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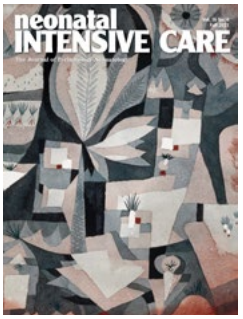

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DEPARTMENTS

Editorial Advisory Board

The Enigma of Autism: Does Labor Management Matter?

BM Petrikovsky MD, PhD

Autism spectrum disorders (ASD) are one of the biggest enigmas of the 21st century. They encompass a group of neuro-developmental disorders characterized by impaired social interaction and a variety of repetitive patterns of behavior.[1] Over the past three decades, the prevalence of ASD has been on the rise in the Western hemisphere,[2,3] posing a substantial public health concern.[4] The lack of understanding regarding the nature and etiology of ASD has led to the formulation of multiple theories regarding its origins, including hypotheses related to vaccines, obstetrical ultrasound, and augmentation of labor among others.[5-7] The role of vaccines in causing ASD has been thoroughly disproven and is no longer a subject of discussion within the scientific community.

Diagnostic ultrasound

Abramowicz reviewed the topic of diagnostic ultrasounds and concluded that there is no peer-reviewed published evidence establishing a causal relationship between prenatal exposure to clinical ultrasound and the development of ASD.[8] Although a mouse study suggests that a prolonged exposure (over 30 minutes) to diagnostic ultrasound can impact neuronal migration, it is unlikely that it is relevant to clinical exposures in humans.[9]

Augmentation of labor

Regarding labor augmentation, a study using detailed birth records and education research databases from North Carolina investigated the association between ASD and labor augmentation among 625,042 live births, including 5,500 children with autism. Among males, multivariate logistic regression showed a weak association between ASD and labor augmentation.[10] However, the study design could not definitively determine if such findings were a result of cause and effect.[6] Reviewers further pointed out that the study failed to indicate the specific agents used for labor augmentation. Additionally, the American Psychiatric Association reported an editorial error in the criteria for diagnosing pervasive developmental disorder not otherwise specified in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, potentially leading to overdiagnosis during a significant portion of the North Carolina study's time frame.[11]

Autism and obstetrical events

A study conducted by Getahun, et al. examined the electronic health records of 594,638 children born in Kaiser Permanente Hospital in Southern California between 1991 and 2009.[4]

Approximately 1 in 88 American children is affected by ASD, with a 4:1 male predominance.[12] Newborns exposed to obstetrical complications during birth were at a 10% increased risk of ASD compared to children who did not experience such complications.[4] The study identified birth hypoxia; the abruption of the placenta, and preeclampsia as the perinatal complications with the highest association with ASD. Other factors such as umbilical cord prolapse, abnormal presentation, poorly managed labor dystocia and low Apgar scores were also linked to ASD. This association may be explained by compromised blood flow to the fetal-placental unit, increasing the risk of ASD.[13]

Practical implications

Despite extensive research efforts, the causes of ASD remain unclear. The recent increase in its prevalence is worrisome, although improved diagnosis and increased awareness may partially explain the rise. It has been postulated that ASD is a multifactorial disease influenced by a combination of genetic and environmental factors that affect critical periods of brain development.[14] While the effect of fetal conditions on the development of childhood disease is recognized, studies of the impact of these conditions during fetal development and its connection to ASD are limited.[15] Continued research into the etiology of ASD is necessary, but based on our current knowledge, we recommend implementing the following precautions:

1. Limit fetal ultrasound exposure, including Doppler, to the minimum necessary.
2. Pay careful attention to the management of fetal hypoxic episodes during pregnancy and labor, striving to avoid even intermittent hypoxia.

Hopefully, further research will provide additional insights into the causes of ASD, enabling improved prevention, early diagnosis, and management of the disorder.

Cesarean delivery and ASD

At first glance, it appears that delivery by cesarean section is associated with an increased risk of ASD.[16] However, although an association between delivery by cesarean section and ASD is possible, a causal relationship has not yet been confirmed. Cesarean section is often performed because of prenatal and intrapartum complications which might be connected to ASD.[16] Many conditions (prematurity, placental abruption, abnormal

BM Petrikovsky is a Professor of Obstetrics and Gynecology, an Editorial Board Member, and ACOG Life Member.

FHRtracings, prolonged labor, shoulder dystocia, etc.) are independent risk factors for ASD, regardless of the mode of delivery. In our anecdotal experience, an elective full-term cesarean section prior to the onset of labor is associated with a lower rate of ASD compared to a cesarean section after labor or a complicated vaginal delivery.[17]

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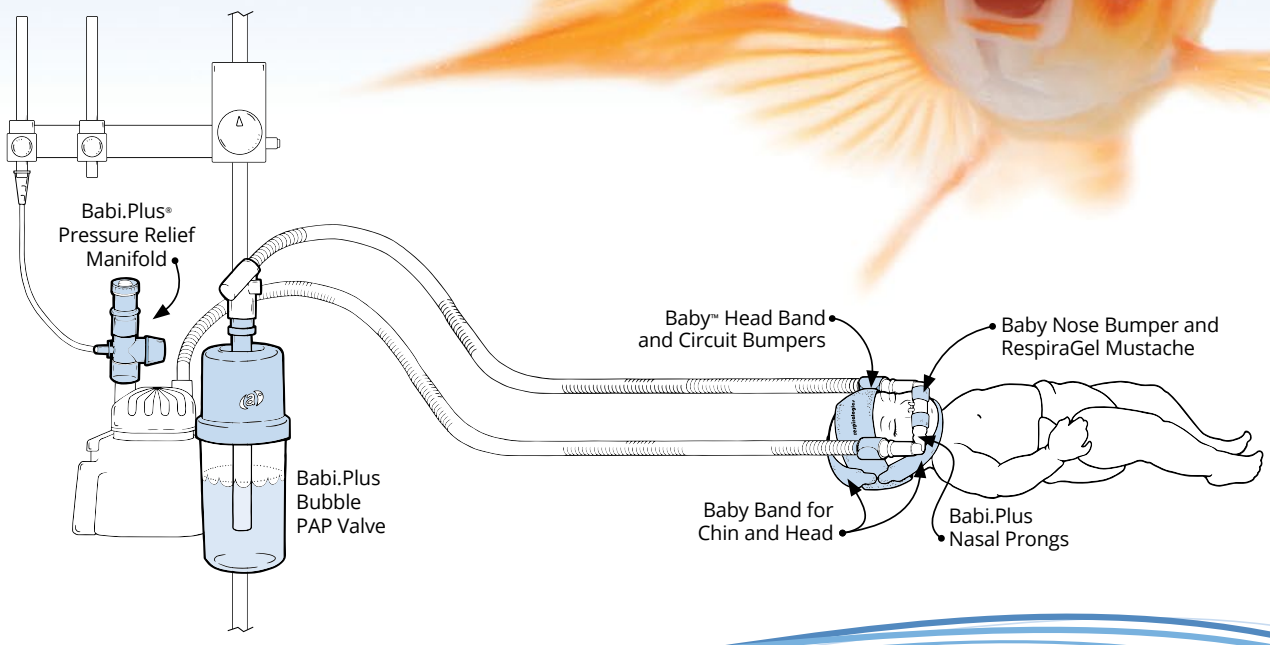

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News

☐ Fall 2023

New AAP Framework Seeks to Help Pediatricians Monitor Premature Babies

A new framework from the American Academy of Pediatrics published aims to aide general pediatricians in better caring for premature babies who are at risk of developing developmental disabilities. About 1 in 10 babies in the United States are born before full term. Even when they are discharged from neonatal intensive care units, these babies are still at risk for conditions like cerebral palsy, autism spectrum disorder, deafness, and severe hearing loss. The framework, published in the journal *Pediatrics*, consolidates existing research into a guide for busy pediatricians to categorize patients as very high risk, high risk, or moderate-low risk for neurodevelopmental disabilities. The guidance also lists key identifiers to help providers flag issues early, such as asymmetry of hand use. Beth Ellen Davis, MD, MPH, a framework author, said the goal is to help pediatricians determine what surveillance and screening they can conduct to promote positive health outcomes. Davis said she wished she had this guidance on caring for children who were born prematurely during her 10 years as a general pediatrician in the US Army Medical Corps.

"I didn't know what I was supposed to do differently with [the former NICU babies]," said Davis, a professor in the Division of Neurodevelopmental Behavioral Pediatrics at the University of Virginia in Charlottesville. For instance, babies born earlier than 28 weeks who have hypoxic ischemic encephalopathy or retinopathy of prematurity (ROP) requiring surgery or intervention are classified as very high risk for the adverse outcomes, including intellectual disability. The authors recommend follow-up and surveillance based on risk level at roughly 9-month intervals until around age 5. Each visit includes assessing for developmental milestones, like walking by 18-months or noting atypical pencil grasp at age 3.

OCD Linked to Adverse Pregnancy and Neonatal Outcomes

Maternal obsessive-compulsive disorder was associated with increased adverse pregnancy, delivery and neonatal outcomes, according to findings from two cohort studies published in *JAMA Network Open*. "We believe that women with obsessive-compulsive disorder (OCD) would benefit from early referral in pregnancy and having access to regular antenatal care with the obstetric care team and also the physicians that routinely take care of their mental health symptoms," Lorena Fernández de la Cruz, PhD, principal researcher at the Centre for Psychiatry Research in the department of clinical neuroscience at Karolinska Institute, Stockholm, told Healio. "Clinicians should work together to reduce these risks, when possible. For example, preeclampsia, for which we observed an increased risk for women with OCD in our study, can be avoided if a good monitoring during pregnancy is in place." Fernández de la Cruz and colleagues conducted two register-based cohort studies in Sweden and British Columbia, Canada. These studies included all singleton births at 22 weeks or more gestation. The Swedish cohort included births from 1999 to 2019, and the British Columbia cohort included births from April 2000 to December 2019. Researchers examined maternal OCD diagnosis recorded before childbirth and the use of serotonin reuptake inhibitors (SRIs) during pregnancy. Researchers assessed pregnancy and delivery outcomes including gestational diabetes, preeclampsia, maternal infection, antepartum hemorrhage or placental abruption, premature membrane rupture, labor induction, mode of delivery and postpartum hemorrhage. Neonatal outcomes included perinatal death, preterm birth, small for gestational age, low birth weight, low 5-minute Apgar score, neonatal

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hypoglycemia, neonatal jaundice, neonatal respiratory distress, neonatal infections and congenital malformations. The Swedish cohort included 8,312 pregnancies among women with OCD that were compared with 2,137,348 pregnancies among unexposed women. Overall, 37.2% of women with OCD were taking SRIs in the Swedish cohort, and 81% were taking SRIs in the British Columbia cohort. Women with OCD who took SRIs during pregnancy had increased risks for several pregnancy, delivery and neonatal outcomes compared with women not taking SRIs. Researchers also observed increased risks for these outcomes among women with OCD not taking SRIs compared with women without OCD. According to Fernández de la Cruz, women with OCD and their health care providers should have all available information and assess risks and benefits of treatment while monitoring any pharmacologic treatment changes and, if indicated and available, other therapeutic options, such as cognitive-behavior therapy, should be explored.

New Study Shows Prolacta's Human Milk-Based Nutritional Fortifiers Save Hospital NICUs Up to $3.4M Annually

Prolacta Bioscience, the world's leading hospital provider of 100% human milk-based nutritional products for critically ill, premature infants, announced a peer-reviewed report demonstrating significant annual cost savings that ranged from $500,000 to $3.4 million per hospital after the implementation of Prolacta's Exclusive Human Milk Diet (Prolacta's EHMD) for preterm infants in the neonatal intensive care unit (NICU). NICU leaders from seven US hospitals varying in size, geographic setting, patient population, and funding levels contributed to the publication in *BMC Pediatrics* titled "Implementing an Exclusive Human Milk Diet for Preterm Infants: Real-World Experience in Diverse NICUs." The study found that of the five hospitals reporting financial data, all realized significant cost avoidance after implementing Prolacta's EHMD, with savings ranging from $515,113 to $3,369,515 per institution annually from a reduction in comorbidities and shorter lengths of stay among very low birth weight (VLBW) infants. Implementation of Prolacta's EHMD resulted in a reduction in the total (medical and surgical) necrotizing enterocolitis (NEC) rate, regardless of the size or level of care of the NICU, as well as reductions in bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and late-onset sepsis—all common complications of prematurity. VLBW infants fed Prolacta's EHMD also experienced shorter NICU stays at five of the seven hospitals, savings ranging from $307,916 to $2,520,000 per institution annually. The study emphasizes that the cost of Prolacta's EHMD represents a fraction of the usual cost of care for a VLBW infant—approximately $12,500 per infant for an EHMD over a 90-day NICU stay, compared to a total NICU cost of $693,000 to $774,000 for 90 days, depending on level of care. A reduction in length of stay has a sizable impact on total cost expenditure compared with the investment in an EHMD. "This study provides real-world evidence that an EHMD is not only effective in reducing comorbidities in very preterm infants but also saves money regardless of the institution's size or level of care," said lead author Jonathan R Swanson, MD, MSc, of the University of Virginia Children's Hospital in Charlottesville. Although protocols differed, feeding volume at initiation of fortification, fortification goals, and criteria for transitioning infants off Prolacta's EHMD were similar among the institutions. All seven hospitals fortified between 60-80 mL/kg/day. Clinical outcomes data for each hospital were obtained either from Vermont Oxford Network (VON) or the institution's NICU database. "While the NICUs participating in this study were diverse, the benefits and cost savings of Prolacta's EHMD were consistently observed, including reduced complication rates, shorter lengths of stay, and reduced costs," said Melinda Elliott, MD, chief medical officer for Prolacta and a practicing neonatologist. "These findings mirror the cost savings seen for years in hospitals adopting Prolacta's fortifiers, including my experience and published research on an EHMD at The Herman & Walter Samuelson Children's Hospital at Sinai in Baltimore."

FDA Panel Backs Sanofi-AstraZeneca's Preventive RSV Therapy

The US Food and Drug Administration advisers have backed the use of Sanofi and partner AstraZeneca's experimental antibody to prevent respiratory syncytial virus (RSV) infections in infants. The advisers voted unanimously in favor of using the antibody, nirsevimab, in newborns and infants to prevent infections in their first RSV season. In a separate 19-2 vote, the panel backed the therapy's use in children aged up to two years who are vulnerable to severe illness through their second RSV season. Swedish Orphan Biovitrum's treatment Synagis is currently the only approved preventive therapy in the United States for high-risk infants against RSV, a leading cause of hospitalizations during an infant's first year of life. Unlike Synagis, which is given as monthly injections, nirsevimab is a long-acting therapy expected to be given once every season to prevent infection regardless of additional medical conditions in infants. "This is probably the closest thing to an RSV vaccine that we have and it really moves the field forward," said panel member Nimish Patel.
Continued on page 16…

From Babies to Baby Hippos; A Vascular Pioneering Legend Answers Questions for His Cherished Customers

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Tim Duvall, Founder of Neo Medical, Inc.

Tell us about your background.
I have a Bachelor of Science degree from UC Berkeley and an MBA from Pepperdine University. Many people ask if I'm a medical doctor or engineer because of the products I've developed, but I have always had a desire to create and invent things. My grandfather was an inventor, my father was a chemist with multiple patents and my mother was a very compassionate and dedicated registered nurse who also inspired me to help others.

I've been in the medical device field since 1993 and have 30 years of experience in critical care products including PICC lines, midlines, regional anesthesia, interventional radiology-specific products and cardiology-specific products. I founded Neo Medical Inc. and the NeoMagic line of products in 2007 to focus on the tiniest and most vulnerable of our patients such as premature infants and young children.

In 2016 I was awarded Technologist of the Year and in 2023 my company was awarded Medical Health Services Company of the Year, both of which were in the State of Nevada.

What made you decide to create, and then manufacture, lifesaving Neonatal devices?
Having looked closely at the products that were available to licensed medical professionals, I found that the Neonatal arena was one of the most underserved parts of the medical device market mainly because of its market size. Therefore, when I started my own small company, I said, "Hey, this market is perfect to focus on and create products from the ground up that are specifically designed for those patients." Also, I have been in many NICU units and have observed the fantastic things that were being done and the need for less traumatic devices; I just wanted to be a part of that endeavor.

When I first started the company, I was brought into a couple of meetings with a Pediatric Vascular Access Specialty group and was specifically asked to bring out the first MST kit for the neonatal world. I jokingly was told I wouldn't be allowed to attend the cocktail party the following year unless I brought a prototype. I thought about it and decided to give it a try. I built a prototype dilator, which was a great device, and years of excellent results reflect this.

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

I also remember being at an Emory University health fair in 2011. I went into a seminar where I saw horrible damage being done to children such as extravasations, one of which resulted in an amputation because of the failure of the device being used. It just hit me very hard, and I decided right then and there that we can do better than this!

That experience resulted in the creation of our extended peripheral IVs (EPIVs) which were the first of their kind to enter the market. Our MST was also the first in the world created for neonates.

What patient population benefits most from your products?
Well, we make products for every patient size, but over the last 10 years our concentration has been in the pediatric and neonatal communities. My company, Neo Medical Inc, was the first one to bring out designs specifically for neonates, but we didn't just take adult products and reduce the size. For example, we didn't take an adult tear-away and put a 2Fr tube on it, instead we redesigned the entire product specific to the patient population it serves.

Which products are most in demand?
Our Mini Neonatal MST Kits, EPIVs, and our silicone and polyurethane PICC lines are the most popular devices we manufacture. Demand for these products has increased so much that we have difficulty keeping them on the shelf! New customers constantly request overnight shipments because they want to transition to our USA-made products because they are more reliable in a critical care environment.

Why do you think your EPIVs and MSTs are in such high demand?
They work incredibly well because our high-quality standards yield great results! We continually improve all facets of our products, and my manufacturing, production, quality, and engineering crews are very keen on carefully monitoring the quality of our products. We see the results in the field and our EPIVs are now backed by three clinical studies and publications.

We are fortunate that 100% of our suppliers are based in North America so we readily have access to raw materials. In addition, our manufacturing is 100% in the USA as well, so our clients know they will receive top quality products, which also drives demand.

How did these products evolve?
Many years of speaking directly to clinicians has allowed me to understand what does, or doesn't, work for them in the field. I look at what they like, but most importantly I consider *what they need*; when a new product is designed, both factors are critical to the successful use of the product. For example, the new product we are designing is due to demand for a smaller catheter for micro- preemies. However, I considered the need to introduce that into very fragile, immature veins which demands close examination of the entire catheter system and how it will be used. My desire is not to just meet demand but to seriously consider how it will be used in the field.

Once a licensed professional commits to an invasive action, they *must* have confidence in the product they are using because it can mean life or death for that tiny patient. This captures my heart and mind *every* time I think of a new product.

What are some of the challenges that practitioners face when choosing a product?
Finding a product that has been designed specifically for a particular patient population can be a challenge. The individuals that choose to save the tiniest patients are heroes on the front line of care; they hone their skills daily and they want the very best product they can find.

Informed decision-making is a hallmark of knowledgeable and successful clinicians. We constantly answer clinical questions by employing licensed medical professionals and engineers to ensure accuracy. When a clinician needs specifications on catheter diameters, we must answer that question immediately. Our goal is to make their procedures as flawless as possible.

Many practitioners have asked about the rumors of another groundbreaking new product you have created. Would you be willing to give us a little information about this and when it will be released?
I had a dream product sitting on my desk for quite a while, but then perfected it for release. It is a 1.2 Fr Reduced Trauma Catheter for Micro-Preemies with an Integrated Introduction System. The concept was fairly simple; the introducer becomes part of the catheter, so it doesn't require a large tear-away introducer to place a very small catheter.

It's patent-pending internationally now and should be a serious game-changer that is slated for release this Fall. My hope is that we can get micro-preemie survival rates up to the same level we have achieved for most babies that are born too soon.

We were told to ask you about the baby hippo story. Tell us about this.
A few years ago, in 2017 the Cincinnati Zoo called Cincinnati Children's Hospital because they had a tiny baby hippo that was born 6 weeks prematurely. The hospital sent over our 3 Fr EPIV along with their PICC Team. I then got a call that we had saved Fiona. I said, "What's a Fiona?" They laughed and explained that they had saved this baby hippo with our product and thanked me. What a great story! Fiona thrived and now weighs over 1300 pounds! They even wrote a children's book about her.

We hope you say, "Never," but do you have any plans for retiring?
No! Okay, everybody gets to that point in their life when they want to move on to the next great adventure, but I will never retire! I have lots of ideas and hopefully will stay involved with what I love best, which is creating new groundbreaking products. Also, I've been involved in youth initiatives in every community where I've lived. My parents believed that your community is only as good as you make it and because of them I intend to always try to make our world a better place!

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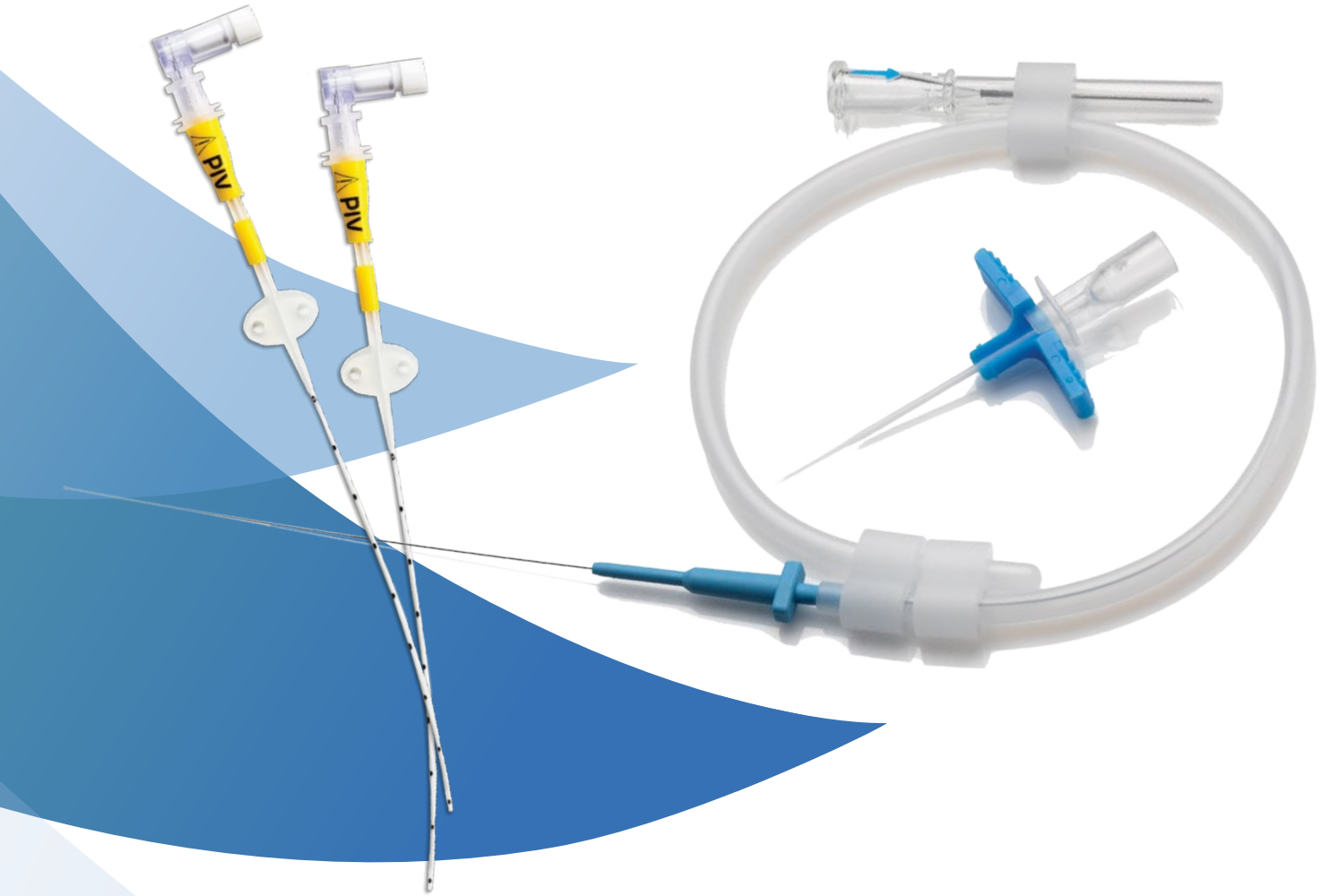

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An HIE Mom Starts a Support Movement

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Betsy Pilon, executive director of Hope for HIE, a global nonprofit that helps families impacted by neonatal and pediatric-acquired hypoxic ischemic encephalopathy.

So many parents in the NICU are told not to socialize with other parents. My stay with my premature infant daughter, almost 20 years ago, was no different. One tiny baby would be placed in an incubator next to a much larger infant and so on and so on. We parents were desperate for connection, for community. It wasn't until I found out about a preemie group in a newsletter in the parent waiting room that I realized there was a lifeline. Years later I would come to find out about the myriad of conditions that land infants in the NICU. One of these was the condition Hypoxic Ischemic Encephalopathy (HIE) and it was then that I learned about Betsy's organization, Hope for HIE (https://hie.support). This organization, in my mind, is not only a lifeline for parents but also for professionals trying to find resources to give to families. I was honored to interview Betsy so as to help continue to spread the word among the professional community in hopes that this would also in turn put a large spotlight on a condition that needs real attention and education.

Deb Discenza (DD): How did Max get diagnosed with HIE and how was it explained to you?
Betsy Pilon (BP): Max stopped moving when I was 37 weeks pregnant. I went into labor and delivery after he failed kick counts, and he was determined to be in significant distress. While he had a heartbeat, it was non-reactive, and he was not "pre-breathing". I was rushed in for an emergency c-section at our local community hospital.

After he was born, he let out a small cry and was immediately intubated, and taken to be assessed. It was determined he needed a higher level of care and qualified for therapeutic hypothermia. We had no idea what that meant, and figured he was "just a little early" and needed breathing support. We did not realize it was neurological for a few days, as we were told this could be something non-neurological. However, at day five after he had rewarmed from cooling and had an MRI, it was determined his brain was injured, suffering from damage to the occipital, frontal and parietal lobes. He spent just under three weeks in the NICU.

Deb Discenza is the mother to a 30-week preemie who is now 19 years old. She runs PreemieWorld.com, home of "The Preemie Parent's Survival Guide to the NICU" sold in bulk to NICUs and non-profit organizations nationwide. In 2020 she was a Co-Founder of the Alliance for Black NICU Families. Interested in the pump program? Please contact us at contact@blacknicufamilies.org.

We did not hear the official diagnosis of Hypoxic Ischemic Encephalopathy until after discharge. We heard the term "encephalopathy" used once during rounds, and when I asked (my husband had to go back to work), I felt dismissed and was told, "It has something to do with the brain, and don't go home and Google it." The initial term used with us was "perinatal depression". His neurologist confirmed HIE at our follow up appointment post-discharge. We received no educational information or connection to support for HIE when we asked in our discharge planning process. It felt like we were pushed off a cliff, and we were told to feel lucky we had a short NICU stay. After we got home, I began Googling and weeded through complex medical journal articles and sites for birth injury attorneys. Eventually, I found three families blogging about their experience and all connected me into a Facebook group, Hope for HIE, with around 200-300 families at the time from all over the world. Everyone had a similar story of a lack of support and education, and there was talk of forming a foundation to build out more support and advocacy for HIE.

Max is 11 years old today. He is "living his best life" every day, but does live with permanent impacts from his HIE including spastic diplegic cerebral palsy, a vision impairment, ADHD and later childhood onset epilepsy stemming from his HIE. Despite these challenges, he's smart, funny, loves basketball, video games, has a wonderful group of friends, and is heading to middle school.

DD: So what educational information were you given in the NICU and out of the NICU?
BP: We were not given any information about HIE in the NICU. We were handed two brochures — one for early intervention services, and one "inviting" us to apply for Medicaid supplemental. I headed to the internet and found families connecting. This group became my lifeline and a call to action to build out support, education and advocacy for HIE. Finding out the incidence of 2-3 per 1,000 live births was frustrating, because there had been no advocacy for this community despite a pretty significant prevalence, HIE being the 2nd leading cause of infant mortality worldwide, and a significant cause of lifelong disabilities across a wide range, and having ONE approved therapeutic treatment.

DD: Hope for HIE was created by other Moms, correct? When did you come into the picture?
BP: I did not start Hope for HIE. I am a torch bearer, "standing on the shoulders of giants." Hope for HIE was started by three

moms like myself, who passed the torch to a group of us who got the organization up and running in 2013. While I have led these efforts, and feel proud of the contributions I have made to grow our global community over the last decade, the vision was set in place before I found Hope for HIE. Hope for HIE belongs, first and foremost, to the global HIE community it connects and serves.

I heeded a call to move the organization forward knowing I could contribute my skill sets in organizational and community development, marketing and communication in healthcare initially just to make the internet a friendlier and more accessible place to be for families who would be searching for support like the rest of us had.

DD: So what are the statistics around HIE?
BP: HIE happens in 2-3 per 1,000 live births in developed countries, and 10-20 per 1,000 live births in low and middle income countries. It's the second leading cause of infant mortality in the world. It can happen to preemies and full term babies, but primarily impacts full term babies.

The largest impact area with HIE is epilepsy. HIE is the leading cause of neonatal seizures, and the leading non-genetic cause of some really aggressive rare seizure disorders such as Infantile Spasms, Lennox-Gastaut Syndrome and ESES/CSWS.

For a long time, HIE was erroneously painted as interchangeable with Cerebral Palsy. Only around 40% of babies born with HIE will develop CP, and HIE only makes up around 10-15% of all CP cases.

There is also a lot of confusion families face with understanding when the medical community refers to "levels" of HIE. There are typically four different references:

- Babies born with HIE are typically assigned a level on the Sarnat scale — mild, moderate, & severe. This matrix drives intervention decisions such as qualification for therapeutic hypothermia. Research has shown this level is not a good predictor of outcome, however.
- Babies born with HIE typically get an MRI, and interpretation will be made on any impact areas that can be seen structurally, and some will assign "levels" of damage severity. This is one piece of a puzzle, and more data has shown it is not the best predictor of prognosis, again one piece of the puzzle, but not the entire puzzle.
- Babies with HIE will receive EEGs in the NICU, and interpretation will be made on the areas of concern that could correspond to findings on the MRI, or may show slowing or spikes. EEGs can change over time. This diagnostic is more of an assessment of how the brain is functioning.
- Clinical outcome is measured against various developmental domains, and gives the most accurate picture of how a baby is doing and progressing.

There is so much complexity with HIE, and part of the difficulty is that we still don't know why some children do better than others.

DD: What are the treatments to date for HIE?
BP: There is one approved treatment currently — therapeutic hypothermia - and only approved for a specific criteria of babies. Babies are cooled down to approximately 91 degrees for 72 hours. It takes approximately 12 hours to bring a baby down to the therapeutic temperature and 12 hours to rewarm. To qualify, a baby should meet the moderate or severe criteria on the Sarnat scale, 36 weeks gestation or greater, and cooling must be initiated within six hours to have a chance of being effective. Cooling has been shown to decrease death and disability by around 40%, meaning it saves more babies, but the level of disability has a wide range. And, it leaves out many babies who may miss the window, be a less gestation, or not qualify for one reason or another, such as a mild presentation – which could actually be more of a severe injury as some babies may have a more mild appearance at birth and some will begin having neonatal seizures 12-24 hours after birth, get an MRI and discover brain injury.

There is an upcoming multicenter study looking at the safety and efficacy of expanding cooling to mild HIE babies that is PCORI-funded and called COOL PRIME.

There is upcoming data to be published that was discussed at the recent Pediatric Academic Society meeting showing cooling preemies caused adverse effects, including increased mortality.

There are several exciting therapeutics in the pipeline in various stages. Some are novel therapeutics – such as the upcoming ReAlta RLS-0071 multicenter study that is set to begin shortly — and some are testing existing medications/therapeutics such melatonin, caffeine, and other neuroprotective agents that have shown preclinical promise and are working through the feasibility of safety and efficacy to move to human trials. Most are following the cooling model of running with cooling as the standard of care, and adding on, initially for moderate to severe presentation babies.

DD: Impressive! So tell me about Hope for HIE and what your organization does for families and the public?
Hope for HIE has built a comprehensive support network of more than 8,500 families worldwide, supported by a staff that includes a full time Executive Director, part-time licensed clinical social worker, certified child life specialist, program manager, and administrative assistant support. Because HIE has such a wide range of impacts and outcomes, we have tailored our support services and programming to best meet the needs of our community, attempting to fill known gap areas, so that all HIE families can access services that sometimes can only be found at Children's Hospitals, such as our Child Life services, but so many need and can utilize. We have built out support programming and services to serve the full family across various demographics and locations.

We are focused on health information literacy, as HIE is filled with lots of complex medical jargon, and families are often thrown into the world of medical complexity with varying educational levels and understanding. Because our families have experienced trauma, and often have children facing medical complexity, with so far, not a lot of effective therapeutics, this is also a vulnerability for our community, and others like ours, for "bad actors" to attempt to peddle unproven treatments that many are either ineffective, unsafe, or both, and typically cost thousands of dollars out of pocket. As resources such as time and money are limited for most people, we want to ensure families have a deep understanding of what has been disproven, what is emerging as having possible benefit, and what is known to have evidence behind it to be effective.

We work to make our resources as accessible as possible, and have a robust translation committee working to not only translate our resources, but also serve as vetted points of contact for families to communicate in their first language.

We also have been building our advocacy and research efforts, collaborating with the top researchers in HIE and related subsequent diagnoses like cerebral palsy and epilepsy, globally. We also elevate the lived experiences of our community and identify advocacy areas of focus where inequity and inaccessibility for our community exists—from the neonatal period through adulthood, and in loss. In particular, the vast majority of NICU support and advocacy has excluded families outside of the premature experience, and thus resources continue to be built without important input from communities like ours, which perpetuates the marginalization of families, in conjunction with the abysmal maternal and infant mortality rates around the world. However, there is a lot of interest thanks to other advocacy groups like the Newborn Brain Society that have shed a light on our community, and the need for better research, care and inclusion.

DD: I agree, we should not be excluding non-premature infant families from support in the NICU. The fact that this happens is really frustrating to me as an advocate for all NICU families. What do you want professionals to know about HIE and about what you are doing? How can they spread the word about your work?

BP: Our neonatal HIE families continue to have inequitable access to longitudinal care and support. Partnering with patient advocacy organizations like ours can help decrease these impacts and accelerate progress in both clinical care and research. We know our community best, we have passionate volunteers and patient-families who want to give back. We just need the opportunity to do so.

We also have built a comprehensive clinical trial support structure based on research, data, and best practices in patient-centered outcomes and are available for consulting on a variety of projects and topics. More information can be found on our website.

There continues to be a significant disparity of awareness and support for our community by the neonatology community. This can be seen strongly in fundraising, messaging and advocacy by leaders in the neonatal space who elevate other communities far over others. This has been attributed to the uncomfortability of taking care of neurological impacted full term babies and the notion of "sad outcomes" for this community, which only adds bias and stigma. Lots of work to do!

DD: Agreed, lots of work to do. Thank you Betsy.

NICUs take notice. Preemies may be a common denominator in your unit but equitable care means access to support and more for *all families* regardless of reason of admission to the NICU. We get it—you are busy. So here is a simple way to help HIE families. Send them to Hope for HIE (https://hie.support) today and know that you are working with a vetted organization making headway in this arena in support, education and yes, studies, too.

News…continued from page 10

Kangaroo Mother Care May Cut Death Risk for Premature Babies by a Third

Kangaroo mother care (KMC), with close skin-to-skin contact between mothers and their low-birthweight newborns, appears to reduce mortality risk by almost one-third, compared with conventional care, according to new research published online in BMJ Global Health. Starting the contact, which involves mothers carrying the newborn in a sling, within 24 hours of birth and continuing it for at least 8 hours a day both appear to amplify the effect on reducing mortality and infection, the paper states. Sindhu Sivanandan, MD, with the department of neonatology at Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, and Mari Jeeva Sankar, MD, in the pediatrics department of the All India Institute of Medical Sciences, New Delhi, looked at existing studies to compare KMC with conventional care and to compare starting the intervention within 24 hours of birth versus a later start. Their review looked at 31 trials that included 15,559 low-birthweight and preterm infants collectively. Of the 31 trials, 27 studies compared KMC with conventional care and four compared early with late initiation of KMC.

Tankless Delivery System Recognized as a 'Technological Breakthrough'

VERO Biotech Inc., a commercial-stage healthcare business dedicated to neonatal intensive care and the acute care hospital community, announced that it will be honored during Premier, Inc.'s annual supplier Innovation Celebration at the 2023 Breakthroughs Conference and Exhibition. VERO Biotech's GENOSYL Delivery System (DS) will be recognized as a "Technological Breakthrough." VERO Biotech's GENOSYL DS—the first tankless nitric oxide delivery system approved by the FDA—will be one of only seven innovations honored during Premier's supplier Innovation Celebration, which recognizes groundbreaking healthcare technologies that have been launched throughout the year and the ways these products are helping to improve the health of communities. "We are honored to receive this recognition from Premier. We are deeply committed to continued innovation so that we may better serve patients, respiratory therapists, and healthcare providers." said Brent V Furse, CEO and President, VERO Biotech. Premier is a leading healthcare improvement company, uniting an alliance of approximately 4,400 US hospitals and 250,000 other providers to transform healthcare. With integrated data and analytics, collaboratives, supply chain solutions, consulting and other services, Premier enables better care and outcomes at a lower cost. GENOSYL DS is the first tankless inhaled nitric oxide delivery system approved by the US Food and Drug Administration (FDA). Inhaled Nitric Oxide dilates pulmonary blood vessels and may be used to improve oxygenation in neonates with hypoxic respiratory failure and pulmonary hypertension. Unlike tank-based systems, GENOSYL DS generates and delivers iNO at the bedside using a small disposable cassette. This eliminates the need for hospitals to manage large, cumbersome tanks, helps to simplify clinical workflow, and streamlines patient care.

Study Shows Prolacta's Fortifiers Significantly Increase Bioactivity

Prolacta Bioscience, the world's leading hospital provider of 100% human milk-based nutritional products for critically ill, premature infants, today announced that *Breastfeeding*

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LungFit PH: Reactions from RTs on their Transition to and Use of this New System

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Heidi Dostal RRT-NPS, Lindsay Eddy RRT and Sarah Burda BSRT, RRT regarding the LungFit® PH system.

LungFit® PH is the most recent nitric oxide delivery device to become commercially available to treat neonates with hypoxic respiratory failure. Approved in June 2022 and with just over a year on the market, we asked a few respiratory therapists to share their transition from traditional cylinder-based systems and experience with the LungFit PH.

The LungFit PH is the first and only FDA-approved system that generates inhaled nitric oxide (iNO) from room air. The 3-in-1 integrated system generates, delivers, and monitors iNO and provides unlimited, on-demand iNO regardless of dose or flow, without the use of cylinders or cassettes.

Responses by Heidi Dostal RRT-NPS, Neonatal-Pediatric Advanced Practitioner, Bryan Health

Can you tell us about your career in respiratory care within the NICU?
I have been a respiratory therapist for 25 years, 15 years in NICU. Respiratory therapy (RT) is heavily involved with the care of NICU babies on respiratory support. We are also part of the neonatal transport team.

How did you find the transition from traditional cylinder-based systems to LungFit PH?
The transition to LungFit PH from the cylinder-based system was very smooth. The staff is good about letting the oncoming shift know when the NO_2 Smart Filter will need to be changed in report. The nursing staff is also good about letting us know when the last 30 minutes of the filter alarm goes off.

What are the advantages of the LungFit PH system compared to other systems on the market?
Our NICU is in a different building from the RT department, and you really had to plan ahead to make sure that we had enough tanks if we were running low. If you had a busy shift, it was easy for that to slip your mind. With the LungFit PH, we are getting into the habit of checking how many filters we have when we switch to a new filter. It is also easier to store the filters than the tanks, along with changing the filter vs tanks. The setup time is shorter for the LungFit PH system than the cylinder-based system.

How has LungFit PH improved NICU workflow?
The time that we would have spent getting the tanks to the NICU, changing the tank, and setup calibration, we can use that time to devote to patient care. Switching the filter is easy and fast.

What has been the initial response to LungFit from the NICU team?
We have had a positive response from the nursing staff, NNPs, and Neonatologists. Overall, there is less confusion about what needs to happen in order to manually ventilate a baby on nitric oxide (ie, which knob to turn, is the nitric oxide set where we need it, etc).

Responses by Lindsay Eddy RRT, Registered Respiratory Therapist, Northshore Edward-Elmhurst

Can you tell us about your career in respiratory care within the NICU?
I have been a NICU respiratory therapist (RT) for a little over a year now after years with adult and pediatric patients, and I love it. In Edward's NICU, respiratory therapists are very valued and work very closely with the NICU nurses and Neonatologists. I was very welcomed into the NICU and have thoroughly enjoyed my time learning and growing in our NICU. As a NICU RT we are responsible for maintaining airways, running ventilators, giving nebulizer treatments, as well as other respiratory treatments that may be ordered. And finally, we are responsible for setting up and running nitric oxide (NO) systems.

How did you find the transition from traditional cylinder-based systems to LungFit PH?
At first, I was nervous about the transition because a cylinder-based system was all I have ever known, and I was very comfortable with it. After setting up a LungFit unit on a patient and getting the system running I felt silly for being nervous. The LungFit system is extremely easy to use, and the setup was quick and seamless. I almost didn't believe it was on and running so quickly. I would say my transition from cylinder to LungFit was very smooth and I am happy with the switch.

What are the advantages of the LungFit PH system compared to other systems on the market?
The biggest advantage to the LungFit system is how quick and easy the system is to set up on patients. The delivery of NO is very fast with the LungFit PH. Aesthetically the LungFit system looks very new and is easy to transport. The screen display is easy to navigate and read, which is very helpful for all staff.

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

How has LungFit PH improved NICU workflow?
The LungFit PH has cut down the time from the physician order to delivery of NO dramatically, which is a huge asset. The nurses and doctors are very pleased with how fast we can set up and run the new nitric system. Timing is very important in NICU and when those patients need something, especially an inhaled gas, they usually need it rather promptly.

What has been the initial response to LungFit from the NICU team?
The initial response was as to be expected with anything new. The NICU team was excited about the new machine and loved the looks of it, but they were nervous about not having tanks and how effective the filters in the LungFit system would be. After using the system for a few days, the team expressed that they really liked the new machine and were happy about the transition. The bagging system was very easy for nursing to navigate and they were very happy about that.

Responses by Sarah Burda BSRT, RRT, Edward Hospital

Can you tell us about your career in respiratory care within the NICU?
I have worked in respiratory care since 1993. 30 years and have seen several changes. I haven't always worked within the NICU but I have been a supervisor and manager for 10 years and been involved in the monthly NICU meeting at my previous employer.

How did you find the transition from traditional cylinder-based systems to LungFit PH?
I find it incredibly easy to use compared to the cylinder-based system or the cassette-based system. It's quick and easy to exchange the filter.

What are the advantages of the LungFit PH system compared to other systems on the market?
Quick setup and delivery to the patient. 12 hours before the filter needs to be changed. Easy to schedule the change of the filter.

How has LungFit PH improved NICU workflow?
Quick and easy setup for having the machine checked out, set up, and ready to go. It's like a grab and go system.

What has been the initial response to LungFit from the NICU team?
RNs were shocked at the machine when we brought it in. It's exciting to bring in a new piece of equipment. I am a little worried about bagging since I haven't needed to do that much. That is the only confusing part, otherwise the setup…easy! Weaning…easy! Showing the doctor or nurse what the patient is receiving…easy.

News…continued from page 16
Medicine has published an independent study demonstrating Prolacta's human milk-based fortifiers (HMBF) reinstate and significantly boost bioactive proteins when added to mother's own milk (MOM) and donor human milk (DHM). The naturally occurring bioactive components in human milk are thought to support infants' immunity, development, growth, and long-term health. The study, "Exclusive Human Milk Diet for Extremely Premature Infants: A Novel Fortification Strategy That Enhances the Bioactive Properties of Fresh, Frozen, and Pasteurized Milk Specimens" was an observational feasibility study that analyzed the bioactive components of human milk to evaluate fortification choices. It was authored by Professor Roy K. Philip, MD, MBA, and colleagues of the University of Limerick School of Medicine, and Bernal Institute, University of Limerick, Ireland. "Freshly expressed mother's milk fortified with HMBF appears to be an optimal nutritional choice for extremely premature infants during the critical early postnatal window of tissue accretion and immunological imprinting," Dr Philip said. "Pasteurized donor human milk showed significantly low bioactive properties in comparison to fresh and frozen MOM; however, the addition of HMBF reinstated and further enhanced bioactivity to partially offset the effects of pasteurization." The study found milk samples fortified with Prolacta's HMBF contained higher protein, fat, and total solids ($p < 0.05$) compared to unfortified samples and those fortified with cow milk-based fortifier (CMBF). HMBF reinstated lactoferrin and α-lactalbumin and exhibited higher protein, fat, and total solids ($p < 0.05$) in comparison to unfortified specimens and those supplemented with CMBF. Samples with added HMBF had the highest ($p < 0.05$) antioxidant activity (AA), suggesting the potential capability of HMBF to enhance oxidative scavenging. "This study highlights the advantages of Prolacta's proprietary processing in retaining important bioactive components," said Melinda Elliott, MD, chief medical officer at Prolacta. "The findings underscore that bioactivity matters and may be a key reason why extremely premature infants fed an Exclusive Human Milk Diet (EHMD) with human milk-based fortifiers fare better, have fewer complications, and go home sooner than those fed a cow milk-based diet."

Dietary Fiber Cut Gestational Diabetes, Preterm Birth
Pregnant women who had a high level of insulin resistance according to their triglyceride and glucose (TyG) index prior to 20 weeks' gestation showed improved glucose metabolism, a reduced risk for gestational diabetes, and significantly fewer preterm births when treated daily with an oral fiber supplement for 5 weeks (gestational weeks 20-24) compared with untreated controls in a single-center, randomized study with 295 women. The fiber supplement intervention did not affect lipid profiles or other maternal and neonatal outcomes. Women who develop gestational diabetes are at risk for maternal and perinatal complications and for type 2 diabetes later in life. High TyG index in the first trimester is associated with gestational diabetes development. Improving glucose metabolism in women with a high TyG index during pregnancy might help prevent gestational diabetes. The study randomly assigned 295 women with a TyG index ≥ 8.5 before 20 weeks' gestation seen at the Department of Obstetrics and Gynecology at the Shanghai General Hospital during June 2021 to July 2022. During gestational weeks 20-24, 97 women received a 12-g dose of oral dietary fiber powder twice daily, and 197 served as controls and received usual care without
Continued on page 25…

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Generate and Deliver Nitric Oxide Within Seconds[2]

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INDICATIONS FOR USE

The nitric oxide from the LungFit PH System is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents. Refer to the full Prescribing Information within the LungFit PH System Operator's Manual before use.

Visit **www.LungFitPH.com** for full Important Safety Information.

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Study Finds Many Benefits of Neurally Adjusted Ventilatory Assist (NAVA) for Newborns

Chris Campbell

Helping newborns be healthy and get stronger is a goal for every neonatal intensive care unit.

Technology is helping clinicians achieve this goal in bigger and better ways, but one study sought to quantify exactly how much for something called Neurally adjusted ventilatory assist — otherwise known as NAVA.

NAVA is a support technology for the respiratory system that is triggered by the electrical activity of the diaphragm (EAdi).

But just how effective is NAVA for newborns in respiratory distress, and is it a reliable index to guide medical staff during weaning and extubation?

That's what the study "Weaning in neurally adjusted ventilatory assist: a prospective interventional study in neonates" sought to find out.

In the study, the authors describe NAVA: "Pressure assistance is provided in proportion to and synchronous with the electrical activity of the diaphragm (EAdi), and its amount is adjustable by the operator via an amplification factor called NAVAlevel.[1]"

The study was produced by Cosi G, Monzani A, Genoni G, De Franco S, Parlamento S, Bona G, et al. through the Neonatal and Pediatric Intensive Care Unit, Maggiore della Carità Hospital, Novara, Italy; Division of Pediatrics, Department of Health Sciences, University of Eastern Piedmont, Novara, Italy.

In the study, 34 newborns with respiratory failure were ventilated with synchronized intermittent mandatory ventilation plus pressure-regulated volume control plus pressure support (SIMV(PRVC)+PS) for 12 hours and switched to NAVAuntil extubation. Ventilator and vital parameters, oxygen saturation (SpO_2)/fraction of inspired oxygen (FiO_2) ratio (S/F), arterialized capillary blood gases (aCBG), and sedatives dose were recorded. The occurrence of reintubation within the first 72 hours, pneumothorax and mortality were evaluated.

What the study found was that NAVA is very safe to use in neonates and the EAdi peak "could be a reliable index to guide the physicians during weaning and extubation."

Chris Campbell is the Senior Editor of Neonatal Intensive Care.

Struggles with pediatric patients

The study authors say that while NAVA has been shown to be effective for newborns, there isn't a lot of data on the subject found through study.

"In pediatric patients, NAVAhas been shown to enhance patient-ventilator interaction and synchrony, improving the outcome of mechanical ventilation by reducing its duration and avoiding ventilator-induced lung injury.[2-7] To synchronize ventilation is a challenge for the neonatologist because of rapid respiratory rates, small tidal volumes, periodic breathing patterns, short inspiratory times, and variable airleaks around the endotracheal tube.[8] Up to now, only few studies about NAVAefficacy and safety in newborns exist, and most of them enrolled a small number of subjects and used NAVAonly for short-term.[9-11] Only three studies evaluated NAVAin a cohort of preterm neonates for longer time (12, 24 and 26 hours, respectively)[12-14] and only one of them was a randomized-controlled trial of NAVAversus conventional mechanical ventilation.[14] In all of these papers, NAVAimproved patient-ventilator synchrony and reduced ventilator assistance with an improvement of ventilation parameters. Furthermore, Longhini et al. reported a decrease in the need of sedation during NAVA[12] and Stein et al. showed no differences in short-term complications like intraventricular hemorrhage (IVH), pneumothorax (PNX) or necrotizing enterocolitis (NEC), compared to conventional mechanical ventilation.[13] Kallio et al. evaluated the length of hospital stay, the need of mechanical ventilation and sedation with no differences between conventional ventilation and NAVA.[14] Aim of our study was to assess in a cohort of newborns the efficacy and safety of NAVA used for a longer period, until extubation. Moreover, we aimed to analyze ventilation parameters during NAVAhelpful to guide the operator during the weaning process."

The Study

The study authors conducted prospective uncontrolled interventional study from January 2015 to June 2016 in the Neonatal Intensive Care Unit (NICU) of the Maggiore della Carità University Hospital (Novara, Italy). "The institutional ethics committee approved the study, written informed consent was obtained from the patient's parents/ guardians," the authors wrote. "The study was in line with principles of the Declaration of Helsinki. All patients requiring mechanical ventilation admitted to the NICU were considered eligible if matching the following inclusion criteria: 1) age <28 days of life; 2) presence of spontaneous breathing effort able to trigger the ventilator;

3) availability of the only NAVAventilator in our NICU (Servo-N ventilator, Maquet Critical Care, Solna, Sweden)."

The patients, once selected, received ventilation using NAVA until the point of extubation, "unless matching the following discontinuation criteria: 1) FiO_2 >0.6 to maintain SpO_2≥90%; 2) persistent hypercapnia, defined as $PcCO_2$>60 mmHg and/or pH<7.25 in spite of a progressive increase of ventilatory support; 3) heart rate (HR) >180 beats/min and/or respiratory rate (RR) >80 breaths/min for more than 15 consecutive minutes."

Out of the 34 newborns included in the study, the media GA was listed by the authors was 33 weeks.

Results

The study authors wrote about the overwhelming success of the NAVA in the study subjects.

"After 6 hours of NAVA, a significant reduction of FiO_2 (0.25 versus 0.32), and peak inspiratory pressure (13 versus 18 mmHg), and a significant increase of S/F (383 versus 316) were found, compared to SIMV(PRVC)+PS," the study said. "Other ventilation, vital and aCBG parameters were similar in both ventilation modes. During NAVA a significant reduction of sedation was shown. All subjects were successfully extubated guided by EAdi peak during weaning. No reintubation, pneumothorax, or death were recorded."

The authors added that: "Notably in our study NAVA delivered an effective ventilation in neonates with different clinical and pathophysiological features."

The authors noted that their study appears to be the first where a "standardized protocol of weaning using NAVA is proposed." The authors write that more studies of newborns are needed to see the effectiveness of NAVA at various points of ventilation.

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Addressing Antibiotic Resistance in the NICU: Managing Antibiotic Use/Overuse is Not Enough

Sushma Krishna, MD

Antimicrobial resistance remains a growing global threat despite intense efforts to combat it. According to the World Health Organization, nearly 5 million deaths were attributed to infections caused by antibiotic-resistant organisms in 2019, and they project that number will double by 2050.[1] Multidrug-resistant microbes are emerging faster than we can develop treatments for them, edging us closer to the return of an era when infections were untreatable.

Current evidence points to liberal and inappropriate antibiotic prescribing, i.e., at doses, for indications, and for durations that disregard established guidelines, as the principal drivers of antibiotic resistance. Regardless of the pathobiological mechanisms underlying this disturbing trend, our best defense against serious infection with antimicrobial-resistant organisms is stronger anti-infectives, an unsatisfactory solution that risks severe side effects for patients and perpetuates the vicious cycle of drug resistance.

Nowhere is the situation more complex and threatening than in the Neonatal Intensive Care Unit (NICU) where the most fragile hospitalized patients are treated. Infection is the leading cause of morbidity and mortality in preterm infants whose premature immune defenses are ill-equipped to combat the latest generation of superbugs. Parents and other visitors, staff and high-touch surfaces in hospital acute care units are often colonized with multidrug-resistant pathogens capable of evading current disinfection procedures.

The adoption of flexible staffing models, in which nurses float between units, enables organisms previously restricted to a particular ward to take up residence in others, as does mobile technology (e.g., x-ray and ultrasound machines, point-of-care diagnostic devices, and multi-use equipment). Frequent instrumentation with indwelling devices that promote sticky biofilm formation, such as vascular and urinary catheters, and nasogastric and endotracheal tubes used during prolonged hospital stays, affords repeated opportunities for the horizontal transfer of mobile antibiotic resistance genes (ARG) from opportunistic pathogens to vulnerable body compartments including the premature infant's developing intestinal tract.

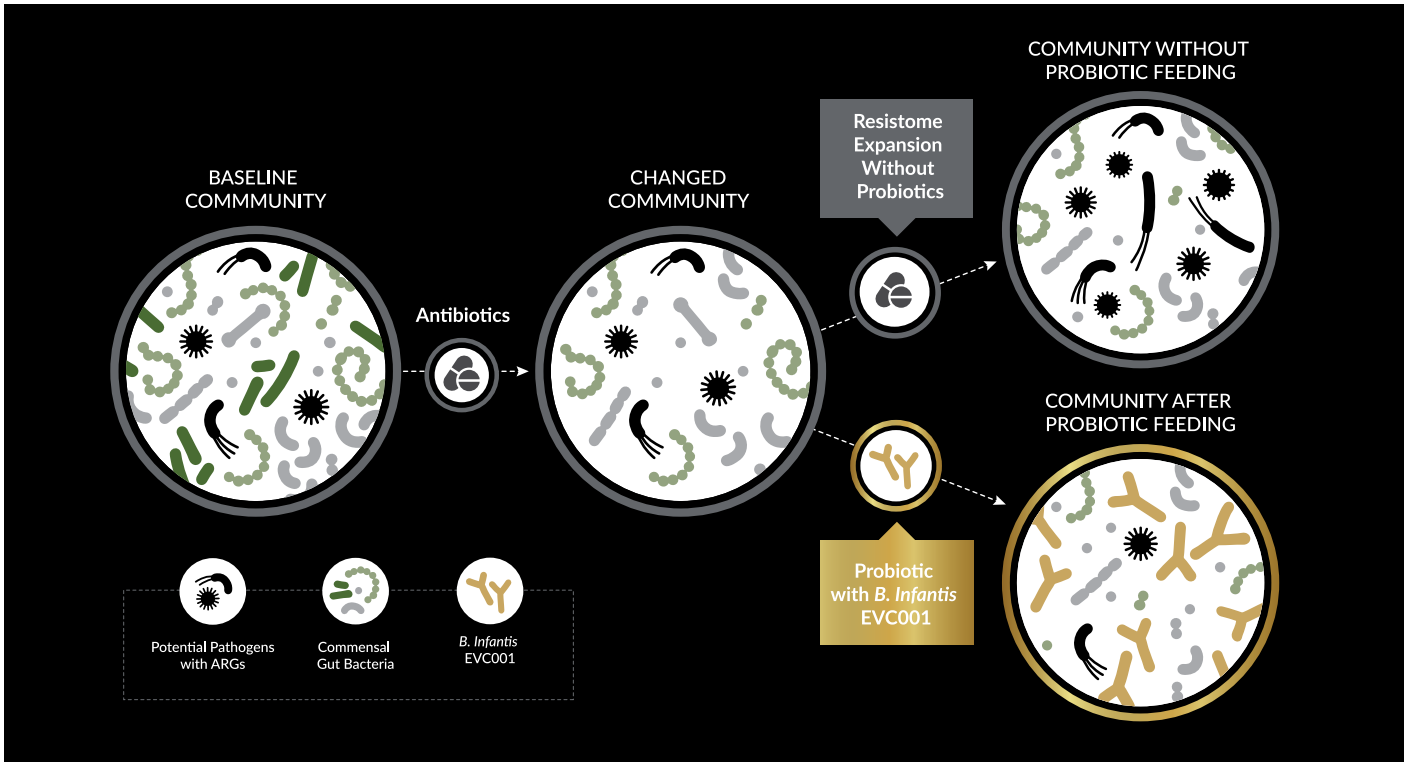
Infection is the leading cause of morbidity and mortality in preterm infants whose premature immune defenses are ill equipped to combat the latest generation of superbugs.

The preterm gut microbiota, a primary site of immune system priming and development, is dysbiotic from birth[2] and unstable,[3] rendering it highly susceptible to colonization with pathogens harboring antibiotic resistance genes. Under conditions of repeated stress, perpetual proinflammatory state, and suboptimal nutrition, pathogens harboring antibiotic resistance genes (ARGs) outcompete health-promoting commensals for nutrients and energy, disrupting intestinal homeostasis and delaying immune system development. Administering broad-spectrum antibiotics under these conditions induces further dysbiosis, reduces host gut microbiota diversity, and permits the emergence of new ARGs. The damaging effects of antibiotics extend beyond the targeted harmful pathogens to the host's commensal resistome (ARGs), a key factor in preserving healthy microbiota composition.

Physician concerns over the susceptibility of preterm infants to serious and life-threatening infections have elevated antibiotics to the most commonly prescribed medication in U.S. NICUs.[2,4,5] According to recent estimates, as many as 75-80% of very low birth weight (VLBW) and extremely low birth weight (ELBW) preterm infants are exposed to antibiotics within the first 72 hours of life, either directly or through intrapartum administration to mothers to avert the risk of early-onset sepsis.[3]

To date, consensus is lacking on appropriate balance between antibiotic stewardship and treating for presumed sepsis in high risk newborns.[6] Notably, the incidence of culture-positive early-onset sepsis in these two groups is less than 10%.[6] And, despite convincing evidence linking prophylactic antibiotic courses longer than 5 days to necrotizing enterocolitis, invasive fungal infections, and death,[3,4] neonatologists lack equipoise in their prescribing practices. Their decisions are informed as much by long-standing NICU culture and personal experience as by universal guidelines or objective clinical and laboratory data. And not without reason.

Sushma Krishna, MD is an Assistant Professor of Pediatrics in the Division of Newborn Medicine at Mount Sinai West. She graduated from SUNY Upstate Medical University before completing her pediatric residency and chief residency at Stony Brook Children's Hospital. She completed her neonatology fellowship at New York Presbyterian-Weill Cornell Medical Center. In addition to probiotics, Dr. Krishna has an interest in neurodevelopmental outcomes of preterm infants.



Preterm infants often do not manifest reliable focal signs of sepsis until quite late. Providing adequate specimen volumes for blood cultures can be challenging and complicates the interpretation of negative results. Thus, in the absence of highly sensitive and specific sepsis biomarkers, as opposed to the non-specific markers of inflammation or stress currently available, physicians have tended to rely on non-specific, softer signs (e.g., decreased activity or tone, feeding intolerance, need for increased respiratory support, and increased apnea and bradycardia events) and have taken the more conservative approach of starting and/or continuing antibiotics for culture-negative infections (CNI).

Furthermore, publication of a study in which C-reactive protein-guided treatment decisions led to a paradoxical *increase* in antibiotic use in premature infants with CNI[4] has done little to convince those caring for VLBW and ELBW infants to abandon empiric antibiotic prescribing and embrace evidence-based decision-making. When faced with these limitations, well-intentioned providers may choose to downplay data showing that prolonged treatment of CNI with inappropriate antibiotics can have harmful consequences due to the risk of antimicrobial resistance and from inadequate treatment of the actual cause of illness.

In response to the alarming rise in antimicrobial resistance, the Centers for Disease Control and Prevention introduced antibiotic stewardship programs (ASP) to best optimize antimicrobial use among hospitalized patients, improve patient outcomes, ensure cost-effective therapy, and reduce adverse sequelae of antimicrobial use. These multidisciplinary, multipronged interventions combine continuous surveillance and periodic reporting with implementation of evidence-based recommendations for appropriate drug selection, dosing, initiation, duration, and discontinuation of antimicrobials.

For premature infants, ASPs have focused on reducing

> Physician concerns over the susceptibility of preterm infants to serious and life-threatening infections have elevated antibiotics to the most commonly prescribed medication in US NICUs.[2,4,5]

empiric antibiotic prescribing after birth and restricting the duration of antibiotic therapy in low-risk situations.[7] In addition, these programs are looking for additional ways to fight antibiotic resistance and suggest that alternative agents such as those that modulate the microbiome warrant further investigation. Stewardship teams comprised of physicians, nurses, pharmacists, epidemiologists, pathologists, and quality improvement specialists monitor community and hospital-acquired infections and present detailed institutional performance reports to hospital leadership and national oversight agencies.[13] All U.S. federally-funded (CMS) hospitals are required to have ASPs for accreditation by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and must report compliance and outcomes data to the National Healthcare Safety Network (NHSN).[8] ASPs are currently the most widely practiced intervention for combating antibiotic resistance in hospitalized patients and slowing the emergence of ARGs. Although ASPs have been in existence for more than half a century, they've become increasingly essential to delivering quality healthcare over the past decade.[8]

Whereas antibiotic stewardship programs in hospitalized patients outside the NICU have recorded noteworthy successes, similar results have not been replicated widely in U.S. NICUs in part due to the aforementioned resistance among providers to changing their practice patterns regarding suspected sepsis.[3,7] Studies reporting unchanged or even improved outcomes in

NICUs employing risk stratification in their sepsis treatment algorithms,[4,9] (i.e., withholding prophylactic antibiotics in preterm infants born via cesarean section to mothers without chorioamnionitis who have not labored, have not substantially altered antibiotic prescribing patterns among those caring for VLBW and ELBW neonates.) And despite evidence that with current specimen-processing technology >90% of blood cultures will turn positive after 36–48 hours of incubation,[4] negative blood cultures have only limited influence on decreasing antibiotic use.

Given the complexities of neonatal care that make it difficult to alter antibiotic prescribing patterns and influence a providers ability to fully embrace the tenets of antibiotic stewardship, growing awareness of the need to mitigate the negative effects of perinatal antibiotic exposure have led some researchers to focus on fortifying the gut microbiota against pathogenic organisms and their resistomes by supplementing human milk-based feedings with probiotics. Adding specific bioactive strains selected for their efficiency in out-competing pathogens for human-milk oligosaccharide-derived energy sources[10] and their efficacy in improving intestinal barrier function, promoting immune system development, and maintaining healthy microbiota composition has produced promising results. In doing so, scientists hypothesize that sepsis events and overall exposure to prophylactic antibiotics will decrease, as will morbidity, mortality, and NICU length of stay.

Studies using select strains of *Bifidobacteria* suggest they have the capacity to perform the aforementioned functions and could complement efforts to reduce, track and diversify Antiboitic use as a means of focusing the preterm infant gut microbiome as a means of curbing burden of antimicrobial resistance in the NICU. In one Canadian NICU,[11] serial stool samples from 21 preterm infants (8 fed *Bifidobacterium* and *Lactobacillus*-containing probiotics, 13 not exposed to the probiotic), and 9 full-term controls, were analyzed using a targeted capture approach. The study's authors reported that administering probiotics during hospitalization prevented persistence of ARGs in the gut microbiome. Furthermore, despite initial similarities among the 3 groups on the first (in-hospital) fecal specimen, the ARG profile of the preterm infants fed probiotics more closely mirrored that of the full-term infants than did the non-probiotic-supplemented group. Additionally, the protective effects seen in the probiotic-supplemented group persisted during the entire 5-month sampling period. The authors recommended further exploring the benefits of probiotic use on the microbiome (and the resistome) in larger groups of infants.

In another prospective multicenter trial including 6 Norway NICUs,[5] 31 infants < 28 weeks gestational age (GA) supplemented with a probiotic formulation containing *B. longum subsp infantis* and *Lactobacillus acidophilus* were compared to 35 infants 28–31 weeks (GA) not given probiotics, and 10 full-term controls. Microbiota composition and ARGs were analyzed using shotgun-metagenome sequencing of fecal samples at 7 days, 28 days, and 4 months. A greater abundance of *Bifidobacterium* was found at 7 days in the probiotic-exposed group compared to the other 2 groups. The extremely preterm infants receiving probiotics had greater antibiotic exposure, but the microbial diversity and resistome did not differ from more mature infants in subsequent samples. The study's authors concluded that probiotic supplementation may reduce the harmful effects of antibiotics on the gut microbiota and commensal antibiotic resistome.

When faced with these limitations, well-intentioned providers may choose to downplay data showing that prolonged treatment of CNI with inappropriate antibiotics can have harmful consequences due to the risk of antimicrobial resistance and from inadequate treatment of the actual cause of illness.

In their prospective study in 2 California NICUs,[12] Nguyen et al. compared ARGs in 31 infants (<32 weeks GA or < 1500 gm) fed human milk supplemented with the probiotic *B. longum subsp. infantis (B. infantis)* with that of 46 infants (>32 weeks GA or >1500 gm) fed human milk without the probiotic, and found a reduced abundance of ARGs and pathogenic organisms harboring them in the probiotic-supplemented group. In addition, the infants not fed probiotics acquired a new ARG type every 2 days on average while in the NICU. However, infants who received probiotics harbored 13.6 fewer ARG types than those not fed probiotics. Importantly, the infants given *B.infantis* were exposed to fewer antibiotics in the week prior to stool sampling, suggesting an association between probiotic supplementation and decreased infection risk. Thus, the authors concluded, the combination of human milk feedings with *B. infantis* may mitigate microbiome-associated risk of morbidity and mortality in hospitalized [preterm] infants.

Future approaches to overcoming antimicrobial resistance must avoid added administrative burden. It also cannot rely on commitment to resource-intensive guidelines naïve to the consequences of restricting treatments in vulnerable patients and ignorant of the potential for culpability. Likewise, interventions that demand strict adherence and require culture change for their success are destined to have limited uptake. Above all, developing new and stronger antimicrobials will only perpetuate the cycle of resistance and cannot be the focus of future solutions. Instead, recruiting the infant's own defenses by bolstering the gut microbiome with safe and effective probiotics added to enteral human milk feedings may offer a promising alternative for addressing the infectious sequelae of prematurity and the threat of increasing antibiotic resistance. This simple and resource-economical treatment has already been adopted safely by NICUs in Canada, Europe, and Australia, and should be investigated further as an adjunct to antibiotic stewardship. Leveraging evidence-based probiotic supplementation alongside antibiotic stewardship recognizes the central role of the infant's immune system in the fight against antibiotic resistance and may be just what's needed to win.

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the fiber supplement. All participants received guidance on how to optimize diet and activity. Forty-six women either dropped out or were lost to follow-up prior to delivery. Participants underwent a 75-g oral glucose tolerance test at 25-28 weeks' gestational age and also underwent additional testing.

Global Push to Tackle Maternal and Newborn Deaths Has Stalled, WHO Report Finds

Progress in reducing deaths during pregnancy and childbirth and among newborn infants has stalled since 2015, and over 60 countries are on track to miss 2030 targets at current rates, a World Health Organization report found. The COVID-19 pandemic, poverty, and worsening humanitarian crises have strained already pressured healthcare systems, the UN agency said in a statement. Annually since 2015 there have been about 290,000 maternal deaths, 1.9 million stillbirths, and 2.3 million newborn deaths within a month after birth, the report said. The combined total represents one death every seven seconds, "mostly from preventable or treatable causes if proper care was available," the WHO said. Countries need to ramp up investment in primary care to see different results, said Anshu Banerjee, the WHO's director of maternal, newborn, child and adolescent health and ageing. More than 190 countries backed a plan in 2014 to cut rates of stillbirth and preventable deaths among infants, and subsequently set up global targets such as reducing the maternal mortality ratio to less than 70 per 100,000 live births. Projections indicate the need to accelerate progress in order to meet those targets, according to the report, which could help save at least 7.8 million lives by 2030 if they are met. Progress was faster between 2000 and 2010 than at any time since, the report showed, blaming funding shortfalls among the primary reasons. Only 12% of 106 reporting countries have fully-financed maternal and newborn health plans, it said. The report also found that only 61% of reporting countries have systems for keeping track of stillbirths. The report found that 10 countries with the highest maternal deaths, stillbirths and neonatal deaths account for 60% of all such deaths globally. India, Nigeria and Pakistan led that list in 2020, according to the report.

Clinic Responsible for Misdiagnosing Newborn's Meningitis, Must Pay Millions

A health system serving three Midwest states must pay millions to the parents of a now 10-year-old boy whose meningitis was misdiagnosed at birth, according to a report in the *Star Tribune*, among other news outlets. The story of the jury verdict begins in 2013, when the boy, Johnny Galligan, was just 8 days old. Alarmed by the newborn's crying, lack of appetite, and fever, his parents, Alina and Steve Galligan, brought him to Essentia-Health-Ashland Clinic, located in Memorial Medical Center, in Ashland, Wisconsin. There, the baby was seen by a family physician, who noted the baby's extreme fussiness and irritability and was concerned that he was being overfed. Without ordering additional tests, the family physician sent the baby home but arranged for the Galligans to be visited by a county nurse the following day. In 2020, the Galligans filed a medical malpractice claim against several parties, Duluth Clinic LTD (doing business as Essentia Health and Essentia Health–Ashland Clinic), and Memorial Hospital. In their suit, Johnny's parents alleged that the collective failure to diagnose their son's severe infection led directly to his permanent brain damage.

The Importance of Thermoregulation in the NICU

Liz Drake MN, RNC-NIC, NNP, CNS, C-ELBW

Introduction

Temperature management is foundational to caring for newborn babies, particularly pre-term infants, but it is almost so basic that it can be overlooked beyond those first moments of life.

At birth, baby transitions from a place inside mom that is about 99 degrees Fahrenheit to a much cooler environment. The delivery team understands the importance of maintaining that baby's temperature so the first steps they take for full term babies is to dry and warm them. For premature neonates, they will often use a plastic barrier to help reduce heat loss.

Hypothermia is an independent variable for neonatal morbidity and mortality, with the evidence revealing that no other factor is as important in newborn survival than thermoregulation.[1,2] In fact, a study of 5,500+ low birth weight babies showed that over 50% were hypothermic upon admission to the neonatal intensive care unit (NICU).

So, why is temperature often not prioritized as highly as other vital signs even though evidence clearly shows a relationship between temperature management and morbidity and mortality rates? And, while preemie temperatures are challenging to regulate, how can we bridge the gap to help improve thermoregulation for all of our NICU babies?

To improve thermoregulation management, we should start with the basics. Understanding physiology of premature babies, the signs of hypo- and hyperthermia and what different temperature modalities reveal about a baby's condition can help prepare us for what interventions may be needed to prevent further temperature instability.

This first of a two-part article series explores why premature babies are at risk for cold stress, methods of heat production in babies born prematurely, the benefits of thermoregulation in a neutral thermal environment (NTE), and signs and complications of infant thermal stress.

Liz Drake is a NICU Clinical Nurse Specialist at CHOC Children's at Mission Hospital, Mission Viejo, CA. Liz and Dräger worked in collaboration to develop this article as part of Dräger's continuing efforts to advance neonatal care through the sharing of insights, knowledge and best practices within the neonatal community.

Why tiny babies need our help

Babies born prematurely are unprepared for life outside of the womb. They have limited stores of metabolic substrates (aka body fat); lack the ability to regulate skin blood flow; cannot constrict/flex for heat conservation or shiver generate heat when they are cold; their immature skin is prone to trans epidermal water loss (TEWL); and their body surface area is three times greater than that of an adult.[3]

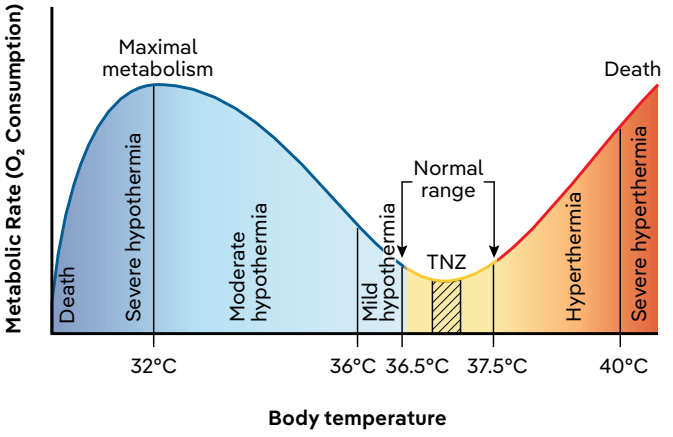
In a premature infant, the hypothalamus, which is the control center for heat production responsible for all our metabolic processes (controls body temperature, hunger, fatigue, sleep, and circadian rhythms), is immature and not functioning at full capacity.[4]

With so many vulnerabilities and no way to communicate when they are too cold or hot, neonates depend on us to be one step ahead of them in their thermoregulation needs—it's in our hands to maintain a neutral thermal environment (NTE).

NTE is defined as "the temperature range where heat production is at the minimum needed to maintain normal body temperature." This is achieved when heat generation to heat dissipation is balanced—what I call the "sweet spot."

Methods of heat production

To understand why cold stress and hypothermia are so common in premature infants, it is important to first understand the difference in how adults and preemies generate body heat.



Adults and children stay warm through the accumulation of white fat as it serves as insulation. When we consume too many calories our bodies convert that into energy reserves in the form of white fat.

In addition to this layer of insulation, adults shiver when they are cold as a form of thermoregulation to keep a steady body temperature. We also can constrict our bodies to preserve heat and can put on a sweater or blanket to get warm or ask a caregiver to do this for us.

Premature babies can't shiver, can't constrict on their own, can't put on more layers or ask a caregiver to put on more layers for them. They have very little subcutaneous (white) fat, but instead have brown fat (brown adipose tissue or BAT) stored for energy between their shoulder blades, adrenals, kidneys, head and neck, and scapula.[iii]

Brown fat metabolism (non-shivering thermogenesis) is the process infants use to produce heat when they are cold[iii] But because these brown fat stores are limited, we as NICU clinicians want babies to conserve them. Their limited ability to maintain their body temperature puts them at high risk to lose and gain heat via evaporation, conduction, convection and radiation.

Benefits of thermoregulation and maintaining the "sweet spot"

The "sweet spot" in thermoregulation of the premature infant refers to when the baby's heart rate is stable, they are sufficiently gaining weight, dual temperatures (axillary and skin temperatures) are aligned, and there are minimal temperature fluctuations.[iii]

Starting off on the right foot with good thermoregulation, and keeping that baby in the sweet spot, will help with outcome predictors and help reduce mortality and co-morbidity rates. Maintaining an NTE where temperature is stabilized makes the care path for baby far easier, minimizing the peaks and valleys of high or low temperatures and subsequent complications.

When a baby is in normothermia, they have a stable metabolic rate and won't, in turn, burn precious calories and have increased oxygen needs that tax already fragile respiratory systems.

Providing this environment is in our hands as NICU clinicians — and it is so powerful that we have the opportunity to stabilize a baby's temperature to get them on the right path for healthy outcomes.

Signs of infant thermal stress

While preterm infants can't tell us when they are cold, there are signs that a baby is suffering from cold stress. It is important for the NICU team to recognize these signs. Below are common signs of cold stress in the premature infant.[iii]

- Below recommended core temperature range (36.5-37.5) (for term infants this range is the same)
- Below recommended skin temperature range (36.2-37.2) (for term infants this range is 36.0-36.5)
- Inverted temp values, such as a high core temperature and decreased skin temperature
- Overt signs: acrocyanosis, mottling, poor perfusion
- Apnea and bradycardia events, increased FiO_2 needs, low resting heart rate and decreased SPO_2
- Decreased activity, lethargy, hypotonia
- Poor feeding tolerance
- Increased residuals
- Hypoglycemia

Potential impact of infant thermal stress

Thermal stress in the premature infant not only causes them to burn their limited brown fat reserves, but it can also lead to a number of life-threatening complications.[i] These include:

Weight loss: Approximately 5% of a newborn's baby's weight is comprised of brown fat. If a baby is burning through these reserves trying to keep warm, they will be losing calories, leading to a calorie deficit and the need for higher caloric intake to improve weight gain.

Poor digestion: Hypothermia can cause reduced perfusion to the baby's gut, compromising their ability to digest feedings well. To increase caloric intake, NICU staff will resort to higher calorie formulas that are even harder for the baby's body to digest.

Necrotizing enterocolitis: The stress, intolerance of feedings, and need for increased caloric intake in an already compromised gut can increase the risk for necrotizing enterocolitis (NEC). Low skin temp can also be the indicator for sepsis which can lead to NEC.

Impaired immune function: This can lead to higher sepsis risk in already high-risk infants.

Respiratory distress due to premature lungs: Babies with compromised cardiorespiratory systems are at an even greater disadvantage when cold as heat production requires oxygen. Increased oxygen consumption can tax a baby's already compromised respiratory function, resulting in hypoxia.

Impaired coagulation: A premature infant under cold stress is at increased risk for intraventricular or pulmonary hemorrhage. Intracranial bleeding can lead to brain damage, cognitive dysfunction, cerebral palsy, and other co-morbidities.

Pulmonary hypertension: Thermal stress can also increase the risk for pulmonary hypertension, which is high blood pressure in the lungs. It's an uncommon condition that forces the heart to work harder to deliver blood to the lungs.

Conclusion

Temperature management and preventing low body temperature at birth for low-birth-weight infants is critically important to survival and long-term outcomes.

NICU teams want the best care and outcomes for the babies in their care so understanding the symptoms and risks of cold stress and how to keep babies in that thermoregulation "sweet spot" is foundational to them providing those babies a great start at life.

The next article offers some best practices for temperature measurement and management of premature babies, and three steps for establishing thermoregulation as a priority in your NICU.

Test your thermoregulation knowledge

"Jesse", a two-day old preemie, born at 27 weeks, has an axillary temperature of 37.6 Celsius and central skin temperature of 35.9 Celsius. The baby's fraction of inspired oxygen (FiO_2) demand has increased incrementally since a procedure performed four hours ago. How should the nursing team interpret these values and what steps should they take to find the root cause of conflicting temperatures?

Read the next article in this series for the answer.

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Warnings and Precautions
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Methemoglobinemia: Methemoglobin levels increase with the dose of Noxivent; it can take 8 hours or more before steadystate methemoglobin levels are attained. If methemoglobin levels do not resolve with decrease in dose or discontinuation of Noxivent, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide: Monitor nitrogen dioxide (NO2) levels. Nitrogen dioxide may cause airway inflammation and damage to lung tissue.

Heart Failure: In patients with pre-existing left ventricular dysfunction, Noxivent may increase pulmonary capillary wedge pressure leading to pulmonary edema.

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The most common adverse reaction of Noxivent is hypotension.

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Nitric Oxide donor compounds may increase the risk of developing methemoglobinemia.

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Please see the full Prescribing Information for additional important Noxivent® safety and risk information.

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Clinical Study of Continuous Non-Invasive Blood Pressure Monitoring in Neonates

Anoop Rao[1], Fatima Eskandar-Afshari[2], Ya'el Weiner[3], Elle Billman[4], Alexandra McMillin[1], Noa Sella[1], Thomas Roxlo[5], Junjun Liu[5], Weyland Leong[5], Eric Helfenbein[6], Alan Walendowski[5], Arthur Muir[5], Alexandria Joseph[4], Archana Verma[4], Chandra Ramamoorthy[4], Anita Honkanen[4], Gabrielle Green[1], Keith Drake[5], Rathinaswamy B Govindan[7], William Rhine[1] and Xina Quan[5]

Abstract: The continuous monitoring of arterial blood pressure (BP) is vital for assessing and treating cardiovascular instability in a sick infant. Currently, invasive catheters are inserted into an artery to monitor critically-ill infants. Catheterization requires skill, is time consuming, prone to complications, and often painful. Herein, we report on the feasibility and accuracy of a non-invasive, wearable device that is easy to place and operate and continuously monitors BP without the need for external calibration. The device uses capacitive sensors to acquire pulse waveform measurements from the wrist and/or foot of preterm and term infants. Systolic, diastolic, and mean arterial pressures are inferred from the recorded pulse waveform data using algorithms trained using artificial neural network (ANN) techniques. The sensor-derived, continuous, non-invasive BP data were compared with corresponding invasive arterial line (IAL) data from 81 infants with a wide variety of pathologies to conclude that inferred BP values meet FDA-level accuracy requirements for these critically ill, yet normotensive term and preterm infants.

Introduction

Every year in the US, nearly half a million sick infants are hospitalized and undergo close monitoring of vital signs such as blood pressure (BP). In critically ill neonates, continuous BP monitoring is achieved by inserting a catheter into the lumen of an artery. This catheterization procedure is risky, invasive, and expensive—it requires skill and time, and infants may require sedation. Multiple attempts may be required to place the catheter due to small arteries.[1-3] A catheter may remain within the artery for several days and can lead to serious complications such as infection, bleeding, clots, tissue, and nerve damage.[1-4]

Non-invasive alternatives to measure BP also have disadvantages. Oscillometry is the most widely used non-invasive method and measures BP by intermittently inflating a cuff. In general, continuous monitoring is preferred over intermittent, cuff-based, oscillometric monitoring for hypotensive neonates because premature neonatal BP values are often too low for an accurate measurement with a conventional cuff[5] and application of the cuff can perturb the patient to artificially elevate the measured BP values.[6] Moreover, the frequent use of cuffs can cause ischemic damage,[7] particularly for patients with fragile skin such as premature neonates.

Other non-invasive techniques have been developed for the measurement of adult BP values, such as volume clamping using partially inflated finger cuffs, pulse transit time analysis using multiple sensors, and pulsewave analysis using cuffs or optical or radiative sensors.[8] These are summarized in Table 1. Almost all methods require calibration with a known BP measurement so that the measured features can be used to estimate BP,[9-11] and none have been adopted for use with neonates. Machine learning (ML) methods can be used to analyze pulse waveform features and derive BP[12] and other hemodynamic parameters.[13] These include neural networks, probabilistic, decision tree, and rule-based induction.

Premature neonates have small wrists akin to an adult's index finger and weigh as few as 400 g. For these infants, there is a critical need for a wearable, continuous, non-invasive BP (cNIBP) monitoring device that is accurate, affordable, and easy to use. For ease of use, it is necessary to overcome the need for calibration. Such a cNIBP device could eliminate the complications associated with IALs and obviate the need for sedation. Rapid and timely attachment could reduce latency for treating hypotension and potentially improve outcomes. Furthermore, less-skilled practitioners could use this device in resource-limited settings or during patient transport.

Here, we investigate the clinical feasibility and accuracy of estimating continuous BP in critically ill neonates with a wearable device (Boppli™, PyrAmes Inc., Cupertino, CA, USA) using ML-based methods without the need for calibration.

Materials and Methods

Device Design and Working Principle

Boppli was designed to meet the BP monitoring requirements and physical dimensions of small, prematurely-born infants. It uses capacitive sensing methods, previously reported.[8] The thin (~50 µm), capacitance sensor array comprises four sensing elements. It is flexible and conforms to the contour of the limb.

[1] Department of Pediatrics, Division of Neonatal and Developmental Medicine, School of Medicine, Stanford University, Palo Alto, CA 94304, USA
[2] Division of Neonatology, LAC+USC Medical Center, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA
[3] Department of Emergency Medicine, Children's Hospital Los Angeles, Los Angeles, CA 90027, USA
[4] Department of Anesthesia, School of Medicine, Stanford University, Palo Alto, CA 94304, USA
[5] PyrAmes Inc., Cupertino, CA 95014, USA
[6] Philips Healthcare, Cambridge, MA 02141, USA
[7] Children's National Hospital, Washington, DC 20010, USA

Table 1. Methods for determining BP. Adapted * from Ref.[8]

	Method	Measurement	Example Companies	FDA
Cuff	Finger, tabletop	Continuous	BMEYE, Finapres, ADI, Biopac, Edwards (ClearSight), CNAP	Yes
	Finger, wearable	Continuous	Caretaker	Yes
	Wrist	Intermittent	Omron, H2Care	Yes
Cuffless	PPG	Continuous	Aktiia, BioBeat, Apple, ASUS, Samsung, Sensifree	Yes
	PWV, PTT	Continuous	Vital Insight, Quanttus, Scanadu, Blumio, Sibel	No
	Tonometer	Continuous	Tensys, HealthStat, LiveMetric	Yes
	Capacitance	Continuous	PyrAmes, Vena Vitals	Submitted

Abbreviations: **PWV**: Pulse wave velocity; **PTT**: Pulse transit time; **PPG**: Photoplethysmography.

This extremely sensitive sensor is coupled with low-power electronics (Figure 1) to achieve a small form-factor and low weight (~12 g). The sensor and electronic components are incorporated into a disposable, foam band designed to ensure a snug fit without imposing excessive pressure on an infant's delicate skin. The band does not use an adhesive, and its materials are hypoallergenic.

The device determines continuous BP in real-time by using two tandem processes: (1) capacitive sensing to quantify each pulse as a waveform, and (2) signal processing and machine learning methods to analyze and process the pulse waveform data to derive the systolic (SBP), diastolic (DBP), and mean arterial pressure (MAP).

Capacitive Sensing

When the band is snugly wrapped around an infants' wrist or foot, the sensor comes in contact with the skin that overlies the artery (Figure 2). In this configuration, the sensor and skin function like a capacitor. Each arterial pulse displaces the overlying skin towards the sensor. This displacement alters the capacitance (ΔC) of the system. With every pulse, the capacitance will fluctuate. This fluctuation in capacitance is sensed by the electronics and is displayed as a waveform ("pulse-waveform"). These unscaled pulse-waveforms directly correlate with arterial BP and are wirelessly transmitted in real-time to a mobile device uniquely paired with each sensor. The capacitance data are collected at 125 Hz, and estimated BP values are updated at approximately 1 Hz.

Pipeline for Real-Time Processing of Pulse Waveforms

The acquired pulse waveform data are streamed in real-time to a custom Android application (App). The App analyzes and displays the pulse waveforms (Figure 2). The measured pulse waveforms require additional signal processing and the application of machine learning trained algorithms to derive the systolic, diastolic, and mean arterial pressure (SBP, DBP, and MAP). These processing steps are summarized in Table 2.

Data Quality

To extract robust parameters for further analysis, the pulse waveform data must have sufficient quality. Raw pulse waveform data from both the IAL and sensor can be noisy for multiple reasons such as active or passive infant movement.

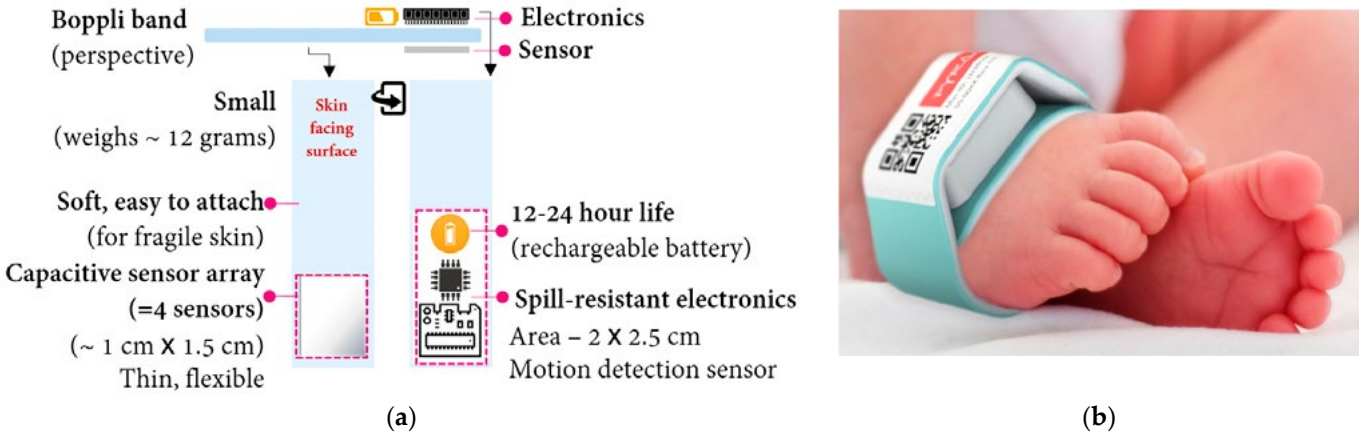


Figure 1. (**a**) Boppli sensor schematic: illustration of the sensor and wearable, continuous, non- invasive BP device for neonates (cross-sectional at the top; aerial view at the bottom); (**b**) Boppli sensor placement around the foot of an infant.

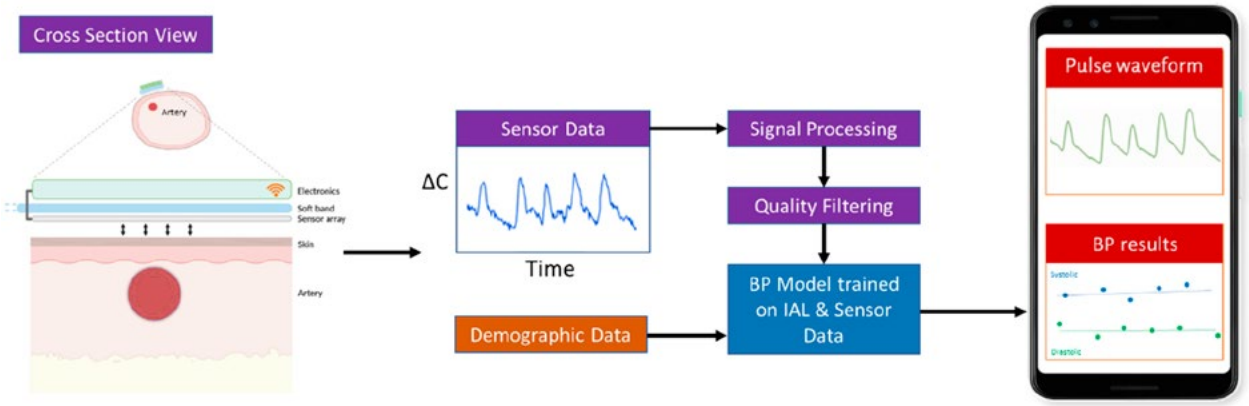


Figure 2. Overview of the working of the sensor and steps to infer blood pressure.

To evaluate the usability of the measured pulse waveforms signal, a visual metric, $|Qv|$, was developed with a scale ranging from 0 (unusable) to 5 (best). This quality scale was based on a visual assessment of secondary peak resolution and the degree of signal noise by comparison to the corresponding IAL data according to a rubric. A training set of 10,000 pairs of Boppli/IAL pulse waveforms with $|Qv|$ and regression coefficients was used to train a convolutional ANN (CNN) model to automatically grade Boppli and IAL pulse waveforms. The outputs of this model are a quality metric $|Q|$ and estimated regression coefficient, r. The methods used to establish data quality are described in.[8]

Signal Processing

To decrease noise and increase signal quality i.e., signal-to-noise ratio (SNR), a Butterworth bandpass filter (order 2) with limits of 0.1 to 20 Hz was used to remove baseline shifts, respiratory effects, and high frequency noise. For infants on high-frequency oscillatory ventilation (HFOV), a notch filter based on the ventilation frequency was used to mitigate the parasitic noise due to subtle motion of the patient.

Artifact Removal

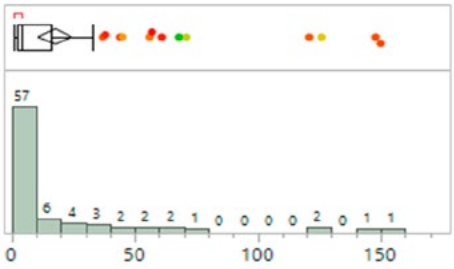
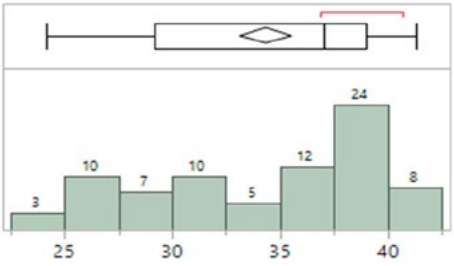
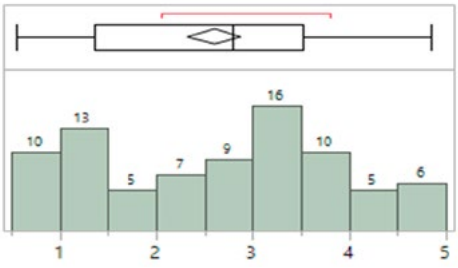
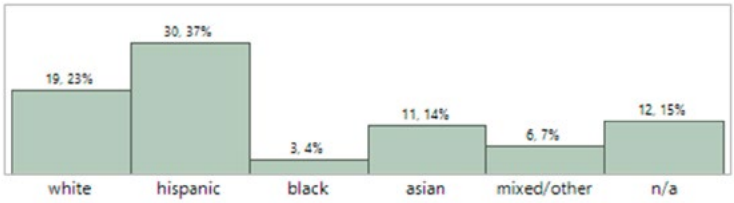
Similarly, if the infant moves, the signal is momentarily distorted and that segment has low data quality $|Q|$ and consequently cannot be used. Both IAL and sensor data were excluded if they did not meet the predefined $|Q|$ and r. The IAL data were also required to have an SNR > 5 and to be within realistic ranges with a minimum value of 0 mmHg and maximum values of 200, 175, and 150 mmHg for SBP, MAP, and DBP, respectively. The

Table 2. Pipeline for real-time processing of pulse waveforms and artificial neural network (ANN) training.

Modules	Steps	Relevance
A. Quality Model	**Select** data **Exclude** data segments **Quality ranking** **Classification elements**	Boppli Band has an array of four sensors. The algorithm chooses data from the best sensor. Infant moves ⇨ pulse waveform excluded if quality value is below the threshold. Automated PW quality rating (0—bad, 5—good) using ANN, correlation coefficient Boppli/IAL. Algorithm automatically *detects* if the pulse waveform is corrupted by HFOV.
B. Signal Processing	**Noise filtering/↑SNR**	If Classification element detects HFOV ⇨ then notch filter. Normalize pulse waveform.
C. BP Model	**CNN trained** on pulse waveform and IAL **SHAPE**	Determines systolic, diastolic, mean arterial blood pressure.
D. Training Data	**Obtain Boppli/IAL data**	Sources: Stanford and CNH patient data warehouse; Stanford Boppli/IAL data collection.
E. Data Curation	**Clean** IAL data **Synchronize** data	Removes artifacts due to motion, damping, and other IAL operational issues. Synchronize Boppli and IAL data taken simultaneously.
F. Training and Testing	**Cross-validation (k-fold)** **Model Ranking**	Inputs: pulse waveform data, age, and weight. Splits data into 10 groups. Takes one group as a test and the remainder as training. Recursively tests model using TensorFlow and proprietary code. Choose best model that minimizes MAE and SD while optimizing slope and correlation coefficient of regression fit of estimated vs. ground truth values.

Abbreviations: **PW**: Pulsewave; **ANN**: artificial neural network; **HFOV**: high frequency oscillatory ventilation; **MAE**: mean average error; **SD**: standard deviation; **IAL**: intraarterial line; **CNH**: Children's National Hospital.

Table 3. Characteristics of the study cohort. Normotensive, not on any inotropic support during the measurement period.

Study Cohort	Patient Characteristics (N = 81)		
Age (days)	Minimum Maximum Average Median	1 150 17 4	
Gestational age (weeks)	Minimum Maximum Average Median	24.14 41.29 34.33 37.00	
Weight (kg)	Minimum Maximum Average Median	**0.55** **4.85** **2.60** **2.80**	
Sex, n (%)	60.5% male, 39.5% female		
Race/Ethnicity			
Primary diagnosis at time of measurement	Cardiac (34), gastrointestinal (3), hyperbilirubinemia (2), multisystem congenital (4), neurological (8), prematurity (21), respiratory (4), Trisomy 21 (1), combination issues (3), and pulmonary hypertension (1) issues		

pulse waveforms which met all these criteria were normalized and used to derive the SBP, MAP, and DBP with the BP model which was developed by using the process described below.

BP Model

The purpose of the BP model is to recognize and correlate certain characteristics of the shape of a pulse waveform to BP values. Once learned, the BP model can automatically infer SBP, DBP, and MAP from the pulse waveforms.

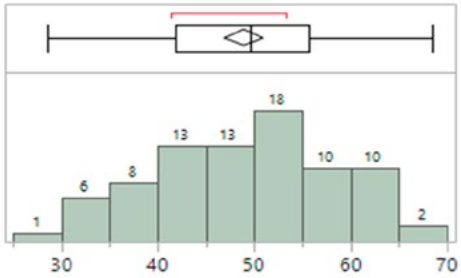
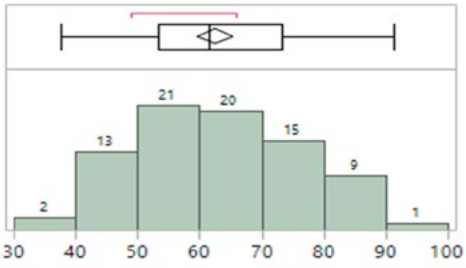
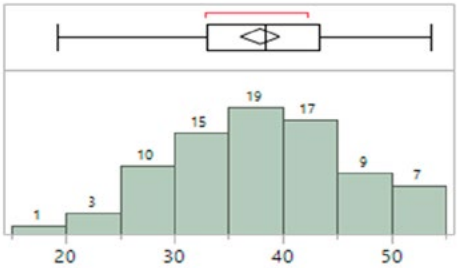
Training Data: To enable learning, we developed an arterial line BP training/learning database by collating de-identified, historical IAL waveforms of infants and pediatric patients previously admitted at Lucile Packard Children's Hospital Stanford (Stanford) and Children's National Hospital and Boppli sensor data collected from patients with arterial lines in place at Stanford. These patient data were associated with patient age and weight but were not labeled with a diagnosis. The IAL and sensor data were processed to improve the signal quality and curated to remove artifacts as described above to make IAL data more suitable for learning.[8]

Training database characteristics:

- A total of 306 infants under 5-years-old in the historical database and 95 patients collected in this study, no exclusions, both sexes.
- Up to 5000 pulse waveforms chosen randomly for each individual from a total of ~25,000 h of training data.
- Same quality preprocessing metrics as the data from the Boppli sensor.

When the IAL and sensor data were taken simultaneously, the two data streams for each patient were synchronized pulse-by-pulse by correlating the amplitudes of the pulse waveform

Table 4. Characteristics of the invasive arterial line data.

IAL MAP (mmHg) individual means	Minimum Maximum Average Median	29 68 49 50	
IAL SBP (mmHg) individual means	Minimum Maximum Average Median	38 91 63 61	
IAL DBP (mmHg) individual means	Minimum Maximum Average Median	19 54 38 38	

signals and heart rates for a set of high-quality windows randomly distributed across the entire time series to obtain a global time lag value. A local time lag was then determined for each individual window to compensate for any missing data. A database was created from the synchronized windows where ground truth BP values were generated from the IAL data and associated with the sensor data for each window.

We used this database to train artificial neural networks to 'learn' features from pulse waveforms which could be correlated to SBP, DBP, and MAP values extracted from the peaks, valleys, and areas, respectively, of the IAL pulse waveforms. Finally, the ANN model was validated (Table 2, Step F) to ensure that it could perform well when presented with real-world data. Because of the limited amount of sensor data, 10-fold cross-validation (CV) sets were used (with 10% of the individuals with sensor data distributed into each CV set) where one set is held out as a test set while the nine other CV sets are used to train the model.

Clinical Study Design

The use of historical IAL data was approved by the Institutional Review Boards at Stanford University (IRB Protocol #47185) and at the Children's National Hospital (IRB Protocol # Pro00014876). The observational study was approved by the Institutional Review Board at Stanford University (IRB Protocol #45892) and conducted in the neonatal (NICU) and cardiovascular intensive care units (CVICU) at Lucile Packard Children's Hospital Stanford. The study complied with all relevant ethical guidelines for human subject research. Written consent was obtained from the parents of the study subjects prior to partaking in the study.

We excluded those infants who were facing imminent demise and those undergoing extra corporeal membrane oxygenation (ECMO). After parental consent, we enrolled infants with umbilical arterial catheters (UACs) or peripheral arterial lines (e.g., radial, femoral, posterior tibial, axillary, or ulnar). The Boppli sensor was placed on an available wrist or foot with the sensor array overlying a pulse point. The wirelessly transmitted pulse waveforms were visualized in the App on a mobile device. The mobile device was kept in close proximity to the patient but not available to the clinical team. This was undertaken to ensure that clinical decisions were not made on the basis of the Boppli readings during the conduct of the clinical study.

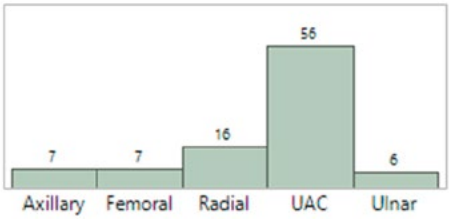
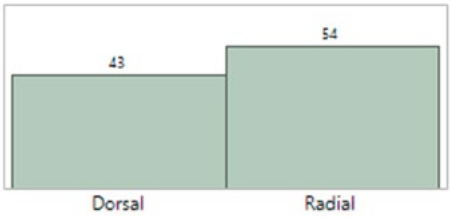
Arterial-Line Data Collection

The catheter (UAC or peripheral arterial line) was connected to an electronic transducer for measuring continuous IAL BP. Measured BP waveforms sampled at 125 Hz were displayed on a Philips Intellivue (Philips Medical Systems, BG Eindhoven, The Netherlands) and stored in the Stanford data warehouse. The IAL data corresponding to each study subject was pre-processed as described above to improve quality and usability.

Correlation and Accuracy Metrics

Finally, we determined if the inferred, sensor-based BP (SBP, DBP, and MAP) correlated with BP from the IAL. Since the eventual clinical use of this device is to be determined by the US Food and Drug Administration (FDA), we compared the Boppli results to the accuracy specifications recommended by the FDA, i.e., a mean average error (MAE) <5 mmHg and standard deviation (SD) <8 mmHg.[14]

Table 5. Characteristics of the IAL and Boppli placement locations.

IAL location(s) (Some patients had more than one IAL)	
Boppli location(s) (Some patients wore more than one Boppli)	

Results

The demographics for 81 infants enrolled in this study are shown in Table 3. These infants were admitted with a wide range of pathologies but were generally normotensive during the period of the study. Table 4 describes the characteristics of the invasive arterial line data. Table 5 provides characteristics of the IAL and Boppli placement locations. The gauge of the catheters used also varied (data not shown). Only patients with a weight below 5 kg and at least ten high-quality pulse waveforms were included in this analysis.

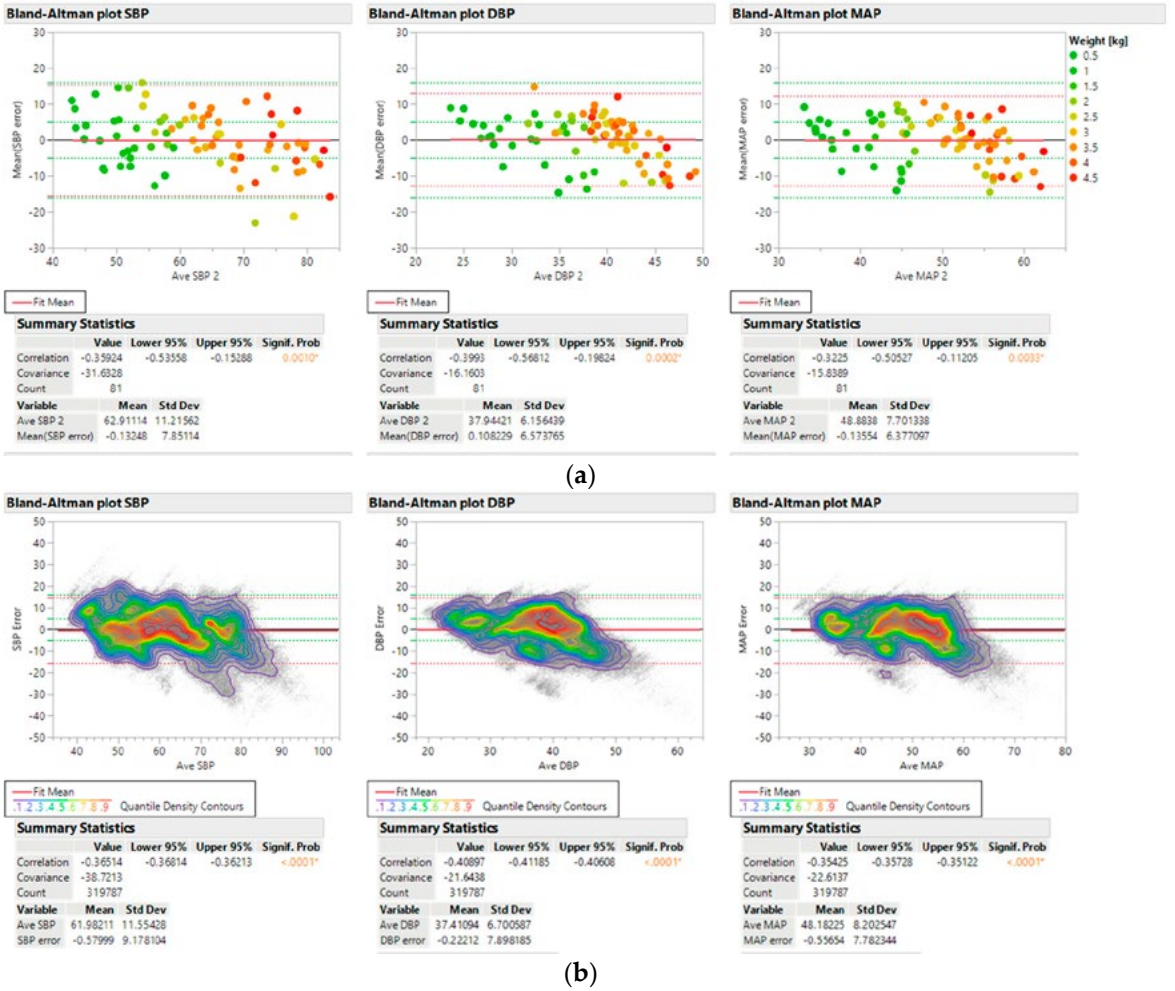


Figure 3. Bland–Altman plots for SBP, DBP, and MAP: (**a**) values averaged over each individual for 81 test patients; and (**b**) all data values without averaging. Bland–Altman plots represent a scatter plot of average versus difference of BP readings constructed for SBP, DBP, and MAP. Points are color coded by patient weight. Red dotted lines indicate 2 * SD of the calculated values. Green dotted lines indicate targets based on FDA guidelines for accuracy of MAE ≤5 mmHg and 2 * SD ≤2 * 8 mmHg. The figures were generated using JMP software version 16.2.0.

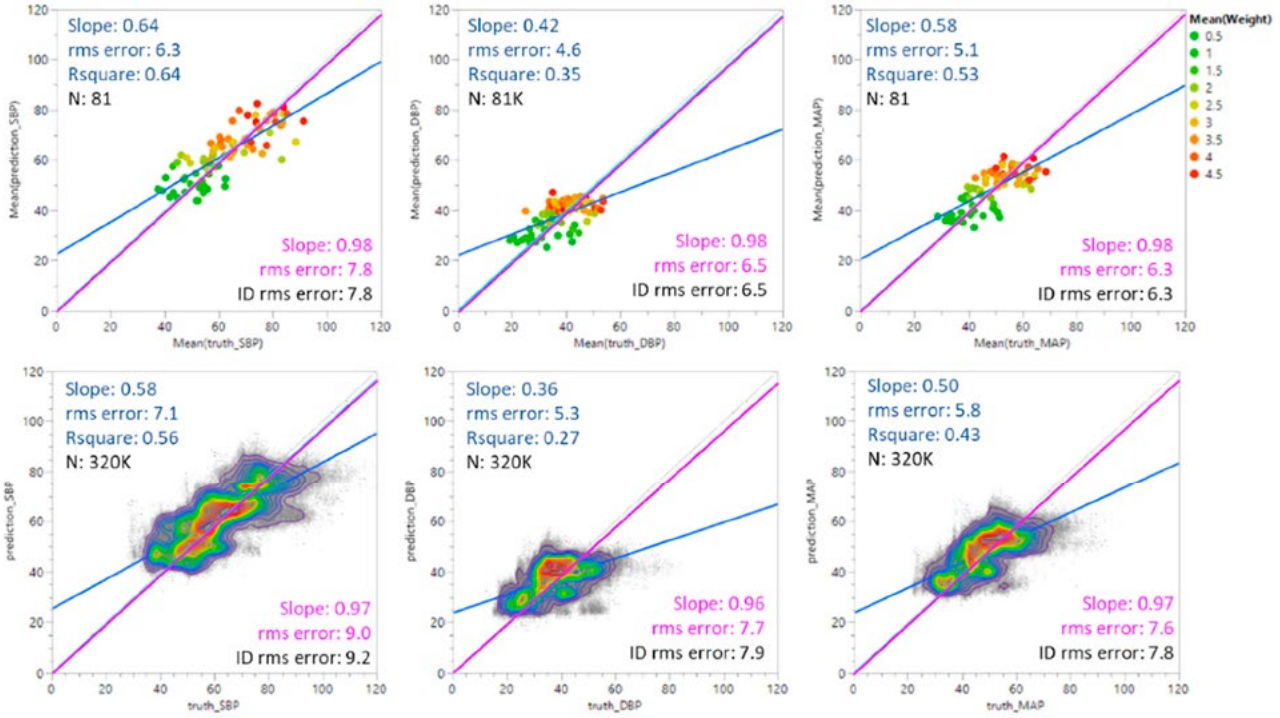


Figure 4. Predicted BP values vs. ground truth values. The blue line represents an unconstrained linear fit to the data. The purple line is a linear fit constrained by a zero-intercept. The grey line is the identity (ID) fit where the predicted values equal the ground truth values. The figures were generated using JMP software version 16.2.0.

cNIBP (Sensor)

The average length of data collection was eight hours per patient, with a minimum of 10 min and a maximum of 14.5 h. The total length of sensor data examined was ~750 h. The data recording was stopped when the arterial line was removed, when the battery ran out (~13–15 h), in anticipation of a procedure, or if the band was removed in error. In some cases, the band was removed or slipped to an incorrect position during extended periods of time, and only poor-quality data were collected during those periods.

Degree of Agreement

Bland–Altman analysis[15] for the mean difference between predicted BP (SBP, DBP, and MAP) and A-line BP demonstrates that SBP, DBP, and MAP predictions are within the FDA specifications when the sensor data $|Q| > 2.5$ and when averaged across each individual to account for the different number of data points per individual (Figure 3a). These analyses were performed in accordance with the guidelines for new BP devices provided by the American National Standards Institute/Association of the Advancement of Medical Instrumentation (AAMI)/International Organization of Standardization (Association for the Advancement of Medical Instrumentation and American National Standards Institute 2003). Predicted values were obtained from the pulse waveform data with the additional inputs of patient age and weight at the beginning of data collection. The points are color coded by patient weight and do not show a systematic trend of error with patient weight or BP values.

Bland–Altman plots with all derived data points without averaging are also shown with contour lines indicating point

Table 6. Summary of degree of agreement for SBP, DBP, and MAP including agreement with FDA guidelines (green) and agreement falling outside FDA guidelines (red).

	Systolic BP		Diastolic BP		Mean Arterial BP		FDA Guidelines	
	MAE	**SD**	**MAE**	**SD**	**MAE**	**SD**	**MAE**	**SD**
Individual averages (N = 81)	−0.1	7.9	0.1	6.6	−0.1	6.4	≤±5 mmHg	<8 mmHg
All points (N = 327 K)	−0.6	9.2	−0.4	7.9	−0.6	7.8		
	r^2	**Slope**	r^2	**Slope**	r^2	**Slope**		
Individual averages (N = 81)	0.64	0.64	0.35	0.42	0.53	0.58		
All points (N = 327 K)	0.56	0.58	0.27	0.36	0.43	0.50		

Table 7. Efficacy by gestational age.

GA	N	MAP			SBP			DBP		
		MAE	SD	Letter Code *	MAE	SD	Letter Code *	MAE	SD	Letter Code *
EPT: <28 wk	15	0.2	6.9	A	−0.0	7.3	A	0.4	7.3	A
MPT: 28–37 wk	38	0.2	6.4	A	0.3	8.3	A	0.4	6.6	A
FT: ≥38 wk	26	−0.9	6.2	A	−0.8	7.8	A	−0.5	6.4	A

* Letter codes not connected by the same letter are significantly different.

densities in Figure 3b. Again, the MAE specifications are met for SBP, DBP, and MAP and there is no systematic trend in error with BP values. However, all three BP values show increased variance and SBP does not meet the SD criterion.

Figure 4 shows predicted SBP, DBP, and MAP values plotted against ground truth values. The top set of plots shows the results for average values weighted by individual; the bottom set shows all predicted values without averaging. Three linear fits are shown in each plot. The blue line shows the unconstrained fit to the data. The purple line shows the fit of the data when the intercept is constrained to be 0. The grey line indicates the ideal (identity) case where predicted values equal the ground truth values with a slope of 1 and an intercept at 0. The root mean square (rms) errors are included for each fit for comparison.

Table 6 summarizes the degree of agreement for SBP, DBP, and MAP.

Effect of Gestational Age

Table 7 summarizes the MAE and SD values for the study population by gestational age at birth (GA) to understand if the BP algorithm is generalizable across the range of GAs found in NICU patients less than 5 kg in weight. The population was separated into three categories of GA: <28 weeks (extremely preterm, EPT), 28-37 weeks (moderately preterm, MPT), and ≥38 weeks (full-term, FT). These categories correspond to the extremes of gestational age as defined by the World Health Organization.[1,4] For MAP and DBP, all subsets meet the efficacy specification of MAE 5 mmHg, SD 8 mmHg. SBP meets the MAE criterion for all subsets but the MPT subset does not meet the SD criterion.

The differences in accuracy between the GA groups were evaluated using the Tukey–Kramer analysis on JMP, a statistical package from SAS. This is a variant of the Tukey HSD method and uses SDs when there is an uneven number of data points per test period. Due to the range of data collection periods and variations in the quality of both IAL and Boppli data with time, the number of points varied by individual.

In the Tukey–Kramer (Tukey HSD) analysis, a letter code is assigned to each test group which can be used to gauge the statistical significance of differences between pairs of test groups. If the comparison of a pair of test groups did not exceed the threshold of significant difference, they were given the same letter code. If the analysis of their SDs exceeded this threshold, they were assigned different letter codes. A given test group may have multiple letter codes if it did not exceed the threshold of significant difference with several other test groups but some of the others differed significantly from one another and thus were given different letter codes. Pairs are considered significantly different if they do not share a letter code. The broader the difference between letter codes between a pair of test groups, the higher the likelihood that the pairs are significantly different. In Table 7, all groups show the same letter code and thus there does not appear to be a significant difference between GA groups.

Figure 5 shows the comparison results for the three GA categories of infants. Data points are colored by patient weight at the time of the study. A good overlap between the mean diamonds (green) and the Tukey–Kramer circles (black) indicates there is no significant difference between the GA groups. All subsets show MAP, SBP, and DBP mean values within the specification for accuracy (green dotted lines at 5 mmHg error) and the 95% confidence level (green dashed lines at 16 mmHg). As such, there does not appear to be an impact of gestational age on accuracy. Similar analyses show no significant trends in efficacy due to age, weight, race/ethnicity, IAL location, or Boppli location.

There is some indication of a significant difference due to sex although the results for both male and female cohorts meet the accuracy (MAE) guidelines. There is more variance for the male subset which exceeds the target of SD 8 mmHg for SBP. The results are shown in Table 8 and Figure 6.

Discussion

A non-invasive approach to monitoring BP is a vital unmet need in neonatal critical care. Currently, there are no commercially available neonatal cNIBP devices. Solving this unmet need can provide better, safer BP monitoring for the ~400,000 NICU patients annually in the US[16] and avoid the pain, stress, and risks of IALs. The novel Boppli cNIBP device can continuously and non-invasively infer BP without the need for external calibration.

Table 8. Efficacy by sex.

	N	MAP			SBP			DBP		
		MAE	SD	Letter Code *	MAE	SD	Letter Code *	MAE	SD	Letter Code *
Female	33	2.0	5.1	A	2.2	6.4	A	1.9	4.9	A
Male	48	−1.6	6.8	B	−1.7	8.4	B	−1.1	7.3	B

* Letter codes not connected by the same letter are significantly different.

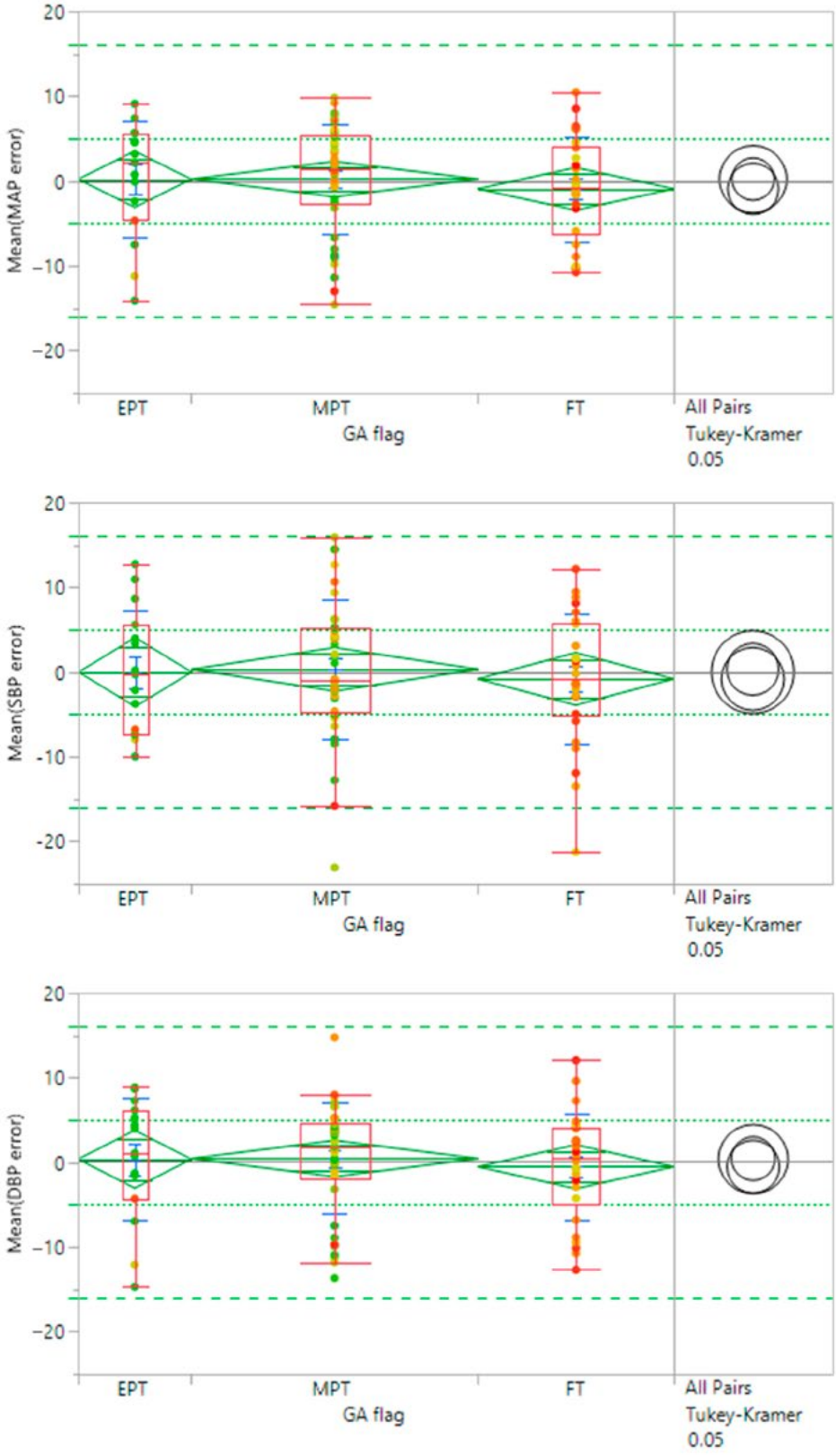


Figure 5. Effect of gestational age (GA) on efficacy. Groups categorized by prematurity are compared through mean diamonds (green) and Tukey–Kramer circles (black). EPT (<28 wks GA), MPT (28-37 wks GA), FT (≥38 wks GA). Overlap between diamonds and circles indicates there is no significant difference between groups. Mean diamonds are contained within the FDA guidelines for accuracy (dotted green lines). Targets for 95% confidence levels are indicated with dashed green lines. Points are color-coded by patient weight.

This is significant because it reduces the nursing burden at the bedside. The device does not use adhesives, which is relevant for premature neonates who lack a protective layer in the skin, i.e., stratum corneum.[17] It is less perturbing to the patient than an IAL, cuff, or other bulky non-invasive options. This device can be strapped on like a wrist-watch and can be used while transporting patients. The electronics can be reused to a lower cost of care. Consequently, this device can change the

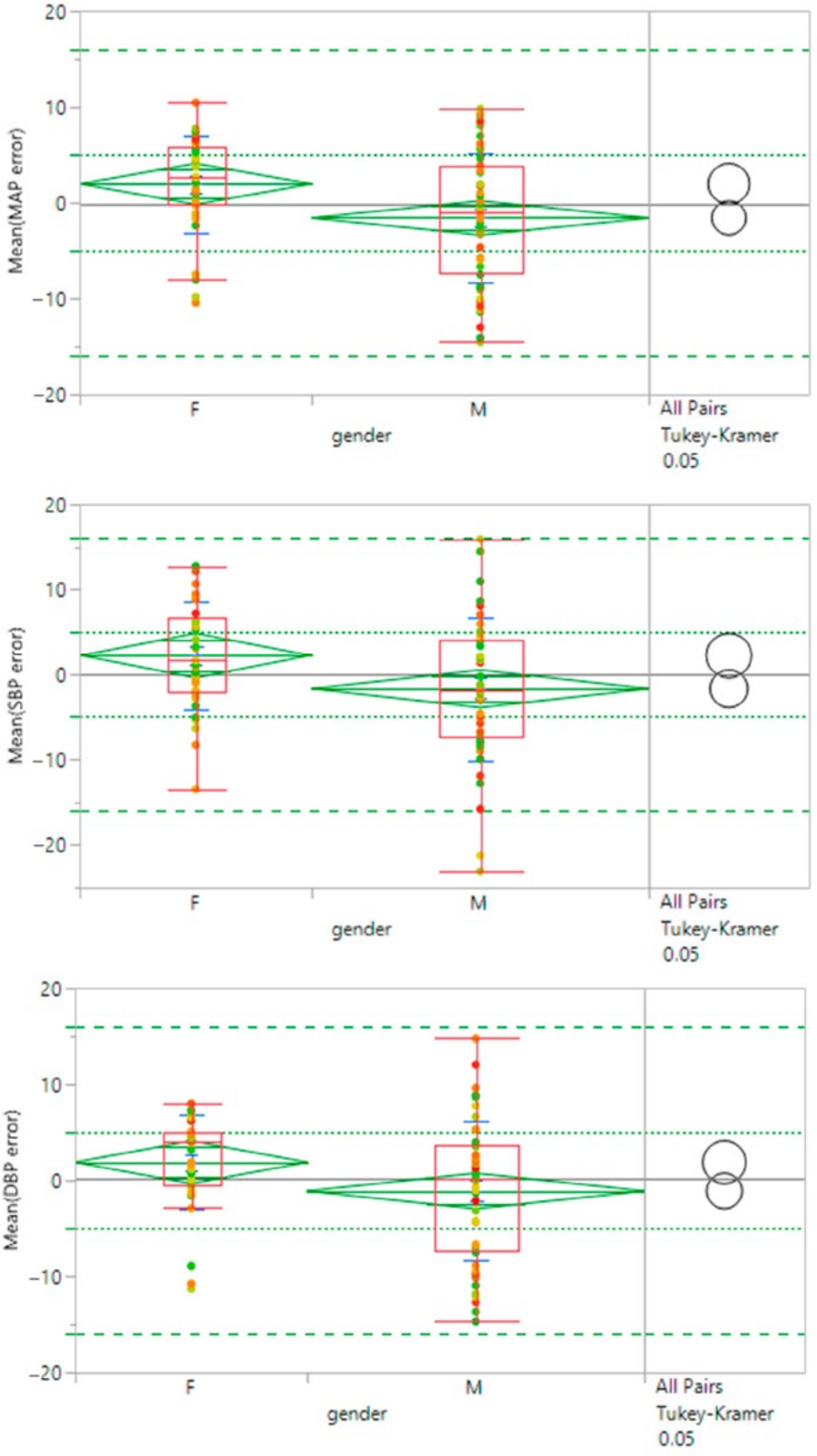


Figure 6. Effect of sex on efficacy. Female and male patient subsets are compared through mean diamonds (green) and Tukey–Kramer circles (black). Minimal overlap between diamonds and circles indicates there is a significant difference between the two groups. Mean diamonds are contained within the FDA guidelines for accuracy (dotted green lines). Targets for 95% confidence levels are indicated with dashed green lines. Points are color-coded by patient weight.

management of neonates by avoiding arterial line placement in neonates who strictly need monitoring for BP issues.

A few prior studies have suggested that non-invasive methods of BP overestimate invasive arterial lines.[18,19] These studies used intermittent, cuff-based methods unlike the continuous, non-cuff-based method described here. Other studies have shown good agreement for non-invasive methods of BP measurement.[5,20] We expect that this device, once cleared by the FDA and adopted for clinical use, will potentially eliminate the complications

associated with invasive arterial lines. This transition will pave the way for enabling continuous non-invasive monitoring, early detection of changes in BP, timely intervention, and tracking of the response to treatment. Although this study focuses on neonates, the technology platform is applicable to all age groups, and limited only by the availability of arterial waveform data for building neural network models.

The study had limitations. All enrolled neonates were critically ill but were normotensive. We acknowledge that the utility of this device and its accuracy is of utmost value in hypotensive patients and such a study is intended in the future. The correlation between a gold-standard arterial line and cNIBP sensor can depend on the precise location of the arterial line. We have not accounted for this issue in the current study. Critically ill infants often have fluids running through their umbilical lines. This can dampen the observed and recorded signals. Comparing the cNIBP signal from a limb to a presumably corrupted waveform, deemed as a "gold-standard" can be inaccurate. Another limitation is due to the blinding of the data to the clinical team which led to periods of time where the data quality was insufficient for analysis. In future studies, we will display the pulsewave to the clinical team to provide a visible cue of data quality. We have observed that the fraction of data with usable quality increases when the clinicians are able to see the Boppli signal in real time.

Our study also has strengths. First, we demonstrated the accuracy of the device in estimating BP in real-world ICU settings and in infants with a wide variety of clinical conditions. Additionally, capturing unscaled data is innovative because it overcomes the need to calibrate for skin type, edema, patient size and shape, sensor positioning, and temperature sensitivity. The BP model was generated with data obtained from 306 patients. We believe that additional data can refine the algorithms and increase accuracy. In several instances, IAL data were distorted due to over/underdamping and artifacts from transducer flushing, kinking of catheters, movement artifacts, BP cuff inflations, and high frequency oscillatory ventilation. However, using filtering techniques, we have extracted underlying cNIBP waveforms. This work is novel and significant because it can impact clinical practice and simultaneously enable real-time analytics.[21]

Conclusions

This study is significant because it addresses a critical gap faced by clinicians treating infants in the neonatal period. We have investigated the accuracy of a novel wearable device that utilizes capacitive sensing and algorithms trained through machine learning in tandem to infer BP, continuously and non-invasively, without external calibration. We showed that the use of the device is feasible for critically ill term and preterm infants with a wide variety of pathologies—from serious cardiac ailments, pre- and post-operative cases, neurologic conditions, and prematurity. The ANN model used in this study is one of several models we have developed to estimate BP in real-time without the need for calibration. The wearable meets the FDA specifications for accuracy and is a practical choice in clinical settings—it is easy to attach and operate and provides continuous BP readings with no latency. A pivotal multi-center study to assess accuracy and submit data to the FDA for device clearance is underway.

Author Contributions

Conceptualization, X.Q., A.R., W.R. and A.H.; methodology, X.Q., A.R., C.R., A.V. and A.H.; software, T.R., J.L., W.L. and A.W.; validation, A.R. and X.Q.; formal analysis, X.Q., J.L., T.R., and W.L.; investigation, X.Q., A.R., T.R., and W.L.; resources, X.Q., A.M. (Arthur Muir) and W.L.; clinical data collection, F.E.-A., Y.W., A.R., E.B., A.M. (Alexandra McMillin), N.S., X.Q. and A.J.; data curation, E.H., W.L., X.Q., A.R., A.W., G.G. and R.B.G.; writing—original draft preparation, X.Q. and A.R.; writing—review and editing, J.L., T.R., W.L. and K.D.; visualization, X.Q. and A.R.; supervision, X.Q. and A.R.; project administration, X.Q. and A.R.; funding acquisition, X.Q. and A.R. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The studies were conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Stanford University (Protocol #45892 and #47185) and the Institutional Review Board of the Children's National Hospital (Protocol #00014876).

Informed Consent Statement

Written informed consent was obtained from all subjects via their Legal Adult Representatives.

Data Availability Statement

Data presented in this document that were generated solely by PyrAmes are available from the corresponding author upon reasonable request. The data are not publicly available due to sensitive personal data that were collected during clinical studies on patients. Data generated or provided by Stanford University and Children's National Hospital are restricted by the terms of contractual agreements and are available upon reasonable request with the permission of those organizations and if the requestor agrees to comply with the European General Data Protection Regulation and not to attempt to trace the origin of the data.

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Citation

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Conflicts of Interest

Y.W., E.B., T.R., J.L., A.W., A.M., W.L., X.Q. and K.D. are/were employees/contractors of PyrAmes. No conflict are reported for A.R., F.E.-A., E.H., A.J., A.V., C.R., A.H., W.R., R.B.G. and N.S.

Code Availability Statement

The custom code used in this study is copyrighted by PyrAmes Inc. Any commercial use including the distribution, sale, lease, license or other transfer of the code to a third party is prohibited. For inquiries regarding commercial use of the code, please contact xquan@pyrameshealth.com.

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High-Value Care Decisions in Neonatal ICU

Estephanie Rivero, MD and Shabih Manzar, MD

Abstract

High-value care (HVC) can be described as a cost-effective medical practice. HVC decisions are not easy in neonatal ICU. It requires astute clinical examination and skills. We present two neonatal cases to elucidate HVC in NICU. In case 1, the infant had poor cord blood gases, but therapeutic hypothermia was not initiated by following the clinical guidelines and performing serial neurological examinations, thus preventing unwarranted whole-body cooling and an extended hospital stay. In case 2, exchange transfusion was avoided by performing serial neurological examinations to assess for BIND (bilirubin-induced neurological dysfunction). In conclusion, treating a laboratory test or a numerical value should be viewed critically. The clinician should follow clinical guidelines and perform good clinical examinations, thereby saving unnecessary high medical costs.

Introduction

High-value patient care (HVC) can be described as a cost-effective medical practice. For many years, families have been burdened by the healthcare system due to the increasing number of unnecessary procedures and treatments. Much of medicine has centered around following guidelines without considering the patient's social determinants of health. In 2012, The Choose Wisely campaign started an initiative to curtail overdiagnosis by involving patients to partake in their medical decisions after being well-informed on recommendations made by national medical organizations. As physicians, we can move towards changing the standard practice of patient care by being financially conscious and inclusive of the community we serve.

Currently, only a few pediatric residency programs throughout the United States have implemented High-Value Care into their curriculum.[1] The lack of training on HVC stems from limited research in low-value care and its impact on the medical system. Incorporating HVC can not only be taught in the typical didactic settings as outlined by Dewan et al.[1] but during the bedside rounds to include families, nurses, and pharmacists.[2] Recently, Holmes et al.[3] proposed two new teaching models, "PPI (Prepare, Process, and Initiate) and SOAP-V (Subjective, Objective, Assessment, and Plan along with Value)," for conducting patient assessment which emphasizes value.[3] These models give a platform for patient advocacy as they aid in reminding us of the humanistic view of medical care.

For this article, we described two cases in which thoughtful clinical examination and following the clinical guidelines prevented an extended hospital stay and exorbitant medical bills.

Case 1

A full-term newborn was delivered via repeat cesarean-section to a gravida 1, para 0 mother with a history of chronic hypertension. The cord gases were obtained as a part of the standard of care. The venous cord gas showed a pH of 7.06, BD -12, while the arterial cord gas showed a pH of 6.98, BD -13. There was no history of any perinatal event, and Apgar scores were 9 and 9 at 1 and 5 minutes of life, respectively. Based on the cord and arterial gases (postnatal arterial blood gas: pH 7.1, BD -16), the infant could have been a candidate for therapeutic hypothermia. However, the on-call team followed the clinical guidelines and performed serial neurological examinations for up to 6 hours of life, as described in recent literature (Figure 1).[4] The infant showed no signs of encephalopathy during her overnight stay in the NICU. She could feed without any issues and was transferred to the nursery before discharge with family. It was evident that following clinical guidelines and good clinical evaluation prevented unwarranted whole-body cooling and an extended hospital stay.

Case 2

A preterm infant was born at 30 weeks gestation via spontaneous vaginal delivery due to premature prolonged rupture of membrane (PPROM). Maternal history was remarkable for advanced maternal age, chronic hypertension, and Rh-negative status. She was gravida 1, para 0. The infant was admitted to NICU for prematurity and developed significant hyperbilirubinemia at 72 hrs. of life. Intensive phototherapy was initiated after levels rose from 2.5 mg/dL to 10.5 mg/dL within 24 hours. Although intensive phototherapy was in effect, he continued to have a slow rise in bilirubin, with the peak being 13.1 mg/dL at 96 hours of life. There were concerns over having to perform an exchange transfusion (Figure 2) as the patient was premature and had rapidly rising bilirubin levels, but we used clinical assessments such as serial neurological examinations to assess for BIND (bilirubin-induced neurological dysfunction).[5] The patient did not demonstrate signs of feeding difficulties, was interactive, had good muscle tone and a normal cry; therefore, the scores did not reflect signs of acute bilirubin encephalopathy. We continued to follow the bilirubin levels closely, which

Estephanie Rivero is a Fellow, Neonatology, Department of Pediatrics School of Medicine, Louisiana State University. Shabih Manzar is an Associate Professor, Department of Pediatrics, School of Medicine, Louisiana State University Health Sciences Center.

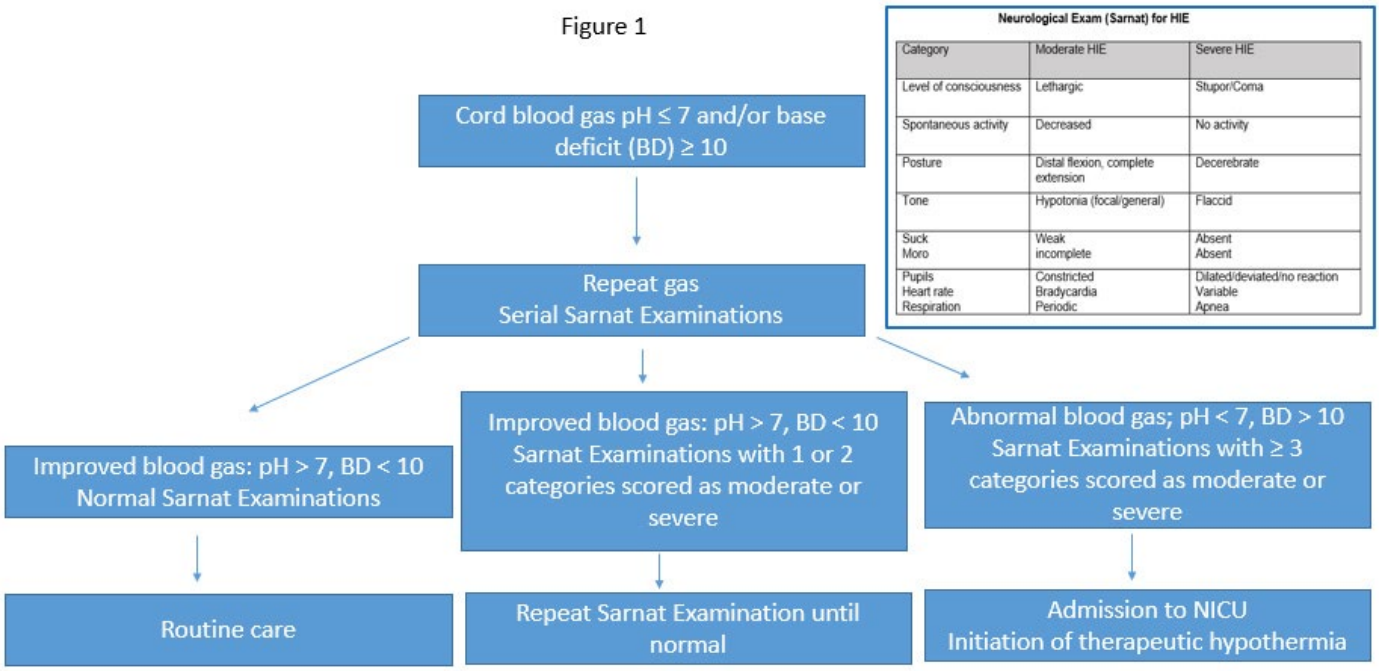

Figure 1. Schematic diagram describing the action plan based on the repeat blood gas and serial Sarnat examinations.

showed a decrease by the 6th day of life. Exchange transfusion was avoided due to our serial examinations.

Discussion

These cases provided evidence that for HVC, it is essential to follow clinical guidelines and the value of clinical examination.

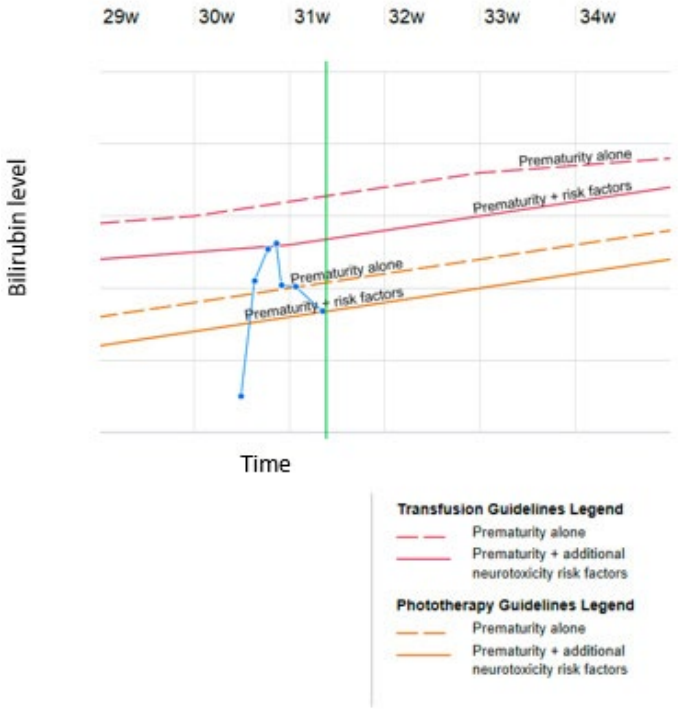

Figure 2. Phototherapy and Exchange transfusion thresholds in preterm infants. The blue line represents the infant's serial bilirubin measurements. Time is on the x-axis, and serum bilirubin is on the y-axis.

The whole-body hypothermia treatment is not only costly but has significant side effects. The exchange transfusion exposes the patient to blood which may lead to transfusion-related complications.

The HVC decisions do require some calculated risk. For example, the risk associated with not performing the exchange transfusion (ET) or therapeutic hypothermia (TH) could not be overlooked, as hypoxic-ischemic encephalopathy and hyperbilirubinemia are detrimental to the infant. In the cases presented above, the infants were observed closely in the intensive care unit so that ET or TH would be instituted immediately in case of deterioration or absolute indications.

Although most guidelines are developed based on evidence, they are still just expert opinions. They are beneficial, as noted in the cases, but a regular update based on changing statistics and current data should be done. The cases focus on the need for teaching adequate clinical skills to interns, residents, and fellows. Technology could not replace the value of bedside clinical skills. Intelligent quotient (IQ) is superior to artificial intelligence (AI) in clinical medicine.

The flip side of holding on to certain investigations and treatments is the fear of litigation. Many practitioners feel obligated to investigate further, which leads to more preventable overdiagnosis. By the examples presented above, it was made clear that an astute clinical observation and management plan could be safely observed without any untoward complications.

In conclusion, clinicians should follow a wholesome approach in the management of clinical cases. Treating a laboratory test or a numerical value should be viewed critically. By following clinical guidelines and performing good clinical examinations, unwarranted high-cost medical interventions could be avoided.

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Empowering Communication and Respiratory Function in Infants: Exploring the Use of the Bias-closed, No-leak Speaking Valve

Kristin King, PhD, CCC-SLP

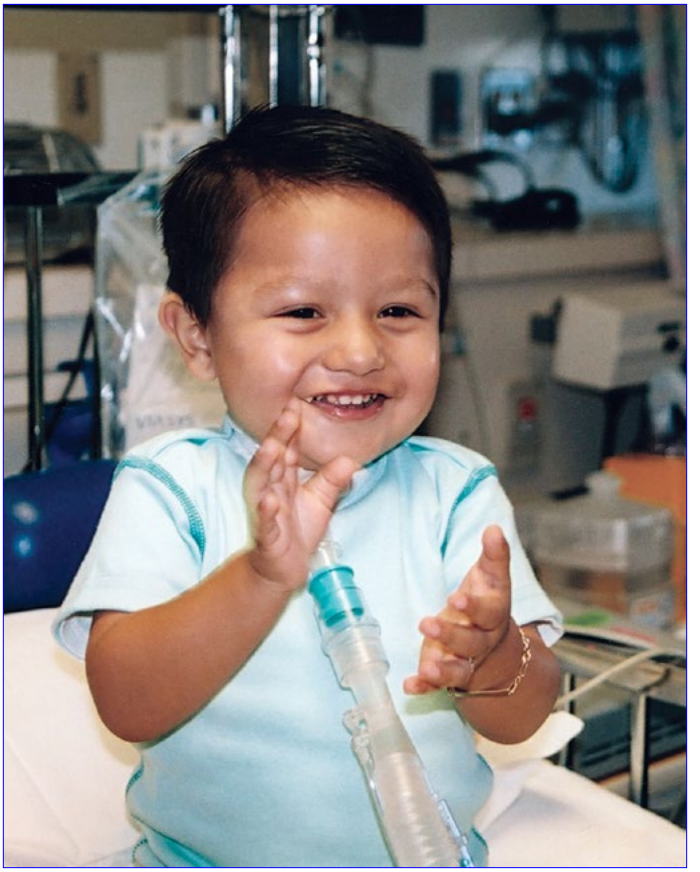
Effective communication and optimal respiratory function are vital for infants to thrive and develop.[1] However, infants with tracheostomies or ventilator dependency face challenges in both areas. The Passy Muir® Tracheostomy & Ventilator Swallowing and Speaking Valve (PMV®) has emerged as a significant tool to assist in pediatric care, allowing infants to vocalize and communicate while improving their respiratory status following placement of a tracheostomy tube for respiratory support. Considering the benefits, considerations, and implications of using the Passy Muir Valve with infants further illustrates potential impact on speech development, swallowing, and overall quality of life.[2]

Use of the Passy Muir Valve

The Passy Muir Valve is a one-way valve that attaches to the tracheostomy tube, redirecting airflow through the vocal folds and out of the mouth. This innovative device enables infants with tracheostomies to produce speech by restoring the natural airflow pathway. Additionally, it helps improve swallowing function and promotes positive pressure ventilation, enhancing respiratory mechanics.[3-5]

Benefits of Using the PMV with Infants

1. **Vocalization and Speech Development:** The Valve plays a crucial role in facilitating vocalization and speech development in infants.[2,6] By redirecting airflow through the vocal folds, it restores the sensation and coordination necessary for vocal production. Early exposure to the valve stimulates speech-like sounds, leading to improved speech patterns and overall communication skills.
2. **Swallowing and Oral Feeding:** Infants with tracheostomies often face challenges in swallowing and oral feeding due to disrupted airflow.[7] The Passy Muir Valve aids swallowing by promoting a closed system during the swallowing process. With the Valve in place, airflow is restored through the upper airway which has been shown to improve swallowing. This reduces aspiration and enables a more natural and efficient oral feeding experience, enhancing nutrition and growth. Research has even shown that use of the Valve during breastfeeding can enhance not only the swallow and latch but improve bonding as the mother is able to provide a more typical feeding experience.[8]
3. **Respiratory Function:** The Passy Muir Valve positively impacts respiratory function in infants. By improving glottic closure during exhalation, it enhances oxygenation, pulmonary mechanics, and the removal of secretions. This not only facilitates weaning from mechanical ventilation but also supports successful decannulation, ultimately promoting respiratory independence.[9]



Communication has a significant impact on a child's progress.

Considerations for Improved Success

While the Passy Muir Valve offers significant benefits, its use with infants requires careful consideration and adherence to

With 25 years of experience in medical, academic, and industry settings, Dr King brings a unique perspective of medical speech pathology. Her research, publications, and teachings focus on traumatic brain injury, swallowing disorders, and critical care (tracheostomy and mechanical ventilation) for both pediatric and adult patient populations. She has been an invited speaker both domestically and internationally and has published in peer-reviewed journals. Currently, Dr King is the Vice President of Clinical Education and Research for Passy-Muir, Inc.

Quality of life and interaction with family have been shown to improve patient outcomes, even in infants and children.

facility policies and procedures. Research has shown that a multidisciplinary team with protocols have more success with Valve use.[10]

1. **Respiratory Stability:** Infants must have stable respiratory status before the introduction of the Valve. Adequate oxygenation, ventilation, and the ability to maintain respiratory stability during valve trials are critical factors to consider.[1]
2. **Size and Comfort:** Comfort and tolerance should be assessed during initial trials, with adjustments made as necessary to ensure optimal function and infant comfort.
3. **Multidisciplinary Collaboration:** Successful implementation of the Passy Muir Valve requires collaboration among various healthcare professionals, including respiratory therapists, speech-language pathologists, nurses, and caregivers.[10] Each member of the team contributes unique expertise to optimize outcomes.
4. **Education and Training:** Caregivers should be provided with comprehensive education and training regarding the proper handling, cleaning, and maintenance of the Passy Muir Valve. They should be familiar with troubleshooting techniques and recognize signs of potential complications, ensuring appropriate intervention when necessary.

Improved Quality of Life for Infants and Families

Having a tracheostomy and subsequent use of the Passy Muir Valve with infants not only enhances their communication and respiratory function but also has a profound impact on their overall quality of life.[11] While most research has been done looking at the psychological wellbeing of adults, it is common sense that the impact of tracheostomies on communication and quality of life would be similar, no matter the age of the patient.

1. **Emotional Connection and Bonding:** Communication plays a crucial role in building emotional connections between infants and their caregivers. The Valve enables infants to express their needs, wants, and emotions, fostering stronger bonds and enhancing the overall caregiving experience.[8]
2. **Self-Expression and Confidence:** The ability to vocalize empowers infants with tracheostomies, allowing them to participate actively in their environment. This increased self-expression promotes self-confidence, autonomy, and a positive sense of self-identity as they develop.[12]
3. **Social Interaction and Inclusion:** Communication skills are essential for social interaction and inclusion. With the Passy Muir Valve, infants can engage more effectively with peers, family members, and healthcare professionals, fostering social development and facilitating integration into various environments.[11,12]

Conclusion

Using a Passy Muir Valve provides a significant advancement in improving communication and respiratory function in infants with tracheostomies or ventilator dependency. By enabling vocalization, enhancing swallowing function, and optimizing respiratory mechanics, the valve empowers infants to communicate, develop speech, and thrive in their environments. However, careful assessment, multidisciplinary collaboration, and proper education are crucial for the safe and efficacious use of the Passy Muir Valve. Ultimately, its use has the potential to profoundly impact the quality of life for infants and their families, promoting positive developmental outcomes and facilitating long-term success.

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Health Literacy in the NICU: Empowering Healthcare Professionals to Enhance Parental Engagement

Jaylee Hilliard, MSN, RN, NEA-BC, CPXP

Health literacy plays a pivotal role in the Neonatal Intensive Care Unit (NICU), where healthcare professionals provide specialized care to newborns requiring intensive medical attention. The topic's significance prompted the development of a National Action Plan to Improve Health Literacy, envisioning a society where individuals have equitable access to precise and actionable health information, person-centered health services are provided, and continuous learning and skills fostering good health are encouraged.[1]

This article explores the concept of health literacy in the NICU setting and its significance for healthcare professionals. By understanding the impact of health literacy, healthcare professionals can better support parents and caregivers, enhance communication, and promote informed decision-making, ultimately improving outcomes for NICU infants.

Defining Health Literacy in the NICU

Health literacy encompasses the skills, knowledge, and abilities required for individuals to access, understand, evaluate, and use healthcare information and services effectively. Health literacy is a complex concept that includes reading, writing, verbal, and numeracy skills in the context of health information.[2,3] Examples include the ability to interpret medication labels, dose medication appropriately, mix powdered formula, relay clinical information to providers, and interpret and navigate digital health information. According to the National Network of Libraries of Medicine, nine out of ten adults do not have the health literacy skills needed to navigate our current healthcare system.[2] It is also well-documented that health literacy is decreased when patients or caregivers are stressed, anxious, sick, or traumatized.[2]

According to a study by Mackley et al., upon NICU admission, 43% of parents were identified as having suspected limited health literacy (SLHL), with this figure decreasing to 32% at the time of NICU discharge.[4] Notably, factors such as parental age, gender, location, and history of healthcare-related employment were not found to be associated with health literacy status at any time. Furthermore, it was observed that 39% of NICU parents with SLHL possessed a college education.[4]

Jaylee Hilliard, MSN, RN, NEA-BC, CPXP, is the Senior Director of Clinical Strategy at AngelEye Health, revolutionizing patient and family support through advanced technology. With extensive experience in nursing leadership and NICU parenting, Jaylee drives product innovation, supports healthcare leaders, and empowers hospitals to achieve the quadruple aim.

In the context of the NICU, health literacy extends beyond the literacy skills of parents and caregivers to include their capacity to comprehend and navigate complex medical information, terminologies and procedures for their child. Examples include drawing up the appropriate amount of medication and administering it through the appropriate route at the appropriate time or following a recipe to fortify milk. Parents often need more hands-on practice opportunities to build the know-how and confidence to effectively identify and troubleshoot problems independently.

Lower health literacy in parents and caregivers is associated with worse child health outcomes.[5,6] Healthcare professionals must recognize health literacy as crucial to their interactions with parents and caregivers. Professionals should acknowledge this population's diverse backgrounds and varying levels of health literacy and adopt a "universal health literacy precautions" approach — that is, to explain concepts in simple and straightforward terms and focus on comprehension.[7] When designing and implementing discharge processes that adequately prepare parents to care for their child after discharge, NICU professionals must recognize that most adults do not have high levels of health literacy.We must shift our "this is how we have always done it" mentality and challenge ourselves, our institutions, and our practices to best support families and caregivers.

The Importance of Health Literacy in the NICU

Enhanced Communication and Collaboration

Acknowledging and addressing the disconnect between professional and parental knowledge and health literacy levels enables healthcare professionals to communicate effectively with parents and caregivers in the NICU. Experts note that parents should not be screened for literacy or health literacy as this often creates shame or overestimates comprehension.[7] Instead, best practices for communicating with parents or other caregivers include using plain language, avoiding medical jargon, employing clear explanations, discussion or hands-on-based teaching and color-coded simple pictures. Effective communication promotes collaboration, enables shared decision-making, alleviates anxiety, builds trust, and helps parents and caregivers feel informed and engaged in their baby's care. Given the frequency of interactions and other contextual factors, NICU systems and the professionals who work in them have a unique opportunity to enhance caregiver/parent health literacy and prepare parents to best care for and advocate for their infants beyond the NICU.

Parents often face challenges when answering questions about fundamental infant care tasks. In the study conducted by Enlow et al., it was revealed that 31% of the 137 participants demonstrated limited health literacy. Interestingly, these scores were not found to be associated with admission characteristics or complications experienced in the Neonatal Intensive Care Unit (NICU). Moreover, lower health literacy scores did not correlate with parents' self-rated readiness for discharge. These findings provide further evidence of the challenges many parents face when answering questions regarding basic infant care tasks. It emphasizes the importance of prioritizing health literacy in their communication and discharge planning processes.[8]

Empowering Parents and Caregivers

Building comprehension and enhancing health literacy equips parents and caregivers with the knowledge and skills necessary to actively participate in their baby's care. It fosters their confidence, encourages them to ask questions, and enables them to make informed decisions. By promoting health literacy, healthcare professionals empower parents and caregivers to become advocates for their baby's needs, leading to better adherence to treatment plans and improved overall outcomes. A study by Patel et al. found that during 635 home visits after NICU discharge, a comprehensive examination of 241 high-risk infants revealed 363 errors.[9] These errors encompassed various aspects such as feeding, medication, equipment, and appointments. No significant associations were found between the presence or absence of errors and infant or maternal demographic factors.[9] Infants' clinical outcomes improve when parents are more engaged during the NICU stay, and the length of stay decreases when parents are educated and empowered.[10,11]

Challenges to Health Literacy in the NICU

Complex Medical Information and Terminology

The NICU environment presents parents and caregivers with an overwhelming amount of complex medical information, making it challenging to understand and process. The NICU often feels other-worldly to parents with unfamiliar terminology, equipment, people, and an environment with unfamiliar sights and sounds from the moment they enter. Each day they may face new experiences, terminology, and more that continue until the day of discharge. There is a paradigm here where families are rarely able to "catch up" to the gap in their knowledge because they are constantly bombarded with new information as their child's condition changes. If you take that coupled with the increased need for engagement, participation, and understanding required to pass the baton to them before discharge, they are set up for failure from the start. Many parents feel overwhelmed or even defeated because of this. Following NICU discharge, many parents of NICU graduates are entrusted with the responsibility of managing complex and ever-changing care routines. Healthcare professionals must recognize this challenge and employ effective communication and education strategies to bridge the gap between medical terminology, skills required to care for their child, and the parents' comprehension level.

Emotional and Cognitive Stressors

Parents and caregivers in the NICU often experience emotional distress and cognitive overload due to their baby's critical condition. These stressors can significantly impact their ability to absorb and retain information.[2,3] Research indicates that a substantial proportion of medical information provided to patients during office visits is promptly forgotten, ranging from 40% to 80%.[12] Furthermore, nearly half of the retained information is found to be inaccurate.

Healthcare professionals should provide support and empathy, an open-discussion style dialogue while delivering information, and allow for repeated explanations and reinforcement. NICU discharge preparation processes (which begin upon admission) must support parents' ability to learn and practice skills until they have reached an appropriate level of competency. Many NICU leaders share that the bulk of education and training is provided to families 48-72 hours before discharge. This information may include drawing up and administering medication, utilizing medical equipment such as home oxygen, or following a recipe to fortify milk properly. Not only is this not enough time for families to learn and retain the information, but it is also certainly not enough time to practice, formulate questions, and experience situations that may require troubleshooting.

Language and Cultural Barriers

Language, cultural differences, and biases can impact effective communication in the NICU. Parents and caregivers may face difficulties understanding and communicating their needs.

In their study, Harris et al. discovered that parents with limited health literacy and limited English proficiency were at the highest risk of making liquid medication dosing errors compared to parents with adequate health literacy and were proficient in English.[13] Cultural nuances and beliefs can affect comprehension, decision-making, and reciprocal trust. Healthcare professionals should employ interpreter services, offer culturally sensitive materials, and engage in cultural humility to bridge the gaps.

Due to language and cultural barriers, families may feel embarrassed or guilty admitting they have questions or may not understand what was shared with them.[3] Most NICUs do not have all the educational resources available to families in their native language. An interpreter can help communicate with the family when consulted during the NICU stay, but families need additional handouts and materials to support their training/educational needs as a reference. Many NICU nurses express guilt or anxiety after attempting to effectively educate, train, and communicate with families with language barriers. Thinking- "I wonder what happened to that family," or "I am worried about how this family will handle caring for their baby when they are home." These are the things that keep some NICU nurses up at night.

Strategies to Enhance Health Literacy in the NICU

Effective Communication Techniques

Healthcare professionals should use plain language, visual aids, and simplified explanations to convey complex medical information.[2] Clear, concise, and visual communication helps parents and caregivers better understand their baby's condition, treatments, and expected outcomes. It is recommended that professionals ensure the family understands what is being communicated before moving on to the next topic.[1] The Joint Commission highlights the "Teach Back" method as an easy and effective communication tool to assess understanding and assist with decision-making.[12,14] Another example of open-ended dialogue includes phrases such as "What questions do you have?" instead of "Do you have any questions?" — signals to families

that questions are a routine and an expected part of medical communication.[15]

Universal Health Literacy Precautions

While limited health literacy is widespread, medical professionals are notoriously inaccurate in predicting who has limited health literacy.[16] For example, a study by Mackley et al. determined no correlation between nurses' subjective assessment of parental comprehension of discharge instructions and the objective measurement of health literacy. Given this, experts recommend that healthcare professionals communicate information utilizing "Universal Health Literacy Precautions."[7] According to the Agency for Healthcare Research and Quality Toolkit, these universal precautions simplify communication, ensure comprehension, and make the healthcare environment easy to navigate and empower parents.[7] This universal practice may be even more critical in the NICU given the high prevalence of stress, feeling overwhelmed, trauma, anxiety, depression, and physical health issues among parents.

Creating a Supportive Environment

Healthcare professionals should foster a supportive environment encouraging questions, active participation, and collaboration. This may include taking the time to sit down with the family at the bedside or even scheduling a care conference with the multidisciplinary team to ensure the family has all of the information they need to make educated and informed decisions regarding their child's care. Professionals can alleviate stress and enhance engagement by addressing emotional and psychological needs, improving outcomes.

Utilizing Health Literacy Resources

Healthcare professionals should provide parents and caregivers with reliable health literacy resources in print and online formats.[6] These resources may include brochures, videos, and websites that offer understandable and evidence-based information about NICU care, developmental milestones, and follow-up support. It is best practice if these materials are created by a multidisciplinary team that includes designers and parents.

Collaborating with Interdisciplinary Teams

Interdisciplinary collaboration is vital in addressing health literacy challenges in the NICU. Social workers, interpreters, and other healthcare team members can provide valuable insights and support in overcoming language and cultural barriers and addressing social determinants of health that may impact health literacy.

Staff Training and Education

Most medical professionals erroneously make assumptions about a parent's health literacy level, and few receive formal training in health literacy.[16] A recent study of pediatric residents by Griffeth et al. found that only 19% of pediatric residents and 26% of pediatric residency faculty were familiar with universal health literacy precautions. Additionally, 37% of residents and 38% of faculty reported not receiving any health literacy training.[16] Continuous professional development programs should include effective communication strategies, health literacy awareness, and cultural competence, motivational interviewing training. By equipping healthcare professionals with the knowledge and skills necessary to navigate health literacy challenges, they can better support parents and caregivers in the NICU. Training for professionals should emphasize parental comprehension as the primary goal and measure of effective communication, no matter the parent's health literacy level.

Health literacy plays a critical role in the NICU, enabling healthcare professionals to enhance parental engagement and improve outcomes for infants in their care. By recognizing the importance of health literacy, healthcare professionals can employ effective communication strategies, address challenges, and provide the necessary support and resources to empower parents and caregivers. With a focus on health literacy, healthcare professionals can promote informed decision-making, strengthen collaboration, and foster a supportive environment in the NICU. Ultimately, by enhancing health literacy, healthcare professionals contribute to the overall well-being and success of NICU infants and their families in the hospital and at home.

AngelEye Health has spent much of this year researching and understanding the need to improve education and discharge processes in the NICU to facilitate a successful transition to home for NICU babies and their families. As we formally sponsor the National Perinatal Association (NPA) to ensure wide distribution and implementation of their recent publication, *"NICU Discharge Preparation and Transition Planning: Guidelines and Recommendations,"* AngelEye is also actively developing solutions to help hospitals effectively implement the guidelines.[17] Its newest solution, Empower, includes automated, relevant, and timely education and resources delivered to families both during the NICU stay and for six months post-discharge. The goal of this new turnkey solution is to address a significant unmet need to help mitigate the issue of health literacy and the challenges faced by staff in empowering families to be their child's best advocate. Empower further amplifies AngelEye Health's mission to equip care teams and empower families of neonatal and pediatric patients to improve outcomes.

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Transcutaneous Monitoring in the NICU: Enabling Proactive Ventilator Management for Quality Patient Care

Dr Shaili Amatya, MD, FAAP, Jennifer Erkinger, MS, RRT-NPS, AE-C, C-NPT, and Ann Donnelly, MS, RRT-NPS

Dr Shaili Amatya, Jennifer Erkinger, and Ann Donnelly from Penn State Children's Hospital discuss the important role of continuous transcutaneous CO_2 monitoring for reducing painful events and proactively managing ventilation in the NICU. The following has been adapted from its original presentation for clarity and brevity.

Introduction

Our team at the Penn State Children's Hospital level IV NICU comprises a large group of people. We are neonatologists, neonatal perinatal medicine fellows, neonatal advanced practice providers, pediatric residents, bedside neonatal nurses, respiratory therapists, speech therapists, pharmacists, and dieticians.

Ventilation Modalities for Neonates in the Penn State Children's Hospital NICU

As seen in Figure 1, our NICU saw 63 very low birth weight (VLBW) patients in 2021, 11 of whom were younger than 26 weeks gestational age. Our guideline is to manage these small babies on gentle ventilation using high-frequency jet ventilators, and the 52 other patients who were more than 26 weeks at gestation were managed on mechanical ventilators.

For conventional mechanical ventilation, our unit utilizes volume-targeted or volume-guaranteed ventilation. For the babies treated with ventilatory support, once they are able to wean to a noninvasive support, we tend to use noninvasive NAVA, or neurally adjusted ventilatory assist. Once stable, they're placed on bubble CPAP, which is our primary mode of continuous positive airway pressure that we provide for our patients. As you can see, we have a lot of respiratory support changes that happen during the hospital stay.

Monitoring Gas Exchange in the NICU

Arterial blood gas (ABG) measurements are the gold standard assessment of gas exchange when monitoring patients in the NICU. However, ABGs are invasive, painful, and only offer a point-in-time measurement. And in some of our tiny patients, there is a lot of blood sampling that is done during their NICU stay.

Shaili Amatya is a Neonatologist and Assistant Professor with Penn State College of Medicine. Jennifer Erkinger is a Pediatric Clinical Specialist, Respiratory Therapist, and Neonatal ECMO Coordinator. Ann Donnelly is a Respiratory Clinical Research Expert and Pediatric Respiratory Therapist.

Penn State Children's Level IV NICU: By the Numbers

The Facility

- 56 beds
  - 18 open beds
  - 4 twin rooms
  - 1 triplet room
  - 27 single family rooms
- 800+ admissions per year
- 13 neonatologists
- 130 staff nurses
- 35 dedicated respiratory therapists

VLBW Admissions (less than 1500 g)

- 2021 | 63 VLBW patients
- 2022 | 72 VLBW patients

Oxygen is monitored noninvasively by pulse oximetry (SpO_2). For carbon dioxide monitoring, we have a few devices that we use for our patients:

End-tidal CO_2 ($etCO_2$) monitor

- CO_2 levels measured at the end of exhaled breaths
- NOTE: Although usually used in the pediatric population, we do use it in our NICU, but it is limited because it is only useful in intubated patients.

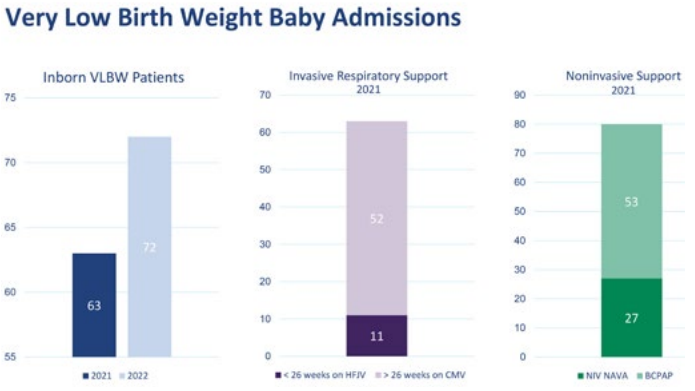

Figure 1. Ventilation modalities used for very low birth weight neonates in the Penn State Children's Hospital NICU.

How Does Transcutaneous CO_2 Monitoring Work?

Transcutaneous CO_2 technology warms the skin at the measurement site to encourage blood flow and the diffusion of gas across the skin. The recommendation for the sensor temperature is 41°C, which allows for this gas to be diffused. A thin electrolyte layer is confined to the sensor surface with a CO_2-permeable membrane, which maintains contact with the skin during monitoring.

CO_2 diffuses through the membrane and into the measurement electrode, where the sensor measures CO_2 by the change in the pH of the electrolyte solution, utilizing a Stow-Severinghaus electrode. This value is then translated into an estimation of arterial CO_2.

Transcutaneous CO_2 ($tcPCO_2$) monitor

- Measures $PaCO_2$ that diffuses through the skin
- Device is placed on the baby's abdomen or forehead

Colorimetric CO_2 detector

- A qualitative assessment of CO_2 detected in the exhaled breath
- Often used during resuscitative measures

CO_2 and the Neonatal Brain

In a term baby, the brain vasculature is fragile but developed. Because of this, autoregulation is present in infants who are more than 36 weeks gestational age. The cerebral blood flow (CBF) remains relatively stable during fluctuations of the partial pressure of CO_2, which leads to a decreased risk of bleeding or hemorrhage.[1]

Preterm babies, on the other hand, have underdeveloped vasculature and an absence of this autoregulation. Preterm babies don't have the ability to maintain CBF, which can become uncontrolled due to changes in the CO_2 levels. As a result, there is an increased risk of hemorrhage.[2]

"$PaCO_2$ is the most potent acute regulator of CBF," researchers wrote in a 2014 study in the Journal of Pediatrics.[3] There are two extremes of pCO_2 levels that we want to avoid. Hypocarbia, in which CO_2 levels are less than 35 mmHg, can lead to cerebral vasoconstriction and decreased CBF. Hypercarbia, in which CO_2 levels are more than 55 mmHg, can lead to cerebral vasodilation and an increase in CBF.

This unstable blood pressure and flow can lead to complications, including intraventricular hemorrhage (IVH). IVH is a bleed in the ventricles of the brain, a common condition in neonates that presents the risk for long-term consequences. We would like to be at a safe range of CO_2 to prevent this dangerous complication, amongst others.

How Transcutaneous CO_2 Monitoring is Used in Penn State's NICU

In Ventilated & Non-Ventilated Patients | Transcutaneous monitoring has helped us to identify rapid changes in lung compliance within the first few hours of life. This allows us to be able to see the changes and make timely ventilator adjustments. With transcutaneous monitoring, we're able to avoid prolonged hypocarbia and hypercarbia, and minimize fluctuations in CO_2 and cerebral blood flow.

Transcutaneous CO_2 monitoring is also feasible with both invasive ventilation and non-intubated patients (which is most of our patients in the NICU). This differs from $etCO_2$ monitoring, which is infeasible for non-intubated patients. We have also been able to use it for postoperative CO_2 monitoring.

To Reduce Blood Draws | By utilizing transcutaneous monitoring, we have been able to minimize the need for repeated blood sampling, while also being able to trend pCO_2 over a period of time.

During Transports | We have found transcutaneous CO_2 monitoring to be reliable during transport of ventilated newborns.

In one case, a very sick baby on an oscillatory ventilator was being transferred to the Penn State Children's Hospital NICU from an outside facility. However, we were not able to take the oscillator in the helicopter transport with us. What we were able to do was once we transitioned the baby to the transport ventilator, we hooked up the transcutaneous CO_2 monitor. This allowed us to manage the ventilator settings in real time by monitoring the transcutaneous CO_2 continuously. Time is of concern during these transports since we're not able to do blood sampling to find out what the blood gas analysis is. So, transcutaneous monitoring is very helpful in allowing us to perform safe transports and manage ventilation better with the continuous measurement of CO_2 to guide us.

Advantages of Transcutaneous CO_2 Monitoring

Transcutaneous CO_2 monitoring is preferred over end-tidal monitoring here in the NICU—again, with the reason that $etCO_2$ monitoring can only be used in intubated patients. In our NICU, we tend to use uncuffed endotracheal tubes because we want to prevent tracheal injury in some of these delicate patients. However, this inadvertently leads to esophageal mixing and causes false $etCO_2$ readings. End-tidal measurement also encounters dead space; this is very significant for our fragile patients, as this can lead to false measurements.[4]

$EtCO_2$ also cannot be used with high-frequency oscillatory ventilators or high-frequency jet ventilators; modes of ventilation that are very much used in extremely preterm patients in our NICU.

Compare that with transcutaneous CO_2 monitoring, which we have been able to use for both intubated and non-intubated patients, and the use of which has increased as more and more

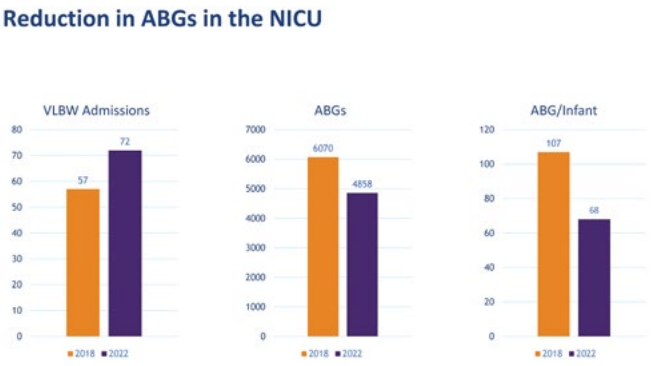

Figure 2. Number of total ABGs, as well as ABGs per infant, taken in the Penn State Children's Hospital NICU before (2018) and after (2022) the implementation of transcutaneous CO2 monitoring.

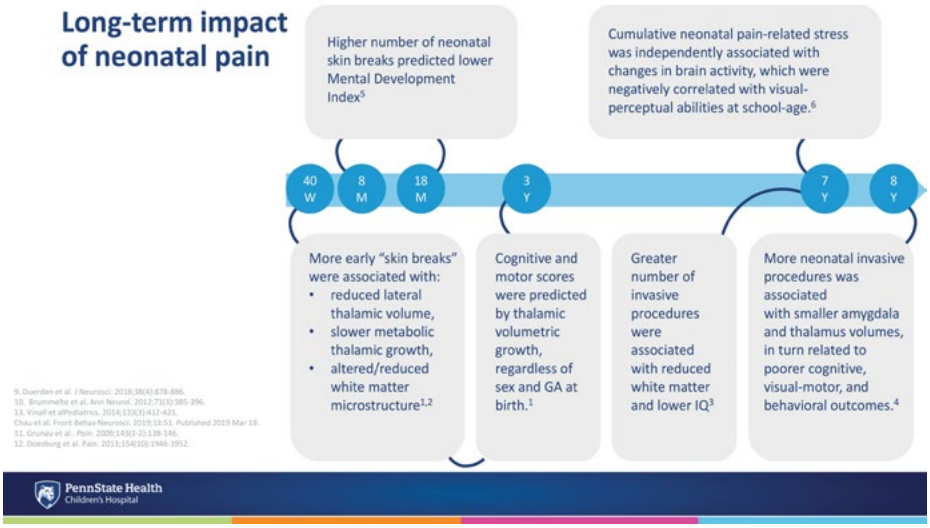

Figure 3. Timeline of the long-term impacts of neonatal pain and early skin breaks, from 40 weeks to 8 years of age.

preterm patients are managed with noninvasive ventilation. When compared to end-tidal monitoring, transcutaneous monitoring has been shown to be equally as accurate in patients with normal respiratory function and more accurate in patients with shunt or ventilation-perfusion inequalities.[5]

Transcutaneous monitoring also helps to prevent excessive blood draws from neonatal patients.[6] The average neonate has about 85 to 105 ml/kg of total blood volume.[7] And out of that, we use about 0.3 ml of blood per blood gas analysis. That's a lot if you think cumulatively of how many blood draws we need to do.

Studies have shown that about 13 to 18 ml/kg of blood loss happens during blood sampling or testing in these patients. Add that to the normal physiological fall in the hemoglobin, and these babies are at high risk of having anemia and requiring blood transfusion, which happens in about 20 to 50% of these patients.[7] Because of this, many institutions are trying to limit unnecessary blood draws and waste, which is something we do in our own NICU.

Impact of Implementing Transcutaneous CO_2 Monitoring in the NICU

As seen in Figure 2, despite an increase in patients in 2022 as compared to 2018, the implementation of transcutaneous CO_2 monitoring contributed to a 36% decrease in blood gas draws per patient in the Penn State Children's Hospital NICU.

How can NICUs reduce painful events?

1. Bundle routine medical interventions with other care procedures to reduce bedside disruption.
2. Utilize noninvasive monitoring wherever applicable, such as transcutaneous monitoring.
3. Anticipate testing procedures to reduce the frequency of blood sampling.
4. Use handheld devices capable of performing several analyses from a single blood sample.
5. Consider using peripheral arterial and central venous catheters in babies who require more than 3 or 4 heel sticks per day.[16]

Why Reducing Pain in the NICU is Important

Another thing that we saw with the use of transcutaneous monitoring was a reduction in painful procedures for our preterm patients. Preterm infants endure 643 procedures in the first four weeks of life for an average of 23 events per day. Over the span of their stay, the average pain exposure is thought to be between 10 and 18 events per day.[8] One of these procedures is blood sampling, which is an important test done in the first week of life in preterm infants for blood gas analysis.

Several studies show how this exposure to pain can have long-term impacts for these neonates. As displayed in Figure 3, neonatal pain, largely driven by blood draws, has consistently been shown to negatively affect neurologic and developmental outcomes, even extending into school age.[9,10,11,12,13]

As a neonatologist, this makes a significant impact on how we manage our premature infants, because we want to make sure that they have a good quality of life and have better neurodevelopmental outcomes down the road.

Less Invasive Care with Noninvasive Monitoring

With noninvasive monitoring modalities, such as transcutaneous O_2, CO_2, glucose, and bilirubin monitoring, and even near infrared spectroscopy (NIRS), we can avoid the need for blood sampling. In the Penn State Children's Hospital NICU, we use pulse oximetry for noninvasive O_2 monitoring, NIRS for some of our sicker patients to avoid blood sampling, and also consider noninvasive therapeutic approaches to provide analgesia to newborns.[16]

Implementing transcutaneous monitoring helps to reduce painful events in the NICU by reducing the need for repeated blood sampling.[6] As a result, there is a reduction of blood loss, which in turn will reduce neonatal anemia, reduce transfusion rates, and overall reduce the number of painful events.

Factors that Impact the Accuracy of Transcutaneous Monitoring

There are some factors that may affect the correlation between transcutaneous monitoring and blood gas values. Hypoperfusion of the skin at the measurement site caused by low cardiac index, presence of circulatory centralization, hypothermia, use

of vasoactive drugs, and arterial occlusive disease may limit accuracy. Skin breakdown, scarring, and edema can prevent adequate diffusion of CO_2 through the skin, also leading to inaccurate measurements.

Additionally, inadequate sensor temperatures, poor sensor application, incorrect measurement sites, and pressure on the sensor could lead to a lack of correlation between transcutaneous monitoring and blood gas values.

In patients with a shunt, the transcutaneous CO_2 sensor and the blood sampling site should be on the same side of the shunt. For example, if the patient has a large patent ductus arteriosus (PDA) causing a left-to-right shunt, the measurement will be inaccurate if the sensor is placed on the right side.

Case Studies: Transcutaneous Monitoring in the Penn State Children's Hospital NICU

In the Penn State Children's Hospital NICU, transcutaneous monitoring is standard of care for all patients who require continuous monitoring. For example, if they're being transitioned from one ventilator to another, if they're transitioning from invasive ventilation to noninvasive ventilation, or if we see that they still have a large scale of changes in their ventilatory status, we use transcutaneous CO_2 monitoring to guide our management.

Case Study 1 | 26 weeks GA, 366 g, transcutaneous monitoring to reduce ABGs and maintain safe CO_2 levels in an extremely low birth weight baby

The baby in our first example had severe fetal growth restriction, with a gestational age of 26 weeks and a birth weight of just 366 g.

The baby was placed on the high-frequency jet ventilator and needed frequent changes, which does happen with these extremely small babies. The transcutaneous sensor was placed on the forehead due to limited surface area on the rest of the body and it correlated pretty well, with the average correlation being ±1.9 mmHg (shown in Figure 4). 113 blood gases were drawn in the first 172 days of life. Once the arterial blood gases began correlating with the transcutaneous monitor, we used transcutaneous monitoring to guide our management rather than frequently repeating the blood gases.

These tiny patients are particularly sensitive to small changes in CO_2 levels, and we saw that the transcutaneous CO_2 measurement had a steep fall to 16 mmHg. Now at this point, as a clinical provider, we questioned: Is the perfusion okay?

Figure 4. Correlation between CO_2 levels measured with transcutaneous monitoring and blood gas analysis.

Is this picking up well? We followed up with an arterial blood gas, which did show that it correlated pretty well, enabling us to change our ventilation management and bring this infant to a normal level again. Examples of correlation seen across 4 separate blood gases are presented in Figure 4.

Case Study 2 | 25 weeks GA, 820 g, transcutaneous monitoring to guide ongoing ventilatory decision-making

At birth, day-of-life 0, this neonate was intubated in the delivery room and placed on a high-frequency jet ventilator as per our guidelines. The first 24 hours were critical, as the baby required 7 blood gas analyses, not just to maintain ventilation, but also to monitor electrolytes and other parameters.

By day-of-life 7, the baby was stable and we were able to extubate to noninvasive NAVA, or neurally adjusted ventilatory assist. Then, by day-of-life 20, the baby had respiratory failure that required reintubation, which does happen with these tiny babies. And again, we did a couple of blood gases to make sure that the transcutaneous monitor was correlating. On day-of-life 25, the support changed to invasive NAVA. And on day-of-life 29, the baby was able to be extubated to noninvasive NAVA. We attempted on day-of-life 33 to see if the baby would tolerate being on bubble CPAP, but the baby did not. So again, the next day required the noninvasive NAVA. On day-of-life 40, we attempted bubble CPAP, but by the next day the baby needed the noninvasive NAVA again.

Once we found that the transcutaneous monitoring and the CO_2 arterial gases were correlating well, we did not use arterial gases in the last 3 weeks to guide our management, despite making multiple ventilatory changes. And the correlation with the transcutaneous monitor was good at ±4.5 mmHg, allowing us to accurately trend the CO_2 to guide our ventilatory management.

Case Study 3 | 40 weeks GA, transcutaneous monitoring to accurately monitor entire patient course

This case study is of a patient who was transferred from an outside hospital to Penn State Children's Hospital. This was a term gestation at 40 weeks and 3 days, and the diagnosis for this baby was idiopathic persistent pulmonary hypertension. This baby, being critically ill, was transferred to the NICU and started on the oscillator with nitric oxide because of the pulmonary hypertension. We placed the transcutaneous monitor on the right abdomen and immediately the transcutaneous monitor was reading pretty high, with values around 100 and 109 mmHg.

An echocardiogram was performed after admission, which showed that there was significantly depressed left and right ventricular heart function and that the patient was in cardiogenic shock. At that point, because of the hypertension, the baby was placed on milrinone, dobutamine, and epinephrine, and the decision was made to start venoarterial extracorporeal membrane oxygenation (VA ECMO).
The moment the baby was placed on the VA ECMO, the transcutaneous reading came down pretty nicely to values around 37, 42, and 48 mmHg, which was maintained during the use of VA ECMO. Once the baby was able to successfully come off ECMO, we continued the transcutaneous monitoring. This continued to correlate and show us the ventilatory status even after we were able to extubate the baby and transition to noninvasive support.

Summary

In summary, transcutaneous CO_2 monitoring enables timely management of ventilation status in patients in the NICU. Used with proper technique, it can provide comparable monitoring to blood gas analysis, and is comparable to end-tidal CO_2 measurement in intubated patients, with the advantage of being compatible with non-intubated patients as well. Transcutaneous CO_2 monitoring can enable ventilator management and prevent blood losses and painful procedures in the NICU.

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WHITEPAPER

Balancing Brain & Lung Protection in the NICU with Transcutaneous CO_2 Monitoring

READ THE **FULL WHITEPAPER**

The very same ventilatory support that can help keep CO_2 within safe ranges for brain protection can also damage the lungs without careful consideration. Failing to deliver enough volume can result in derecruitment and atelectasis. Delivering too much risks overdistension and volutrauma.

In this way, the brain and the lungs are in constant tension – what protects one can harm the other. To prioritize lung protection and avoid potentially harmful airway pressures, respiratory teams may employ a strategy of permissive hypercapnia, which can help keep plateau pressures within a safe range, but could put the brain at risk. Prioritizing the brain may require increased ventilator settings that damage the lungs. In these scenarios continuous visibility to CO_2 can be a powerful, even vital, tool to balance both priorities.

Continuous CO_2 monitoring can be a valuable tool when care teams employ permissive hypercapnia, as it can allow them to keep a close eye on how the patient is responding and to react quickly to unexpected changes or spikes.

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