THE OFFICE OF THE OFFICE OFFICE OF THE OFFICE OFFIC

The Journal of Perinatology-Neonatology

THANK YOU To Our Clinical Heroes



Passy Muir is proud to support the clinical professionals who continue to care for vulnerable patients with tracheostomy during this crisis. We are committed in our efforts to provide only the best products and support for healthcare professionals and the patients they serve.

Real heroes wear masks below their eyes.









TRY IT FOR FREE! neotech-neonatalic.com

No Tape On the Skin

NeoBar[®] ET Tube Holder

Featuring NeoBond[®] Hydrocolloid! Which helps to decrease the risk of damage to fragile skin.

NeoBar offers the ideal balance between security and comfort.



©2020 Neotech Products LLC. All rights reserved.

Request your free samples online at neotech-neonatalic.com



neonatal INTENSIVE CARE

Vol. 33 No. 4 Fall 2020

Table of Contents

DEPARTMENTS

5 News

ARTICLES

- 15 Standardizing Blood Drawing Technique in the NICU
- 17 Implementation of a Human Milk & Breastfeeding Committee
- 19 Building Bridges for NICU Families
- 21 Building a Business Case for Nutrition Technology in the NICU
- 23 Plan of Care: Overview of ECMO
- 26 Effects of Early Fortification on Morbidity
- 29 Top 3 Considerations When Evaluating a Probiotic
- 32 Intact Survival to Discharge of the Tiniest Baby
- 34 Modified Apgar Score for Premature Infants (MASPI)
- 38 Comparing Nasal High-Flow Therapy and CPAP for Newborns in Nontertiary Special Care Nurseries
- 41 Sodium Supplementation in Preterm Infants
- 42 Comparing the Efficacy of Three Positive Pressure Ventilation Devices
- 48 Association Between Admission Hypothermia And Outcomes In Very Low Birth Weight Infants In China

Editorial Advisory Board

Arie L. Alkalay, MD Clinical Professor of Pediatrics David Geffen School of Medicine Pediatrician, Cedars-Sinai Los Angeles, CA

M. A. Arif, MD Professor of Pediatrics & Head, Neonatology National Institutes of Child Health Karachi, Pakistan

Muhammad Aslam, MD Associate Professor of Pediatrics University of California, Irvine Neonatologist, UC Irvine Medical Center Orange, CA

Edward Austin, MD Austin-Hernandez Family Medical Center Compton, CA

Richard L. Auten, MD Assistant Professor of Pediatrics Duke University Medical Center Durham, NC

Bruce G. Bateman, MD Department of Obstetrics & Gynecology University of Virginia Charlottesville, VA

Sandy Beauman, MSN, RNC-NIC CNC Consulting Albuquerque, NM

David D. Berry, MD Wake Forest University School of Medicine Winston-Salem, NC

Melissa K. Brown, BS, RRT-NPS, RCP Faculty, Respiratory Therapy Program Grossmont College El Cajon, CA

D. Spencer Brudno, MD Associate Professor of Pediatrics Medical Director, Pediatric Therapy Medical College of Georgia Augusta, GA

Curtis D. Caldwell, NNP UNM School of Medicine, Dept of Pediatrics Albuquerque, NM

Ed Coombs, MA RRT-NPS, ACCS, FAARC Marketing Director – Intensive Care Key Application Field Manager – Respiratory Care, Draeger Medical Telford, PA

Jonathan Cronin, MD Assistant Professor of Pediatrics Harvard Medical School Chief Neonatology and Newborn Medicine Unit Department of Pediatrics Massachusetts General Hospital for Children Boston, MA

Michael P. Czervinske, RRT Neonatal and Pediatric Critical Care University of Kansas Medical Center Kansas City, KS

Professor Adekunle H. Dawodu Director, International Patient Care and Education, Cincinnati Children's Hospital Cincinnati, OH

Jayant Deodhar, MD Associate Professor of Clinical Pediatrics Children's Hospital Center Cincinnati, OH

Leonard Eisenfeld, MD Associate Professor of Pediatrics University of Connecticut School of Medicine Division of Neonatology Connecticut Children's Medical Center Hartford, CT

Sami Elhassani, MD Neonatologist Spartanburg, SC

Ivan Frantz, III, MD Chariman of Department of Pediatrics Chief, Division of Newborn Medicine Tufts University School of Medicine Boston, MA Philippe S. Friedlich, MD Associate Professor of Clinical Pediatrics Children's Hospital of Los Angeles Los Angeles, CA

G. Paolo Gancia, MD Neonatologist, Terapia Intensiva Neonatale-Neonatologia, Cuneo, Italy

George A. Gregory, MD Professor of Pediatrics and Anesthesia University of California San Francisco. CA

Charles J. Gutierrez, PhD, RRT, FAARC Neurorespiratory Clinical Specialist, J.A. Haley VA Hospital and Assistant Professor, Pulmonary, Critical Care & Sleep Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL

William R. Halliburton, RRT, RCP Neonatal Respiratory Care Coordinator Department of Respiratory Care Hillcrest Baptist Medical Center, Waco, TX

Mary Catherine Harris, MD Associate Professor of Pediatrics Division of Neonatology University of Pennsylvania School of Medicine The Children's Hospital of Philadelphia Philadelphia, PA

David J. Hoffman, MD Clinical Associate Professor of Pediatrics Penn State College of Medicine Staff Neonatologist The Reading Hospital and Medical Center West Reading, PA

Michael R. Jackson, RRT Newborn Intensive Care Unit Beth Israel Hospital, Boston, MA

Chang-Ryul Kim, MD Associate Professor of Pediatrics College of Medicine Hanyang University Kuri Hospital Seoul, South Korea

David M. Kissin, BS, RRT Perinatal/Pediatric Specialist Maine Medical Center, Portiand, ME

Sheldon Korones, MD Director of Newborn Center College of Medicine, Memphis, TN

Scott E. Leonard, MBA, BA, RRT Director of Respiratory Therapy, EEG, Neurophysiology George Washington University Hospital Washington, DC

Raymond Malloy, MHA, RRT Director of Pulmonary Care Thomas Jefferson University Hospital Philadelphia, PA

Paul J. Mathews, PhD, RRT, FCCM, FCCP, FAARC Associate Professor of Respiratory Care University of Kansas Medical Center

University of Kansas Medical Center Kansas City, KS **William Meadow**, MD

Professor of Pediatrics Co-Section Chief, Neonatology Comer Children's Hospital The University of Chicago, Chicago, IL

David G. Oelberg, MD Center for Pediatric Research Eastern Virginia Medical School Children's Hospital of The King's Daughters Norfolk, VA

Rahmi Ors, MD Director, Department of Neonatology and Pediatrics Professor of Pediatrics and Neonatologist Meram Medical Faculty Necmettin Erbakan University Konva. Turkev

T. Michael O'Shea, MD, MPH Chief, Neonatology Division Wake Forest University School of Medicine Winston-Salem, NC Lisa Pappas, RRT-NPS Respiratory Clinical Coordinator NICU University of Utah Hospital Salt Lake City, UT

G. Battisita Parigi, MD Associate Professor of Pediatric Surgery University of Pavia, Italy

Richard Paul, MD Chief, Maternal & Fetal Medicine Department of Obstetrics & Gynecology University of Southern California Los Angeles, CA

Max Perlman, MD Professor of Pediatrics The Hospital for Sick Children Toronto, Ontario, Canada

Boris Petrikovsky, MD Director, Prenatal Diagnostic Unit Services New York Downtown Hospital New York, NY

Arun Pramanik, MD Professor of Pediatrics Director of Neonatal Fellowship Louisiana State University Health Sciences Center, Shreveport, LA

Benamanahalli K. Rajegowda, MD Chief of Neonatology Lincoln Medical and Mental Health Center Professor of Clinical Pediatrics Weill Medical College of Cornell University, NY

Ruben D Restrepo, MD RRT FAARC FCCP Coordinator of Research Professor - Division of Respiratory Care UT Health San Antonio 7703 Floyd Curl Dr, San Antonio, TX

Koravangattu Sankaran, FRCP(C), FAAP, FCCM Professor of Pediatrics and Director of Neonatology and Neonatal Research

Department of Pediatrics Royal University Hospital University of Saskatchewan Saskatoon, Saskatchewan, Canada

Istvan Seri, MD, PhD Professor of Pediatrics Head, USC Division of Neonatal Medicine University of Southern California, Los Angeles, CA

Tushar A. Shah, MD, MPH Division of Neonatology Cincinnati Children's Hospital Medical Center Cincinnati, OH

Dave Swift, RRT Ottawa Hospital – Civic Site Campus Coordinator (Professional Practice) & Special Care Nursery Charge Therapist Respiratory Therapy Team Lead National Office of the Health Care Emergency Response Team (NOHERT) Subject Matter Expert, Health Canada

Jack Tanner NICU Clinical Coordinator U Mass Memorial Hospital Worcester, MA

Otwell D. Timmons, MD Carolinas Medical Center Charlotte, NC

Maya Vazirani, MD, FAAP Board Certified Neonatology and Pediatrics Lancaster. CA

Max Vento, MD Associate Professor of Pediatrics Chief, Pediatric Services Neonatologia Hospital Virgin del Consuelo Valencia, Spain

Dharmapuri Vidyasagar, MD Professor of Pediatrics Department of Pediatrics University of Illinois Chicago, IL

News

Fall 2020

The Benefits of Human Milk Detailed in Meta-analysis

Prolacta Bioscience, the world's leading hospital provider of 100% human milk-based nutritional products, announced the results of a new meta-analysis involving more than 450 very low birth weight (VLBW) premature infants. The report, published in Neonatology Today, found those fed a diet of human milk had a lower risk of complications and/or death when Prolacta's 100% human milk-based fortifiers were added to mother's own milk or donor human milk rather than cow milk-based fortifiers. To support the rapid growth that takes place during their first weeks of life, very preterm infants typically require a nutritional fortifier added to their feeds to provide the calories and protein they need. There are two kinds of fortifiers available: cow milk-based and Prolacta's 100% human milk-based. Numerous studies have demonstrated that VLBW infants fed cow milkbased products, rather than human milk-based fortifiers, may have a greater risk of adverse outcomes, including late-onset sepsis, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) and mortality. However, few studies have directly compared outcomes of the use of cow milk-based versus human milk-based fortifiers among VLBW infants fed a base diet of human milk (as opposed to cow milk-based formula or a combination of the two). To address this question using as much of the available evidence as possible, Lucas et al. gathered

data from three studies, including two prospective, randomized clinical trials, and compared outcomes of 453 preterm infants fed a base diet of mother's or donor milk and fortified with Prolacta's fortifiers or cow's milk-derived fortifier (CMDF). Meta-analyses of data from the three studies showed that when compared with the Prolacta human milk-derived fortifier (HMDF) group, the CMDF group was associated with: 40% higher risk of a positive mortality/morbidity index in the CMDF group (RR = 1.4; P = 0.006), when the same index from the O'Connor et al. study10 was applied to the combined meta-analysis; 2.4-fold higher risk for retinopathy of prematurity (ROP) (RR = 2.4; P = 0.001); 3.3fold higher risk for NEC (RR = 3.3; P = 0.008). "These findings provide additional evidence that adding a cow milk-based fortifier to mother's or donor milk not only reduces the health benefits of that milk, but increases the risk of complications and mortality," said Melinda Elliott, MD, chief medical officer of Prolacta. "In contrast, nurturing these vulnerable infants with an exclusive human milk diet that includes Prolacta's 100% human milk-based fortifiers not only increases their odds of survival, but also reduces the risk of the most serious complications. Human milk for human babies just makes sense."

Revision Urged to Guidelines on Caffeine in Pregnancy

Doctors should advise pregnant women and women planning to become pregnant to abstain completely from caffeine, according to a new narrative review in BMJ Evidence Based Medicine. "For the wellbeing of mothers and babies, health authorities are well-overdue to take a more realistic and responsible position in relation to maternal caffeine consumption," the report's author, Professor Jack E James of Reykjavik University in Iceland, said in an email. "In short, caffeine should be avoided altogether during pregnancy." The American College of Obstetricians and Gynecologists (ACOG) and several other health authorities state that moderate consumption of caffeine in pregnancy is not harmful, with some, including ACOG, defining this amount as less than 200mg daily. In the UK, "Based on current scientific opinion, the Food Standards Agency (FSA) advises pregnant and breast-feeding women not to have more than 200mg of caffeine over the course of a day, which is roughly two mugs of instant coffee or one mug of filter coffee," the FSA said. The US Department of Agriculture (USDA) defers to physicians in its

neonatal INTENSIVE CARE

ISSN 1062-2454 Published five times each year by

Goldstein and Associates, Inc.

10940 Wilshire Blvd., Suite 600 Los Angeles CA 90024 Phone: 310-443-4109 Fax: 310-443-4110 E-mail: s.gold4@verizon.net Web: www.nicmag.ca

Publisher/Editor in Chief Steve Goldstein Managing Editor Christopher Hiscox

Senior Editor Vincent Terrier

News Editor Chris Campbell

Associate Editor Jordana Hammeke, Susan Goldstein

Circulation, Coverage, Advertising Rates: Complete details regarding circulation, coverage, advertising rates, space sizes, and similar information are available to prospective advertisers. Closing date is 45 days preceding date of issue.

Change of Address: Notices should be sent promptly to Circulation Department. Provide old mailing label as well as new address; include zip code or postal code. Allow two months for change.

Editorial Contributions may be sent by e-mail and will be handled with reasonable care: however, publishers assume no responsibility for safety of art work, photographs, or manuscripts. Every precaution is taken to ensure accuracy, but the publishers cannot accept responsibility for the correctness or accuracy of information supplied herein or for any opinion expressed. Editorial closing date is the first day of the month preceding month of issue.

©2020 by Goldstein & Associates, Inc. All rights reserved. Reproduction in whole or in part without written permission is strictly prohibited.

Cover: Abstraction. Artist: Abraham Walkowitz, American, b. Tyumen, Russia, 1878-1965 2015-2020 Dietary Guidelines for Americans, stating: "Women who are capable of becoming pregnant or who are trying to, or who are pregnant, and those who are breastfeeding should consult their health care providers for advice concerning caffeine consumption." Eighty-two percent of pregnant women in the US, and 91% in France, report consuming caffeine daily, James notes in his report. Caffeine easily crosses the placenta. he added, and is known to affect neural processes, including brain networks that control respiration and heart function. He analyzed 48 observational studies and meta-analyses of maternal caffeine consumption reporting at least one of six negative outcomes: miscarriage; stillbirth, low birthweight/small for gestational age; preterm birth; childhood acute leukemia and childhood overweight and obesity. Thirty-seven observational studies reported 42 separate findings, including 32 showing increased risk of harm due to caffeine in all outcomes except preterm birth, while 10 didn't find an association or were inconclusive. Out of 17 meta-analyses, 14 found associations between caffeine and miscarriage, stillbirth, low birth weight and/or small for gestational age and childhood acute leukemia. "Certainly, there is no evidence to suggest that caffeine benefits either mother or baby. Therefore, even if the evidence were merely suggestive, and in reality it is much stronger than that, the case for recommending caffeine be avoided during pregnancy is thoroughly compelling," James said. "It is important for the public to understand that caffeine is not the benign substance it is often portrayed to be. Unfortunately, the position of many health authorities to date has been disappointing in this regard," he added. "The idea that there is a safe level of maternal caffeine consumption is a myth that is strongly at odds with the scientific evidence. This accepting attitude towards caffeine and pregnancy must change." In an emailed statement, ACOG said that it does not plan to change its guidelines at present. "Our guidance remains that moderate caffeine consumption, less than 200 mg per day, does not appear to be a major contributing factor in miscarriage or preterm birth," Dr Christopher Zahn, MD, ACOG's vice president of Practice Activities, said. "ACOG's clinical guidance is based on a thorough expert review of the most current evidence and is routinely reviewed every 18-24 months. ACOG Committee Opinion, 'Moderate Caffeine Consumption During Pregnancy' was reaffirmed this year," he added. "While this study will likely be included in the next review, there is nothing that warrants immediate change to the current guidance."

Black Newborns Less Likely to Die When the Treating Physician Is Also Black

While research has shown that Black newborns in the US die at three times the rate of white newborns, a new study suggests that those numbers might improve when the race of the physician is concordant with the child's. Based on data from 1.8 million births between 1992 and 2015, researchers found the in-hospital death rate among Black newborns was one third lower when these babies were treated by a Black physician, rather than a white one, according to the results published in the Proceedings of the National Academy of Sciences. The research doesn't hold the key to why concordance might be beneficial to Black infants, said study coauthor Rachel Hardeman, Blue Cross Endowed Professor of Health and Racial Equity at the University of Minnesota-Twin Cites School of Public Health, in Minneapolis. "That's the million-dollar question," Hardeman said. "What we know from previous research is that there are issues around racism and implicit bias and that when physicians are short on time or in stressful situations, they are much

more likely to rely on implicit biases." To take a closer look at whether patient-physician concordance could make a difference in Black newborn survival, Hardeman and her colleagues modeled data from the State of Florida's Agency for Healthcare Administration, which provides a census of patients admitted to Florida hospitals. Those data include detailed information on both the mother and the newborn, including race; comorbidities: outcomes; and the name, specialty certifications, and date of licensure of the treating physician. While the database did not include the physician's race, the researchers determined that from publicly available photos. For their analysis, the researchers only included data on Black and white newborns and Black and white physicians. Overall, they found the raw mortality rate for white newborns was 289 per 100,000 births, while the raw mortality rate for Black newborns was 784 per 100,000 births. When the researchers analyzed newborn death rates by race of treating physician, they found that under the care of a white physician, Black newborns experienced 430 more fatalities per 100,000 births than white newborns. Under the care of Black physicians there was a big difference: there were 173 more fatalities per 100,000 births among Black newborns compared to white newborns. That's a difference of 257 deaths per 100,000, the authors note.

When the researchers looked specifically at white newborns treated by white physicians, they did not find a similar benefit from concordance. Ultimately, the researchers determined that the "mortality penalty" for Black newborns is 39% lower under the care of a Black physician than under a white physician.

Federal Investigation Finds Hospital Violated Patients' Rights

A prominent women's hospital here violated patients' rights by singling out pregnant Native American women for COVID-19 testing and separating them from their newborns without adequate consent until test results became available, according to a federal investigation disclosed to New Mexico In Depth and ProPublica. Lovelace Women's Hospital did not admit to any wrongdoing but reported that the practice has been halted. Hospital officials submitted a plan to fix problems identified by investigators, including a promise to conduct internal audits to ensure compliance with state and federal regulations and COVID-19 screening guidance. "The Department of Health will assure that the plan of correction is fully and effectively enacted," said New Mexico Secretary of Health Kathyleen Kunkel, the state's highest-ranking public health official. "The Division of Health Improvement will be conducting an unannounced onsite survey to verify compliance." Investigators with the state Health Department, who are contracted to conduct site surveys for the US Centers for Medicare and Medicaid Services, or CMS, launched their inquiry after an article by New Mexico In Depth and ProPublica reported that the hospital had targeted Native American mothers for COVID-19 testing based on their tribal-area ZIP codes, then separated them from their newborns while awaiting test results. All patients were screened upon arrival at the hospital with forehead temperature checks and standard questionnaires. But starting in late April, according to the report, patients with home ZIP codes on the hospital's list were treated as "persons under investigation" and tested for COVID-19. That practice stopped May 28, investigators were told - one week after New Mexico In Depth and ProPublica first approached a hospital official about newborns being separated from Native American mothers. The practice, while meant to stop the spread of COVID-19, was described by clinicians and

health care ethicists as racial profiling. Isolating expectant mothers as though they had the virus created a stressful birth experience, a clinician noted. Separating newborns from mothers awaiting lab test results denied them early skin-toskin contact and breastfeeding, which studies have shown can affect bonding. Investigators concluded that the hospital failed to protect patients' rights by implementing an "informal policy to target patients that live on Native American reservations for COVID testing, and [to] separate mother and baby while test results were pending, and did not provide clear options for these patients to request or refuse COVID testing and separation from their babies." was written," said Nguyen, who used this as an example of why protocols and strategies to reduce risk of parental refusal of neonatal therapies should be informed by, and consistent with, state laws. Because of the low levels of vitamin K in infants, the rate of bleeding within the first few months of life is nearly 2%, according to figures cited by Nguyen. It falls to less than 0.001% with administration of intramuscular vitamin K. Families who refuse intramuscular vitamin K often state that they understand the risks, but data from a survey Nguyen cited found this is not necessarily true. In this survey, about two-thirds knew that bleeding was the risk, but less than 20%

> understood bleeding risks

intracranial

hemorrhage,

and less than

10% were aware

that there was

potential for a

fatal outcome.

"This is a huge

piece of the

counseling,"

Nguyen said.

with parents

involve the

most infant

stores are

or gastro-

intestinal,

intracranial

hemorrhage

does occur,

outcomes can be

devastating. Up

to 25% of infants

who experience

an intracranial

die, while 60%

of those who

survive have

some degree

hemorrhage

and these

"The discussion

should explicitly

explanation that

the risks include brain bleeds and

death." Although

bleeds attributed

to low vitamin K

mucocutaneous

puzzle for

included

Parental Refusal of Neonatal Therapy a Growing Problem Parents who refuse one indicated neonatal preventive therapy often refuse others even when the reasons are different, according to an update at the Pediatric Hospital Medicine 2020 Virtual. This finding indicates the value of preparing policies and strategies to guide parents to appropriate medical decisions in advance. "Elimination of nonmedical exceptions to vaccinations and intramuscular vitamin K made it into two of the AAP [American Academy of Pediatrics] top 10 public health resolutions, most likely because refusal rates are going up." reported Ha N



Nguyen, MD, of the division of pediatric hospital medicine at Stanford (Calif.) University. Importantly, state laws differ. For example, erythromycin ointment is mandated in neonates for prevention of gonococcal ophthalmia neonatorum in many states, including New York, where it can be administered without consent, according to Nguyen. Conversely, California does not mandate this preventive therapy even though the law does not offer medico-legal protection to providers if it is not given. "There is a glaring gap in the way the [California] law of neurodevelopmental impairment, according to Nguyen. Oral vitamin K, which requires multiple doses, is not an appropriate substitute for the recommended single injection of the intramuscular formulation. The one study that compared intramuscular and oral vitamin K did not prove equivalence, and no oral vitamin K products have been approved by the Food and Drug Administration, Nguyen reported. "We do know confidently that oral vitamin K does often result in poor adherence," she said.

Small NY Study: Mother-Baby Transmission of COVID-19 Not Seen

All infants born to a cohort of 31 COVID-19-positive mothers tested negative for the virus during the height of the New York surge, according to a study out of New York-Presbyterian Hospital. "It is suggested in the cumulative data that the virus does not confer additional risk to the fetus during labor or during the early postnatal period in both preterm and term infants," concluded Jeffrey Perlman, MB ChB, and colleagues in Pediatrics. But other experts suggest substantial gaps remain in our understanding of maternal transmission of SARS-CoV-2. "Much more needs to be known," Munish Gupta, MD, and colleagues from Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, said in an accompanying editorial. The prospective study is the first to describe a cohort of U.S. COVID-19-related deliveries, with the prior neonatal impact of COVID-19 "almost exclusively" reported from China, noted the authors. They included a cohort of 326 women who were tested for SARS-CoV-2 on admission to labor and delivery at New York-Presbyterian Hospital between March 22 and April 15th, 2020. Of the 31 (10%) mothers who tested positive, 15 (48%) were asymptomatic and 16 (52%) were symptomatic. Two babies were born prematurely (one by Cesarean) and were isolated in negative pressure rooms with continuous positive airway pressure. Both were moved out of isolation after two negative test results and "have exhibited an unremarkable clinical course," the authors reported. The other 29 term babies were cared for in their mothers' rooms, with breastfeeding allowed, if desired. These babies and their mothers were discharged from the hospital between 24 and 48 hours after delivery. "Visitor restriction for mothers who were positive for COVID-19 included 14 days of no visitation from the start of symptoms," noted the team. They added "since the prepublication release there have been a total of 47 mothers positive for COVID-19, resulting in 47 infants; 4 have been admitted to neonatal intensive care. In addition, 32 other infants have been tested for a variety of indications within the unit. All infants test results have been negative." The brief report outlined the institution's checklist for delivery preparedness in either the operating room or labor delivery room, including personal protective equipment, resuscitation, transportation to the neonatal intensive care unit, and early postresuscitation care. "Suspected or confirmed COVID-19 alone in an otherwise uncomplicated pregnancy is not an indication for the resuscitation team or the neonatal fellow," they noted, adding delivery room preparation and management should include contact precautions. "With scrupulous attention to infectious precautions, horizontal viral transmission should be minimized," they advised.

Stillbirth Incidence Increases During COVID-19 Pandemic

The incidence of stillbirth has increased since the COVID-19 pandemic began, according to a comparative study of pregnancy outcomes in a London hospital. "The increase in stillbirths may have resulted from indirect effects such as reluctance to attend hospital when needed (eg, with reduced fetal movements), fear of contracting infection, or not wanting to add to the National Health Service burden," Asma Khalil, MD, of St George's University of London and coauthors reported in JAMA. To further assess reported changes in stillbirth and preterm delivery rates during the pandemic, the researchers began a retrospective study of pregnancy outcomes at St George's University Hospital in London. They compared two periods: from Oct 1, 2019, to Jan 31, 2020 as the pre-COVID-19 period and from Feb 1, 2020, to June 14, 2020 as the pandemic period. The median age

of the mother at time of birth in both periods was 33 years. The prepandemic period had 1,681 births, and the pandemic period had 1,718 births. Although there were found to be fewer nulliparous women and fewer women with hypertension in the pandemic period, the incidence of stillbirth in that period was significantly higher (n = 16 [9 per 1,000 births]) than in the prepandemic period (n = 4 [2 per 1,000 births]) (difference, 7 per 1,000 births; 95% confidence interval, 1.83-12.0; P = .01). The pandemic rate remained higher when late terminations for fetal abnormality were excluded (difference 6 per 1,000 births; 95% CI 1.54-10.1; P = .01). None of the pregnant women who experienced stillbirth had COVID-19 symptoms, and none of the postmortems or placental exams indicated infection. There were no significant differences between the two periods in regard to births before 37 weeks' gestation, births after 34 weeks' gestation, neonatal unit admission, or cesarean delivery.

Cerclage in Twin Pregnancies Reduces Perinatal Mortality

Among women with twin pregnancies and asymptomatic cervical dilation before 24 weeks, cerclage reduced perinatal mortality and preterm birth, according to a randomized controlled trial. The trial, which was published in the American Journal of Obstetrics and Gynecology, included 30 patients at 8 centers. The investigators stopped the trial early because perinatal mortality occurred more often in the group that did not receive the intervention. The research suggests that a combination of physical exam–indicated cerclage, indomethacin, and antibiotics decreased the incidence of spontaneous preterm birth and prolonged the period from diagnosis to delivery by an average of 5.6 weeks, compared with no cerclage.

"We've already incorporated this cerclage into our practice and have been able to offer this to pregnant mothers with twins with great success," senior author Vincenzo Berghella, MD, said in a news release. "These results have the potential to change practice and help many more women have healthy twin babies," said Berghella, director of the division of maternal fetal medicine at Thomas Jefferson University in Philadelphia. More research is needed to establish a standardized approach, but the trial should "open physicians' perspectives to think about how, in selected cases and with the proper approach, cerclage can work well," said Ozhan M. Turan, MD, PhD, director of the division of maternal and fetal medicine and director of fetal therapy and complex obstetric surgery at University of Maryland in Baltimore. Although many physicians use cerclage for twin pregnancies in select situations, the practice is not well established. "If you look at the guidelines or books, mostly everyone thinks that doing a cerclage in twins is not a good idea," Turan said in an interview. In the present trial, the researchers controlled for many factors and carefully selected patients with no signs of preterm labor or infection. It is not simply a matter of saying, "Do the stitch," he said. "But it is proven: if you select patients well and use the appropriate approach, then you could improve the outcome." The study is the first randomized controlled trial of physical exam-indicated cerclage focused on twins, according to its authors. It enrolled patients between July 2015 and July 2019. In the end, the researchers analyzed data from 30 pregnancies, rather than the originally intended 52. They stopped the trial after a data and safety monitoring board considered it "unethical to continue the study due to the considerable perinatal mortality in one of the arms ... and requested to unmask the arms of the study," the researchers said. Perinatal mortality occurred in 18% of neonates in the cerclage group (6 of 34), compared with 77% in the group

Are you bubbling?

Babi.Plus is the standard of care for non-invasive ventilation, providing a gentle approach to improve ventilation and optimize neonatal outcomes.

To start optimizing ventilation in your NICU contact us at <u>4info@respiralogics.com</u>

Δ





3545 Airway Drive, Suite 104 • Reno, NV 89511 775 954 0160 • www.respiralogics.com without cerclage (20 of 26). All perinatal mortality cases were associated with delivery before 24 weeks.

OB-GYNs Struggle to Keep Pace With Changing COVID Knowledge

In early April, Maura Quinlan, MD, was working nights on the Labor and Delivery unit at Northwestern Medicine Prentice Women's Hospital in Chicago. At the time, hospital policy was to test only patients with known COVID-19 symptoms for the SARS-CoV-2 virus. Women in labor wore N95 masks, but only while pushing - and practitioners didn't always don proper protection in time. Babies came and families rejoiced. But Quinlan looks back on those weeks with a degree of horror. "We were laboring a bunch of patients that probably had COVID," she says, and they were doing so without proper protection. She's probably right. According to one study in the New England Journal of Medicine, 13.7% of 211 women who came into the labor and delivery unit at one New York City hospital between March 22 and April 2 were asymptomatic but infected, potentially putting staff and doctors at risk. Quinlan already knew she and her fellow Ob/Gyns had been walking a thin line and, upon seeing that research, her heart sank. In the middle of a pandemic, they had been racing to keep up with the reality of delivering babies. But despite their efforts to protect both practitioners and patients, some aspects slipped through the cracks. Today, every laboring patient admitted to Northwestern is now tested for the novel coronavirus. Across the country, hospital labor and delivery wards have been working to find a careful and informed balance among multiple competing interests: the safety of their healthcare workers, the health of tiny and vulnerable new humans, and the stability of a birthing mother. Each hospital has been making the best decisions it can based on available data. The result is a patchwork of policies, but all of them center around rapid testing and appropriate protection.

Living Near Gas Flaring Sites May Increase Risks

Women living near oil and gas production sites where natural gas is flared may be at a higher risk of giving birth preterm, a team of California researchers reported on Wednesday. Analysis of more than 23,000 birth records from 2012 through 2015 reveals a 50% higher chance of pre-term birth for women living within three miles (5 km) of Texas' Eagle Ford shale basin than for women who lived farther away, according to the study. "Our study finds that living near flaring is harmful to pregnant women and babies," said co-author Jill Johnston, an environmental health scientist at the University of Southern California. The research, published in the journal Environmental Health Perspectives, adds to evidence linking pollution with poorer pregnancy outcomes. Another study in June found a correlation between air pollution or higher outdoor temperatures and increased chances of having a preterm or stillborn baby. Those findings, in the Journal of the American Medical Association, resulted from analyzing 70 studies covering 32 million births. It also found that black women were disproportionately at risk. In the new study, by scientists at USC and UCLA, the association between preterm births and flaring proximity was seen only among Hispanic and Latina women, who made up 55% of the study population. No effect was seen among non-Hispanic White women, who comprised 37% of the total. Preterm babies are at higher risk of respiratory and cardiovascular illness, as well as developmental delays. The team said it was the first to look at birth outcomes in relation to oil and flaring, which has seen a sharp increase in southern Texas' Eagle Ford and other shale hubs. Flares can release chemicals such as benzene, carbon monoxide and

nitrogen oxides, along with fine particulate matter, heavy metals and black carbon.

Too Many Children Receive Opioids/Steroids for Pneumonia and Sinusitis

A significant percentage of children receive opioids and systemic corticosteroids for pneumonia and sinusitis despite guidelines, according to an analysis of 2016 Medicaid data from South Carolina. Prescriptions for these drugs were more likely after visits to EDs than after ambulatory visits, researchers reported in Pediatrics. "Each of the 828 opioid and 2,737 systemic steroid prescriptions in the data set represent a potentially inappropriate prescription," wrote Karina G Phang, MD, MPH, of Geisinger Medical Center in Danville, Pa., and colleagues. "These rates appear excessive given that the use of these medications is not supported by available research or recommended in national guidelines." To compare the frequency of opioid and corticosteroid prescriptions for children with pneumonia or sinusitis in ED and ambulatory care settings, the investigators studied 2016 South Carolina Medicaid claims, examining data for patients aged 5-18 years with pneumonia or sinusitis. They excluded children with chronic conditions and acute secondary diagnoses with potentially appropriate indications for steroids, such as asthma. They also excluded children seen at more than one type of clinical location or hospitalized within a week of the visit. Only the primary diagnosis of pneumonia or sinusitis during the first visit of the year for each patient was included. The researchers included data from 31,838 children in the study, including 2,140 children with pneumonia and 29,698 with sinusitis. Pneumonia was linked to an opioid prescription in 6% of ED visits (34 of 542) and 1.5% of ambulatory visits (24 of 1,590) ($P \le .0001$). Pneumonia was linked to a steroid prescription in 20% of ED visits (106 of 542) and 12% of ambulatory visits (196 of 1,590) ($P \le .0001$). Sinusitis was linked to an opioid prescription in 7.5% of ED visits (202 of 2,705) and 2% of ambulatory visits (568 of 26,866) ($P \le .0001$). Sinusitis was linked to a steroid prescription in 19% of ED visits $(510 \text{ of } 2,705) \text{ and } 7\% \text{ of ambulatory visits } (1,922 \text{ of } 26,866) (P \le 1000 \text{ m})$.0001). In logistic regression analyses, ED visits for pneumonia or sinusitis were more than four times more likely to result in children receiving opioids, relative to ambulatory visits (adjusted odds ratio, 4.69 and 4.02, respectively). ED visits also were more likely to result in steroid prescriptions, with aORs of 1.67 for pneumonia and 3.05 for sinusitis.

"I was disappointed to read of these results, although not necessarily surprised," Michael E Pichichero, MD, a specialist in pediatric infectious diseases and director of the Research Institute at Rochester (NY) General Hospital, said. The data suggest that improved prescribing practices may be needed, "especially in the ED," wrote Dr Phang and colleagues. "Although more children who are acutely ill may be seen in the ED, national practice guidelines and research remain relevant for these patients." Repeated or prolonged courses of systemic corticosteroids put children at risk for adrenal suppression and hypothalamic-pituitary-adrenal axis dysfunction. "Providers for children must also be aware of the trends in opioid abuse and diversion and must mitigate those risks while still providing adequate analgesia and symptom control," they wrote.

Platform Expanded by Company

Masimo Corporation announced a significant expansion to the Masimo SafetyNet platform with the introduction of Radius T° , a wearable, wireless sensor that provides continuous

My first seizure could have been trying to tell you something.

When the first seizure strikes a newborn, be aware of and consider testing for **molybdenum cofactor deficiency** (MoCD).¹ This neurological disease can present with intractable seizures and trigger a pattern of progressive brain damage that is often fatal.^{1·3}

Every minute counts, so use the **STAT** approach to make an early treatment decision:

See a seizure?

Think MoCD.

Assess for sulfites.

Time to call Origin Biosciences.

Contact Origin Biosciences at (617) 322-5165 to learn about an investigational treatment for MoCD Type A.

References: 1. Mechler K et al. *Genet Med.* 2015;17(12):965-970. 2. Schwahn BC et al. *Lancet.* 2015;386(10007):1955-1963. 3. Atwal PS et al. *Mol Genet Metab.* 2016;117(1):1-4.



Origin Biosciences is a member of the BridgeBio family. ©2019 Origin Biosciences. All rights reserved. PRC-006 09/19 body temperature measurements. By augmenting the already powerful Masimo SafetyNet, which features Radius PPG tetherless pulse oximetry, with Radius T°, the remote patient management solution becomes capable of tracking four key vital signs-oxygen saturation, respiration rate, pulse rate, and now temperature-making it an ideal solution for assessing the status of patients with suspected or low-acuity COVID-19, among many other remote patient management uses. Unlike spot-check thermometry solutions, Radius Tº measures body temperature continuously, providing remote notifications when a patient's temperature is outside a clinician-specified range — giving peace of mind to caregiver and patient alike. Masimo SafetyNet uses a tetherless, wearable single-patient-use Masimo SET Measure-through Motion and Low Perfusion pulse oximetry sensor to monitor a patient's blood oxygen saturation and pulse rate, as well as respiration rate, perfusion index, and PVi. Masimo SafetyNet is designed to help manage the surge in COVID-19 patients while maintaining distance from other patients and providers, allowing hospitals to expand remote patient monitoring into alternative care spaces, including overflow locations, emergency recovery facilities, and home care settings. The telehealth platform combines tetherless pulse oximetry-and now also Radius Tº continuous temperature measurement-with a cloud-based remote data capture and surveillance platform accessible from a patient's Android or iOS smartphone or smart device. Monitoring key physiological data provides clinicians with the ability to assess patient status and facilitates awareness of the need for intervention. Temperature measurement by patients at home typically occurs intermittently, at the prompting of a clinician, and is prone to poor compliance in the collection and reporting of data to healthcare providers in a timely, consistent fashion. A patient taking their temperature at regular or semi-regular intervals may only notice a spike in temperature hours after a fever has begun, or may not even be aware of it, delaying possible clinical intervention. In contrast, Radius Tº collects data continuously and seamlessly, recording trend data and automatically notifying remotely when a clinician-specified high temperature threshold is breached, without any action needed on the patient's part. By eliminating inconsistent manual measurements and concerns about patient compliance, while providing continuous insight into changes in body temperature, Radius Tº is intended to significantly improve patient status assessment workflows. Radius T° is small, light, and comfortable, and is easily applied to the chest. Each showerproof, single-patient-use sensor lasts up to 8 days and can be worn throughout the day and night, allowing patients to continue normal daily activities while still being monitored. Applied to the skin, Radius T^o uses proprietary algorithms to measure the patient's body temperature, not just external skin temperature, with laboratory accuracy within $\pm 0.1^{\circ}$ C, whereas other thermometry solutions typically have laboratory accuracy within ±0.2°C. Using Bluetooth, Radius T° provides this continuous data to the Masimo SafetyNet app on the patient's smartphone and via secure cloud to clinicians back at the hospital, allowing them to track and trend a patient's body temperature, helping them to spot potential deterioration in patient status using the web-based Masimo SafetyNet Clinician Portal. Joe Kiani, Founder and CEO of Masimo, said, "We're proud to add this noninvasive, continuous, wearable thermometer solution to our growing family of remote patient management solutions. Masimo SafetyNet has already helped clinicians effectively care for countless patients during the pandemic. With the addition of Radius Tº, Masimo SafetyNet becomes an even more useful tool for remotely managing patients with COVID-19 and many other

health concerns." Radius T^o is indicated for use on patients 5 years and older. Radius T^o is not FDA 510(k) cleared; the device is marketed under the FDA's Enforcement Policy for Clinical Electronic Thermometers During COVID-19.

Study Results Released on Screening for Newborns

Masimo announced the results of a prospective study published in the International Journal of Neonatal Screening in which researchers in Marrakesh, Morocco, conducted the first Moroccan study on critical congenital heart disease (CCHD) screening for newborns using Masimo SET pulse oximetry. The authors concluded that "Our results encourage us to strengthen screening for CCHD by adding pulse oximetry to the routine newborn screening panel." Slitine and colleagues sought to improve early detection of CCHD in Morocco by studying the feasibility of implementing CCHD screening using pulse oximetry. From March 2019 to January 2020, 8,013 asymptomatic newborns at Mother and Child Hospital (part of the Mohammed VI University Hospital of Marrakesh), who were "normal" according to neonatal examination using the current standard, were screened for CCHD in accordance with American Academy of Pediatrics (AAP) guidelines, including pre- and post-ductal oxygen saturation measurement, using Masimo Rad-97 and Radical-7 Pulse CO-Oximeters with Masimo SET pulse oximetry sensors. The researchers found that, of the 8,013 infants screened, 7,998 newborns had a negative screen (99.82%) and 15 newborns were screen positive (0.18%). Of those 15, five were later diagnosed with CCHD and five with non-critical CHD; five were false positives (three of which had other underlying conditions). Of the 7,998 infants who passed, there was one false negative, an infant who was later diagnosed, at 2 months of age, with coarctation of the aorta. The researchers noted that the screening test was "easy, simple, reliable, reproducible, acceptable, discriminating, well-accepted by parents and caregivers, and did not involve parental anxiety." They also noted that "Pulse oximetry has a good specificity and sensitivity and thereby fulfills the criteria for screening. Additionally, most of the data in the literature suggest a favorable cost-effectiveness of this technique." The authors concluded, "Screening for CCHD is a reliable method for the early detection of critical congenital heart disease and even non-cardiac conditions. We think that it will have positive repercussions on infant mortality and morbidity in Morocco. It is an optimal test and it adapts perfectly to our context. We hope to implement it locally and nationally, as consistent with international best practice for newborn screening, to allow for timely detection of the infants born with CCHD in Morocco." Although the researchers at times use the term pulse oximetry generally, the specific pulse oximetry technology used in this study, as noted, was Masimo SET. To date, six other large published CCHD screening studies, as well as additional, smaller studies, have used Masimo SET. Cumulatively, the large studies represent 284,800 infants, which includes the largest CCHD study to date, of 122,738 newborns. All of these CCHD studies with Masimo SET pulse oximetry showed improved screening sensitivity with the use of Masimo SET alongside clinical assessment when compared to routine physical exam alone. With its ability to accurately measure through motion and low perfusion, alongside its performance in outcome studies, Masimo SET stands out as the established choice of pulse oximetry technology for clinicians and policy makers hoping to implement CCHD screening processes.

Fortifiers Helped Infants Grow

Prolacta Bioscience, the world's leading hospital provider of

100% human milk-based nutritional products, announced the results of an independent, multicenter study of 394 extremely premature infants that demonstrated the benefits of an early versus late fortification feeding protocol. According to this study, the use of Prolacta's fortifiers in the first days of life helped premature infants achieve better growth and is associated with significantly less bronchopulmonary dysplasia (BPD)/chronic lung disease of prematurity (CLD), all without compromising safety. The study was led by author Robert K Huston, MD, and published in the Journal of Neonatal-Perinatal Medicine. Lung health is an important short- and long-term outcome for preterm infants. However, because the lungs are among the last organs to mature in the womb, lung dysfunction such as BPD/CLD is common in preterm infants. Neonatal nutrition is a critical consideration in addressing lung health; however, many neonatal intensive care units (NICUs) delay adding a fortifier to extremely premature infants' feeds due to the risk of complications associated with cow milk-based fortifiers. This study showed that adding Prolacta's human milk-based fortifiers in the first days of life resulted in greater growth velocities for weight and head circumference and a 15% reduction in BPD/CLD (P = 0.008), compared with infants who received late fortification. These benefits were seen without an increase in complications. Infants who received early fortification in the study did not show significant increases in necrotizing enterocolitis (NEC) or surgical NEC, life-threatening complications that limit the use of early fortification with cow milk-based fortifiers. The Huston Early Fortification Study investigators compared the outcomes of infants born weighing 500 to 1,250 g whose feedings included mother's own milk, donor milk when needed, and Prolacta's human milk-based fortifiers at less than 60 mL/kg/day (early

fortification) or greater than 60 mL/kg/day (late fortification). "The Huston Early Fortification Study provides further data to support the practice of early fortification in extremely premature infants," said Melinda Elliott, MD, chief medical officer of Prolacta Bioscience. "Not only was early fortification proven safe, it also enhanced growth and reduced the incidence of BPD."

CDC Revises COVID-19 Risks During Pregnancy as Research Lags

In late June, after three months of near silence on the topic, the Centers for Disease Control and Prevention finally weighed in on a question of critical importance to millions of American women and families: How dangerous is the coronavirus for pregnant women and new mothers? The CDC had been asserting that pregnant women don't seem to be at higher risk for severe complications from the virus. As recently as late May, a spokesperson told ProPublica, "Current evidence shows pregnant women have the same risk of severe illness from Covid-19 as adults who are not pregnant." Then, the agency abruptly changed its tone. In its first examination of data on Covid-19 in pregnancy, the CDC found that expectant mothers with the virus had a 50 percent higher chance of being admitted to intensive care and a 70 percent higher chance of being intubated than nonpregnant women in their childbearing years. Pregnant Latina and Black women were infected at significantly higher rates than White women, researchers reported. As of July 2, at least 30 expectant and new mothers with the virus had died. That news was sobering enough. But what many experts found really worrisome were the glaring gaps in data that the study exposed. The CDC acknowledged that crucial



health information was missing for about three-quarters of pregnant women with the virus, including whether they had preexisting conditions or required an ICU stay or mechanical ventilation. For the vast majority of US women of reproductive age who tested positive — about 326,000 women through June 7 — there was no information about pregnancy status at all. Researchers couldn't even say how many of the hospitalized mothers-to-be — 31.5 percent of the pregnant women in the study - had been admitted because of Covid-19, versus how many were in the hospital for other reasons, such as giving birth. The flawed CDC report highlights a problem that OB-GYN providers and researchers in the US have been fretting about since the pandemic began. Because emerging diseases can have catastrophic consequences for pregnant women and their babies, close monitoring of new illnesses in this vulnerable population is important. So is rapid communication with providers trying to keep their patients safe. But the US public health system's efforts to understand the impact of the coronavirus in mothers and babies have been flat-footed, scattershot and agonizingly slow.

'Time to Lay to Rest' Fears About Dolutegravir Birth Defects

The longer researchers have looked for evidence of neural tube defects linked with dolutegravir treatment of HIV at the time of conception the fewer incident cases they've found. The newest data, based on 3,591 deliveries among women in Botswana infected by HIV and treated with dolutegravir at the time of conception during a little more than 5.5 years through April 2020, showed that dolutegravir use at conception linked with 7 cases of neonatal neural tube defects (NTDs), a 0.19% rate that exceeded comparator rates by about 1 in every 1,000 deliveries, far below the 0.94% rate initially found and that raised a red flag 2 years ago. "The prevalence of NTDs among infants born to women on dolutegravir at conception may be stabilizing at approximately 2 per 1,000," said Rebecca Zash, MD, during the virtual meeting of the International AIDS conference. "This small absolute risk for neural tube defects is far outweighed by the potential benefits from dolutegravir" for better tolerability than alternative drugs and fewer drug-drug interactions. "This should allow for broader use of dolutegravir in women," added Zash, an HIV specialist at Beth Israel Deaconess Medical Center and codirector of the Placental Scientific Working Group of the Harvard University Center for AIDS Research, both in Boston. "What this has taught us is that women are not a niche population" of people infected with HIV, but rather constitute about half of HIV patients worldwide. "Maintaining gender equity in HIV treatment requires safety data for treatments during pregnancy," she said during a press briefing. The new findings mean that it's "time to lay to rest" concerns about neural tube defects in infants born to women treated with dolutegravir, "given the incredible benefits of dolutegravir," commented Monica Gandhi, MD, professor of medicine and associate chief of the division of HIV, infectious disease, and global medicine at the University of California, San Francisco. Another benefit from removing any caveats about use of dolutegravir in women who could become pregnant is that it would simplify treatment recommendations and make dolutegravir the unqualified firstline agent for treating HIV infection, Dr Gandhi said during the briefing. "It's super reassuring to have these data, as the incidence of NTDs goes down and down," she added. Following the alarm raised by initial findings from the Tsepamo study in 2018, Zash and associates first updated their data through March 2019, when they reported a revised cumulative NTD incidence rate of 0.3%. The Tsepamo study began by following

the pregnancy outcomes of women at eight Botswana sites during August 2014-July 2018, representing 45% of the country's deliveries. This expanded to 18 sites and 72% of deliveries during July–September 2018, and then starting in September 2019 the scope slightly reduced to 16 Botswana sites with 70% of the nation's deliveries. Folate supplementation to women who might conceive is vital, but remains spotty in Botswana. "Folate supplementation is a no-brainer, but has had really slow adoption in many countries," Zash said. "Folate supplementation, especially in food so that everyone gets it, will reduce NTDs by half." The two most recent cases of infants born with a NTD to mothers who had been on dolutegravir at conception occurred in mothers who had received no folate supplementation, Zash reported.

Neonatal SARS-CoV-2 May Present With Hypoxemia Without Respiratory Distress

Neonatal SARS-CoV-2 infection may present in the first days of life with clinically significant hypoxemia in a newborn that doesn't have overt signs of respiratory distress or require oxygen therapy, one case report suggests. "In mild disease, there may be non-specific signs such as poor feeding that alert the care-providers, before signs of respiratory distress are noted," said Dr Shaili Amatya, an assistant professor in neonatal-perinatal medicine at Penn State Health Children's Hospital in Hershey, Pennsylvania, who wasn't involved in the study. "The physiological mechanisms underlying the effects in infants versus older children are unknown," Amatya said by email. "The immature immune system of children may respond to SARS-CoV-2 differentially in various age groups." The case, highlighted in Pediatrics, involved a full-term male newborn with an uncomplicated vaginal delivery with Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively. On the second day after delivery, the mother developed a fever and had a nasopharyngeal swab that was positive for SARS-CoV-2; the infant was subsequently swabbed, and also positive. Mother and baby were transferred to an airborne isolation room. After 48 hours, the newborn developed poor sucking and perioral cyanosis without signs of respiratory distress. The baby's respiratory rate was 15 to 20 per minute, heart rate was 120 beats per minute, and blood pressure was normal. Cardiac abnormalities were ruled out by echocardiogram, and PCR on the nasopharyngeal specimen ruled out other respiratory viruses. The baby was moved to the NICU, where he was put on 30% inspired oxygen via high flow nasal cannula. Lung ultrasound at this point didn't show consistent abnormalities, and chest radiograph showed mild bilateral ground glass opacities. After 36 hours, no major abnormalities were found on CT scan. Fifty hours after NICU admission, the infant improved enough to have respiratory support discontinued. He was fed maternal expressed milk via nasogastric tube for 48 hours, then was able to bottle feed. At day 18, the baby was discharged. On days 15 and 21, his qualitative PCR for SARS-CoV-2 remained positive, the researchers note. This suggests that newborns could be a source of horizontal transmission, the study team concludes in Pediatrics.

Premature Infants Go Home Earlier

A retrospective study indicates that premature infants' stays in neonatal intensive care units (NICUs) are reduced anywhere from 4.5 to 22.9 days when fed Prolacta Bioscience 100% human milk-based products as a part of an Exclusive Human Milk Diet (EHMD). Additional research suggests that infants with *Continued on page 22...*

Standardizing Blood Drawing Technique in the NICU

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Stacia Nickell RN, Shift Coordinator at Riley Children's Hospital, which implemented the use of the Hummi Micro Draw in its 60-bed NICU.

Standardizing Blood Drawing Technique in the NICU: A follow up 2 years after implementation of the Hummi Micro Draw Blood Transfer System at Riley Children's Hospital, Indianapolis, IN, a Level IV NICU.

This follow up interview looks at the recognized benefits of using this unique closed system for Central Line blood draws over the last 2 years? What potentially unexpected benefits does standardization of technique and improved line management bring to the Blood Draw procedure in the Neonate in terms of improved clinical outcomes and reduced economic costs?

Background

In August of 2018 Riley Children's Hospital implemented the use of the Hummi Micro Draw in its 60 bed NICU. The system was implemented for blood draws on Umbilical Arterial Catheters, Umbilical Venous Catheters and PICC Central Line Catheters (>2.5Fr). The Hummi System was implemented over the next year into 4 other NICUs in the IU Health System in an effort to standardize line setup and technique for blood draws throughout the network.

This interview was conducted after approximately 2 years of product utilization with Riley Childrens Hospital with input from key staff members: Stacia Nickell RN, Shift Coordinator, Laura Blaizer, RN Clinical Nurse Specialist and Rebecca Rose, MD, Neonatologist.

Neonatal Intensive Care: What were your original goals in implementing the Hummi Micro Draw system in your NICU? Stacia Nickell: As mentioned in our first interview, Riley Children's receives the sickest newborns in the state of Indiana. Access to draw blood can be a big issue with these infants. Prior to using the Hummi Micro Draw we had trialed several different closed blood draw systems and were running into problems with line clearance and flushing when running TPN, Glucose, Lipids etc. with our then current system when drawing ABGs and Labs. Lab values were often inaccurate because the in line device was difficult to clear when used with Central Venous lines, often requiring 3mL or more of clearance. We observed higher than desirable infection rates possibly due in part to blood residual in the devices after drawing which was not clearing without up to 3mL of flush. Blood exposure during use was also a problem with some of the systems we trialed.

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

We were looking to reduce our infection rates, improve line setup, standardize and simplify the blood drawing procedure and easily access the line in place to draw blood without excessive clearance and flushing required. The risk for IVH development due to large fluid shifts during blood drawing was also an issue.

NIC: What were some of the key clinical benefits you recognized during the first year of using the Hummi Micro Draw device?

SN: With the Hummi Micro Draw system we were able to standardize our line setup, as well as standardizing our clearance and flush volumes for both Arterial and Venous placed lines. We standardized our waste holding from 3mL down to 1mL of blood and we do not have inaccurate labs. We do run TPN, Glucose through the Central Venous lines and with the Hummi Micro Draw it is very easy to flush any catheter after the blood draw with only 0.6mL of flush. Actually we do not need to draw any blood up into the line itself when using the Hummi system, as the waste and sample are taken directly from inside the catheter hub with this sampling method.

The great thing about the Hummi System is that it can be used successfully when any fluid is being administered through any type of line, Central or Venous. The clearance draw volumes are small and the small amount of flush (0.6mL) completely clears the catheter after the blood draw. More importantly we observed a significant reduction in infection rates compared to the previous 2 years.

Our work flow has improved as we change our fluids with an aseptic technique and the Hummi Micro Draw System fits easily into this process. The packaging is user friendly and it works nicely with our new line setup with minimal components compared to other systems. The Hummi System has made our process for blood draw more streamlined, and is very easy to use and easy to teach how to use.

NIC: In addition to improvements in work flow, reduced CLABSI rates, standardization of blood draw technique across the Health System and IVH Risk Reduction, what economic benefits have you recognized that might be attributable to the implementation of the Hummi Micro Draw after 2 years of ongoing use
SN: We continually review our infections, clinical results, outcomes, issues etc. as a group of practitioners system wide. One area where we saw a marked improvement in the last 2 years was in the reduction of the incidence of re-draws of blood



The Hummi Micro Draw System: Closed Blood Draw for Central Lines

The lowest volume movement of any closed system for neonatal blood drawing that also provides standardization of technique across all types of Central Lines, improves line setup and reduces infection risk and IVH risk



The Hummi Micro Draw System for Standardization and Reduced Infection Risk:

Standardizing Blood Draw Technique and Line Setup
Significantly reduces clearance and flush volumes
Eliminates all open accesses to line for Blood Draw
Eliminates Blood Residual in line and line components
Closed access ports for sampling, flushing and line change
Now available fully integrated into the Umbilical Catheter

Hummingbird Med Devices, Inc. 1283 Elger Bay Road, Suite D Camano Island, WA 98282 Ph. 949-300-6265

see the Hummi Micro Draw closed system at **www.hummingbirdmed.com**

sampling due to contaminated or inaccurate blood test results. Patient safety has been improved and the economic cost of redrawing blood samples has been significantly reduced.

For example: Riley Children's does on average 30 blood draws per day. Prior to implementing the Hummi Micro Draw we were seeing on average 10 re-draws of blood samples per day. In 2019-2020 we are seeing re-draws on average of 2 per day. This is a reduction in re draws of 80%. The average cost of a re-draw is \$200. Previously this re-draw rate resulted in increased lab costs of \$730,000 annually. The current re draw rate of only 2 per day has resulted in an average annual savings on blood re- draws of \$584,000 annually.

The Hummi Micro Draw system has given us a more consistent standardized method with which to draw labs. This consistency and ease of use has contributed greatly to this cost savings.

NIC: What other notable benefits have you observed that affect both patient safety and help to reduce costs?
SN: We have implemented a number of changes in an ongoing effort to reduce CLABSI rates. Consistency of practice overall is very important. Using the Hummi Micro Draw system with simple concise direction on how to draw and standardized guidelines for the amounts we clear and flush has helped to reduce our CLBASI rate in that everyone is consistent in the use of this blood drawing device. Each CLASBSI costs the hospital approximately 35-40,000 dollars to treat, so reducing even one can greatly save money and length of stay, as well as reduced morbidity and mortality.

Over the 4-year period from 2015 – 2018 we experienced on average 14 CLABSIs per year. This cost to treat was on average \$525,000 per year. In 2019 – 2020 we are averaging 2 CLABSIs annually, which was 0.38 per 1000 line days in 2019. This represents an 85% reduction in CLABSI and an annual cost savings of \$450,000 annually in CLABSI costs. We attribute much of these savings to the nursing staff being very consistent with line care, line maintenance and standardized blood drawing techniques in which the Hummi Micro Draw has been a large part. This represents a reduction in CLABSI cost from \$525,000 annually to \$75,000 annually.

NIC: Outside of the Cost Savings you are seeing with the implementation of these specific clinical and patient safety improvements over the last 2 years, how has Riley Children's Hospital been measured for these significant clinical improvements?

SN: Due to our many quality improvement projects we have been able to appreciate an increase in our ranking in the US News and World report on NICUs in the United States. One area that really affects a NICU's ranking nationally is a decrease in the CLASBI rates. In our case, we feel in large part this can be attributed to consistency in the way we have improved our line care and blood drawing practices. This consistency in drawing practices relates specifically to the adoption of the Hummi Micro Draw system. We ranked 45th Nationally in 2017-18 and we were very pleased to enjoy an increase our National NICU ranking to 14th in the 2019-20 report.

Implementation of a Human Milk & Breastfeeding Committee for Neonatal Nurses

Lisa G Dell, BSN, RN, IBCLC and Diane L Spatz, PhD, RN-BC, FAAN

Introduction

At Children's Hospital of Philadelphia (CHOP), there is a strong culture regarding promoting the use of human milk. The Spatz 10-step model (2018) is utilized to ensure the use of human milk and breastfeeding despite infant-mother dyad separation, a challenge in the Neonatal/Infant Intensive Care Unit (N/IICU) setting. CHOP has a Human Milk Management Center (HMMC) with milk technicians who fortify and optimize mothers' milk as warranted, including the ability to make skim milk for infants with chylothorax. In 2014, CHOP was approved to become a nonprofit milk bank as part of the Human Milk Banking Association of North America (HMBANA). As a HMBANA milk bank, not only are we able to provide pasteurized donor human milk (PDHM) for infants as a bridge to mother's own milk, but all of our mothers who have extra milk can donate right on-site (Spatz 2018).

In order to disseminate evidenced-based practice protocols, current research, and ensure optimal human milk and breastfeeding outcomes, CHOP has a hospital-wide breastfeeding committee as well as unit-based committees. The N/IICU committee is the most active of the unit-based committees.

Hospital-Wide Committee

There is nursing representation from every inpatient unit from CHOP Main hospital, as well as from our Care Network sites (pediatric primary care). In addition, there are a variety of interdisciplinary colleagues also actively involved including: International Board-Certified Lactation Consultants (IBCLC), registered dietitians, speech language pathologists, and social workers.

The committee meets monthly to discuss research regarding human milk and breastfeeding, hospital policy & procedure updates, HMMC and milk bank updates, World Breastfeeding Week, and more. The committee is responsible for dispersing policies and procedures throughout the organization and updating their peers with current research to ensure best practices for human milk, lactation, and breastfeeding (Spatz, 2018).

Lisa G Dell is a Clinical Staff Nurse, Children's Hospital of Philadelphia (CHOP), Newborn Infant Intensive Care Unit (N/IICU), and chair of the N/IICU Breastfeeding Committee. Diane L Spatz is a Professor of Perinatal Nursing & the Helen M Shearer Professor of Nutrition, University of Pennsylvania School of Nursing, and Nurse Scientist for the Lactation Program, Children's Hospital of Philadelphia. This manuscript was written at the request of Medela, LLC. Nurses at CHOP have the opportunity to take a two-day Breastfeeding Resource Nurse (BRN) course which awards the nurse 14.0 Pennsylvania State Nurses Association (PSNA) credits upon completion of both days. This class provides nurses with information regarding the science of human milk, how to support mothers & families, and technology education regarding breast pumps and milk transfer scales. In order to stay current, staff must take the four-hour BRN refresher class every two years after the initial course. The BRN refresher course provides nurses with 3.75 PSNA credits. The BRN refresher course focuses on new research and policy and updates in clinical practice procedures (Spatz, 2005; Froh, Flynn-Roth, Barton, & Spatz, 2015; Spatz, Froh, Flynn-Roth, & Barton, 2015; Spatz, 2018).

N/IICU Breastfeeding Committee

The unit-based Neonatal/Infant Intensive Care Unit Breastfeeding Committee (N/IICU BFC) is the most active sub-group of the hospital-wide committee. The mission of the N/IICU BFC is to promote and support the mother's decision to provide human milk for her infant. The committee is committed to providing excellent family-centered care through parent and staff education, while utilizing and conducting innovative breastfeeding research (N/IICU BFC mission statement).

The N/IICU BFC is led by two co-chairs, both Breastfeeding Resource Nurses who also went on to pursue their IBCLC certifications. Members of the committee include nurses from all five areas of our N/IICU, our IBCLCs, clinical supervisor of the lactation team, student interns, and our PhD-prepared nurse scientist in lactation. Members serve as important resources with knowledge of CHOP standards, procedures and patientfamily education materials. Various project opportunities are available, such as becoming a unit representative. The N/IICU has 101 beds and is split into five separate units; each of the five units has two representatives for the N/IICU BFC. The N/IICU BFC meetings are held monthly with an agenda of topics to be discussed during the meeting, along with minutes from the previous meeting to be reviewed.

Projects

In order to be an active member of the committee, members are asked to attend two meetings a year and participate in at least one project, including audits of our lactation equipment, two-healthcare provider checks and more. To ensure there is a hospital-grade breast pump and human milk warmer at every infant's bedside, the unit representatives perform monthly inventory. It is preferred for mothers to have access to a hospital-grade pump with computer chip technology in order to ensure a robust milk supply for their hospitalized child (Froh et. al., 2015). Unit representatives also perform two-healthcare provider human milk administration check audits; these checks ensure the proper human milk product is received by the right patient (Spatz, 2018).

Journal club is an extremely effective component of the N/IICU BFC. A different member of the committee each month selects a current research article and develops a post-test for the article. Members who complete the journal club post-test can earn 1.0 PSNA credit for each test completed. Therefore, in one year, nurses can earn up to 12.0 PSNA credits (almost half of what they need for re-licensure).

Screensavers are another popular project opportunity for members of the committee. Each month a new screensaver is developed by members of the committee and placed on every N/IICU computer. Topics include items such as milk storage times, importance of oral care with fresh milk, updates on the milk bank, and World Breastfeeding Week (WBW).

The N/IICU BFC also partners with the N/IICU Developmental Care Team and Child Life Services to implement a Kangaroo-a-thon annually. International Kangaroo Care Day is celebrated May 15th. The Kangaroo-a-thon encourages all families to engage in skin-to-skin contact with their infants. Families and staff are entered into raffles upon participating/ assisting in kangaroo care with gift card awards. The N/IICU BFC makes flyers, screensavers, and candy bags with Kangaroo-ing facts for staff and assists with fundraisers.

The N/IICU committee participates in the hospital-wide WBW celebration by making posters for the hospital-wide poster competition. Posters are displayed both in the main lobby as well as on the unit. During WBW, the N/IICU committee members provide re-education for all nurses on the unit with different topics each year, such as pre- and post-weights, PDHM, and use of the breast pump. The hospital also hosts WBW Grand Rounds which our committee members participate in (Spatz, 2018). During WBW Grand Rounds, the BRN STAR Award is also presented. The N/IICU has had more recipients of the STAR Award than any other area in the hospital. The BRN STAR is for the nurse who epitomizes support (S), teaching (T), advocacy (A) and serving as a resource (R) for the families and all staff in the unit.

Members of the N/IICU BFC also assist with facilitation of our pumping and breastfeeding support group, Group of Empowered Moms (GEMs) (Kristoff, Wessner, & Spatz, 2014). GEMs encourages peer relationships among mothers and provides education and support for the provision of human milk and breastfeeding for their hospitalized infants (Kristoff, Wessner, & Spatz, 2014).

Conclusion

We hope that by sharing our experiences and positive outcomes of our unit-based N/IICU BFC that other neonatal nurses will be inspired to replicate this model at their institutions. Nurses are the largest and most trusted group of health care professionals and they play a critical role in ensuring that families receive expert evidence-based lactation support and care (Spatz, 2010).

References

- Froh, E. B., Flynn-Roth, R., Barton, S., & Spatz, D. L. (2015). The voices of breastfeeding resource nurses. *Journal of Obstetric, Gynecologic, and Neonatal Nursing*, 44(30), 419-425. doi:10.1111/1552-6909.12565.
- 2 Froh, E.B., Hallowell, S., & Spatz, D.L. (2015). The use of technologies to support human milk & breastfeeding. *Journal* of *Pediatric Nursing*, 30(3), 521-523. doi: 10.1016/j. pedn.2015.01.023
- Kristoff, K. C., Wessner, R., & Spatz, D.L. (2014). The birth of the GEMs group. *Advances in Neonatal Care*, 14(4), 274-280. doi: 10.1097/ANC.00000000000065
- 4 Spatz, D. L. (2005). Report of a staff program to promote and support breastfeeding in the care of vulnerable infants at a children's hospital. *Journal of Perinatal Education*, *14*(1), 30-38. doi:10.1624/105812405X23630
- 5 Spatz, D. L. (2010). The critical role of nurses in lactation support. Journal of Obstetric, Gynecologic, and Neonatal Nursing, 39(5), 499-500. doi:10.3928/08910162-20101027-04
- 6 Spatz, D.L (2018). Beyond BFHI: The Spatz 10-step and breastfeeding resource nurse model to improve human milk and breastfeeding outcomes. *Journal of Perinatal & Neonatal Nursing*, *32*(2), 164-174. doi:10.1097/ JPN.00000000000339
- 7 Spatz, D.L., Froh, E.B., Flynn-Roth, R., & Barton, R. (2015). Improving practice at the point of care through the optimization of the breastfeeding resource nurse model. *Journal of Obstetric Gynecologic & Neonatal Nursing*, 44(3), 412-418. doi: 10.1111/1552-6909.12570

Building Bridges for NICU Families

Deb Discenza

It was September 5, 2003 and I was 7.5 months pregnant with my first child. I was all alone in a grocery store bathroom an hour outside of town in hysterics because my water had broken and I knew it. I had had a few hiccups during my pregnancy but my OB seemed unconcerned about my jitters a month before about the potential for preterm labor. I noted to her that I had been born a little early myself and she ignored my concerns telling me I was a first time mother and would be late rather than early.

Remembering that, I felt betrayed as I cleaned up my tears and the gushing fluid as much as humanly possible to head out to the front office to call my doctor.

Fast forward I was rushed back to town (110 mph by my husband who should not have been driving) and to our hospital at the doctor's request. A little over 30 hours later, despite every intervention possible and getting the very traumatic live tour of the labor and delivery wing that coincided with the weekend I was supposed to have my maternity tour, my daughter was born at 30 weeks gestation at 2 lbs 15.5 oz. The tiny but fierce kitten cry erupting from my daughter's mouth gave me real hope. But little did I know that the shock and trauma of her 38-day stay in the NICU, the re-admission to the pediatric unit, almost a decade and a half of specialists would be the emotional and physical marathon of my life.

So a year ago, when I first met Rebecca South and heard about her program launch, Families' Bridge to Caring Hands[®], I knew at last that someone was doing something to empower parents in a way that was clinically sound and emotionally strong. I felt it important to bring Rebecca's program to a higher level of attention because of its strength, its bottom-line hospital savings and its focus on finally giving NICU moms the attention they need and deserve.

Deb Discenza (DD): Rebecca, you came to this program with a unique perspective on the preemie experience, yes? Rebecca South (RS): I've been a NICU nurse since 1994 and have always loved working with preemies and families. I am the

Deb Discenza runs PreemieWorld.com, an educational products company full of free items for educating families. PreemieWorld's flagship product, The Preemie Parent's Survival Guide just published its second edition and is on sale at PreemieWorld.com. In addition, Mrs Discenza is the founder of the 15+ year old global Inspire Preemie Community, free for parents at https://preemie.inspire.com. mother of twin girls and so I have a unique perspective when it comes to the challenges our NICU parents face.

DD: Indeed you have understanding from all sides of the equation here. When did you conceive of this program's idea? Was it a "lightbulb" moment?

RS: In 2013, I saw a gap in the care of moms in the high risk OB arena—and these moms were not at all prepared for what was to come if they delivered early and had a baby in the NICU. I always called these moms 'the forgotten moms' as we never really paid attention to them until they delivered. So, as part of my work in our NICU and the career advancement program at my hospital, I conceived Families' Bridge to Caring Hands[®] and piloted the program in 2014-16. We worked with over 200 families during this time.

DD: Wow, impressive. Walk me through the program.

RS: Families' Bridge to Caring Hands[®] (FBCH) NICU Navigator Nurse program targets antepartum mothers with a high probability of delivering an infant who will be admitted into the NICU. The program methodology provides structured staff training, accompanied by parent resources to aid in lowering stress and providing potential parents of infants in the NICU with a clear view of what's ahead. Our goal is to prepare parents to become engaged members of the NICU care team.

This program provides evidence-based training to perinatal nurses (antepartum, labor and delivery, postpartum, and lactation), with additional training to NICU RNs as NICU Navigator Nurses, to give psychosocial support to families and mothers while on bed rest. Education content is derived from research and literature which indicates that lowering the stress levels of potential parents of infants in the NICU results in improved outcomes for both the parents and the infant following delivery. Our program trains designated NICU Navigator Nurses to work with potential parents of NICU infants by providing structured information throughout their stay in the antepartum unit and continues up to the infant's NICU admission. This oneon-one clinical support has improved staff-parent communication which allows for better parent focus on the infant's care post-delivery.

In addition to the clinical staff training, Families Bridge to Caring Hands provides antepartum mothers with various educational resources utilizing the patient portal on our website (login access required) at time of admission, during and after their hospital stay. This customized content can be accessed via computer, tablet or smartphone and comes preloaded with educational material which correlates with the training provided to the mother by NICU Navigator Nurses and perinatal staff nurses.

DD: You really work hard to lessen a mother's stress, I really like that. I have to assume that this program saves time and money for the team, yes?

RS: Our preliminary data shows that babies whose mothers are in the Families Bridge program have a shorter length of stay in the NICU (as much as three days shorter) and mothers report improved bonding and less anxiety in taking their babies home. As for time savings, the program really supports the NICU staff, in that the parents, on admission, are already 'educated and prepared' and so the staff time in education and support is less.

DD: It appears that you have a lot of fans of this program. Let the voices of hospitals and parents commence:

"Families' Bridge to Caring Hands[®] provides such an amazing opportunity for our families and has a 'triple E effect.' As a result of participating and using the portal, we now have EDUCATED, EMPOWERED and ENGAGED parents." —Sheri, Nurse Supervisor/Navigator

"As a Neonatologist, I go into these families' room and explain what to expect when their baby is admitted into the NICU. It's nice to have a trained NICU nurse to follow up and answer clinical questions, reinforcing what was discussed during the consult."

"The Families' Bridge program has helped me to show my patients evidence-based, realistic information, which eases their stress." — Antepartum Nurse

"The program allowed us to have a glimpse into the possibilities, and our nurse was open and honest with us. We appreciated this so much and felt so much more aware and prepared." —Antepartum Mom

"This is an incredible resource and has really helped address many of my concerns. Having a Nurse Navigator made my transition to the NICU less intimidating and stressful."—Antepartum Mom

DD: Is there anything else you would like people to know about your program?

RS: We have a passion for impacting families/babies who are born in disproportionate share or underserved hospitals—many of which do not have budgets to offer these types of programs. Our goal is for hospitals to have access to this program for minimal cost, so our team is active in pursuing grant funding to assist in implementation and ongoing costs of the program.

DD: That is so important, Rebecca. Thank you for speaking with me.

Imagine a healthcare system that provides families with support pre-NICU and post-NICU to navigate the emotional and physical stressors involved. Imagine a family entering the NICU with far less trauma and more hope through information. Imagine better patient satisfaction and even better, improved post-NICU outcomes as a result of this program. Sadly I had to go through extensive trauma to get where I am today as an advocate. But I wouldn't wish that on anyone else. And you shouldn't wish that on your families going forward. Families' Bridge to Caring Hands[®] is a real, well thought out program that requires minimal resources to implement in your hospital to save time and money and so much heartache. Please reach out today: https:// familiesbridge.com/

Building a Business Case for Nutrition Technology in the NICU

Tracy Warren

We have seen tremendous technological breakthroughs in neonatal care in the past fifty years that have advanced care and improved infant outcomes. From state-of-the-art monitors for pulse ox, blood pressure, and heart rate, to warmers, human milk fortifiers and other novel nutritional interventions. However significant gaps in care still remain, and the pressure is building to find the best gadget or technology to improve care for our most vulnerable patients.

As a unit within a hospital, NICUs contribute solid profit margins, affording them an opportunity to invest in new technologies to further advance care and optimize workflow. However, few clinicians see their role as one of building a business case for a new technology, and while outcomes are a priority, nothing trumps the almighty dollar in health care.

Building a business case requires a clinical champion to not only think about outcomes and performance improvement but how purchasing technology can improve the economic profile for the hospital or unit. Does it allow for increased billing or greater profitability? If we make the investment in this technology, how can we recoup the cost and over what period of time? This is not what clinicians went to medical school for, and this business case burden can often stymie projects which can't articulate clear metrics, both operational, clinical and economic. Some vendors assist these clinical champions by creating tools to demonstrate how a NICU can perform better, improve outcomes and lower cost, which is essential to supporting her/him in bringing in the business-types to get the required approvals.

An area that has tremendous promise in building a solid business case is in standardization of care and reducing the burden of reporting, whether to quality collaboratives or internal quality improvement projects. As EMRs capture trillions of datapoints, technology that "talks to" the EMR can greatly enhance care and support a strong return on investment. The perfect example is nutrition.

Nutrition is an essential part of NICU care and requires substantial resources, yet adverse outcomes, such as growth failure, remain high. Not all units have the good fortune of having a dedicated registered dietitian and many neonatologists aren't comfortable prescribing nutrition and ascertaining the optimal plan for infants who are struggling. Hospitals have invested in

Tracy Warren, Co-founder and CEO, Astarte Medical @TracyAstarte; tracy@astartemedical.com substantial labor resources, whether RDs, nurses or others who extract data from an EMR, run calculations—on a calculator or in a spreadsheet—and then create care plans. Interestingly enough, those calculations and plans are often not captured in the EMR leaving the "secret sauce of success" in the circular file.

> Successful progression from parenteral to enteral to oral feeding is key to achieving appropriate growth and development.

Studies have shown that the implementation of a standardized feeding strategy has effectively minimized practice variability, accelerated the attainment of enteral and oral feeding milestones, reduced central line days and decreased length of stay without increasing adverse morbidities. Technology, with a backbone of math, 0s and 1s, can automate and standardize many of the aspects of nutrition planning and enable efficient use of time and resources increasing time at the bedside and empower clinicians to practice at the top of license. Successful progression from parenteral to enteral to oral feeding is key to achieving appropriate growth and development. Moreover, initiation of early enteral nutrition reduces parenteral nutrition use which can average \$1436/day. Given nutrition is embedded in the DRG and other bundled payments, this increases profit for the hospital. As infants achieve full feeds faster, central line days are reduced, which then reduces the risk of CLABSI, a hospital acquired condition that is not reimbursed. For hospitals that have at-risk contracts with payers or Medicaid ACOs, optimizing discharge planning and reducing length of stay can improve profits and performance metrics as well.

Neonatal nutrition is complex but providing the preterm infant with optimal nutrition to achieve the same growth and development of the healthy, growing fetus is the next imperative in neonatal critical care. Clinicians must be relentless in providing top quality care in the face of time constraints, a growing catalog of available and often expensive dietary options, staying current on the vast amount of new research, all while assessing the overall impact on infant outcomes. A person at the bedside cannot possibly know all about an infant's metabolism, growth, development, nutrition, changes over time, influence of diseases and treatments, and all related outcomes. Technology is the answer and as more hospitals embrace clinical decision support for such challenging elements of care, they will benefit from increase profits, reduced risk and optimal performance measures.

References

- Jadcherla SR, Dail J, Malkar MB, McClead R, Kelleher K, Nelin L. Impact of Process Optimization and Quality Improvement Measures on Neonatal Feeding Outcomes at an All-Referral Neonatal Intensive Care Unit. JPEN J Parenter Enteral Nutr. 2016;40(5):646-655.
- 2 Stefanescu BM, Gillam-Krakauer M, Stefanescu AR, Markham M, Kosinski JL. Very low birth weight infant care: adherence to a new nutrition protocol improves growth outcomes and reduces infectious risk. Early Hum Dev. 2016;94:25-30.
- 3 Edwards TM, Spatz DL. Making the case for using donor human milk in vulnerable infants. Adv Neonatal Care. 2012;12(5):273-280. doi:10.1097/ANC.0b013e31825eb094

News...continued from page 14

bronchopulmonary dysplasia (BPD), a common complication of prematurity, may benefit the most from an EHMD when it comes to shortening their hospital stays. A retrospective study published in the Journal of Perinatology found that 293 infants between gestational ages 23 and 34 weeks and birth weights between 490 and 1,700 g who received Prolacta's fortifiers as part of an EHMD achieved full feeds at faster rates and ultimately reduced their NICU stay by 4.5 to 22.9 days, compared with infants fed their mother's milk with a cow milk-based fortifier or a combination of mom's milk with cow milk-based fortifier and formula. Frontiers in Pediatrics published findings from a study of more than 12,000 premature infants born at ≤ 28 weeks indicating that among the 41% who developed BPD, hospital stays were 19 days longer on average (P = .001) than those who did not develop BPD. A secondary analysis of a study that originally looked at the impact of Prolacta's cream fortifier on growth among premature infants weighing 750 to 1,250 g showed that adding Prolacta's human milk-based cream fortifier to an EHMD resulted in an average stay in the NICU that was 12 days shorter, from 86 days without the cream supplement to 74 days when it was used. In this study, the infants with BPD may have benefited the most from the addition of Prolacta's cream fortifier, with 17 fewer days in the NICU, from an average of 121 to 104 days (P = .08). This updated analysis was published in Breastfeeding Medicine in 2016. A 2019 study published in Advances in Neonatal Care compared 104 infants born weighing ≤ 1,250 g who received an EHMD to a similar group of 101 infants who received cow milk-based fortifier. In this study, an EHMD was associated with decreased rates of BPD (P = .018) and sepsis (P = .06) and an average five-day reduction in length of hospital stay. "The goal of all parents with a premature infant in the NICU is to bring their baby home as soon as possible. When you add the concerns about exposure to hospital-based infections for both the parents and the baby, that desire for discharge is stronger than ever," said Melinda Elliott, MD, chief medical officer of Prolacta. "The clinical evidence shows an EHMD including Prolacta's products helps to overcome the complications of prematurity, resulting in better health outcomes and shorter hospital stays in the NICU."

Neotech Earns B Corp Certification

Neotech announced its newly earned B Corp certification, furthering a commitment to using business as a force for good. "Since its inception, Neotech has always strived to

create a lasting impact and do the right thing. Becoming certified as a B Corp is a natural step for Neotech," said Henry Heyman, Neotech Consultant. "It's a way to solidify many of the amazing initiatives and choices Neotech has already made." Certifying as a B Corporation goes beyond product or service level certification. B Corp Certification is the only certification that measures a company's entire social and environmental performance. The B Impact Assessment evaluates how a company's operations and business model impacts its workers, community, environment, and customers. From supply chain and input materials to charitable giving and employee benefits, B Corp Certification assures that Neotech is meeting the highest verified standards of social and environmental performance. "We are extremely happy that Neotech Products has joined our community of Certified B Corporations," said Lindsey Wilson, B Lab Senior Associate, Business Development. "Neotech's existing culture and values align perfectly with the global B Corp movement to redefine success in business to balance both profit and purpose. With their dedication to their customers, their employees, and the community, Neotech serves as an excellent example of People Using Business as a Force for Good," Wilson continued. In conjunction with the B Corp initiative, Neotech has recently launched the Being the Difference charitable giving program. Being the Difference launched in May 2020 with three newlyformalized opportunities to individuals and organizations in need: Product Donations, Monetary Donations and Scholarship Aid. Additionally, Being the Difference encompasses our two existing Research Grant programs.

Plan of Care for a Neonate: Overview of ECMO

Gabriela Ortiz, BSRT, RCP

What is ECMO?

Extracorporeal Membrane Oxygenation (ECMO) may be considered as an elective, advanced form of life support to treat infants, children, and adults in respiratory and/or cardiac failure. Though conventional ventilatory management, including Nitric Oxide and High Frequency Oscillatory Ventilation (HFOV), do help save the lives of neonates with respiratory failure, there are still those who cannot overcome their disease process within an adequate amount of time, and therefore mortality occurs. ECMO is only used for patients who are responding poorly to optimal ventilatory, surgical, and medical treatment. Roeleveld and Mendonca (2019) reported a 40% hospital survival rate in neonatal cardiac ECMO modalities. As with all invasive modalities, risk factors increase, involving pre- and post-placement impacts, age, cardiac/lung anomalies, vascular complications, previous life support, and drug therapies (Roeleveld and Mendonca, 2019). In rare cases a patient may be awake and alert; however, sedating a patient is preferred as this may prevent stress, ventilator dyssynchrony, and dislodgments of the ventilator circuitry. Jenks, Tweed, Gigli, Venkataraman, and Raman (2017) conducted a survey of ECMO centers to determine practice pattern changes for ventilator strategies, extubation, bronchoscopy, and tracheostomy, when comparing neonate, pediatric, and adult centers. Their results showed that centers are extubating their patients and proceeding with tracheostomies and bronchoscopies, with 45% using percutaneous tracheostomies and 19% open, surgical tracheostomies. Hines and Hansell (2003) discussed the use of ECMO with tracheal reconstruction surgery as a means to allow patients to stabilize and recover while receiving venoarterial support, then it can be switched to veno-venous to allow the lungs to rest. They report using bronchoscopy to evaluate progress and develop the plan of care.

Gabriela Ortiz has been in the field of respiratory care since 2006. She has lived in Southern California all her life, graduating from California Paramedical College with her Associates degree in respiratory care, then gaining her Bachelor's degree in respiratory as well. She has used her clinical knowledge to advance into clinical education and unique sales roles, being responsible for selling critical care ventilation products into the ICU, PICU and respiratory care of acute and subacute hospitals in Southern California. Gabriela is recognized for her compassion and is invited as a guest speaker at trade schools, Better Breather's Group and the ALS Association-Golden West Chapter Support Groups to educate on the transition of invasive therapies following tracheostomy. The Extracorporeal Life Support Organization (ELSO) reported that as of 2017, over 87,366 patients have been treated with ECMO worldwide, including 35,598 neonates. Most neonatal cases treated with ECMO have a primary respiratory diagnosis (78%), with the remainder of cases having a primary cardiac diagnosis. Approximately 4% of the cases underwent extracorporeal cardiopulmonary resuscitation (ECPR). Within the ELSO registry, it is reported that there is a decrease in ECMO use, accounting for <10% of therapy (ELSO, 2017).

What does ECMO do?

ECMO is a temporary artificial heart and lung, requiring closer attention than with traditional ventilation, due to the precision of ventilator settings which affect circulation and ventilation much more quickly. Blood is drained from the venous systems using large percutaneous cannulas where oxygen is added, and carbon dioxide is removed. The two most common applications of ECMO are the veno-arterial (VA) and veno-venous (VV) also known as central or peripheral ECMO (Kaiyun Gu, Ya Zhang, Bin Gao, Yu Chang, and Yi Zeng, 2016). In both modalities, blood is drained from the venous system then oxygenated outside of the body. In veno-arterial ECMO, a venous cannula is placed in the right femoral vein for extraction and an arterial cannula is placed into the right femoral artery for infusion. In VA ECMO, blood is returned to the arterial system when there are problems with the heart and lungs. In veno-venous ECMO application, the cannula is placed in the right femoral vein for drainage and right internal jugular vein for infusion. With VV ECMO, the blood is returned to the venous system and used only when there are lung issues.

Indications & Management

According to ELSO Registry criteria, term or late preterm neonates (34 -36 weeks of gestation) with unmanageable, severe respiratory and/or cardiac failure, a high probability of mortality, and a potentially reversible etiology are considered for ECMO therapy. If a neonate's respiratory and cardiac disorder can be reversed, it is feasible for ECMO to safely support the patient, allowing the child time to rest and heal which may help with progression of developmental milestones. Contraindications for therapy include those patients with irreversible anomalies, brain damage, and neonates less than 34-week gestation (ELSO, 2017).

Once the initial respiratory and hemodynamic goals have been achieved, the blood flow is maintained at that goal rate. Frequent assessment and adjustments are facilitated by continuous venous oximetry, which directly measures the oxyhemoglobin saturation of the blood in the venous limb of the ECMO circuit.



Settings are maintained at near-maximum with flow rates to optimize oxygen delivery in VV ECMO. In contrast, the flow rate used during VA ECMO must be high enough to provide adequate perfusion pressure and venous oxyhemoglobin saturation, measured on drainage blood, but low enough to provide sufficient preload to maintain left ventricular output. Aggressive diuresis is necessary once the child is stable on ECMO to prevent fluid-over load. Ultrafiltration can be easily added to the ECMO circuit if inadequate urine output presents. Left ventricular output is rigorously monitored during VA ECMO because left ventricular output can become worse (ED ECMO, 2017). As with many invasive therapies, complications do arise, bleeding that can become difficult to control, vascular insufficiency, and neurological impairments. For this reason, it is not practical to use ECMO to treat a disease process that is not reversible within 7 to 30 days. Thrombolytics, such as heparin will be necessary to maintain patency of the circuit and to reduce clotting complications (Van Ommen, Neunert, and Chitlur, 2018).

Perspective from a respiratory therapist on the role of the respiratory care practitioner in the initiation and maintenance of the ECMO procedure?

Extracorporeal Membrane Oxygenation (ECMO), Extracorporeal Life Support (ECLS) and Cardiopulmonary Support (CPS), Extracorporeal Cardiopulmonary Resuscitation (ECPR) are acronyms that all refer to the setting up of cardiopulmonary bypass via mechanical circulatory support systems. Since ECMO provides both cardiac and respiratory support, this therapy is often supported and maintained by respiratory therapists, just like traditional ventilation.

In most situations, the doctor accesses and places the cannulas, then respiratory therapists maintain and support the patient's needs with ECMO. Whether ECMO is via veno-arterial ECMO (VA-ECMO) or veno-venous ECMO (VV-ECMO), support and maintenance of ECMO requires closer attention than traditional ventilation, due to the precision of settings affecting circulation and ventilation quicker.

At what point in a neonate's course would you consider using ECMO therapy as a replacement for nitric oxide? Nitric oxide (NO) is a pulmonary vasodilator without significant effects on the systemic circulation. It improves oxygenation and ventilation, reduces the need for extracorporeal membrane oxygenation (ECMO), and lowers the incidence of chronic lung disease and death among infants with respiratory failure. However, ECMO provides prolonged mechanical support for patients with reversible heart or lung failure. The technology is capable of effectively and safely supporting respiration and circulation in neonates with severe reversible respiratory failure and a declining clinical presentation.

The special technology, of a heart-lung machine is needed to oxygenate the blood of babies with higher acuity breathing difficulties. ECMO is for babies with extremely limited lung function. It does the job of the heart and lungs, passing lifegiving oxygen into the blood and circulating it. It gives babies with lung problems time to grow and heal. It is most often used to support medical treatment of respiratory problems like pulmonary hypertension, pneumonia, and others. Nitric oxide has largely superseded ECMO as the standard of care for newborn pulmonary problems, but ECMO still plays a role in neonatal care.

A bridge to recovery

As Roeleveld and Mendonca (2019) state, "bridge to recovery, bridge to long-term support, or bridge to decision making" (e.g., diagnostic work-up, organ donor), ECMO has become not only a rescue treatment but also an elective support during diagnostic and therapeutic procedures. As research and experience is still needed, neonatal ECMO continues under sedation to reduce oxygen consumption, stress, and dislodgment of circuitry. According to ELSO, overall survival to hospital discharge is 72% for patients treated with ECMO for neonatal respiratory disease (ELSO, 2017). As the bridge to recovery continues, those with tracheostomies can use Passy Muir® Valves to help expedite weaning, allow communication with parents through crying and cooing, improve progression with developmental growth, and improve quality of life.

References

- Bahrami, R. K. and Van Meurs, K. P. (2005). ECMO for neonatal respiratory failure. *Seminars in Perinatology*, 29(1), 15-23. doi.org/10.1053/j.semperi.2005.02.004
- Costa, J., Dirnberger, D. R., Froehlich, C. D., Beaty, C. D., Priest, A., & Ogino, M. T. (2020). Awake Neonatal Extracorporeal Membrane Oxygenation. *ASAIO Journal*, 66(5), e70-e73. doi: 10.1097/MAT.000000000001029.
- Extracorporeal Life Support Organization. (2017). Guidelines for neonatal respiratory failure. (1.4.),
 5. Retrieved from https://www.elso.org/Portals/0/ ELSOGuidelinesNeonatalRespiratoryFailurev1_4.pdf
- Hibbs, A., Evans, J. R., Gerdes, M., Hunter, J. V., & Cullen, J. A. (2001). Outcome of infants with bronchopulmonary dysplasia who receive extracorporeal membrane oxygenation therapy. *Journal of Pediatric Surgery*, *10*, 1479-84. doi: 10.1053/jpsu.2001.2702
- Hines, M. H. and Hansell, D. R. (2003). Elective extracorporeal support for complex tracheal reconstruction in neonates. *Annals of Thoracic Surgery*, 76(1), 175-179. doi: 10.1016/s0003-4975(03)00129-2.
- Jenks, C. L., Tweed, J., Gigli, K. H., Venkataraman, R. & Raman, L. (2017). An international survey on ventilator practices among extracorporeal membrane oxygenation centers. *ASAIO Journal*, *63*(6), 787-792. doi: 10.1097/ MAT.000000000000575.

- Kaiyun Gu, A.D.E., Ya Zhang,B.C., Bin Gao, F.G., Yu Chang, A.G., & Yi Zeng,A. (2016). Hemodynamic differences between central ECMO and peripheral ECMO: a primary CFC study. *Medical Science Monitor*, 22, 717–726. doi: 10.12659/ MSM.895831
- Methodist MD. (2019). Methodist Hospitals ECMO Program. Methodist Health, San Antonio TX. Retrieved from https:// sahealth.com/about/newsroom/methodist-hospital-s-ecmoprogram-receives-national-acclaim
- Roelveld, P. P. and Mendonca, M. (2019). Neonatal cardiac ECMO in 2019 and beyond. *Frontier in Pediatrics*, *7*, 327. doi: 10.3389/fped.2019.00327
- Van Ommen, C. H., Neunert, C. E., & Chitlur, M. B. (2018). Neonatal ECMO. Frontiers in Medicine (Lausanne), 5, 289. doi: 10.3389/fmed.2018.00289

Benefitting Extremely Preterm Infants: Effects of Early Fortification on Morbidity

Melinda J Elliott, MD FAAP

Introduction

As advancements continue to be made at hospital neonatal intensive care units (NICUs), an increasing number of infants born extremely prematurely are surviving to hospital discharge. While survival rates are improving, our clinical focus remains: reduce patient morbidities and maximize patient potential for long-term health through the use of the best and most costeffective modalities available.

Recently, mounting evidence has demonstrated that adoption of an exclusive human milk diet (EHMD), with early use of Prolacta's human milk-based fortifiers, to feed infants born extremely prematurely is one cost-effective¹ way to minimize morbidity^{2,3,4} and promote long-term health.⁵ An EHMD is one that is devoid of any cow milk-based products and where all of the macronutrients (protein, fat, carbohydrate) are derived from only human milk.

Impact of Early Adoption of Prolacta's EHMD Human Milk Fortifiers

A new study on the importance of initiating 100% human milk fortifiers sooner rather than later has been published by Huston and colleagues. This was a multicenter retrospective cohort study of 394 infants with a birth weight of 500 to 1250 g who were fed Prolacta's EHMD. The investigators compared early fortification, starting at ≤ 60 mL/kg/day of enteral feeding volume, with late fortification, which was initiated at > 60 mL/ kg/day of enteral feeding volume. The infants who received early fortification had better growth metrics, including greater weight gain velocity (12.9 ± 2.6 vs 13.3 ± 2.6 g/kg/day; P = 0.03) as well as a reduction in bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD) (42.6% vs 27.6%; P = 0.008). Adjusted multiple regression analysis found early fortification was independently associated with improved growth velocity for weight (P = 0.007) and head circumference (P = 0.021), as well as a decreased occurrence of CLD (P = 0.004) and less negative changes in z scores for weight (P = 0.022) and head circumference (P = 0.046) from birth to discharge.²

Dr Melinda Elliott is a practicing neonatologist and chief medical officer of Prolacta Bioscience where she serves as the voice of the patient, working to ensure that the needs of critically ill and premature infants are being articulated and that the relevant treatment and product opportunities are identified. As an experienced neonatologist and researcher in neonatal intensive care, Elliott has committed her career to the care of vulnerable premature infants and has researched the benefits of an EHMD for extremely low birth weight premature infants in the NICU.

Impact of Early Feeding on BPD

Another study that demonstrated the benefits of early feedings on lung health was recently presented in poster format at the 2019 Congress of joint European Neonatal Societies (jENS).⁶ In this study, Wyble et al conducted post hoc analyses of publications by Sullivan,⁷ Hair,⁴ and Assad,¹ as well as an analysis of unpublished data from the Tampa Mednax Neonatal Group, to determine the impact of timing of feeds on BPD among infants with a birth weight of ≤ 1250 g.

The authors uncovered benefits of early feeding in all the data sets, and these were particularly notable when Prolacta's EHMD was adopted. In the Sullivan data set, delay to first enteral feeding and increased number of days to full feeds were both associated with an increased rate of BPD/CLD among those who received an EHMD. For every additional day to first feed, the odds of developing BPD were increased by 9.9%. For every additional day to full feeds, the odds of developing BPD were increased by 5%. Notably, a link between timing of feeds and BPD was not observed among infants fed cow milk products in this data set.⁷ Assad et al started feeds earlier than the Sullivan group and again a link was observed between longer time to full feeds and a higher rate of BPD, this time among those who received both an EHMD and cow milk products.1 From the Hair et al data set, they demonstrated a significant association between fewer days on total parenteral nutrition (TPN) as a surrogate marker for time to full feeds and lower rate of BPD.⁴ Analysis of the unpublished data out of Tampa revealed that a shorter median time to first feed was associated with less BPD. For every additional day of delay in first feed, the odds of developing BPD increased 2.3-fold.6

Clinical Evidence on the Impact of Prolacta's EHMD

It is important to interpret these new findings within the context of a larger body of literature that demonstrates reduction in feeding intolerance as well as improved morbidity and mortality among extremely preterm infants fed Prolacta's EHMD, compared with a diet that includes cow milk-based products. This evidence led us to adopt Prolacta's EHMD in March of 2012 at The Herman & Walter Samuelson Children's Hospital at Sinai in Baltimore, Maryland, for infants born ≤ 28 weeks gestational age and/or ≤ 1500 g at birth. We published a retrospective study of our experience in 2016, which included 293 infants of gestational ages 23 to 34 weeks and birth weights 490 to 1700 g.¹ We compared outcomes among those who received either:

• Prolacta's EHMD that included human milk (mother's own milk or donor milk) plus human milk-based fortifier

- Mother's own milk plus cow milk-based fortifier
- A mixed combination of mother's own milk with cow milkbased fortifier or formula
- Formula alone

In our study led by Assad, infants fed Prolacta's EHMD were less likely to experience feeding intolerance (P < 0.0001) and necrotizing enterocolitis (NEC) (P < 0.011). In addition, the number of days to full feeds was lower (P < 0.001), and total hospitalization costs were lower by up to \$106,968 USD per infant (P < 0.004) with adoption of an EHMD.¹

Two years before our study, Abrams et al⁸ analyzed the same Sullivan data set used by Wyble et al in combination with another data set by Cristofalo et al,⁹ for a total of 260 infants born extremely prematurely with a birth weight ≤ 1250 g. Of these infants, 167 received a diet consisting of human milk fortified with a human milk-based fortifier (EHMD), and the remaining 93 received variable amounts of cow milk-based protein. Mortality (2% vs 8%; *P* = 0.004) and NEC (5% vs 17%; *P* = 0.002) were both significantly lower in the EHMD group. The authors calculated that every 10% increase in the volume of milk containing cow protein was associated with a 17.9% increased risk of late-onset sepsis (*P* < 0.001).

Importantly, duration of parenteral nutrition (PN) was eight days shorter in the subgroup of infants receiving a diet containing < 10% cow milk than among those who received \geq 10% cow milk (P < 0.02).⁸ This oftentimes overlooked outcome is important because longer time on PN among premature infants is associated with greater incidence of several morbidities, including central line-associated bloodstream infections and PN-associated liver disease.¹⁰ In addition, shorter time to full enteral intake is associated with better neurodevelopmental outcomes.¹¹

In 2019, Delaney Manthe et al demonstrated that the adoption of Prolacta's EHMD in their center resulted in reductions in both per-patient evaluations for late-onset sepsis (P = 0.0027) and cases of BPD (P = 0.018).³

This year, Lucas et al published a subgroup analysis of the Sullivan data set, this time including only the 114 infants who received only their mother's own milk as a base diet plus fortification (infants who received preterm cow milk-based formula were excluded). When the infants who received 100% human milk-based fortifier were compared head to head with those who received cow milk-based fortifier, risk of NEC (relative risk [RR] 4.2; P = 0.038) and surgical NEC or death (RR 5.1; P = 0.014) were both greater among those who received the cow milk-based fortifier.¹² In addition, the infants who received the cow fortifier had reduced head circumference gain (P = 0.04).¹²

In 2018, one of the few prospective, blinded, randomized trials comparing human milk-based fortifier with cow milk-based fortifier was published. In it, 127 infants born in Toronto, Canada, weighing < 1250 g at birth and fed mother's own milk or donor milk (as needed) were randomized to receive fortification with either human milk-based or cow milk-based fortifier. The authors concluded there was no significant difference between the two groups with respect to a mortality and morbidity index they created, but the P value of 0.07 narrowly missed significance. While not powered to determine

differences between the two groups in terms of individual morbidity outcomes, severe retinopathy of prematurity (ROP) was observed significantly less often in the EHMD group (1.6% vs 10.2%; P = 0.04). While not reaching the statistical significance level of 0.05, the incidence of late onset sepsis was nearly cut in half with the use of Prolacta's EHMD, from 23% to 12.5%, P = 0.07.¹³

Because small sample size may have contributed to the lack of significant outcomes in the O'Connor trial, Lucas et al in 2020 conducted a pooled analysis of the data sets from O'Connor, Sullivan, and our group.¹⁴ When data from all three studies were analyzed together, a diet containing cow milk, compared with Prolacta's EHMD, was associated with a greater risk of NEC (RR 3.3; P = 0.008), ROP (RR 2.4; P = 0.001), feeding intolerance (RR=3.4; P=0.001), and the same combined morbidity/mortality index used in the O'Connor trial (RR 1.4; P = 0.006).

Conclusion

When considering the impact of an intervention, it is important to evaluate the sum of the evidence. Studies exploring the impact of Prolacta's EHMD with human milk-based fortifiers in extremely preterm infants have limitations, from inconsistencies regarding the use of preterm formula to small sample sizes. These studies vary in design, patient populations, number of subjects, and other factors. Rather than being viewed as a limitation, this variability adds validity to their similar conclusions. Different NICU types in varying parts of the world have studied an EHMD. They have used slightly different feeding protocols on slightly different patient populations, yet all involve low birth weight or very/extremely premature infants. Given the variability of the studies, it is powerful that they all show similar health outcomes for premature infants. This is very unlikely to be a chance discovery. After evaluating the body of evidence, it is clear that extremely premature infants fed Prolacta's EHMD including human milk-based fortifiers likely have a lower risk of several morbidities and possibly even mortality. There also appear to be benefits to initiating human milk-based fortifiers sooner rather than later. Importantly, these clinical benefits appear to be so substantial that they also translate to cost savings for the NICU.

References

- 1 Assad M, Elliott MJ, Abraham JH. Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. *J Perinatol.* 2016;36(3):216-220. doi:10.1038/ jp.2015.168
- 2 Huston R, Lee M, Rider E, et al. Early fortification of enteral feedings for infants <1250 grams birth weight receiving a human milk diet including human milk based fortifier. *J Neonatal Perinatal Med.* 2020;13(2):215-221. doi:10.3233/ NPM-190300
- 3 Delaney Manthe E, Perks PH, Swanson JR. Team-based implementation of an exclusive human milk diet. Adv Neonatal Care. 2019;19(6):460-467. doi:10.1097/ ANC.000000000000676
- 4 Hair AB, Peluso AM, Hawthorne KM, et al. Beyond necrotizing enterocolitis prevention: improving outcomes with an exclusive human milk-based diet. *Breastfeed Med.* 2016;11(2):70-74. doi:10.1089/bfm.2015.0134 Published correction appears in *Breastfeed Med.* 2017;12(10):663. doi:10.1089/bfm.2015.0134.correx
- 5 Bergner EM, Shypailo R, Visuthranukul C, et al. Growth, body composition, and neurodevelopmental outcomes at 2 years

among preterm infants fed an exclusive human milk diet in the neonatal intensive care unit: a pilot study. *Breastfeed Med.* 2020;15(5):304-311. doi:10.1089/bfm.2019.0210

- 6 Wyble L, Ferry J, Vaughan E, Lee M. Earlier, more rapid feeding of exclusive human milk diet leads to lower incidence of bronchopulmonary dysplasia (BPD). Presented at: 3rd Congress of joint European Neonatal Societies; Maastricht, Germany.
- 7 Sullivan S, Schanler RJ, Kim JH, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milkbased products. *J Pediatr*. 2010;156(4):562-567.e1. doi:10.1016/j.jpeds.2009.10.040
- 8 Abrams SA, Schanler RJ, Lee ML, Rechtman DJ. Greater mortality and morbidity in extremely preterm infants fed a diet containing cow milk protein products. *Breastfeed Med.* 2014;9(6):281-285. doi:10.1089/bfm.2014.0024
- 9 Cristofalo EA, Schanler RJ, Blanco CL, et al. Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. *J Pediatr*. 2013;163(6):1592-1595.e1. doi:10.1016/j.jpeds.2013.07.011
- 10 Calkins KL, Venick RS, Devaskar SU. Complications associated with parenteral nutrition in the neonate. *Clin Perinatol.* 2014;41(2):331-345. doi:10.1016/j.clp.2014.02.006
- 11 Cormack BE, Harding JE, Miller SP, Bloomfield FH. The influence of early nutrition on brain growth and neurodevelopment in extremely preterm babies: a narrative review. *Nutrients*. 2019;11(9):2029. doi:10.3390/nu11092029
- 12 Lucas A, Boscardin J, Abrams SA. Preterm infants fed cow's milk-derived fortifier had adverse outcomes despite a base diet of only mother's own milk. *Breastfeed Med.* 2020;15(5):297-303. doi:10.1089/bfm.2019.0133
- 13 O'Connor DL, Kiss A, Tomlinson C, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born weighing <1250 g: a randomized clinical trial. *Am J Clin Nutr.* 2018;108(1):108-116. doi:10.1093/ajcn/nqy067
- 14 Lucas A, Assad M, Sherman J, Boscardin J, Abrams S. Safety of cow's milk-derived fortifiers used with an all-human milk base diet in very low birth weight preterm infants. *Neonatol Today*. 2020;15(7):3-13. Accessed July 22, 2020. http://www. neonatologytoday.net/newsletters/nt-jul20.pdf

Top 3 Considerations When Evaluating a Probiotic for Standard of Care in the NICU

Rebbeca M Duar, PhD and Megan Landrum, MS, RD

Routine neonatal care, antibiotics and prolonged hospitalization can have detrimental effects on the infant gut microbiome. These often-unavoidable practices, together with gestational age and immune immaturity, place preterm infants at uniquely elevated risk for developing gut dysbiosis.¹ In neonates, the consequences of dysbiosis range from feeding intolerance¹ to serious infections and life-threatening conditions, such as sepsis and necrotizing enterocolitis (NEC).² Evidence suggests administration of the appropriate probiotic can be an effective approach to shift the neonatal gut microbiome toward a more protective balance of microbes.³ However, with the variety of products available, as well as range of claims and formulations, choosing the right probiotic can be an overwhelming task. To facilitate this process, three important considerations are recommended when evaluating a probiotic for the NICU.

Scientific evidence of efficacy and proven mechanism of action

Arguably, the most important aspect when choosing a probiotic is the level of evidence-based data to support efficacy. Evidence from peer-reviewed and appropriately controlled studies is imperative, both for safety and to support anticipated beneficial effects. Importantly, data must be available at the strain-level, as the functions and benefits of a given strain are not generalizable to other probiotics of the same species.⁴

Clear mechanism of action for each strain is another key aspect in probiotic evaluation. In the NICU, pathogenic species from hospital surfaces invade the susceptible preterm gut, further exacerbating dysbiosis and contributing to nosocomial infections.⁵ The overabundance of pathogens triggers intestinal inflammation and enterocyte injury, which are thought to be significant risk factors in the development of NEC and sepsis.6 Probiotic strains with an elucidated mechanism to displace pathogenic bacteria in the infant gut, along with demonstrated immunomodulatory properties which in turn reduce enteric inflammation, are likely to have the most success improving outcomes in this population. Thus, it is recommended for probiotic products to contain strains that naturally colonize the healthy infant gut. These probiotics have a better chance of colonizing in high numbers and out-competing harmful bacteria, while having a favorable interaction with the immune system.7

Dr Duar is a Sr Scientist of Microbiology at Evolve BioSystems. Megan Landrum is a pediatric dietitian and Senior Manager of Medical Sales, Training and Development at Evolve BioSystems. Specific species of bifidobacteria are the first colonizers of the healthy infant gut and play key roles in early immunological development. B. longum subsp. infantis (B. infantis) is the most adept at colonizing the infant gut by utilizing oligosaccharides from human milk. B. infantis is also associated with improving gut barrier function.^{7,8} Feeding *B. infantis* in combination with human milk favorably alters the microbiome of term and preterm infants.^{7,9} In a clinical study, feeding B. infantis EVC001 was effective in significantly reducing the abundance of pathogenic bacteria¹⁰ known to carry virulence factors,¹¹ as well as reducing inflammatory responses.¹² Mechanistically, B. infantis EVC001 displaces pathogens by competing for nutritional resources in the gut and producing antimicrobial compounds in the form of organic acids, mainly lactate and acetate.¹³ These organic acids reduce the colonic and fecal pH, which furthers discourages the growth of acid-sensitive pathogens.¹⁴ Infants fed EVC001 also experienced significantly less degradation of the protective gut mucosal barrier compared to infants not fed the probiotic.¹⁵ The EVC001 strain was isolated from a healthy breastfed infant and its benefits in neonates are supported by a growing number of peer-reviewed studies, 10-12, 15, 16 making B. infantis EVC001 an ideal probiotic strain for use in the NICU.

Product formulation and presentation

When it comes to probiotic formulation, powdered and liquid forms are the two main options. Powdered probiotics are more widely available due to the lower manufacturing costs. However, the use of powdered products in the NICU is heavily discouraged.¹⁷ Powdered probiotics can aerosolize up to three feet in distance when opened, contaminating surrounding surfaces and hands of the opening operator.18 This may increase the risk of central line infections and cross-colonization between patients. In the absence of alternatives, guidelines recommend handling powdered products at a designated location separate from patient care areas. These additional safety requisites often involve laborious multi-department logistical coordination which can be disruptive to day to day operations of the NICU staff. Additionally, careful sanitation steps and aseptic technique are required to prevent the inadvertent introduction of pathogens during preparation, and once reconstituted, some ingredients can serve as media for the multiplication of infectious bacteria. For these reasons official guidelines from the Academy of Nutrition and Dietetics (AND) and the Centers for Disease Control and Prevention (CDC) recommend, whenever possible, liquid product formulations should be chosen for use in the NICU.¹⁷

Ask the following questions when evaluating probiotics for your NICU

- Is there sufficient and rigorous evidence-based data to support the mechanism of action and function of each individual strain?
- Is the CFU count of each strain clear and guaranteed at time of use?
- Are the other ingredients in the product safe & tolerable for preterm infants?
- What's the origin of the strain and is it a natural colonizer of the infant gut?
- Is the product manufactured on a dedicated line to prevent cross contamination during manufacturing?
- Does the manufacturer follow current Good Manufacturing Practices (cGMP?)
- Is the company able to provide a certificate of conformance, including stability and viability, for each batch of product?
- Is the product in the most appropriate form for the NICU (liquid) and does it comply with the official guidelines outlined by the Academy of Nutrition and Dietetics (AND) and Centers for Disease Control and Prevention (CDC)?

Liquid probiotic formulations have many advantages. In contrast to powdered probiotics, which require mixing with larger volumes, liquid formulations allow for small volume administration, compatible with initiation of trophic feeds.⁴ Liquid preparations in food grade oils, such as MCT oil, prevent aerosolization allowing bedside handling. MCT oil also creates a protective layer for oxygen sensitive organisms, ensuring probiotic viability, and facilitates flowability reducing the risk of clogging the enteral feeding tube. Finally, liquid formulations in single-serve vials eliminate the risk of product crosscontamination from repeated access to a central container.

Manufacturing, quality and safety

When providing a probiotic to vulnerable NICU patients, manufacturing, quality and safety are imperative. Key considerations when evaluating quality of a probiotic product include accurate labeling, transparent quality testing and verifiable bacterial counts for each individual strain listed on the product label. In a recent position statement, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) stated, "manufacturers should provide certificates of compliance and analysis to be able to address at least strain identity, purity, viability at end of shelf life, and antibiotic susceptibility and resistance profiles".¹⁹ These recommendations were issued in part in response to reports of manufacturers suspected of inflating the total bacterial counts (listed as colony forming units [CFU]) of multi-strain products and/or inaccurately listing bacterial strains on the label.²⁰ Health professionals should be wary of these unethical practices and ensure the probiotic label lists strain designation and visibility to the individual counts for each bacterial strain. Manufacturers must also be able to provide a certificate of conformance upon request, to confirm the product is labeled correctly, free of contamination and viable until time of administration to the NICU patient. Finally, because certain bacterial strains are particularly susceptible to temperature fluctuations, manufacturing and distribution must be protected by cold chain to ensure viability at time of administration.

Taken together, rigorous scientific evidence proving efficacy, product formulation and quality of manufacturing are critical aspects to consider when evaluating a probiotic and could make the difference in achieving important health outcomes in NICU patients. Choosing probiotics from companies committed to verifying the identity and safety of their ingredients is of upmost importance. For the NICU, follow guidelines from the ADA and the CDC,^{17,21} and steer away from powdered products. Ensure your probiotic of choice is manufactured under the highest quality standards and is protected by cold supply chain to ensure viability. To make this process easier, the table below provides criteria for evaluating probiotic options for your unit.

References

- Grier, A.; Qiu, X.; Bandyopadhyay, S.; Holden-Wiltse, J.; Kessler, H.A.; Gill, A.L.; Hamilton, B.; Huyck, H.; Misra, S.; Mariani, T.J. Impact of prematurity and nutrition on the developing gut microbiome and preterm infant growth. *Microbiome* 2017, *5*, 158.
- 2. Henderickx, J.G.; Zwittink, R.D.; van Lingen, R.A.; Knol, J.; Belzer, C. The preterm gut microbiota: an inconspicuous challenge in nutritional neonatal care. *Frontiers in cellular and infection microbiology* 2019, *9*, 85.
- Athalye-Jape, G.; Patole, S. Probiotics for preterm infants– time to end all controversies. *Microbial biotechnology* 2019, 12, 249-253.
- Deshpande, G.C.; Rao, S.C.; Keil, A.D.; Patole, S.K. Evidencebased guidelines for use of probiotics in preterm neonates. *BMC medicine* 2011, 9, 92.
- Brooks, B.; Olm, M.R.; Firek, B.A.; Baker, R.; Thomas, B.C.; Morowitz, M.J.; Banfield, J.F. Strain-resolved analysis of hospital rooms and infants reveals overlap between the human and room microbiome. *Nature communications* 2017, *8*, 1-7.
- Neu, J.; Pammi, M. Necrotizing enterocolitis: The intestinal microbiome, metabolome and inflammatory mediators. In Proceedings of Seminars in Fetal and Neonatal Medicine; pp. 400-405.
- Underwood, M.A.; German, J.B.; Lebrilla, C.B.; Mills, D.A. Bifidobacterium longum subsp. infantis: champion colonizer of the infant gut. Pediatric research 2015, 77, 229.
- 8. Chichlowski, M.; Guillaume De Lartigue, J.; Raybould, H.E.; Mills, D.A. Bifidobacteria isolated from infants and cultured on human milk oligosaccharides affect intestinal epithelial function. *Journal of pediatric gastroenterology and nutrition* 2012, 55, 321.
- Underwood, M.A.; Kalanetra, K.M.; Bokulich, N.A.; Lewis, Z.T.; Mirmiran, M.; Tancredi, D.J.; Mills, D.A. A comparison of two probiotic strains of bifidobacteria in premature infants. *The Journal of pediatrics* 2013, *163*, 1585-1591. e1589.
- Frese, S.A.; Hutton, A.A.; Contreras, L.N.; Shaw, C.A.; Palumbo, M.C.; Casaburi, G.; Xu, G.; Davis, J.C.C.; Lebrilla, C.B.; Henrick, B.M., et al. Persistence of Supplemented *Bifidobacterium longum* subsp. *infantis* EVC001 in Breastfed Infants. *mSphere* 2017, 2, doi:10.1128/ mSphere.00501-17.
- Casaburi, G.; Frese, S.A. Colonization of breastfed infants by *Bifidobacterium longum* subsp. *infantis* EVC001 reduces virulence gene abundance. *Human Microbiome Journal* 2018, 9, 7-10, doi:10.1016/j.humic.2018.05.001.
- Henrick, B.M.; Chew, S.; Casaburi, G.; Brown, H.K.; Frese, S.A.; Zhou, Y.; Underwood, M.A.; Smilowitz, J.T. Colonization by *B. infantis* EVC001 modulates enteric inflammation in exclusively breastfed infants. *Pediatr Res* 2019, 10.1038/ s41390-019-0533-2, doi:10.1038/s41390-019-0533-2.
- 13. Duar, R.M.; Henrick, B.M.; Casaburi, G.; Frese, S.A. Integrating the ecosystem services framework to define dysbiosis of the breastfed infant gut: the role of *B. infantis*

and human milk oligosaccharides. *Frontiers in Nutrition* 2020, 7, 33.

- 14. Duar, R.M.; Kyle, D.; Casaburi, G. Colonization Resistance in the Infant Gut: The Role of *B. Infantis* in Reducing pH and Preventing Pathogen Growth. *High-throughput* 2020, *9*, 7.
- Karav, S.; Casaburi, G.; Frese, S.A. Reduced colonic mucin degradation in breastfed infants colonized by *Bifidobacterium longum* subsp. *infantis* EVC001. *FEBS Open Bio* 2018, 8, 1649-1657, doi:10.1002/2211-5463.12516.
- Casaburi, G.; Duar, R.M.; Vance, D.P.; Mitchell, R.; Contreras, L.; Frese, S.A.; Smilowitz, J.T.; Underwood, M.A. Early-life gut microbiome modulation reduces the abundance of antibioticresistant bacteria. *Antimicrobial Resistance & Infection Control* 2019, *8*, 1-18.
- 17. Robbins, S.T.; Meyers, R. Infant Feedings: Guidelines for Preparation of Human Milk and Formula in Health Care Facilities; American Dietetic Associati: 2011.
- Hennequin, C.; Kauffmann-Lacroix, C.; Jobert, A.; Viard, J.; Ricour, C.; Jacquemin, J.; Berche, P. Possible role of catheters in Saccharomyces boulardii fungemia. European Journal of Clinical Microbiology and Infectious Diseases 2000, 19, 16-20.
- 19. van den Akker, C.; van Goudoever, J.; Shamir, R.; Domellöf, M.; Embleton, N.; Hojsak, I.; Lapillonne, A.; Mihatsch, W.A.; Canani, R.B.; Bronsky, J. Probiotics and preterm infants: a position paper by the ESPGHAN Committee on Nutrition and the ESPGHAN Working Group for Probiotics and Prebiotics. *J Pediatr Gastroenterol Nutr* 2020, *1*.
- Lewis, Z.T.; Shani, G.; Masarweh, C.F.; Popovic, M.; Frese, S.A.; Sela, D.A.; Underwood, M.A.; Mills, D.A. Validating bifidobacterial species and subspecies identity in commercial probiotic products. *Pediatric research* 2016, *79*, 445-452.
- 21. CDC, FDA advise against powdered formula in NICUs. *AAP News* 2002, *20*, 219-219.

Intact Survival to Discharge of the Tiniest Baby in the State of Louisiana

Kate A Degatur, MD, Shabih Manzar, MD, Nitin Walyat, MD

Acknowledgements

We are deeply appreciative of the efforts of our NICU team, including our neonatal nurse practitioners, staff nurses, respiratory therapists, and other supportive staff. This could not have been possible without their help and hard work. Lastly, we would like to congratulate the mother for making it thorough. She was very supportive all along.

Summary

We are reporting here the survival of the tiniest baby in the State of Louisiana. The infant was born at 23 weeks of gestation with birth weight of 320 grams (~11 ounces). Infant had no major comorbidities at discharge. She will be followed up at our high-risk developmental clinic to assess her growth and development.

Case

The infant was born to a 35-year-old G2P0202 at a gestational age of 23-2/7 week. Mother has a past medical history of abnormal Pap smear of cervix, anemia, gestational hypertension, sickle cell anemia, and trichimoniasis. The pregnancy was complicated by pre-eclampsia with severe features, absence on ultrasound Doppler flows, sickle cell disease, and intrauterine growth restriction (IUGR). All her prenatal labs were reported to be normal. She received betamethasone, magnesium sulphate, and ceftriaxone prior to delivery. There was no history of maternal fever.

The infant was delivered by cesarean section for fetal indication. Infant was intubated for secondary apnea; the endotracheal tube placement was confirmed with CO_2 colorimeter. For heart rate less than 60 beats per minute, she was given cardiac compression and required two doses of epinephrine. After stabilizing the heart rate and saturations, she given a dose of surfactant. Apgar scores were 3 and 7 at one and five minute, respectively. Figure 1 showed her picture after birth.

NICU course (a brief synopsis)

The infant was initially placed on high frequency oscillator ventilator and umbilical catheters were placed. Few days later, she was placed on non-invasive ventilator and percutaneous

Kate A Degatur is a Pediatric Chief Resident; Shabih Manzar is an Attending Neonatologist; Nitin Walyat is a Director NICU; Department of Pediatrics, College of Medicine, Louisiana State University of Health Sciences, 1501 Kings Highway, Shreveport, LA 71130. Address correspondence to: Shabih Manzar, MD, 1501 Kings Highway, Shreveport, LA 71130, Telephone: 318-626-1623 Fax: 318-698-4305, Email: smanza@lsuhsc.edu



Figure 1. Picture after birth



Figure 2. Picture at discharge

catheter was placed. She was started on donor breast milk via nasogastric tube. Among the significant event, she developed a right-sided pneumothorax for which she received a chest tube that was removed later. She had persistent pneumatocele on the left lung, managed conservatively.



Figure 4. Schematic representation of co-morbidities

She was discharge at 4 month of life at post menstrual age of 40 weeks. The time line from conception to discharge was: Last Menstrual Period 8/17/2019, Expected Date of Delivery 5/23/2020, Date of Delivery 1/27/2020 and Date of discharge 5/27/2020. At discharge she was on 0.5 L, 100% oxygen and tolerating all feeds per oral. Figure 2 showed the picture of her at discharge.

Discussion

As per the tiniest babies registry, survival to discharge of two cases have been reported from the State of Louisiana (LA).¹ One was a 369 grams female born at 26 weeks of gestation reported in 1994 from New Orleans and the other one was 350 grams female born at 25 weeks gestation reported from Baton Rouge. Our baby, with birth weight of 320 grams, born at 23 weeks gestation at Shreveport, is therefore the tiniest surviving baby from LA. Also, per registry, she is the twentieth tiniest baby nationally.

As noted in most of the tiniest cases, the surviving infants were intrauterine growth restricted (IUGR). Our infant was also an IUGR (Figure 3). The follow up postnatal growth of weight and head circumference is depicted in the figure 3 for comparison. Among the major co-morbidities, the infant had mild-moderate bronchopulmonary dysplasia (BPD) and Stage 2, Zone 2 retinopathy of prematurity (ROP). Infant did not have any metabolic bone disease, intraventricular hemorrhage, or periventricular leukomalacia. Infant did not require any surgeries (Figure 4).

The infant will be followed up closely for growth and developmental milestones. We wish her all the best.

Reference

1 https://webapps1.healthcare.uiowa.edu/TiniestBabies/ getInfantList.aspx

The Modified Apgar Score for Premature Infants (MASPI)

Shabih Manzar, MD

Abstract

Introduction: Apgar score (AS) has been traditionally used to assess newborn physiological status at birth. It has five components: viz. heart rate, respiration, tone, reflex irritability, and color. Prematurity influences the AS. Reflex irritability and muscle tone are affected by the maturity of the infant resulting in an assignment of lower AS to preterm infants. Therefore, we devised the 3-component AS; the MASPI (Modified Apgar score for Premature Infant). To look at its feasibility, we conducted this pilot study.

Methods: The study was approved by the Louisiana State University Institutional Review Board without the need for written informed consent because the study did not involve any intervention and the data were collected without identifiers. For the 3-component AS, we eliminated the tone and reflex. AS makes no allowance for intubation or positive pressure ventilation (PPV), so we added these under respiration component. We changed the color component to pulse oximeter oxygen saturation (SpO₂) as assessment of color is not only subjective but also prone to erroneous scoring. The pilot study was conducted in the month of August 2019. Preterm birth was defined as infant born at less than 37 completed weeks of gestation per antenatal ultrasound. Infants vigorous at birth and not requiring pulse oximetry were not included in the study. All premature births were attended by the NICU team consisting of resident, nurse, respiratory therapist and neonatal nurse practitioner (NNP). NICU attending neonatologist was present for all deliveries less than 28 weeks gestation. The 3-component AS sheet was completed for each delivery attended by the principal investigator (PI). Once the data was completed from the delivery room, the PI matched the 3-component AS with the corresponding cord pH and a segment of fetal heart rate (FHR) tracing 30 minutes prior to delivery.

Results: During the study month, a total of 32 preterm infants were delivered. Pulse oximetry was performed on all infants less than 29 weeks. The data were collected on these infants that constituted 25% of all preterm births for the month.

Conclusion: Obtaining the 3-component AS was feasible in preterm infants. This score is more logical and objective. A score of 5 at 5 minutes indicates reassuring status in preterm infants.

Shabih Manzar is from the Department of Pediatrics, College of Medicine, Louisiana State University of Health Sciences, Shreveport, USA. Email: smanza@lsuhsc.edu Telephone: 318-626-1623. **Keywords:** Apgar Score, Preterm Infants, Heart rate, Saturations, Respiration

Statement of Ethics: The study was approved by the Louisiana State University Institutional Review Board without the need for written informed consent.

Acknowledgments: I would like to thank the neonatal nurse practitioners, residents, nurses, and respiratory therapist for their help in clinical care of all the preterm infants in the delivery room.

Introduction

Since the inception of Apgar score (AS) in 1952,¹ it has been used to describe clinical status of newborn infant at birth. AS measures five subjective components of cardiopulmonary status. The limitation of AS has been being recognized by the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn and American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice.² The factors that can influence AS include maternal sedation or anesthesia, congenital malformations, trauma, interobserver variability and most importantly the gestational age. A healthy preterm infant with no evidence of asphyxia may receive a low score only because of immaturity.

Prematurity influences the validity of Apgar score (AS).³ Catlin et al⁴ described the effects of gestation on AS. As components of the AS, such as reflex irritability, muscle tone, and respiratory effort, are affected by the maturity of the infant, premature infants are inevitably assigned lower AS. Therefore, there is growing need to revisit AS for this special group of infants.

Categories of Preterm Infants



Figure 1. Categories of Preterm infants.

We devised the 3-component Apgar Score for the premature infants. We eliminated the tone and reflex response from the traditional AS. Tone and reflex activity are gestational age dependent and should be assessed using Ballard score.⁵ AS makes no allowance for intubation or positive pressure ventilation (PPV), so we added these under respiration, as premature babies often need these interventions. We limited the score to three components: heart rate, respiration and oxygen saturation, as these three reflects the cardio-pulmonary status of the newborn at birth (Appendix 1). We changed the color component of AS to pulse oximeter oxygen saturation (SpO₂). Assessment of color is not only subjective but also prone to erroneous scoring. Newborn (NB) infants display acrocyanosis which may potentiate lower score on color. Also, dark skinned NBs are difficult to assess on color.

In recent years, Neonatal Resuscitation Program (NRP)⁶ has included pulse oximetry as an integral part of NB assessment at birth. Oxygen saturation obtained by pulse oximetry (SpO₂) is an objective way of assessing oxygenation than skin color assessment. Premature babies invariably get SpO₂ measurements in the delivery room. Therefore, we eliminated color and replaced it with SpO₂. The score range for SpO₂ was selected basing on timings to acquire a certain percentage of oxygen saturation, 1 minute 65% and 5 minute 85%, as described in NRP.

Materials and Methods

The study was approved by the Louisiana State University Institutional Review Board without the need for written informed consent because the study did not involve any intervention and the data were collected without identifiers. The pilot study was conducted in the month of August 2019. Preterm birth was defined as infant born at less than 37 completed weeks of gestation per antenatal ultrasound. Infants vigorous at birth and not requiring pulse oximetry were not included in the study. All premature births were attended by the NICU team consisting of resident, nurse, respiratory therapist and neonatal nurse practitioner (NNP). NICU attending neonatologist was present for all deliveries less than 28 weeks gestation. The 3-component Apgar score sheet (Appendix) was completed for each delivery attended by the principal investigator (PI).

Once the data was completed from the delivery room, the PI matched the score with the corresponding cord pH and a segment of fetal heart rate (FHR) tracing 30 minutes prior to delivery. The cord pH was noted from electronic data system on EPIC[®], Wisconsin while FHR tracings were obtained from the OBiX[®], Perinatal Data System, Clinical Computer System, Inc., Elgin.

Results

During the study month, a total of 32 preterm infants were delivered. Pulse oximetry was performed on all infants less than 29 weeks. The data were collected on these infants that constituted 25% of all preterm births for the month (Figure 1). The 3-component AS was recorded in 7 out of 8 infants (one infant was born at 23 weeks with birth weight of 310 gram and was provided comfort care). Table 1 depicts the individual details.

Due to malfunction of probe/monitor, we were unable to obtain pulse oximeter on one infant for first minute of life (case 5). None of the infant received a score of 6. One point subtracted for respiratory component (positive pressure ventilation (PPV) in the form of continuous positive airway pressure (CPAP) or intubation). We noted normal cord pH and base deficit in all cases. Fetal heart rate tracings corresponded well to the 3-component AS (normal baseline with MASPI of 4 at one-minute, case 2 and 7).

Discussion

Obtaining the 3-component AS was feasible in all cases except for one where we encountered technical difficulty with probe/ oximeter. To avoid interobserver variability, only PI obtained the score. In comparison to traditional Apgar score, we noticed the MASPI as more logical and objective. A score of 5 at 5 minutes indicates reassuring status while a score of 5 in traditional Apgar score is worrisome. As seen in example 2 (Appendix), the traditional AS could be very subjective. A score of 7 gives a false sense of reassurance. A score of 7 could be 2+2+1+1+1 (heart rate 2, respiratory score 2 although the baby is intubated and receiving PPV; color 1 as baby might not be completely pink and reflexes and tone scored 1 each, as these are subjective). Use of 3-component AS would eliminate these variations and subjectivity.

The 3-component AS is a pioneer concept as it takes into consideration the use of positive pressure ventilation (PPV), continuous positive airway pressure (CPAP) and intubation in its evaluation. Establishment of adequate ventilation soon after birth is essential for tissue oxygenation. Oxygen content and delivery on the other hand is dependent upon hemoglobin, oxygen saturation and cardiac output (CO). CO is a product of stroke volume and heart rate. Soon after birth, a heart rate of greater than 100 beats per minute and oxygen saturation of greater than 85% could be taken as a surrogate for adequate oxygen content and delivery, provided hemoglobin and stroke volume remains constant. The three components that include heart rate, respiratory efforts and SpO₂ thereby providing the crude information about cardiopulmonary status at birth. The inclusion of PPV, CPAP and intubation in MASPI further strengthens the scoring. Preterm infants due to their immature respiratory efforts mostly require PPV in first few minutes of life and should get a lower score than vigorous preterm infant of same gestation.

None of the infant in the study group received rescue dose of surfactant in the first five minutes of life. All infants were resuscitated with initial FiO₂ of 21-30% as per Neonatal Resuscitation Program (NRP)⁶ guidelines that recommend to initiate resuscitation with 21% to 30% O₂ keeping preductal SpO₂ of 60%-65% at 1 min; 65%-70% at 2nd min; 70%-75% at 3rd min; 75%-80% at 4th min and 80%-85% at the end of 5 minutes. The SpO₂ values between 5 and 10 minutes of life should be 85%-95%. Provision of supplemental oxygen soon after birth affects the SpO₂. Kumar⁷ in a recent review showed that the mean SpO₂ values were 50%, 53% and 69% at 1 min; 77%, 83% and 95% at 5 min and 92%, 92% and 98% at 10 min in 21%O₂, 40%O₂ and 100%O₂ groups respectively. Basing on the data, he concluded that the key determinant of neonatal resuscitation is the heart rate rather than oxygenation. Limiting oxygen exposure at resuscitation by starting low (21%O₂-30%O₂) and titrating the oxygen concentration upwards to target the above saturation limits in the first ten minutes after birth, not only decreases the oxygen load but may also decrease the risk for BPD.8

The strength of this pilot study was the comparison with traditional Apgar score, cord pH/BD and FHR tracing. The

Table 1. Summary of the Study Findings

Case no	Gestational Age (weeks)	Birth weight (Grams)	Apgar score 1/5 minutes	3-C, AS 1/5 minutes	Cord pH/ BD	Fetal Heart Tracing	Delivery Indication
1	28 ^{4/7} (Twin A)	930	1/7	1/4	7.30/1.9	Low Baseline, good vari- ability	SIPE CS
2	28 ^{4/7} (Twin B)	1200	6/8	4/4	7.28/1.2	Normal baseline	SIPE CS
3	24 ^{4/7}	660	5/8	3/4	7.4/0.7	Variable decelerations	PTL SVD
4	24 ^{6/7}	660	1/4/7	2/4	N/A	Variable decelerations	PTL CS (Fetal malposition)
5	27 ^{3/7}	1310	6/8	T/D	7.35/1.6	Late decelerations	PTL SVD
6	25 0/7	900	5/8	4/5	7.37/0.6	Variable decelerations	PTL CS (fetal omphalocele)
7	26 ^{6/7}	620	6/8	4/5	7.31/0.5	Normal baseline	Preeclampsia CS

3-C, AS: Three component Apgar Score

Cord gas pH (venous)/BD: Base Deficit

1/5: at one and five minutes, 10 minutes if five minutes less than 5

PTL: Preterm Labor

SVD: Spontaneous Vaginal Delivery

CS: Cesarean Section

SIPE: Superimposed Preeclampsia

N/A: Not Available; T/D: Technical Difficulty (probe not working)

weakness is the preliminary nature of the data with small sample size. A national data base with inclusion of increase number of preterm infants will further validate our findings. A score of 4-5 is reassuring, however, the need for continuous respiratory support and supplemental oxygen warrants reassessment. The other potential flaw—as presented in Appendix—is using the same value of pulse oximetry (for example 75%) at 1 and 5 minutes. A SpO₂ of 75% could be inadequate at 5 minute but excessive a 1 minute, so, we do need a specific scale of oximetry values for each observation point. Similarly, the respiratory component of the score of 0-1-2 would be very close, as PPV could be provided via endotracheal tube or thorough T-Piece or bag and mask.

Conclusion

Obtaining the 3-component AS was feasible in preterm infants. The score is more logical and objective. A score of 5 at 5 minutes indicates reassuring status.

Future

The 3-component AS holds a good future. NRP guidelines suggest ECG monitoring during resuscitation.⁹ With the availability of one touch application of NeoHeart[™] ECG pad, the heart rate component of the score would become more objective. Delayed cord clamping (DCC) has been advocated by AAP.¹⁰ The feasibility of neonatal resuscitation with an intact cord has been studied recently.¹¹ In preterm infant, with DCC and need for bedside resuscitation, the 3-component score would be a very useful tool in assessing the resuscitation and well-being of the infant.

Appendix

The 3-component Apgar Score for Premature Infants (MASPI)

	Score 0	Score 1	Score 2
Heart Rate	Absent	<100	>100
Respiration	Absent or Intubated	Gasping or Use of PPV	Good cry or Breathing spontaneously
Pulse Oximetry (SpO ₂)*	< 65%	65% - 85%	>85%

PPV- Positive Pressure Ventilation

*SpO₂ based on NRP oxygen saturation chart from NRP Textbook.⁶ The 3-component AS ranges from 0-6

Example 1

A 32-week premature infant *at birth* is noted to have a heart rate of 80, gasping and SpO_2 of 70% – the 3-component AS would be 1+1+1=3.

At five minutes, the heart rate is 140, good cry and SpO_2 is 90% – the 3-component AS would be 2+2+2 = 6.

The 3-component AS is expressed as 3 and 6 at one and five minutes, respectively.

Example 2

A 23-week premature infant *at birth* is noted to have a heart rate of 80, no respiratory efforts, intubated by 40 seconds, SpO_2 of 60% – the 3-component AS would be 1+0+0 = 1.

At *five minutes*, the heart rate of 150, she is provided PPV, SpO_2 is 90% – the 3-component AS would be 2+1+2=5.

The 3-component AS is expressed as 1 and 5 at one and five minutes respectively.

References

- 1 Apgar V. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg*. 1953;32:260–267
- 2 The Apgar Score. American Academy of Pediatrics Committee on Fetus and Newborn; American College of Obstetricians and Gynecologists Committee on Obstetric Practice. *Pediatrics*. 2015; 136:819-22. doi: 10.1542/peds.2015-2651.
- 3 Hegyi T, Carbone T, Anwar M, et al. The Apgar score and its components in the preterm infant. *Pediatrics* 1998;101:77–81
- 4 Catlin EA, Carpenter MW, Brann BS IV, et al. The Apgar score revisited: influence of gestational age. *J Pediatr* 1986;109:865–868
- 5 Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New **Ballard Score**, expanded to include extremely premature infants. *J Pediatr*. 1991; 119:417-23
- 6 American Academy of Pediatrics and American Heart Association. Textbook of Neonatal Resuscitation. 7th edition. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association; 2016
- 7 Kumar VHS. Oxygen saturations in premature infants at resuscitation. Where is the evidence? *Pediatr Dimensions*. 2016: 91-94. doi: 10.15761/PD.1000120
- 8 Vento M, Moro M, Escrig R, Arruza L, Villar G, et al. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. *Pediatrics*. 2009; 124: e439-449.
- 9 ECG monitoring in the Delivery room. *NRP instructor update*. 2018 Vol 27 no 1
- Delayed Umbilical Cord Clamping After Birth. *Pediatrics* 2017; 139 (6). doi: 10.1542/peds.2017-0957
- 11 Katheria AC, Sorkhi SR, Hassen K, Faksh A, Ghorishi Z, Poeltler D. Acceptability of Bedside Resuscitation With Intact Umbilical Cord to Clinicians and Patients' Families in the United States. *Front Pediatr.* 2018; 26 (6):100 doi:10.3389/ fped.2018.00100

Comparing Nasal High-Flow Therapy and CPAP for Newborns in Nontertiary Special Care Nurseries

Chris Campbell

When it comes to respiratory support for newborn infants, clinicians want to know what the most effective form of therapy is to use on such fragile patients.

There is nasal continuous positive airway pressure (CPAP), but there is also an alternative in nasal high-flow therapy. But when it comes to their use in nontertiary special care nurseries, the efficacy of high-flow therapy compared to CPAP is considered "unknown," according to a 2019 study out of Australia.

The study is called Nasal High-Flow Therapy for Newborn Infants in Special Care Nurseries, and it's by Dr Brett Manley and a team of researchers with the Hunter Trial Investigators in Australia and funded by the Australian National Health and Medical Research Council and Monash University.

The researchers performed a multicenter, randomized, noninferiority trial involving newborn infants (<24 hours of age; gestational age, ≥31 weeks) in special care nurseries in Australia. What they report is that "nasal high-flow therapy was not shown to be noninferior to CPAP and resulted in a significantly higher incidence of treatment failure than CPAP when used in nontertiary special care nurseries as early respiratory support for newborn infants with respiratory distress."

Background

Clinicians look to use the most noninvasive form of respiratory support with newborn infants. That means trying to avoid using mechanical ventilation through an endotracheal tube, the study says.

One issue that medical facilities in Australia deal with are the distances between difference levels of care. "In Australia, infants for whom ongoing mechanical ventilation is indicated are typically transferred to a tertiary-level neonatal intensive care unit (NICU)," the authors write. "Owing to potentially large distances between regional or rural nontertiary special care nurseries and metropolitan NICUs, a transfer may result in family disruptions, with associated psychosocial and financial costs."^{1,2}

CPAP is considered "beneficial and cost-effective," the authors write, and it is associated with a lower incidence of treatment failure or transfer to a NICU than supplemental oxygen alone.³

Chris Campbell is the Senior Editor of Neonatal Intensive Care.

"Infants with respiratory distress now routinely receive CPAP in large special care nurseries in Australia. However, CPAP may be associated with an increased incidence of pneumothorax,4 and experienced medical and nursing specialists are required in order to provide CPAP safely and effectively; this precludes its use in smaller special care nurseries in Australia⁵ and around the world. Nasal high-flow therapy is an increasingly popular alternative to CPAP for neonatal respiratory support.⁶⁻⁸ Highflow therapy delivers heated, humidified gas at flows of greater than 1 liter per minute through small binasal prongs. It has a simple interface that is easier to use and appears to be more comfortable than CPAP, and it is preferred by parents and nurses.^{9,10} We previously found that when used in tertiary-level NICUs as primary respiratory support for preterm infants born at a gestational age of 28 weeks 0 days to 36 weeks 6 days, high-flow therapy resulted in a significantly higher incidence of treatment failure than did CPAP.¹¹ However, special care nurseries have far more mature infants with fewer coexisting conditions than do NICUs; they also differ from NICUs with respect to medical and nursing experience and the ratio of providers to patients. For these reasons, highflow therapy may be well suited to special care nurseries. Since most late-preterm and term infants with respiratory distress receive treatment in special care nurseries, data to guide respiratory support in this setting are relevant to many thousands of infants in developed countries each year."12

The Study

The authors said they performed the multicenter, randomized, noninferiority High-Flow Use in NonTertiary Centres for Early Respiratory Distress (HUNTER) trial in Australian special care nurseries to "test the hypothesis that high-flow therapy is noninferior to CPAP as primary respiratory support for newborn infants with early respiratory distress."

According to the study, "Newborn infants with respiratory distress and a birth weight of at least 1200 g were assigned to treatment with either high-flow therapy or CPAP."

According to the study, "A total of 754 infants (mean gestational age, 36.9 weeks, and mean birth weight, 2909 g) were included in the primary intention-to-treat analysis. Treatment failure occurred in 78 of 381 infants (20.5%) in the high-flow group and in 38 of 373 infants (10.2%) in the CPAP group (risk difference, 10.3 percentage points; 95% confidence interval [CI], 5.2 to 15.4). In a secondary per-protocol analysis, treatment failure occurred in 49 of 339 infants (14.5%) in the high-flow group and



Used on over a quarter of a million babies globally.

The F&P Bubble CPAP System is designed to help babies make the transition to unassisted breathing. Not only is it non-invasive, it is also designed to protect the infant's lungs through world-leading humidification technology.



10



www.fphcare.com

in 27 of 338 infants (8.0%) in the CPAP group (risk difference, 6.5 percentage points; 95% CI, 1.7 to 11.2). The incidences of mechanical ventilation, transfer to a tertiary neonatal intensive care unit, and adverse events did not differ significantly between the groups."

Results

The authors found in their study that CPAP was "statistically superior" compared with the high-flow therapy. "In the intention-to-treat analysis, treatment failure within 72 hours after randomization occurred in 78 of the 381 infants (20.5%) randomly assigned to high-flow therapy and in 38 of the 373 infants (10.2%) randomly assigned to CPAP (risk difference, 10.3 percentage points; 95% confidence interval [CI], 5.2 to 15.4). High-flow therapy was therefore not shown to be noninferior and, since zero was excluded from the 95% confidence interval, CPAP was statistically superior," the study says. "In the per-protocol analysis, treatment failure within 72 hours after randomization occurred in 49 of the 339 infants (14.5%) in the high-flow group and in 27 of the 338 infants (8.0%) in the CPAP group (risk difference, 6.5 percentage points; 95% CI, 1.7 to 11.2), also indicating that high-flow therapy was not noninferior to CPAP.

"High-flow therapy was successful in approximately 80% of the infants and, with CPAP available as backup treatment when primary highflow therapy failed, there was no increase in the need for mechanical ventilation or NICU transfer or in adverse events. It is plausible that the use of backup CPAP was responsible for avoiding intubation or NICU transfer in up to 32 of 78 infants (41%) in the high-flow group with treatment failure. Our previous noninferiority studies of high-flow therapy in preterm infants also showed that the use of backup CPAP prevented intubation in almost half the infants in whom highflow treatment failure occurred.^{11,13} Infants in the high-flow group received respiratory support for a median of 5 hours longer and supplemental oxygen for a median of 4 hours longer than the infants in the CPAP group, but the clinical importance of these differences is uncertain. Interpretation of these results may vary according to the circumstances of individual treatment centers. Important considerations include the number of staff, staff expertise, and the distances to treatment centers offering mechanical ventilation. Although high-flow therapy was not noninferior, the facts that CPAP served as effective backup therapy and that many infants were successfully treated with high-flow therapy mean that these results may not preclude a role for high-flow therapy in treating some newborn infants."

Conclusion

In conclusion, in this trial with a margin of noninferiority of 10 percentage points, we found that high-flow therapy was not noninferior to CPAP. High-flow therapy resulted in a significantly higher incidence of treatment failure than CPAP when used as early respiratory support for newborn infants with respiratory distress in nontertiary special care nurseries.

References

- 1 Argus BM, Dawson JA, Wong C, Morley CJ, Davis PG. Financial costs for parents with a baby in a neonatal nursery. J Paediatr Child Health 2009; 45: 514-7.
- 2 Aagaard H, Hall EOC, Ludvigsen MS, Uhrenfeldt L, Fegran L. Parents' experiences of neonatal transfer: a meta-study of qualitative research 2000-2017. Nurs Inq 2018; 25(3): e12231.
- 3 Buckmaster AG, Arnolda G, Wright IM, Foster JP, Henderson-Smart DJ. Continuous positive airway pressure therapy for

infants with respiratory distress in non-tertiary care centers: a randomized, controlled trial. Pediatrics 2007; 120: 50918.

- 4 Ho JJ, Subramaniam P, Davis PG. Continuous distending pressure for respiratory distress in preterm infants. Cochrane Database Syst Rev 2015; 7: CD002271.
- 5 Buckmaster A. Nasal continuous positive airway pressure for respiratory distress in non-tertiary care centres: what is needed and where to from here? J Paediatr Child Health 2012; 48: 747-52.
- 6 Roberts CT, Owen LS, Manley BJ, Davis PG. High-flow support in very preterm infants in Australia and New Zealand. Arch Dis Child Fetal Neonatal Ed 2016; 101: F401-F403.
- 7 Shetty S, Sundaresan A, Hunt K, Desai P, Greenough A. Changes in the use of humidified high flow nasal cannula oxygen. Arch Dis Child Fetal Neonatal Ed 2016; 101: F371-F372.
- 8 Motojima Y, Ito M, Oka S, Uchiyama A, Tamura M, Namba F. Use of high-flow nasal cannula in neonates: nationwide survey in Japan. Pediatr Int 2016; 58: 308-10.
- 9 Roberts CT, Manley BJ, Dawson JA, Davis PG. Nursing perceptions of highflow nasal cannulae treatment for very preterm infants. J Paediatr Child Health 2014; 50: 806-10.
- 10 Klingenberg C, Pettersen M, Hansen EA, et al. Patient comfort during treatment with heated humidified high flow nasal cannulae versus nasal continuous positive airway pressure: a randomised cross-over trial. Arch Dis Child Fetal Neonatal Ed 2014; 99: F134-F137.
- 11 Roberts CT, Owen LS, Manley BJ, et al. Nasal high-flow therapy for primary respiratory support in preterm infants. N Engl J Med 2016; 375: 1142-51.
- 12 Chow SSW, Le Marsney R, Hossain S, Haslam R, Lui K. Report of the Australian and New Zealand Neonatal Network 2013. Sydney: ANZNN, 2015.
- 13 Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med 2013; 369: 1425-33.

Sodium Supplementation in Preterm Infants: Osmolality Matters

Shabih Manzar, MD

Abstract

Hyponatremia is a common problem in the preterm infants that often require oral sodium supplementation. The standard sodium chloride (NaCl) solution contains 1 mmol of NaCl/ml. Addition of 2 mmol of NaCl increases the osmolality to 700 mOsm/kg, which could be detrimental to premature gut. In this paper we suggest maximizing the breast milk fortification as the treatment of hyponatremia rather than using NaCl. If NaCl supplementation is used, it should be divided into multiple doses.

Sodium Supplementation in Preterm Infants: Osmolality Matters

Treatment of hyponatremia is essential in preterm infants. Oral supplementation is often required which affects the osmolality. The osmolality of the enteral feeds should not exceed 450 mOsm/kg.¹ Human breast milk has an osmolality of around 300 mOsm/kg, while that of full fortified human milk is around 400 mOsm/kg. Higher osmolality of enteral feedings predisposes to gut injury.² Among the treatment choices for hyponatremia, we compared the effect on osmolality of breast milk fortification and oral sodium chloride (NaCl) solution.

We present the example of a preterm infant who weighs 1500 grams. She is receiving 150 ml/kg/day of fortified breast milk (22 calories). Her serum sodium is 128 mmol/L or 128 mEq (We will use mmol and mEq interchangeability as Na and Cl are both monovalent ions). The Na deficit is about 6.3 mEq (135 – 128 × weight × 0.6), which should be replaced. Now let us compare the Na supplementation with increasing fortification versus NaCl.

Breast milk (BM) contains about 15-17 mg of Na or 0.65 to 0.74 mEq per 100 ml (mg × valence \div atomic weight, Na atomic weight = 22.99 amu). One 5 ml-vial of Enfamil[®] liquid fortifier contain about 0.3 mEq of Na. To make a 22 or 24 calorie formula, 1 or 2 vials are added in 50 and 25 ml of BM, respectively. As per the company information, the sodium content per 100 ml of 22 calorie fortified BM is about 1.6 mEq, while the 100 ml of 24 calorie fortified BM contains about 2.0 mEq of Na. The osmolality does not alter significantly by adding extra fortifier—in fact, it remains about 36 mOsm/kg for 22 and 24 calories. Earlier Steele et al,³ had shown similar results. Now let us look at the oral NaCl solution. The standard solution contains

Shabih Manzar is an Associate Professor, Department of Pediatrics, School of Medicine, Louisiana State University Health Sciences Center. Telephone: 318-626-1623, Fax: 318-698-4305, Email: smanza@lsuhsc.edu.

1 mmol on NaCl/ ml, that is 58.44 mg, out of which 22.99 is Na. If we supplement the infant with 1 mEq/kg/day of oral NaCl, the dose would be 1.5 mmol (1mEq \times 1.5 kg), which will increase the osmolality significantly (Figure). If we divide the dose into



Figure 1. Graph showing the effect of NaCl on osmolality

which is 2.4 mEq/kg/day. To bring the serum Na up from 128 mmol to 135 mmol/L, the better option would be to increase the fortification to 24 calories, which will increase the Na intake to 4.5 mEq Na (3 mEq/kg/day) rather than adding oral NaCl solution supplement. If oral NaCl is to be used, it should be divided into 4-6 doses to decrease the osmolality.

References

- Srinivasan L, Bokiniec R, King C, Weaver G, Edwards AD. Increased osmolality of breast milk with therapeutic additives. Arch Dis Child Fetal Neonatal Ed. 2004; 89: F514-7.
- 2 Goldblum OM, Holzman IR, Fisher SE. Intragastric feeding in the neonatal dog. Its effect on intestinal osmolality. Am J Dis Child. 1981 Jul; 135(7):631-3.
- 3 Steele JR, Meskell RJ, Foy J, Garner AE. Determining the osmolality of over-concentrated and supplemented infant formulas. J Hum Nutr Diet. 2013;26(1):32-37. doi:10.1111/j.1365-277X.2012. 01286.x

Supplementary References

- https://www.enfamil.com/products/enfamil-human-milkfortifier-acidified-liquid
- http://neofax.micromedexsolutions.com/neofax/WebHelp/ Content/Enteral%20Formula/Using_Enteral_Formula.htm

Na per day,

Comparing the Efficacy of Three Positive Pressure Ventilation Devices Used by Medical Students on a Neonatal Resuscitation Simulator

Sergio Agudelo Pérez, María José Maldonado, Oscar Gamboa, Ana María Triana, Mauricio Agudelo & Orlando Clavijo Auza

Background: Positive pressure ventilation is the most frequently used intervention for the resuscitation of newborns. It should guarantee pressures and volumes in safe and effective ranges to establish appropriate pulmonary ventilation and prevent pulmonary injury. The objective of this study was to compare the efficacy of ventilation of three manual PPV devices used on a neonatal resuscitation simulator by medical students.

Methods: An experimental two-factor (device and student) study design with several replications of the experiment (a ventilation cycle performed by a student in one minute with each device) was used. Students in their last year of school of medicine at the Universidad de La Sabana were included. The data were collected using a pressure sensor. The peak inspiratory pressure (PIP), the positive end-expiratory pressure (PEEP) by ventilation, and the respiratory rate per minute were recorded for each participant. Pressure in safety range was used as efficacy endpoint.

Results: 30 students were included in the study. With the selfinflating bag (SIB) and the flow-inflating bag, a higher percentage of PIP and PEEP was found to be ineffective. No device exceeded the maximum PIP. The use of the disposable Neo-Tee[®] T-piece resuscitator resulted in PIP within the safety range 3.20 times more frequently and in PEEP within the safety range 963.8 times more frequently compared with the SIB.

Conclusions: The disposable Neo-Tee[®] T-piece resuscitator was found to be the most efficacy device for manual ventilation, when used by inexperienced personnel for neonatal resuscitation.

Introduction

Approximately 10% of newborns require neonatal resuscitation at birth; positive pressure ventilation (PPV) is the most common intervention used for newborn resuscitation.^{1,2} During PPV, it is recommended to use a peak inspiratory pressure (PIP) between 20 cm and 30 cm H₂O. Appropriate PIP establishes the functional residual capacity and generates reflexes that stimulate the onset of spontaneous breathing.¹ The application of PIP lower than these values has been associated with nonresponse to neonatal resuscitation manoeuvres.^{3,4} It is recommended a positive end-expiratory pressure (PEEP) of between 5 cm and 8 cm H₂O should be applied.⁵ It has been

The authors are with the School of Medicine, Universidad de La Sabana, Campus del Puente del Común, Chia, Cundinamarca, Colombia. reported that this PEEP improves the clinical response to the resuscitation manoeuvres, reduces the need for endotracheal intubation, improves the response to the surfactant, and decreases pulmonary injury and atelectotrauma.⁶ Excessive volume and/ or pressure induce pulmonary injury, especially in the premature baby.^{1,7} Therefore, VPP should be with pressures within the ranges of safety for establishing appropriate pulmonary ventilation while limiting pulmonary injury. The operator of the device must quickly and appropriately adjust the pressure and rate to the recommended ranges.¹

Different devices are available to perform positive pressure ventilation to the newborn in the delivery room. The T-piece resuscitator is designed to supply respirations with a previously adjusted PIP and PEEP. Most studies with T-piece resuscitator have been performed with the Neopuff[™], and it seems to be the most effective and safest device.⁷ The T-piece resuscitator is currently available in a disposable (Neo-Tee®). The availability of Neopuff[™] in health centers of 1 and 2 level with limited economic resources is null. The self-inflating bag (SIB) is the most frequently used device, and its effectiveness depends on the operator's profession and experience.^{8,9} In studies using neonatal simulators, the SIB is the least safe, effective, and reliable device in terms of pressure and volume.¹⁰⁻¹² The flowinflating bag its safety and effectiveness is better than that of the SIB.13 The World Health Organization (WHO) recommends the use of the SIB in settings with limited economic resources, recognizing the need to establish neonatal resuscitation guidelines for resource-limited settings where the presence of specialized health personnel and technical resources may be insufficient to meet the International Liaison Committee on Resuscitation (ILCOR) recommendations.14

The pressures and volumes generated by the device are operator dependent and variable, primarily when non-specialized or inexperienced personnel operate the device. In the Colombian context, the availability of specialized personnel or with experience in the care of newborns is limited in low- and medium-complexity health centers. In Colombia, trainees in their last year of medical school are the trained professionals who provide first- and second-level care health.

The objective of this study was to compare the efficacy, defined as the pressures generated for the PIP and PEEP in safety ranges, of three positive pressure ventilation devices to be used by trainees in the last year of medical school on a neonatal resuscitation simulator.

Methods

The Ethics Committee of the Universidad de La Sabana approved the study protocol. The student population signed their informed consent to participate.

An experimental two-factor study design with several replications of the experiment (a ventilation cycle performed by a student in one minute with one device) was applied. The first factor was related to the type of device, and the second was related to the student. Medical students from the Universidad de La Sabana in their last year of school and in their internship year in the Clínica Universidad de La Sabana were included.

The following devices were used: 1. AMBU[®] 220 ml SIB with PEEP regulator valve; 2. Flow-inflating bag (Mercury Medical 0.5 liter Hyperinflation System with pressure gauge); 3. Disposable T-piece resuscitator (Mercury Medical Neo-Tee[®]). A Merlin Medical triangular facemask with a padded edge and of an appropriate size for the simulator was used for all three devices. The neonatal resuscitation simulator that was employed was a PEDI[®] S320 model.

The data collection was performed by a pressure sensor with a flow signal acquisition system to detect the air insufflated into the neonatal simulator. The pressure sensor was placed at the site designed for the manometer of the device and connected to the pressure transducer. The system was composed of an Autonics TK45 reference control with a digital display and was configured to acquire the pressure transmitter signal of a 0-2 psi pressure gauge, ZHYQ model PT124B-216. Using an RS-485-to–USB communication interface, the data were sent to a Windows XP computer platform and were saved in a flat file.



Figure 1(a). Median PIP for the three devices. The red dot lines indicate maximum and minimum limits for the PIP.



Figure 1(b). Median PEEP for the three devices. The red dot lines indicate maximum and minimum limits for the PEEP.

Table 1. Multilevel analysis of PIP and PEEP.				
Variable	OR	95% CI		
PIP				
Self-inflation bag	1	1		
Flow-inflation bag	1.20	(0.95 to 1.51)		
Disposable T-piece resuscitator	3.19	(2.49 to 4.09)		
PEEP				
Self-inflation bag	1	1		
Flow-inflation bag	39.98	(14.58 to 109.62)		
Disposable T-piece resuscitator	963.82	(285.71 to 3251.38)		

Autonics DAQMaster software was used to acquire the data for subsequent statistical analysis.

devices were connected to a gas source. For each participant, the PIP and PEEP for ventilation and the respiratory rate per minute was recorded for each device used.

Design

Prior to the start of the study, the students took the Neonatal Resuscitation Programme course taught by certified instructors. The course consisted of two parts. The first theoretical and selfstudy by the students. The second practical part, where special emphasis was placed on the proper mask seal and the proper use of VPP device to ensure that this was not a factor influencing the results. Before to the data collection, the participants had time to practice with each device under the supervision of instructor, who reviewed the proper technique with a checklist. Once participant demonstrated correct use of the devices, the data collection phase began. Each student used the three devices to perform a cycle of PPV for one minute on the simulator with the mask device. They were asked to perform ventilations with a PIP of 25 cm H₂O and a PEEP of 5 cm H₂O at a rate 40 times per minute. A random list in Excel used to determine both the sequence of the operators and the sequence of the devices that each operator used. Each device had an analogue pressure gauge that the participants could observe while they provided ventilations. The SIB was used with the pressure release valve opened and with the PEEP regulator valve fitted. The three

Sample size estimation

A sample size of 30 individuals was estimated for an analysis of variance for repeated measures using the following parameters:¹⁵ significance level (α) 0.05, power (β) 0.8, mean effect size (intraclass correlation coefficient, ICC) 0.35, correlation between measures 0.5, number of repetitions (K) 3.

Information processing and statistical analysis

Descriptive analyses were performed by calculating median for the PIP, PEEP, and respiratory rate per student per device type. The results are presented in graphs. Two dichotomous variables were established—one for PIP, and one for PEEP; these variables received a value of one when PIP or PEEP were within the safety range. The safety range for PIP was defined as a value between 20 cm and 40 cm H_2O ; for PEEP, the value was between 5 cm and 8 cm H2O. To determine the effectiveness of the devices for achieving appropriate ventilation, two multilevel analysis models for dichotomous variables were constructed with a random slope (device) and intercept (student): one for PIP and another for PEEP. The first level of the model



Figure 2. Respiratory rate for the three devices by student. The red dot lines indicate respiratory rate indicated.

Table 2. Summary of comparative studies including the positive pressure ventilation devices.					
Study	Subjects	Devices	Intervention	Main Findings	
Hawkes et al. (2012) [9]	Professional work in neonatal intensive care unit.	NEOPUFF Others	Quality review. Emphasis on the evidence comparing the NEOPUFF to other manual ventilation devices in neonatal resuscitation. In newborn infants and simulator Measure: PIP, PEEP, Tidal Volume, Mask Leak	T-piece resuscitator (NEOPUFF) include the delivery of inflating pressures closer to predetermined target pressures with least variation, the ability to provide prolonged inflation breaths and more consistent tidal volumes.	
Finer et al. (2001), [10]	Neonatal Nurses Neonatal Nurse practitioners Neonatal staff Fellows Paediatric residents Neonatal Respiratory therapists	Disposable anesthesia type bag Jackson-Rees (JR) type anesthesia bag Neopuff™	Use neonatal simulator to evaluate the use of three devices. Recorded ventilating Pressure: PIP PEEP	Neopuff [™] most consistently delivered pressures within the required ranges. PIP and the PEEP were significantly higher when respiratory therapists used the flow-inflation bag	
Bennet et al. (2005), [13]	Neonatologists Neonatal respiratory therapists Neonatal fellows Pediatrician Pediatric residents Neonatal nurse practitioners Neonatal nurses	Neopuff™ Flow-inflation bag. Self-Inflating Bag	Use neonatal simulator and using a continuous pressure recording system. Evaluated the ability to deliver a consistent PIP of 20 or 40 cm H ₂ O and a PEEP of 5 cm H ₂ O during 30 s of ventilation.	Most accurate and reliable device for delivering pressure within safe ranges was the Neopuff [™] , which had a maximum PIP that was lower than the other devices, while the SIB had a lower PEEP value compared with the other devices	
Roehr et al. (2010), [12]	Pediatricians Obstetricians Anesthesiologist Neonatal nurses Midwives	self-inflating bag T-piece resuscitator (Neopuff™)	Use premature neonatal simulator and recorded pressure measurement: PIP Vt	SIB generated more PIP and tidal volume (Vt) than the Neopuff [™] . Professional experience had no significant impact on the level and the variability of Vt or PIP provided.	
Bassani et al. (2012), [17]	Professional work in neonatal intensive care: Physicians Resident physicians Physiotherapists Nurses Nursing technicians	Self-inflating bag	Use a test lung (adjusted to simulate the lungs of an intubated term newborn. Use 5 different handling techniques. Evaluated whether the manual technique and the user's profession affected positive pressure ventilation in terms of PIP, Vt, and ventilatory frequency.	Profession had an influence on the Vt and respiratory rate. Therapists delivered significantly greater values for these parameters than the other professionals did. Most of the professionals delivered pressures and volumes that exceeded recommendations, combined with insufficient respiratory rates.	
Szyld et al. (2012), [18]	Professional work in neonatal intensive care: divided in two groups according to experience: Group 1 (experts): professionals with less than 5 years in practice. Group 2: (Beginners) Included professionals with less than 5 years of experience.	Self-inflating bag Neopuff™	Neonatal reanimation simulator. Evaluated the precision of the pressure administered by professionals and its relationship with the operator's experience.	Significant differences in the respiratory rate, which was higher than required when ventilation was provided by the inexperienced staff. The T-piece provided lower PIP while both SIB, higher than the target. Both SIB and novice participants were associated with higher VR.	
Prado et al. (2013), [19]	Trained and non- trained medical professionals were studied.	Self-inflating bag T-piece resuscitator Babypuff™	Compared the influence of professional experience and training on the variability and effectiveness of manual ventilation. Ability to perform a sustained inflation Lung. Use intubated mannequin and recorded delivered pressure: PIP and PEEP and Vt.	No influence of professional training on the effectiveness of the ventilation.	

represented the repetitions, and the second level represented the students. The dependent variable was whether PIP or PEEP was within the safety range for each repetition. The model used the formula $Y_{ij}=(B_0+a_j)+(B+b_j)*x_{ij}+e_{ij}$, where Yij is the dichotomous variable (PIP or PEEP) for repetition i of student j; B0 and B are the intercept and the average effect of the device, respectively; xij is the predictor variable (type of device); aj is the effect of the student on the intercept; and bj is the effect of the student on the slope. The information was processed using the STATA[®] program.

Results

Figure 1A and 1B shows the median for PIP and PEEP. With the SIB and the flow-inflation bag, ineffective pressure occurred a higher percentage of times. None of the devices resulted in excessive pressure.

The multilevel analysis of PIP showed the flow-inflation bag resulted in ventilation within the safety rage 1.20 times more frequently than the SIB, which was not a significant; in comparison, the disposable T-piece resuscitator was 3.20 times more frequently within the safety range than the SIB was. A comparison of the confidence interval between the flow-inflation bag and the T-piece resuscitator showed that the T-piece resuscitator did not include the interval of the flow-inflation bag and therefore was superior (Table 1).

The multilevel analysis of PEEP showed that PEEP was 40 times more frequently in the safety range with the flow-inflation bag compared with the SIB and 963.8 times more frequently in the safety range with the disposable T-piece resuscitator than with the SIB. A comparison of the confidence intervals of the flow-inflation bag and the T-piece resuscitator showed that the interval of the latter did not include the interval of the flow-inflation bag and therefore was superior (Table 1). No student met the required 40 breaths per minute (Figure 2).

Discussion

We evaluated trainees in their last year of medical school and who will be performing their social service practice in level I and II health care centers in our country. Our study found that the disposable T-piece resuscitator (Neo-Tee®) delivered pressures (PIP and PEEP) within the range of safety more frequently than the other devices tested, and the results were statistically significant. These findings suggest that the use of this device by non-expert trained personnel can improve respiratory assistance for the neonate and can be a possible cost-effective alternative in level I and II health care settings with limited economic resources.

Studies using neonatal simulators have been conducted to examine the safety and effectiveness of different devices when used by personnel with experience and expertise in neonatal resuscitation at high complexity hospitals with neonatal units. Neopuff[™] appears to be superior over the other devices in terms of the consistency and safety of pressure in simulation scenarios. Table 2 summarizes the studies comparing positive pressure devices. We found no studies comparing the use of these three devices in trainees.

Unlike these studies, which generally included neonatal care unit staff and with expertise in neonatal resuscitation, we evaluated the devices when used by students with no experience in neonatal care. Similar to these studies, we found that the SIB did not generate PEEP in reliable ranges, even with the use of the PEEP valve. However, we did not find excessive PIP at hazardous levels with any of the devices evaluated, unlike the studies mentioned above. The studies have not included alternatives to Neopuff[™] such as the disposable T-piece resuscitator. We found, that the disposable T-piece resuscitator (Neo-Tee[®]) was the safest and most effective device in terms of pressures compared with the SIB and the flow-inflation bag.

In our study, as in some of the mentioned, we found problems with the required respiratory rate; regardless of the device used, none of the evaluated practitioners administered frequencies in the required ranges, and all rates were well below recommendations. The literature indicates that the user's profession, experience, and expertise influence the respiratory rate administered during neonatal resuscitation. Morley and his team¹⁶ found that PEEP in self-inflating resuscitation bag with PEEP valve varied in relation to the respiratory rate. At a respiratory rate of fewer than 20 per minute, PEEP decreased more frequently than when respirations were administered at 60 times per minute since the pressure drops over time. The PEEP delivered was unrelated to the gas flow into the device. Dawson and his team¹⁷ when comparing SIB, flow-inflating bag and T-piece resuscitator, found that each device was able to provide PEEP, but this in relation to the correct use of the device; but the device that provide most accurate PEEP was the T-piece resiscitator. Given the findings of our study and others with respect to operator experience, we recommend strengthening the training of first-level personnel in the use of the devices, particularly in terms of the frequency with which the respirations are administered, to improve the PPV technique.

One limitation of the study was that it did not include the Neopuff[™] device, which according to the literature seems to be the safest and most reliable option in neonatal resuscitation in the delivery room. With the methodology proposed in the present study it was possible to accurately measure the quality of the ventilation pressures of the evaluated devices. Measured pressures for the disposable T-piece resuscitator are similar to those measured in the Neopuff[™] studies. In addition, the Neopuff[™] for the 1 and 2 level care centers is not available in our environment and therefore was beyond the scope of the study, which was to compare available devices in first-level care. Adapting neonatal resuscitation recommendations to settings with limited resources, especially in poor countries, where approximately 90% of neonatal deaths occur, would decrease neonatal morbidity and mortality.

Conclusion

The Neo-Tee® disposable T-piece resuscitator is safe and effective for the ventilation of newborns when it is used by trainees who are inexperienced in handling critical newborns and are evaluated using a simulator; and can be used as an alternative ventilation device in first- and second-level settings. The respiratory rate achieved is related to the personnel's training and expertise. The adaptation of the ILCOR recommendations to the contexts of countries with limited resources should be continued as a cost-effective measure in neonatal care.

Acknowledgements

We gratefully acknowledge the assistance of the medical students, the paediatrics service, and the Clínica Universidad de La Sabana.

What is already known on this topic?

Approximately 10% of newborns require neonatal resuscitation at birth; positive pressure ventilation (PPV) is the most common intervention used for newborn resuscitation.

NeopuffTM it the most effective and safest device. The availability of NeopuffTM in health centers of 1 and 2 levels with limited economic resources is null.

The self-inflating bag is the most frequently used device, and its effectiveness depends on the operator's profession and experience.

What this study adds

Disposable T-piece resuscitator delivered pressures (PIP and PEEP) within the range of safety.

The use of this device by non-expert trained personnel can improve respiratory assistance for the neonate.

Can be a possible cost-effective alternative in level I and II health care settings with limited economic resources.

References

- 1 Polin RA, Fox WW, Abman SH. Fetal and Neonatal Physiology. Fourth Edition Vol 1. Philadelphia: Elsevier Saunders (2011).
- 2 Wyckoff MH, Aziz K, Escobedo MB, et al. Neonatal Resuscitation 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation.132 (18), 543-560 (2015).
- 3 Perlman JM, Risser R. Cardiopulmonary resuscitation in the delivery room: Associated clinical events. Arch Pediatr Adolesc Med 149(1), 20-25 (1995).
- 4 Carbine DN, Finer NN, Knodel E, et al. Video Recording as a Means of Evaluating Neonatal Resuscitation Performance. Pediatrics 106(4), 654-658 (2000).
- 5 Kattwinkel J, Perlman JM, Aziz K, et al. Neonatal Resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 122(18), 909-919 (2010).
- 6 Hooper S, Pas TA, Lewis R, et al. Establishing functional residual capacity at birth. Neo Reviews 11(9), 474-483 (2010).
- 7 Leone TA, Finer NN, Rich W. Delivery Room Respiratory Management of the Term and Preterm Infant. Adv Respir Care Newborn 39(3),431-440 (2012).
- 8 Augustine JA, Seidel DR, McCabe JB. Ventilation performance using a self-inflating anesthesia bag: Effect of operator characteristics. Am J Emerg Med 5(4),267-270 (1987).
- 9 Finer NN, Rich W, Craft A, et al. Comparison of methods of bag and mask ventilation for neonatal resuscitation. Resuscitation 49(3),299-305 (2001).
- 10 Hussey SG, Ryan CA, Murphy BP. Comparison of three manual ventilation devices using an intubated mannequin. Arch Dis Child Fetal Neonatal Ed 89(6), 490-493 (2004).
- 11 Roehr CC, Kelm M, Fischer HS, et al. Manual ventilation devices in neonatal resuscitation: Tidal volume and positive pressure-provision. Resuscitation 81(2),202-205 (2010).
- 12 Bennett S, Finer NN, Rich W, et al. A comparison of three neonatal resuscitation devices. Resuscitation 67(1), 113-118 (2005).
- 13 Kanter RK. EValuation of mask-bag ventilation in resuscitation of infants. Am J Dis Child 141(7), 761-763

(1987).

- 14 http://www.who.int/maternal_child_adolescent/documents/ basic_newborn_resuscitation/en/
- 15 Barcikowski RS, Robey RR. Sample Size Selection in Single Group Repeated Measures Analysis (1985).
- 16 Morley CJ, Dawson JA, Stewart MJ, et al. The effect of a PEEP valve on a Laerdal neonatal self-inflating resuscitation bag. J Paediatr Child Health 46(1-2),51-56 (2010).
- 17 Dawson JA, Gerber A, Kamlin COF, et al. Providing PEEP during neonatal resuscitation: Which device is best? J Paediatr Child Health 47(10), 698-703 (2011).

Association Between Admission Hypothermia And Outcomes In Very Low Birth Weight Infants In China

Yong-hui Yu^{1*}, Li Wang¹, Lei Huang², Li-ling Wang³, Xiao-yang Huang⁴, Xiu-fang Fan⁵, Yan-jie Ding⁶, Cheng-yuan Zhang⁷, Qiang Liu⁸, Ai-rong Sun⁹, Yue-hua Zhao¹⁰, Guo Yao¹¹, Cong Li¹², Xiu-xiang Liu¹³, Jing-cai Wu¹⁴, Zhenying Yang¹⁵, Tong Chen¹⁶, Xue-yun Ren¹⁷, Jing Li¹⁸, Mei-rong Bi¹⁹, Fu-dong Peng²⁰, Min Geng²¹, Bing-ping Qiu²², Ri-ming Zhao²³, Shi-ping Niu²⁴, Ren-xia Zhu²⁵, Yao Chen²⁶, Yan-ling Gao²⁷ and Li-ping Deng²⁸

Abstract

Background: The objective of this prospective, multicentre, observational cohort study was to evaluate the association between admission hypothermia and neonatal outcomes in very low-birth weight (VLBW) infants in multiple neonatal intensive care units (NICUs) in China.

Methods: Since January 1, 2018, a neonatal homogeneous cooperative research platform-Shandong Neonatal Network (SNN) has been established. The platform collects clinical data in a prospective manner on preterm infants with birth weights (BWs) < 1500 g and gestational ages (GAs) < 34 weeks born in 28 NICUs in Shandong Province. These infants were divided into normothermia, mild or moderate/severe hypothermia groups according to the World Health Organization (WHO) classifications of hypothermia. Associations between outcomes and hypothermia were tested in a bivariate analysis, followed by a logistic regression analysis.

Results: A total of 1247 VLBW infants were included in this analysis, of which 1100 infants (88.2%) were included in the hypothermia group, 554 infants (44.4%) in the mild hypothermia group and 546 infants (43.8%) in the moderate/ severe hypothermia group. Small for gestational age (SGA), caesarean section, a low Apgar score at 5 min and intubation in the delivery room (DR) were related to admission hypothermia (AH). Mortality was the lowest when their admission temperature was 36.5 ~ 37.5 °C, and after adjustment for maternal and infant characteristics, mortality was significantly associated with AH. Compared with infants with normothermia (36.5 ~ 37.5 °C), the adjusted ORs of all deaths increased to 4.148 (95% CI 1.505-11.437) and 1.806 (95% CI 0.651-5.009) for infants with moderate/severe hypothermia and mild hypothermia, respectively. AH was also associated with a high likelihood of respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), and late-onset neonatal sepsis (LOS).

Conclusions: AH is still very high in VLBW infants in NICUs in China. SGA, caesarean section, a low Apgar score at 5 min and intubation in the DR were associated with increased odds of hypothermia. Moderate/severe hypothermia was associated with mortality and poor outcomes, such as RDS, IVH, LOS.

¹Department of Neonatology, Shandong Provincial Hospital Affiliated to Shandong First Medical University and Shandong University, No. 234, Jingwu Road, Huai Yin District, Jinan 250021, Shandong, China. Full list of author information is available at the end of the article.

Background

Preterm infants have difficulty maintaining body temperature after birth due to a high surface area-to-mass ratio, little subcutaneous adipose tissue, a thin stratum corneum and inadequate brown fat, especially among very low-birth weight (VLBW) infants.^{1,2}

Neonatal hypothermia (temperature below 36.5 °C) is a vital risk factor for neonatal mortality and morbidity in preterm infants.³⁻⁵ Laptook et al⁶ reported that hypothermia increased the risk of mortality by 28% for every 1 °C drop in body temperature. In a multicentre study, Caldas et al⁷ reported that admission hypothermia (AH) was significantly associated with early neonatal death regardless of hospital performance. In Korea, Lee et al⁸ reported that 74.1% of 5860 VLBW preterm infants with a gestational age (GA) < 33 weeks and hypothermia were admitted to neonatal intensive care units (NICUs), which was associated with high mortality and several important morbidities. Wilson et al⁹ reported that hypothermia occurred in 53.4% of 5697 infants born at a GA < 32 weeks in a population-based study with samples from 11 European countries and that admission hypothermia (AH) after very preterm birth was a significant problem associated with an increased risk of early and late neonatal death. In an analysis of risks associated with AH in preterm infants in the Canadian Neonatal Network, Lyu et al¹⁰ showed that both hypothermia and hyperthermia were associated with increased risks of adverse outcomes. However, in China, clinical data on AH in premature infants are scarce, and most of the studies include small samples from a single centre.¹¹

The aim of this study was to examine the association between AH and neonatal outcomes in VLBW infants in multiple NICUs in China.

Methods

This prospective, multicentre, observational cohort study was carried out over a period of 12 months, from January 1, 2018, to December 31, 2018, in 28 NICUs in Shandong Province, China. The 28 recruited hospitals included 14 teaching hospitals and 14 non-teaching hospitals, with averages of 59 and 40 beds in the neonatology departments and NICUs, respectively.

Data quality and control

Since January 1, 2018, a homogeneous neonatal cooperative research platform Shandong Neonatal Network (SNN) has been implemented. The admission temperatures, mortality

incidence and morbidity data of VLBW infants born in 28 level II and level III NICUs in Shandong Province were collected prospectively. The database provided maternal, delivery, and neonatal data until the first NICU discharge, and the data were collected by trained staff using a standardized operating procedure.^{12,13} The admission temperature was defined as the infant's axillary or rectal temperature measured at admission to the NICU within 1 h after birth, in accordance with local routines. Axillary temperature tested with mercury thermometer on admission was the most common method used in NICUs, accounting for 79.2%. However, rectal temperature tested with mercury thermometer was rare, accounting for 4.2%. Body temperature mostly was measured under the arm for 5 min accompanying by nurses with mercury thermometer (45.8%).¹⁴ The entered data were analysed for statistical adjustment for possible confounders in a multivariate analysis.

Population

Study population

The study population included all infants with a birth weight (BW) less than 1500 g and GA less than 34 weeks who were admitted to the NICUs of 28 level II or level III hospitals in China from January 1, 2018, to December 31, 2018, and their mothers.

Exclusion criteria

Infants who were out-born, who had redirection of intensive care¹⁵ including congenital abnormalities and who were missing temperature data were excluded.

Study variables

Dependent variable

The dependent variable was hypothermia.

Independent variables

The following perinatal variables were considered independent variables: gestational diabetes mellitus (GDM), maternal hypertension, premature rupture of membranes (PROM) (> 18 h), antenatal use of full course of steroid, and caesarean section. The following neonatal variables were considered independent variables: multiple births (twins or more), sex, GA, BW, small for gestational age (SGA) (defined as a BW lower than the 10th percentile of the intrauterine growth curve of 2013-Fenton), Apgar scores at 1 min and 5 min, and intubation in the delivery room. Poor outcomes included respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), necrotizing enterocolitis (NEC), late-onset neonatal sepsis (LOS), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and extrauterine growth retardation (EUGR).

Operational definitions

Hypothermia was defined as an axillary temperature of less than 36.5 °C, according to the WHO.³ Cold stress or mild hypothermia was defined as a temperature 36.0 °C to 36.4 °C, moderate hypothermia was defined as a temperature 32.0 °C to 35.9 °C, and severe hypothermia was defined as a temperature below 32 °C.

Normothermia was defined as a body temperature between 36.5 $^{\rm o}{\rm C}$ to 37.5 $^{\rm o}{\rm C}.$

Redirection of intensive care was defined as limited care (not intensifying medical treatment) or withdrawal of care. 15

The diagnostic criteria of RDS, IVH, NEC and ROP were according to the *Practice of Neonatology (5th Edition)*.¹⁶

LOS was diagnosed by the clinical manifestations of systemic infection after 3 days of birth and abnormal values for 2 or more of the following non-specific infection indicators: WBC < 5 × 10⁹/L or WBC > 20 × 10⁹/L; C-reactive protein (CRP) ≥ 10 mg/L; platelets (PLTs) ≤ 100 × 10⁹/L; and procalcitonin (PCT) > 2 ng/ml. If the blood or cerebrospinal fluid culture was positive, then culture-positive septicaemia was diagnosed.¹⁷

BPD was defined as the requirement of any inspired fraction oxygen above 0.21 at the corrected GA of 36 weeks.¹⁸ EUGR was defined according to the growth curve of 2013-Fenton, when BW, head circumference and body length were all <P10 at discharge or at a corrected GA of 36 weeks.¹⁹

Statistical analysis

Demographic data are expressed as medians [M (Q_{l_i}, Q_{3})] or percentages. In the univariate analysis, we used the Kruskal-Wallis test or chi-square test. We then evaluated the odds ratios (ORs) according to admission temperature using a multivariate logistic regression analysis, with adjustment for factors that had a P < 0.1 in the univariate analysis. We also estimated curves for mortality according to the admission temperature. P < 0.05 was considered statistically significant. The statistical analyses were conducted using SPSS v 25.0 (SPSS Inc., Chicago, Illinois).

Results

A total of 1582 in-born infants with a BW < 1500 g and GA < 34 weeks were enrolled in the study on their day of birth; 93 infants were excluded because they were outborn. Additionally, 150 infants with redirection of intensive care and 92 infants with missing temperature data were excluded. The remaining 1247 infants were included in this analysis (Fig. 1). The final cohort had a median BW and GA of 1250 (480-1499) g and 29 (24.1-33.9) weeks, respectively.

Hypothermia

The mean (SD) admission temperature was 35.8 °C (0.6 °C), ranging from 32 °C to 37.5 °C. Only 11.8% of the study population had an admission temperature in the WHO recommended range of 36.5 °C to 37.5 °C. A total of 88.2% of infants had an admission temperature lower than 36.5 °C, including 554 infants (44.4%) in the mild hypothermia group and 546 infants (43.8%) in the moderate/severe hypothermia group. No hyperthermic (> 37.5 °C) infants were identified. The distributions of infants across the range of admission temperatures are reported in Fig. 2.

Association between hypothermia and risk factors and mortality and major morbidity in VLBW infants

The univariate analysis was found that the risk factors including BW, SGA, caesarean section, antenatal steroid use, a low 5-min Apgar score, intubation in the DR and maternal hypertension and the adverse outcomes including RDS, IVH, LOS and EUGR were associated with hypothermia (Table 1). After adjusting for risk factors using logistic regression, SGA, caesarean section, antenatal steroid use, intubation in the DR, a low 5-min Apgar score, RDS, IVH and LOS remained significantly associated with moderate/severe hypothermia (Tables 2 and 3).

The adjusted ORs of death increased to 1.806 (95% CI 0.651 - 5.009) and 4.148 (95% CI 1.505 - 11.437) for infants with mild





Fig. 1 Flow diagram of the study population. A total of 1582 in-born infants with a BW < 1500 g and GA < 34 weeks were enrolled in the study on their day of birth; 93 infants were excluded because they were out-born. Additionally, 150 infants with redirection of intensive care and 92 infants with missing temperature data were excluded. The remaining 1247 infants were included in this analysis, of which 1100 infants (88.2%) were included in the hypothermia group, 554 infants (44.4%) in the mild hypothermia group and 546 infants (43.8%) in the moderate/severe hypothermia group



Fig. 2 Temperature distribution of VLBW infants. Only 11.8% of the study population had an admission temperature in the WHO recommended range of 36.5 °C to 37.5 °C. A total of 88.2% of infants had an admission temperature lower than 36.5 °C, including 554 infants (44.4%) in the mild hypothermia group and 546 infants (43.8%) in the moderate/severe hypothermia group. No hyperthermic (> 37.5 °C) infants were identified

hypothermia and moderate/severe hypothermia at NICU admission, respectively. The analysis of the correlation between admission temperature and death showed that the relationship was not a linear but a quadratic function equation and was statistically significant (P < 0.05) (Fig. 3).

Discussion

This is the first prospective, multicentre, observational cohort study with a large sample size to investigate the association between mortality and major morbidity with hypothermia in China. Our study demonstrated that infants with hypothermia,

Table 1 Characteristics of normothermic and hypothermic VLBW infants

	Moderate/severe hypothermia $n = 546$	Mild hypothermia n = 554	Normothermia n = 147	P*
GA [weeks, $M(Q_{1}, Q_{3})$]	29 (28, 31)	30 (28, 31)	30 (28, 31)	0.048
BW [g, <i>M</i> (<i>Q</i> ₁ , <i>Q</i> ₃)]	1230 (1050, 1370)	1280 (1100, 1400)	1280 (1130, 1430)	0.001
SGA	144 (26.4)	127 (22.9)	23 (15.6)	0.022
Sex (boy)	287 (52.6)	282 (50.9)	80 (54.4)	0.711
Caesarean section	425 (77.8)	398 (71.8)	73 (49.7)	< 0.001
Multiple birth (twins or more)	104 (19.0)	111 (20.0)	22 (14.9)	0.379
Antenatal use of full course of steroid	270 (49.5)	234 (42.2)	43 (29.3)	< 0.001
Apgar score at 1 min < 7	212 (38.9)	193 (34.8)	42 (28.6)	0.057
Apgar score at 5 min < 7	208 (38.1)	148 (26.7)	16 (10.9)	< 0.001
Intubation at DR	215 (39.4)	157 (28.3)	15 (10.2)	< 0.001
Maternal hypertension	248 (45.4)	227 (40.9)	41 (27.9)	0.001
GDM	64 (11.7)	65 (11.7)	18 (12.2)	0.983
PROM	236 (43.2)	193 (34.8)	52 (35.4)	0.023
Death	93 (17.0)	40 (7.2)	5 (3.4)	< 0.001
RDS	453 (82.9)	404 (72.9)	70 (47.6)	< 0.001
BPD	77 (14.1)	75 (13.5)	18 (12.2)	0.191
IVH	86 (15.7)	35 (6.3)	4 (2.7)	< 0.001
NEC	31 (5.6)	17 (3.1)	5 (3.4)	0.087
LOS	198 (36.3)	170 (30.7)	32 (21.7)	0.002
ROP	44 (8.1)	42 (7.6)	13 (8.8)	0.873
EUGR	301 (55.1)	271 (48.9)	63 (42.8)	0.014

Data are presented as the median or n (%)

Abbreviations: GA Gestational age, BW Birth weight, SGA Small for gestational age, PROM Premature rupture of membranes, DR Delivery room, GDM Gestational diabetes mellitus, RDS Respiratory distress syndrome, BPD Bronchopulmonary dysplasia, IVH Intraventricular haemorrhage, NEC Necrotizing enterocolitis, LOS Lateonset neonatal sepsis, ROP Retinopathy of prematurity, EUGR Extrauterine growth retardation

* Kruskal-Wallis or chi-square test

particularly moderate/severe hypothermia, had adverse outcomes with relatively high rates of death; these findings are consistent with previous reports.^{20,21} The multivariate analysis showed that the OR of death was 4.148 for VLBW infants with moderate/severe hypothermia at NICU admission in our study. Sindhu et al²² reported that a reduction in an infants' body temperature is the primary cause of 18-42% of annual infant mortality worldwide. A recent study by Tay et al²³ reported that hypothermia at NICU admission in extremely preterm infants was independently associated with mortality. Our study showed that mortality was inversely related to admission temperature, although the relationship was not linear but rather a quadratic curve. A quadratic curve indicated that there was an admission temperature range with the lowest death rate, and hypothermia should be avoided in vulnerable VLBW infants.

The univariate and multivariate analyses showed that adverse outcomes in VLBW infants, including RDS, IVH and LOS, were associated with AH. This is consistent with the results of previous studies.^{24,25} Laptook et al⁶ reported that hypothermia

	Adjusted OR ^b (95% CI) ^a		
	Moderate/Severe hypothermia	Mild hypothermia	Normothermia
GA	0.873 (0.744, 1.024)	0.955 (0.818, 1.114)	1.000
BW	1.000 (0.999, 1.001)	1.000 (0.999, 1.001)	1.000
Caesarean section	3.808 (2.411, 6.015)	2.547 (1.647, 3.939)	1.000
Antenatal use of full course of steroid	2.035 (1.344, 3.083)	1.592 (1.059, 2.393)	1.000
Apgar score at 5 min < 7	2.206 (1.093, 4.453)	1.643 (0.815, 3.314)	1.000
Intubation at DR	3.107 (1.515, 6.371)	2.552 (1.247, 5.221)	1.000
PROM	1.203 (0.803, 1.802)	0.935 (0.628, 1.392)	1.000
Maternal hypertension	1.191 (0.730, 1.942)	1.100 (0.681, 1.778)	1.000
SGA	2.009 (1.149, 3.512)	1.521 (0.879, 2.631)	1.000

Abbreviations: OR Odds ratio, CI Confidence interval, GA Gestational age, BW Birth weight, SGA Small for gestational age, PROM Premature rupture of membranes ^a ORs with P < 0.05

^b Adjusted for caesarean section, BW, SGA, Apgar score < 7 at 5 min, and intubation in the DR

Table 3 Multivariate analysis of the association between mortality and major morbidity and hypothermia

	Adjusted OR ^b (95% CI) ^a			
	Moderate/Severe hypothermia	Mild hypothermia	Normothermia	
Death	4.148 (1.505, 11.437)	1.806 (0.651, 5.009)	1.000	
RDS	5.028 (3.169, 7.979)	3.205 (2.099, 4.895)	1.000	
BPD	1.366 (0.862, 2.166)	1.185 (0.734, 1.912)	1.000	
IVH	9.813 (3.353, 28.719)	2.914 (0.984, 8.632)	1.000	
NEC	0.692 (0.228, 2.104)	0.567 (0.186, 1.726)	1.000	
LOS	2.081 (1.284, 3.373)	1.697 (1.063, 2.707)	1.000	
ROP	1.339 (0.626, 2.862)	1.206 (0.580, 2.506)	1.000	
EUGR	1.430 (0.901, 2.267)	1.094 (0.706, 1.695)	1.000	

Abbreviations: OR Odds ratio, CI Confidence interval, RDS Respiratory distress syndrome, BPD Bronchopulmonary dysplasia, IVH Intraventricular haemorrhage, NEC Necrotizing enterocolitis, LOS Late-onset neonatal sepsis, ROP Retinopathy of prematurity, EUGR Extrauterine growth retardation ^a ORs with P < 0.05

^b Adjusted for caesarean section, BW, SGA, Apgar score < 7 at 5 min, and intubation in the DR

increased the risk of sepsis by 11% for every 1 °C drop in body temperature. Miller et al²⁶ reported that moderate/ severe hypothermia significantly increased the incidence of several morbidities, including death, high-grade IVH and lateonset sepsis. Chang H-Y et al²⁷ reported that hypothermia was associated with IVH and RDS. Hypothermia leads to increased oxygen consumption, which leads to hypoxemia, which in turn leads to pulmonary vasoconstriction, the reduced release of pulmonary surfactant and decreased work by respiratory muscles, increasing respiratory distress in these vulnerable preterm infants.²⁸

In this study, we found that the incidence of hypothermia was 88.2%. The incidence of hypothermia at admission to the NICU in VLBW preterm infants was 31-78% in previous studies.^{29,30} In a retrospective observational study, Lyu et al¹⁰ showed that the incidence of hypothermia was 35.6%. In Taiwan, Chang H-Y²⁷ reported that the incidence of hypothermia was 76.8%. Compared with the above international data, the incidence of AH in China is significantly higher. A retrospective analysis was conducted on infants born between January 1 and December 31, 2017 to determine key causes of hypothermia.¹⁴ This study found that

inadequate measures were taken to keep warm in the process of neonatal resuscitation and in-hospital transportation. In addition, medical personnel are not aware of the harm of hypothermia in preterm infants.

The results showed that AH was associated with SGA, caesarean section, intubation at DR, and a low 5-min Apgar score. Caesarean delivery may contribute to hypothermia, as operating rooms are often kept at cool temperatures to maintain a comfortable operating environment. Johannsen et al³¹ showed that a relatively high ambient temperature in the DR may also prevent hypothermia in preterm infants in addition to the above mentioned methods to stabilize body temperatures of VLBW infants. The WHO has recommended that delivery or resuscitation room temperatures be set at a minimum of 25 °C, with a suggested range of 25-28 °C,³ which, anecdotally, is not often the case. SGA is associated with a large surface area-tobody mass ratio, decreased subcutaneous fat, high body water content, and immature skin, leading to increased evaporative water and heat losses;³² therefore, SGA was also a risk factor for AH. A low 5-min Apgar score and intubation at DR may be associated with increased resuscitation efforts, an increased



resuscitation time and inadequate thermal measures.^{8,33} Therefore, heat preservation measures should be included in the management of premature infant resuscitation and the "golden hour" after birth.³⁴

AH was also associated with antenatal steroids. The interpretation of this variable requires special care. During the study period, prenatal use of glucocorticoids is only considered complete prenatal steroid therapy. Pregnant women at risk for preterm delivery are often associated with serious complications, for example maternal hypertension, unexplained uterus contraction. The mothers with hypertensive disorders of pregnancy may be monitored more closely and was higher rates of antenatal corticosteroid use.³⁵ These risk factors cause a higher incidence of asphyxia in preterm infants, leading to a statistical analysis that affected this variable. Therefore, the statistical significance of antenatal steroids has no clinical significance.

Our study had several limitations. We investigated only the incidence of hypothermia and studied the association between hypothermia and poor outcomes; we still have not conducted a quality improvement project considering VLBW infants. Based on the results of this study, our next research project will be to carry out a multicentre quality improvement project to reduce the incidence of hypothermia according to international evidence-based practices for improving quality (EPIQs).

Conclusion

AH is still very high in VLBW infants in NICUs in China. SGA, caesarean section, a low Apgar score at 5 min and intubation in the DR were associated with increased odds of hypothermia. Moderate/severe hypothermia was associated with mortality and poor outcomes, such as RDS, IVH, LOS.

Abbreviations

VLBW: Very low-birth weight; NICU: Neonatal intensive care unit; AH: Admission hypothermia; GDM: Gestational diabetes mellitus; GA: Gestational age; RDS: Respiratory distress syndrome; IVH: Intraventricular haemorrhage; NEC: Necrotizing enterocolitis; LOS: Late-onset neonatal sepsis; BPD: Bronchopulmonary dysplasia; ROP: Retinopathy of prematurity; EUGR: Extrauterine growth retardation

Acknowledgements

We would like to thank Yuan Shi, Professor, from Chongqing Children's Hospital and Zhang-bin Yu from Nanjing Maternal and Child Health Hospital of Nanjing Medical University for assistance with this research project.

Authors' contributions

YHY, the corresponding author, doctorate, and professor of medicine, designed the study, trained and supervised the data collectors, interpreted the results and revised the manuscript. The first author, namely, LW, played a role in the analysis and interpretation of the data and in preparing and drafting the manuscript. The co-first authors, namely, LH, LL-W, XY-H, XF-F, YJ-D, CY-Z, QL, AR-S, YH-Z, GY, CL, XX-L, JC-W, ZY-Y, TC, XY-R, JL, MR-B, FD-P, M-G, BP-Q, RM-Z, SP-N, RX-Z, YC, YL-G, and LP-D participated in the design of the study, the collection and interpretation of the data and writing the manuscript. All authors listed on the manuscript approved the submission of this version of the manuscript and take full responsibility for the manuscript.

Funding

This study was supported by the Shandong Key Research and Development Project (2018GSF118163) and Shandong Provincial Medical Health Technology Development Project (2017WS009). The funder of our study is the corresponding author of this study, professor Yong-hui Yu. She is responsible for designing research, training and supervising data collectors, interpreting results and revising manuscript in this study.

Availability of data and materials

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Ethics approval and consent to participate

The Institutional Review Board of Shandong Provincial Hospital Affiliated with Shandong University approved this project (Approval Number: LCYJ: NO. 2019-004). All authors have signed written informed consent and approved the submission of this version of the manuscript and take full responsibility for the manuscript. The legal guardian of all participants signed an informed consent form that their data could be used for various clinical studies.

Author details

¹Department of Neonatology, Shandong Provincial Hospital Affiliated to Shandong First Medical University and Shandong University, No. 234, Jingwu Road, Huai Yin District, Jinan 250021, Shandong, China. ²Shandong Provincial Maternity and Child Health Care Hospital, Jinan, China. ³Qianfo Shan Hospital Affiliated to Shandong University, Jinan, China. ⁴Qilu Hospital of Shandong University, Jinan, China. ⁵Jinan Maternity and Child Health Care Hospital, Jinan, China. ⁶Yantai Yuhuangding Hospital, Yantai, China. 7Weifang Maternity and Child Health Care Hospital, Weifang, China. ⁸Linyi People's Hospital, Linyi, China. 9Linyi Women's and Children's Hospital, Linyi, China. ¹⁰Affiliated Hospital of Weifang Medical College, Weifang, China. ¹¹Taian Central Hospital, Taian, China. ¹²Liaocheng People's Hospital, Liaocheng, China. ¹³Binzhou Medical University Hospital, Binzhou, China.¹⁴Zaozhuang Maternity and Child Health Care Hospital, Zaozhuang, China.¹⁵Taian Maternity and Child Health Care Hospital, Taian, China. ¹⁶Dongying People's Hospital, Dongying, China. ¹⁷Affiliated Hospital of Jining Medical College, Jining, China. ¹⁸The Second Affiliated Hospital of Shandong First Medical University, Jinan, China. ¹⁹Jinan Central Hospital, Jinan, China. ²⁰Liaocheng Second People's Hospital, Liaocheng, China. ²¹Jinan Second Maternity and Child Health Care Hospital, Jinan, China. ²²Tengzhou Central Hospital, Tengzhou, China. ²³Ju County People's Hospital, Rizhao, China. ²⁴Zibo Maternity and Child Health Care Hospital, Zibo, China. ²⁵People's Hospital of Linzi District, Zibo, China. ²⁶Central Hospital of Shandong Provincial Affiliated to Shandong University, Jinan, China. 27 Dezhou People's Hospital, Dezhou, China. ²⁸Heze Municipal Hospital, Heze, China.

References

- 1 Aylott M. The neonatal energy triangle. Part2: thermoregulatory and respiratory adaption. Paediatr Nurs. 2006;18:38–42.
- 2 Bissinger RL, Annibale DJ, et al. Thermoregulation in very low-birth-weight infants during the golden hour. Adv Neonatal Care. 2010;10:230–8.
- 3 World Health Organization, Department of Reproductive Health Research. Thermal protection of the newborn: a practical guide.

- 4 Geneva: Division of Reproductive Health (Technical Support), World Health Organization; 1997. p. 56.
- 5 Hammarlund K, Sedin G. Transepidermal water loss in newborn infants. VI. Heat exchange with the environment in relation to gestational age. Acta Paediatr Scand. 1982;71:191– 6.
- 6 Costarino A, Baumgart S. Modern fluid and electrolyte management of the critically ill premature infant. Pediatr Clin N Am. 1986;33:153–78.
- 7 Laptook AR, Salhab W, Bhaskar B, Neonatal Research Network, et al. Admission temperature of low birth weight infants: predictors and associated morbidities. Pediatrics. 2007;119(3):e643–9. https://doi.org/10. 1542/peds.2006-0943.
- 8 Caldas JP, Ferri WAG, Marba STM. Admission hypothermia, neonatal morbidity, and mortality: evaluation of a multicenter cohort of very low birth weight preterm infants according to relative performance of the center. Eur J Pediatr. 2019;5:6.
- 9 Lee NH, Nam SK, Lee J. Clinical impact of admission hypothermia in very low birth weight infants: results from Korean neonatal network. Korean J Pediatr. 2019;62(10):386– 94.
- 10 Wilson E, Maier RF, Effective Perinatal Intensive Care in Europe (EPICE) Research Group. Admission hypothermia in very preterm infants and neonatal mortality and morbidity. J Pediatr. 2016;175:61–67.e4.
- 11 Lyu Y, Shah PS, Ye XY. Association between admission temperature and mortality and major morbidity in preterm infants born at fewer than 33 weeks' gestation. JAMA Pediatr. 2015;169:e150277.
- 12 Wan XL, Su SY, Tang J, Hu YL, Cheng H, Peng WT, et al. Effect of goldenhour body temperature bundle management on admission temperature and clinical outcome in preterm infants after birth. Zhongguo Dang Dai Er Ke Za Zhi. 2018;20(8):613–7.
- 13 Wang L, Yu Y-h, Shandong Multicenter Study Coordination for Admission Hypothermia in Neonatal Intensive Care Units. Evidence-based practice for improving quality to to reduce the incidence of admission hypothermia: a multicentered study protocol. Chin J Based Pediatr. 2019;14(2):121–3.
- 14 Choi CW, Park MS. Data management and site-visit monitoring of the multicenter registry in the Korean Neonatal Network. J Korean Med Sci. 2015; 30(Suppl 1):S19–24.
- 15 Yu Y-h, Shandong Multicenter Study Coordination for Admission Hypothermia in Neonatal Intensive Care Units. Hypothermia on admission in both very low and extremely low birth weight infants in Shandong province: a multicentered survey. Chin J Perinat Med. 2019;22(8):553–9.
- 16 Eventov-Friedman S, Kanevsky H, Bar-Oz B. Neonatal end-oflife care: a single-center NICU experience in Israel over a decade. Pediatrics. 2013; 131(6):e1889–96.
- 17 Shao X-m, Ye H-m, Qiu X-s. Practice of neonatology (5th edition). Beijing: People's Medical Publishing House; 2019.
- 18 Schlapbach L, Graf R, Woerner A, et al. Pancreatic stone protein as a novel marker for neonatal sepsis. Intensive Care Med. 2013;39(4):754–63.
- 19 Jobe AH, Bancalari E, et al. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723–9.
- 20 Clark RH, Thomas P, Peabocy J, et al. Extrauterine growth restriction remains a serious problem in prematurely born neonates. Pediatrics. 2003;111(5): 986–90.
- 21 Darcy AE. Complications of the late preterm infant. J Perinat Neonatal Nurs. 2009;23(1):78–86.
- 22 de Almeida MF, Guinsburg R, Sancho GA, et al. Hypothermia and early neonatal mortality in preterm infants. J Pediatr.

2014;164(2):271-275.e1.

- 23 Sindhu R, Ramachandran PV, Jothi Clara M, et al. Reducing early neonatal heat loss in low resourced context an Indian exemplar. Int J Caring Sci. 2015;8(1):140–8.
- 24 Tay VY, Bolisetty S, Bajuk B, et al. Admission temperature and hospital outcomes in extremely preterm infants. J Paediatr Child Health. 2019;55(2): 216–23.
- 25 Silverman WA, Balnc WA, et al. The effect of humidity on survival of newly born premature infants. Pediatrics. 1957;20:477–86.
- 26 Buetow KC, Klein SW, et al. Effect of maintenance of 'normal' skin temperature on survival of infants of low birth weight. Pediatrics. 1964;34: 163–70.
- 27 Miller SS, Lee HC, Gould JB, et al. Hypothermia in very low birth weight infants: distribution, risk factors and outcomes. J Perinatol. 2011;31(suppl 1): S49–56.
- 28 Chang H-Y, Sung Y-H, Wang S-M, et al. Short- and long-term outcomes in very low birth weight infants with admission hypothermia. PLoS One. 2015; 10(7):e0131976.
- 29 Pomerance JJ, Madore C, et al. Effect of temperature on survival of infants with RDS. Pediatr Res. 1974;8(4):449.
- 30 Bhatt DR, White R, Martin G, et al. Transitional hypothermia in preterm newborns. Perinatol. 2007;27:S45–7.
- 31 Boo NY, Guat-Sim Cheah I, Malaysian National Neonatal Registry. Admission hypothermia among VLBW infants in Malaysian NICUs. J Trop Pediatr. 2013; 59(6):447–52.
- 32 Johannsen JKI, Vochem M, Neuberger P, et al. Does a higher ambient temperature in the delivery room prevent hypothermia in preterm infants < 1500 g. Z Geburtshilfe Neonatol. 2017;221(5):235–40.
- 33 Pinheiro JMB, Boynton S, Furdon SA, et al. Use of chemical warming packs during delivery room resuscitation is associated with decreased rates of hypothermia in very lowbirth-weight neonates. Adv Neonatal Care. 2011; 11(5):357– 62.
- 34 Costeloe K, Hennessy E, Gibson AT, et al. The EPICure study:outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics. 2000;106(4):659–71.
- 35 Croop SEW, Thoyre SM, Aliaga S, McCaffrey MJ, Peter-Wohl S. The golden hour: a quality improvement initiative for extremely premature infants in the neonatal intensive care unit. J Perinatol. 2020;40(3):530–39.
- 36 ElSayed E, Daspal S, Yee W, et al. Outcomes of singleton small for gestational age preterm infants exposed to maternal hypertension: a retrospective cohort study. Pediatr Res. 2019;86(2):269–75.



Protecting Neonates for Over 25 Years

Trust clinically proven Masimo SET[®] pulse oximetry to safeguard your most precious patients.

When it comes to treating your most vulnerable patients, there is no room for compromise. Masimo Signal Extraction Technology[®] (SET[®]) overcomes the limitations of conventional pulse oximetry with the ability to measure through motion and low perfusion—advances that are especially beneficial to clinicians caring for delicate neonates.

Masimo SET^{*} pulse oximetry is used to monitor more than

200 million patients

per year around the world¹

Masimo SET^{*} is the primary pulse oximetry technology at

9 of the top 10

hospitals according to the 2019-2020 U.S. News & World Report Best Hospitals Honor Roll² Over 100 studies

have shown that Masimo SET* outperforms other pulse oximetry technologies³

¹Estimate:Masimodataonfile.²https:/health.usnews.com/health-care/best-hospitals/articles/best-hospitals-honor-roll-and-overview ³Comparativestudiesincludeabstractspresentedatscientificmeetingsandpeer-reviewedjournals.Clinicalstudiesonpulseoximetryandthe benefits of Masimo SET® can be found at http://www.masimo.com/clinical-evidence.

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician. See instructions for use for full prescribing information, including indications, contraindications, warnings, and precautions.

S Masimo

Discover how clinically proven Masimo SET[®] can support your neonatal patients.

masimo.com

© 2020 Masimo. All rights reserved. PLCO-004084/PLMM-11736A-0620 PLLT-11196A

A WIDE SPECTRUM of HMOs^{*,†} Mother-Made, Not Lab-Created





100% HUMAN MILK-BASED NUTRITION

For more information on HMOs, please visit www.prolacta.com/HMOs

*Human milk oligosaccharides

tBarile D, Lebrilla CB, German B, Rechtman DJ, Lee ML. Oligosaccharide prebiotics present in a breast milk based human milk fortifier. Presented at Hot Topics in Neonatology. Washington DC December 2008

