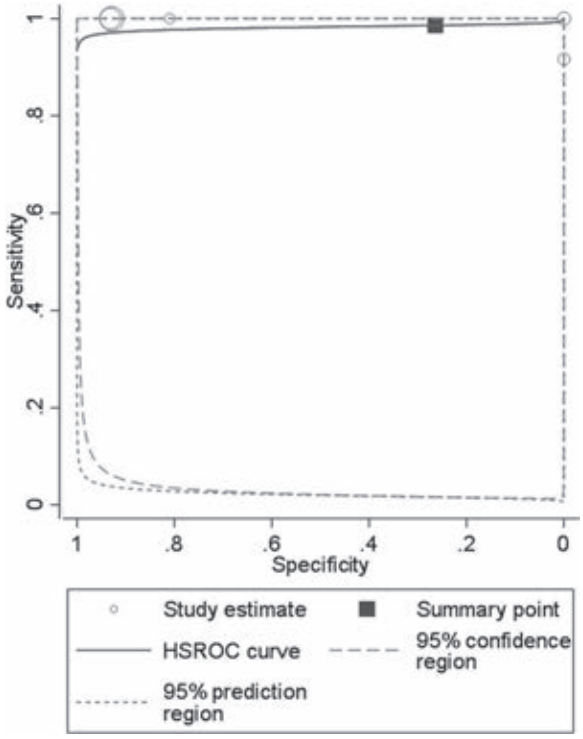

Fig. 1 Summary receiver operator characteristics (SROC) curve

The included studies were performed between 1972 and 2011 in three different countries and comprised a total of 316 infants. The outbreaks reported in the studies were caused by four different bacteria species (*Klebsiella pneumoniae*, *Citrobacter diversus*, *Serratia marcescens*, *Acinetobacter baumannii*). Birth weight ranged from 725 to 4300 g, while gestational age ranged from 25 to 40 weeks. None of the studies reported on ethnicity of participants. In all but one study, screening was performed once a week. Only one of the studies reported the definition used for sepsis. All five studies reported on control measures used to manage the respective outbreak.

The results of the risk of bias assessment using the QUADAS-2 tool are summarized in the last column of Table 1. As confounding of the predictive performance of the screening due to co-interventions (measures applied to control the outbreak) cannot be excluded in any of the studies, all five studies were judged to be at high risk of bias.

Table 2 shows sensitivity, specificity, prevalence, positive and negative predictive values for the five included studies. All but one study had 100% sensitivity in detecting the respective pathogen. This corresponded to high negative predictive values in the respective studies. Specificity was high (81–93%) in three studies, but zero in two. Consequently, positive predictive values ranged between 18 and 57%.

Although the results of the single studies showed heterogeneity, we decided to pool sensitivity and specificity measures to get overall estimates. Pooled sensitivity across all studies was 98% (95% CI 60% to 100%), while pooled specificity was 26% (95% CI 0.5% to 96%). Pooled diagnostic odds ratio was 25.2 (95% CI 0.04 to 14542). Figure 1 shows the summary receiver operating characteristics (SROC) plot.

According to GRADE, evidence quality for all four outcomes (true positives, true negatives, false positives, false negatives) was assessed to be low. This was due to high risk of bias and inconsistency of study estimates.

Discussion

In this study, we extended a previously published systematic review on the performance of body surface screening in neonates at NICUs to outbreaks settings. In contrast to routine settings where both sensitivity and specificity of the screening were found to be low,[2] during outbreaks sensitivity of sepsis prediction by colonization by Gram-negative bacteria was nearly 100%, whereas specificity was still insufficient. Low specificity may be explained by the fact that carriers of Gram negative outbreak pathogens are predominantly colonized and do not necessarily develop infection. Infection rates depend on factors of the pathogen (eg virulence), the host (eg immunodeficiency) and the route of transmission (eg transmission during invasive procedure versus by skin contact) and do differ from outbreak to outbreak. The low specificity of the screening is of relevance when considering it for clinical routine, where screening results may be misinterpreted as strong predictors of Gram-negative sepsis. Consequently, this may result in less prudent antibiotic administration.

In outbreak situations it is of importance to identify all cases in order to apply adequate control measures and understand the mode of transmission. Beyond identification of infants at risk for developing sepsis, the major objective of screening is to identify all infants carrying the outbreak pathogen. The here found low specificity in predicting sepsis should not hinder from performing a systematic screening in outbreak situations to implement hygiene measures.

In any case one has to consider that the evidence base comprised only report of five outbreaks, and evidence quality was low due to high risk of bias.

This extension of a previously published systematic review has several strengths. Using a structured approach and an established evidence grading system, we were able to conduct the first systematic review on this topic in outbreak situations. By focusing on outbreaks, we investigated a setting where the background prevalence of both colonization and disease (sepsis) can be expected to be considerably higher than under routine conditions.

Limitations

The limitations of this systematic review are mainly caused by the limited evidence base. In the previous review on routine screening, we were able to perform subgroup analyses according to sampling site and bacteria species. Interestingly, these analyses revealed that, under routine conditions, the screening performed differently in some bacteria species. Unfortunately, such an analysis was not possible here as the evidence base was too small. As in the previous review, risk of bias clearly limits the value of the data and decreases the quality of the evidence.

The main result of our systematic review confirms that during outbreaks caused by Gram-negative bacteria, body surface screening in neonates has a high sensitivity in detecting newborns at risk of sepsis. Thereby, the screening procedure can be considered to be a useful component of a bundle of interventions used during outbreaks and is prerequisite for the control of outbreaks that are caused by person to person transmission. However, data are more heterogeneous regarding

specificity of the screening. Ideally, more studies should be conducted to broaden the evidence base.

Authors' contributions

JS, TH and SH developed the concept of this study. JS and TH performed the searches, extracted the data and wrote the first draft of the manuscript. SH and TE provided important intellectual input to revised the draft. TH is the guarantor of this study. All authors read and approved the final manuscript.

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The End of an Error

Part two of a three-part series looks at how understanding the root causes of mistakes involving infant feeding management can help prevent them in the NICU.

Kelley Karp MSN, BS RN

Introduction

In Part 1 of this article series, we covered some cognitive behaviors that allow for errors to occur or fail to be prevented.

Here, in part 2 of "The End of an Error," we will continue to explore the *why* behind these errors related to the human factors that support them. We will then switch gears — to discuss the specific operational factors that influence errors in feeding management.

> "The gradual process through which unacceptable practice or standards become acceptable. As the deviant behavior is repeated without catastrophic results, it becomes the social norm for the organization."[1]

Human Factors

Normalization of Deviance and the Work Around

Normalization of deviance, or what I like to call operational deviance, was first coined in 1996 by psychologist Diane Vaughn after the Challenger shuttle disaster.

"The gradual process through which unacceptable practice or standards become acceptable. As the deviant behavior is repeated without catastrophic results, it becomes the social norm for the organization."[1]

Commonly referred to as a "workaround", the term describes the way we operationalize deviations or departures from established rules.

Inherently, workarounds are created when staff does not have the right tools or processes to do their jobs. A workaround is created because they feel they "have to" and this becomes the accepted practice. More often than not, where there are workarounds there are errors which defeats the entire purpose of implementing policies, practices, or technologies.

As nurses, it is in our DNA to root out flaws or deficiencies with any new process or technology. I feel confident in saying the collective "we" become frustrated when mandated to follow a process or use a particular technology if; it hinders our workflow without positively impacting patient safety, or unnecessarily takes precious time away from our patients and families. Speaking generally, I believe it is natural for nurses to create workarounds once we have established workflow inefficiencies.

In 2010 an article was published titled, "The Normalization of Deviance in Healthcare Delivery".[1] This publication discussed the following classifications of errors:

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Active Error, which refers to the failure of a healthcare professional to follow established procedures, practices, or standards.

Latent Errors, defined as laws of weaknesses in a system's defenses that allow the former to break said defenses, reach patients, and cause harm.

While we can all quickly find examples of these weaknesses, below are some of the proposed reasons latent errors occur:[1]

- Rules are perceived as stupid or inefficient.
- The work itself, along with new technology, can disrupt work behaviors and rule compliance.
- The belief that I am breaking the rules for the good of my patient.

The latent error is where we truly uncover the systemic issue; when an event which started as an Active Error is deemed acceptable and not quashed, others will follow suit perpetuating the normalization and acceptance of the workaround. Additionally, the article discusses how the occurrence of these deviations becomes part of the operational norm. A weakened safety net allows for the acceptance of future active errors, continuing the cycle of deviance.

There is a delicate balance between operational deviance and simply trying to work in a safer, more efficient way. One could argue these points from either side. What is established as the appropriate way to do things may not, in reality, be the best practice.

Ultimately, you have to ask: if the processes and systems were better, leaving no need to circumvent the established procedure, would the deviance still occur?

Error Identification

As previously stated, the root causes of errors are multifactorial.

So far, we have covered some of the contributing cognitive and human factors. What other factors impact the occurrence of errors in these processes?

I am sure that many of you are familiar with the FMEA, but lets review. You begin with mapping out the steps in a process, then work through failure modes or at what points could something go wrong. Failure causes — why would this happen and then the failure affects — what would happen if this event occurred. Each item is given a score or priority, and then teams decide to evaluate change based on their findings.

Why are we talking about this? There are a handful of studies that have documented the utilization of this methodology for infant feeding management. Each found that there are between 32-282 potential failure modes that require a human to detect and prevent while the authors believed that 55% are unlikely to be discovered.[2,3]

The reason to touch on this here is that the different institutions found a varying number of and specific potential failure points. It is not that one or the other is incorrect, it simply highlights that in every institution the workflows and resources are vastly different. These differences have a significant impact on people and their processes, creating the potential for errors.

We will not go in-depth to review each of those studies,[2,3] here, we are focusing on the *why*. In these examples, thorough process evaluation and then targeted interventions occurred. Yet, even after the intervention, errors still happened. Was something missed? Probably not. Still, this shows us that with the vast complexity of the infant feeding management process simply correcting for process errors is not sufficient. The cognitive challenges and human factors need to be a part of the conversations, evaluations, and interventions.

Contributing Factors

Let's review some day to day workflows and operational challenges experienced by NICU staff. This is where we will see some specific error points come to life. Below you'll find examples of workflow challenges and some of the causes.

The bottle lifecycle is incredibly complex; Figure X depicts one permutation of the path a bottle can travel. See how many hands, state and/or location changes can occur?

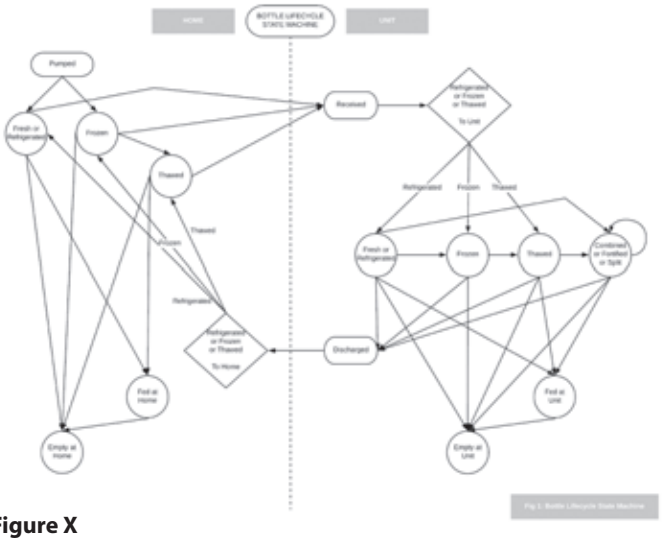


Figure X

Bottle Pathway in Figure Y – a further development of the life cycle. In its simplest iteration, it is still a highly complex process. Though the set up may be different and various staff could own separate parts of this process, every institution experiences this. With this level of complexity, and considering everything that has been discussed, it would be foolish to not expect errors.

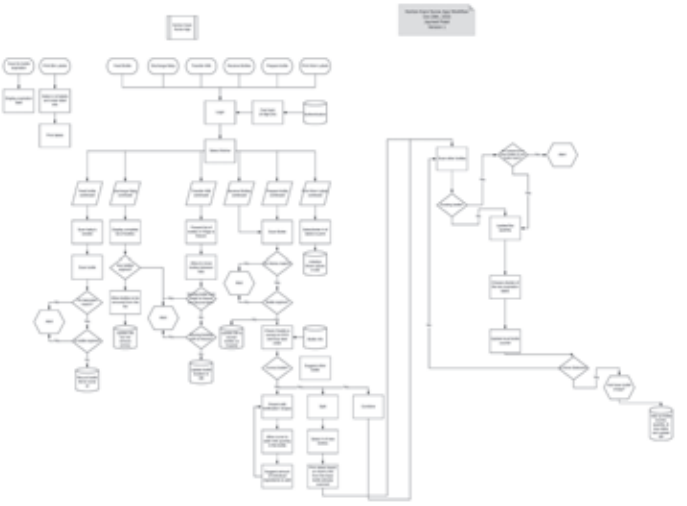
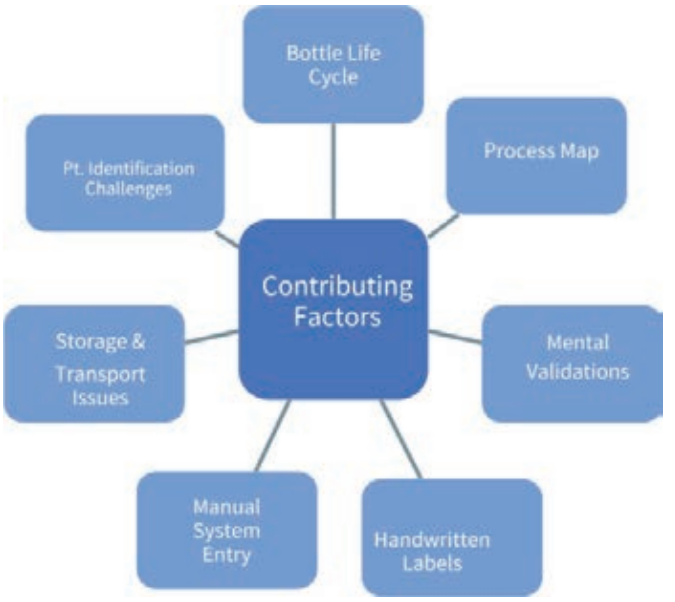


Figure Y

Storage and Transport – Practically every institution faces challenges regarding a lack of ample storage for maternal and donor milk. Some institutions are forced to limit the amount a family can store at the hospital.

Many freezers have bins with open lids (either because they are too full or the lids have long since disappeared). Patient bins may be poorly labeled or, worse, not labeled at all. Milk bottles are placed directly on the shelves or have fallen out of the container. How can a safe process be maintained under these conditions?

Bottles are then transferred from home to the hospital. Milk is received, stored, prepared, and delivered. Refer back to Figure X and Figure Y for the physical movement of a bottle.



Handwritten labels – In most situations, mothers hand write date and time pumped on the label. One study showed that 18%

of errors occurred from handwritten labels, wrong information written, illegible handwriting, etc. Staff then have to receive those bottles into the hospital and manage the entire process from this point. If they start with incorrect information, how can the process be executed accurately and safely?

Manual system entry – If an institution is using any form of scanning system where data needs to be manually entered transcription of this information, incorrect or incomplete data, are all opportunities for error.

Patient identification challenges – Unique naming is complicated in the neonatal population, especially when you have multiples. The new Joint Commission requirement for infant naming convention has improved this issue, but challenges persist.[4]

Conclusion

We have covered identified failure points for all facets of feeding management, the majority of which go undetected, unappreciated, unreported, and unresolved. Given this, the true breadth of the issues is not realized.

As we have continued to explore, infant feeding management is extraordinarily complex and involves multiple processes and players.

Part 1 of "The End of an Error" covered the cognitive failures and mental validations that impact the potential for error.

Here in part 2, we focused on how human factors influence processes and contribute to errors as well as detailed examples of failure points.

In Part 3 we will discuss the current state of electronic management of infant feeding and opportunities to improve safety in these processes.

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Oxidative Stress as a Primary Risk Factor for Brain Damage in Preterm Newborns

Isabella Panfoli[1], Giovanni Candiano[2], Mariya Malova[3], Laura De Angelis[3], Valentina Cardiello[3], Giuseppe Buonocore[4] and Luca A Ramenghi[3]*

The risk of oxidative stress is high in preterm newborns. Room air exposure of an organism primed to develop in a hypoxic environment, lacking antioxidant defenses, and subjected to hyperoxia, hypoxia, and ischemia challenges the newborn with oxidative stress production. Free radicals can be generated by a multitude of other mechanisms, such as glutamate excitotoxicity, excess free iron, inflammation, and immune reactions. Free radical-induced damage caused by oxidative stress appears to be the major candidate for the pathogenesis of most of the complications of prematurity, brain being especially at risk, with short to long-term consequences. We review the role of free radical oxidative damage to the newborn brain and propose a mechanism of oxidative injury, taking into consideration the particular maturation-dependent vulnerability of the oligodendrocyte precursors. Prompted by our observation of an increase in plasma Adenosine concentrations significantly associated with brain white matter lesions in some premature infants, we discuss a possible bioenergetics hypothesis, correlated to the oxidative challenge of the premature infant. We aim at explaining both the oxidative stress generation and the mechanism promoting the myelination disturbances. Being white matter abnormalities among the most common lesions of prematurity, the use of Adenosine as a biomarker of brain damage appears promising in order to design neuroprotective strategies.

Keywords: adenosine, biomarker, oxidative stress, prematurity, white matter lesions

Introduction

Oxidative stress is the consequence of an imbalance in the ratio among pro-oxidants and anti-oxidants in the cell.[1] Free radicals, ie, molecules bearing unpaired electrons, non-radical Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) are collectively called oxidants, as they can easily lead to radical chain reactions (Table 1). ROS/RNS are generated from metabolic redox reactions[2] mostly by the respiratory chain,[3] but also by microsomal cytochrome P450 system and by the immune response.[4] Antioxidants, either endogenously produced or exogenously assumed, include enzymes, vitamins, minerals, and other substances (summarized in Table 1), which act neutralizing the excess of free radicals and protecting the cells against the harmful effects of oxidants.[1]

When the production of ROS exceeds the antioxidant defenses, or antioxidant levels are low, as is the case in the preterm newborn, oxidative stress usually occurs to the detriment of all of the cellular macromolecules.[5] In adults, oxidative stress is recognized as a major contributing factor to the pathogenesis of a number of cardiovascular and neurological diseases, malignancies, diabetes, aging, inflammation and others.[2,6] Despite these deleterious effects, low or moderate concentrations of free radicals are necessary for many fundamental cellular functions, including host defenses.[7]

Oxidative Stress As Pathogenic Factor In The Preterm Infant

The oxidant/antioxidant status balance is a process that begins before birth,[8] and premature infants are particularly susceptible to oxidative stress.[9,10] Most of the complications of prematurity, such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and punctate white matter lesions (PWML), appear related to oxidative stress,[11,12] mostly occurring due to a mismatch among the free radical production and the anti-oxidative capacity of the premature neonate.[10] Accordingly, Saugstad hypothesized that all of these complications may belong to one entity, "the oxygen radical disease of neonatology".[13] This topic was recently reviewed by Buonocore et al.[14]

Birth exerts the challenge of a hyperoxic insult due to the sudden exposure to a normoxic environment (100 mmHg oxygen tension, PO_2) of an organism primed to develop in a hypoxic (20-25 mmHg, PO_2) environment as the womb is. For this reason, current indications on neonatal resuscitation highlight the importance of starting respiratory support using the lowest oxygen concentration to reduce the postnatal oxidative stress.[15] A randomized trial performed on neonates of 24-34 weeks

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TABLE 1 | Main oxidants and anti-oxidants.

Oxidants	Anti-oxidants
Free radicals Hydroxyl radical, superoxide peroxyl, lipid peroxyl	**Enzymes** Superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase
Reactive Oxygen Species (ROS) Peroxide, singlet oxygen, hypochlorous acid and lipid peroxides	**Vitamins** A, C, E
Reactive Nitrogen Species (RNS) Hydrogen nitric oxide, nitrogen dioxide, nitrous acid, peroxynitrite, dinitrogen trioxide	**Minerals** Se, Mn, Cu and Zn
	Other substances glutathione, melatonin, thiols, coenzyme Q, acetylcysteine, carotenoids and flavonoids

Table summarizes the most common oxidants and the main endogenous and exogenous antioxidants.

gestational age who received resuscitation demonstrated that the use of room air, instead of 100% O_2 as the initial resuscitation gas resulted lower oxidative stress, decreasing respiratory morbidities.[16]

Together with hyperoxia, other main risk factors for oxidative stress exposure in preterm infants are hypoxia, ischemia, infections, and immune response activation, mitochondrial dysfunction, Fenton reaction due to both free iron and endothelial cell damage.[17] Hypoxia has been demonstrated to be a risk factor for oxidative stress in preterm newborns. In a study conducted on 34 hypoxic and 15 healthy preterm newborns, plasma concentration of hypoxanthine, total hydroperoxide (TH), and AOPP were assessed both in umbilical cord blood immediately after birth and in peripheral blood on postnatal day 7.[18] Levels of these markers were significantly higher in hypoxic newborn at birth and at day 7 than in the healthy controls. Interestingly, a significant increase in TH and AOPP levels in non-hypoxic preterm newborns at day 7 was also observed, indicating that oxidative stress also occurs in non-hypoxic babies.[18]

Moreover, antioxidant defense mechanisms are incompletely developed or deficient in preterm newborns.[19] Preterm infants show reduced antioxidant defense mechanisms, including decreased levels of vitamin E, β-carotene, melatonin, ceruloplasmin, transferrin, and erythrocyte superoxide dismutase (SOD).[10] In a study on 100 preterm and 100 full-term neonates, plasma levels of vitamin A, vitamin E, and catalase were found significantly lower while plasma level of MDA, a marker of lipid peroxidation, was significantly higher in the preterm than in the full-term newborns, especially in those ones who developed NEC or BPD.[20] A prospective study evaluated the concentration of vitamin D, glutathione peroxidase, SOD, MDA, and AOPP on 31 term neonates with hypoxic-ischemic encephalopathy (HIE) in comparison to 30 healthy term neonates.[21] It was found that Vitamin D level, GP, and SOD were statistically lower on the first day of life in the study group compared to controls, while MDA levels were significantly higher in the study group.[21] Although to date it has been difficult to design effective antioxidant therapies,[19] the possibility can be envisaged to use particular kinds of antioxidants, such as melatonin, and effective free radical scavenger[22-24] and to design prophylactic antioxidant therapies also before birth.

Oxidative Stress-Related Brain Injury

Advances in neonatal care allow preterm neonates to survive,[25] but especially the very-low-birth-weight infants (VLBW) are at high risk to develop brain gray (GM) and white matter (WM) maturational disturbances, which may lead to neurodevelopmental disabilities.[26,27]

A study conducted on 119 consecutive premature infants admitted to neonatal intensive care units demonstrated a significant reduction in both cerebral cortical and deep nuclear GM volume and a subsequent increase in cerebrospinal fluid assessed with brain magnetic resonance at term equivalent age (TEA), in preterm infants compared with term infants.[28] Along with gestational age at birth, the major predictor of altered cerebral volumes was the presence of cerebral WM injury, that most significantly correlated to neurodevelopmental outcome.[28]

Cerebral WM injury is a full-spectrum of lesions named periventricular leukomalacia (PVL), that occurs in two overlapping forms: cystic PVL, in which the periventricular focal necrosis is macroscopic and evolves to multiple cysts; and non-cystic PVL, in which the focal necrosis are microscopic and evolve principally to glial scars.[29] Evidence of PVL is found in 25 to 75% of VLBW infants with neuropathological examination.[10] The incidence of cystic PVL declined significantly starting from late nineties of last century, now occurring in a minority of infants with abnormal neurodevelopmental outcome.[30] Contemporary cohorts of preterm survivors commonly display milder forms of injury, primarily diffuse white matter injury (DWMI) and punctate white matter lesions (PWML), that even though do not involve pronounced neuronal loss may be also associated with a clear WM damage and neurodevelopmental disabilities.[29,31,32] DWMI and PWML are currently the most common causes of brain injury in preterm infants.[33,34] Signs of DMWI occurs in about 50% of very low birth weight infants,[35] while more than 10% of premature infants <32 weeks develop lesions visible at MRI performed at term corrected age. Oxidative stress is among the main causes of PWML.[36-41] In fact, the optimal concentration of oxygen for resuscitation of very preterm infants is currently strictly monitored.[15] Risk factors for the development of PWML and for oxidative stress production are similar, including hyperoxia, hypoxia, ischemiareperfusion, hemorrhage, and maternal/fetal inflammation.[33] Inflammatory microglial response in cerebral white matter can generate free radicals.[42] A number of epidemiological studies have shown an association between infections and cerebral palsy[43] and intrauterine T cell activation and risk of cerebral lesions.[44] VLBW infants with neonatal sepsis were shown to have increased rates of cerebral palsy and WM lesions, by a large cohort study.[45] Another mismatch among demand and supply in the premature babies would regard insulin-like growth factor 1 (IGF-1), a mitogenic hormone involved in growth and metabolism. Increased chemical energy demand but low IGF-1 concentrations characterize preterm birth, which appears associated with complications such as especially ROP.[46,47]

Oligodendroglial Precursor Injury As The Main Cause Of Brain Damage

It has been reported that brain injury mostly affects WM, being oligodendroglial death the most important cause of PVL and PWML.[35,48,49] Studies on both human brain and animal models assessed that the developing oligodendrocyte (OL) is the principal cellular target.[49,50] All of the cited risk factors can cause toxicity to the oligodendroglial precursors. For example,

TABLE 2 | Main antioxidant Treatments.

Treatment	Mechanism of action	References
Caffeine	Free radical scavenger and adenosine receptor antagonist; Anti-inflammatory and anti-apoptotic.	Endesfelder et al. (59)
Erythropoietin	Anti-apoptotic, anti-oxidative and anti-inflammatory with angiogenic and neurogenic effects.	Rangarajan et al. (60), Maiese et al. (61)
Melatonin	Direct scavenger of oxygen free radicals, particularly the hydroxyl radical; Indirect antioxidant via stimulation of antioxidant enzymes.	Reiter et al. (62), Gitto E et al. (63), Miller et al. (64), Vladan et al. (24)
Allopurinol	Decrease free radical formation; Xanthine oxidase inhibitor; Directly scavenging free radicals.	Kaandorp et al. (65), Van Bel F et al. (66)
Quercetin	Increases survival against oxidative insults in neuronal culture.	Dajas et al. (67)

Table reports the most common strategies contrasting oxidative stress employed to protect preterm brain from white matter injuries.

proinflammatory cytokines produced in response to hypoxia and infection can become toxic to the oligodendroglial precursor cells (pre-OL).[43] Glutamate excitotoxicity and free radical injury have recently been implicated in pre-OL death.[39] Free iron, in turn causing oxidative stress, contributes to the onset of the OL dysmaturation.[18]

In addition, oxidative stress reduces the expression of differentiation-promoting genes, such as Olig1, Olig2, and Sox10 in pre-OL, and increases the expression of differentiation-inhibiting genes (ID2 and ID4), resulting in the interruption of OL maturation.[51]

Although there is evidence of an imbalance between antioxidant and oxidants, the ultimate cause of oxidative stress and molecular bases for the maturation-dependent vulnerability of the pre-OL to injury in a window of time ranging from 30 to 34 weeks of gestational age is yet unknown. We have recently proposed a bioenergetics hypothesis, correlating the oxidative stress generation to the significant increase of plasma Adenosine (Ado) concentration observed in some VLBW infants.[52] Ado production may be triggered by the oxygen challenge and the untimely sensory stimulation consequent to premature birth. In particular, the pain sensory pathways would be primarily triggered by the invasive procedures routinely performed in intensive care units. A prospective randomized controlled trial evaluated the reduction of procedural pain 150 preterm newborns (gestational age 27-32 weeks) both pharmacological and non-pharmacological treatments to reduce the procedural pain in preterm newborn.[41] Moreover, our recent unpublished data demonstrate that Ado concentration at day 15 was significantly associated with brain WM lesions evidenced using MRI performed at TEA. The underlying mechanism leading to myelination disturbances of the premyelinating preOLs, would be the consequence of the signal conveyed by Ado, which is a potent promoter of the preOLs differentiation.[48,53,54]

Free radical production consequent to hypoxia and ischemia/reperfusion, together with the low caloric intake after birth in the premature babies may cause a slowing down of the oxidative phosphorylation, diminishing high-energy compounds.[18,55]

Future Directions

Many authors accept the hypothesis that free radicals persists to the damage of the premature brain. Consequently, to prevent long-term sequelae of oxidative stress, it is necessary to early diagnosis the presence of an oxidative stress damage by a validate panel of biomarkers, which could also represent the first step in delineating potential therapeutic interventions. To date, different biomarkers have been proposed to measure oxidative stress in the newborn. Plasma prostanoids were validated as biomarkers of oxidative stress injury to neurons.[56] Visfatin, an adipocytokine involved in oxidative stress was also proposed[57] as a new marker of oxidative stress in preterm newborns. Ado blood concentration at day 15 after birth[52] may represent a biomarker to foresee premature brain injury, but further studies are needed to assess its diagnostic value in preterm infants.[58]

Recently, novel treatment strategies have been proposed to counteract damages induced by oxidative stress in preterm infants (see Table 2), including the Ado antagonist caffeine.[68] Considering the cited low postnatal IGF-1 concentrations in preterm infants, associated to ROP and other complications, a supplementation with recombinant human IGF-1 and its binding protein rhIGFBP-3 has been suggested.[47] The preterm hypoxic status has been addressed by administration of erythropoiesis-stimulating agents (ESAs) in particular erythropoietin (EPO), that was shown to display low plasma levels. ESAs reduced the need for blood cell transfusions and decreased rates of IVH, and NEC.[69] However, although promising, early EPO administration was not recommended by a Cochrane Systematic Review, due to its limited benefits[69] and its beneficial effect appears to require further studies.

In conclusion, despite gaps still present in our knowledge of the mechanism of oxidative stress production in the pathogenesis of brain damage in the premature newborn, this organ remains at major risk especially for the prolonged vulnerability of white matter at certain gestational ages during which preterm newborns undergo intensive care treatment. There is a need for new and accurate neonatal biomarkers of brain injury that can foresee those babies at higher risk of developing brain injury thus needing neonatal neuroprotection, by new therapeutic interventions centered on reversal of the processes that promote dysmaturation, one of the more important being oxidative stress.

Author Contributions

Both LR and IP devised main conceptual ideas and outlines. IP took the lead in writing the manuscript. All authors provided critical feedback and discussed the manuscript.

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Conflict of Interest Statement

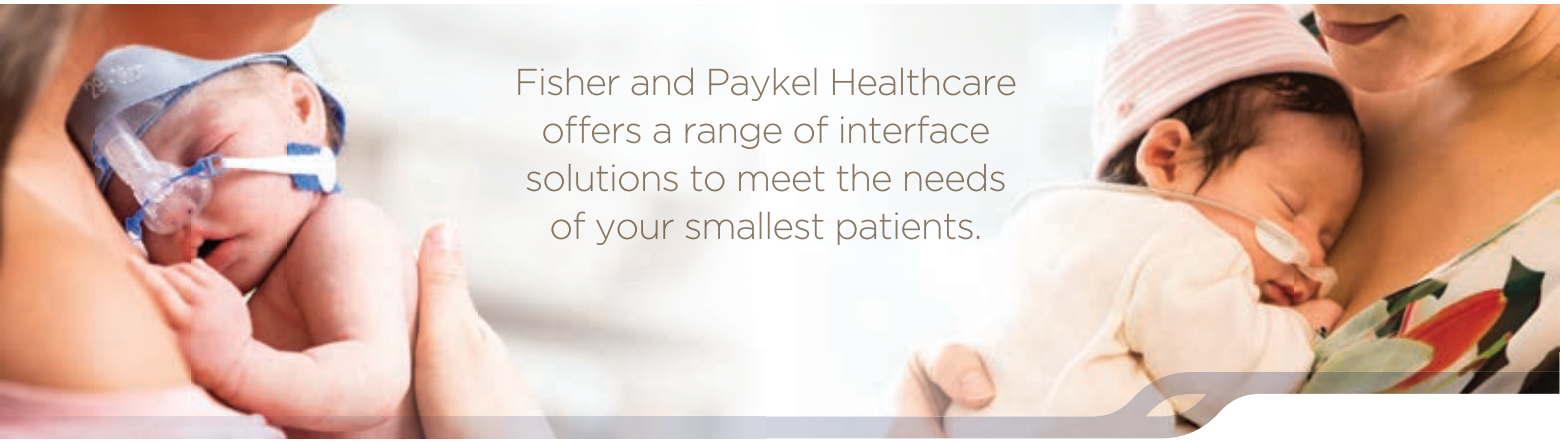
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

News…continued from page 15

ROP screening criteria, so that we can save many premature infants the stress of eye examinations and focus our efforts on those babies most at risk for blindness." Dr Binenbaum of Children's Hospital of Philadelphia and colleagues note that about 70,000 infants a year in the US receive ROP examinations but as few as 5% may require treatment. To develop modified screening criteria, the researchers examined data from a retrospective multicenter cohort study conducted in 29 hospitals in the US and Canada involving 7483 premature infants at risk for ROP. Examinations were deemed necessary if any of the following applied: hydrocephalus, a gestational age of less than 28 weeks, a body weight of less than 1051 g and a weight gain of less than between 120 and 170 g over the course of 10 to 39 days postpartum. This model correctly predicted all of the 459 children with type 1 ROP and 466 of 472 (98.7%) of those with type 2 ROP. The approach also reduced the number of infants who required examinations by 2269 (30.3%). "With validation," say the investigators, "the Postnatal Growth and ROP Study criteria could be incorporated into ROP screening guidelines to reduce the number of infants who require examinations in North America." But as Dr Binenbaum pointed out, "The next step is to validate these new criteria before considering clinical use." For that, he added, "a second study is nearly complete."

F&P FlexiTrunk

F&P Optiflow Junior 2



Fisher and Paykel Healthcare offers a range of interface solutions to meet the needs of your smallest patients.

There is evidence-based guidance supporting the use of CPAP and NHF therapy in the NICU. A Cochrane Review published in 2016 by Wilkinson et al. included data from six post-extubation RCTs that compared the efficacy of CPAP and NHF for post-extubation support.

CPAP and NHF for post-extubation care

GESTATIONAL AGE (WEEKS): 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40

< 28 weeks GA

CPAP first

as there is limited data and insufficient evidence to change clinical practice

Consider NHF once stable to:

- Reduce nasal trauma and head molding
- Facilitate developmental care

≥ 28 weeks GA

NHF first + Rescue CPAP

as data from large RCTs suggests that NHF is equivalent to CPAP, with less nasal trauma and no difference to adverse events

Consider CPAP as as "rescue" therapy if required

Willkinson et al. *Cochrane Database of Systematic Review.* 2016.

In infants ≥ 28 weeks gestational age, compared to CPAP, NHF is associated with:

- **NO DIFFERENCE** in rate of **treatment failure**
- **NO DIFFERENCE** in rate of **re-intubation**
- **SIGNIFICANT REDUCTION** in rate of **nasal trauma**
- **NO DIFFERENCE** in rates of **other adverse outcomes** such as death, pneumothorax, or bronchopulmonary dysplasia

Manley et al. 2013

N Engl J Med.

- 303 infants
- Single center in Australia
- Primary outcome: Treatment failure within 7 days

Collins et al. 2013

J Pediatr.

- 132 infants
- Single center in Australia
- Primary outcome: Treatment failure within 7 days

Liu et al. 2016

Chinese J Pediatr.

- 256 infants
- Single center in China
- Primary outcome: Treatment failure within 7 days

Campbell et al. 2006

J Perinatol.

- 40 infants
- Single center in USA
- Primary outcome: Need for intubation

Mostafa-Gharehbhagi et al. 2015

Zahedan J Res Med Sci

- 85 infants
- Single center in Iran
- Primary outcome: Treatment failure within 3 days

Yoder et al. 2013

Pediatrics

- 432 infants (226 in post-extubation arm)
- Centers: 4 in USA, 1 in China
- Primary outcome: Need for intubation within 72 hours

**NHF: Nasal High Flow, CPAP: Continuous Positive Airway Pressure, NICU: Neonatal Intensive Care Unit; RCT: Randomized Controlled Trial*

Wilkinson et al. *Cochrane Database Sys Rev.* 2016. Manley et al. *NEJM.* 2013. Yoder et al. *Pediatrics.* 2013. Collins et al. *J Pediatr.* 2013. Liu et al. *Chinese J Peds.* 2016. Campbell et al. *J Perinatol.* 2006. Mostafa-Gharehbhagi et al. *Zahedan J Res Med Sci.* 2015.

This information collates data from published literature, but does not overrule expert clinical judgement in patient management.

Please contact your local representative for further information.

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*For babies weighing between 500 and 1250 g. Outcome measures were statistically based on mean weight data.

†Based on the assumption that preterm mother's own milk provides 67 kcal and 1.6 g of protein per 100 mL.

References: **1.** Hair AB, Hawthorne KM, Chetta KE, et al. Human milk feeding supports adequate growth in infants <1250 grams birth weight. *BMC Research Notes*. 2013;459(6):1-8. **2.** Abrams SA, Schanler RJ, Lee ML, Rechtman DJ. Greater mortality and morbidity in extremely preterm infants fed a diet containing cow milk protein products. *Breastfeed Med*. 2014;9(6):281-285. **3.** Hair AB, Peluso AM, Hawthorne KM, et al. Beyond necrotizing enterocolitis prevention: improving outcomes with an exclusive human milk-based diet. *Breastfeed Med*. 2016;11(2):70-74. **4.** Ganapathy V, Hay JW, Kim JH. Costs of necrotizing enterocolitis and cost-effectiveness of exclusively human milk-based products in feeding extremely premature infants. *Breastfeed Med*. 2012;7(1):29-37. **5.** Koletzko B, Poindexter B, Uauy R, eds. Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. *World Review of Nutrition and Dietetics*; vol 110. Basel: Karger; 2014:300-305.

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