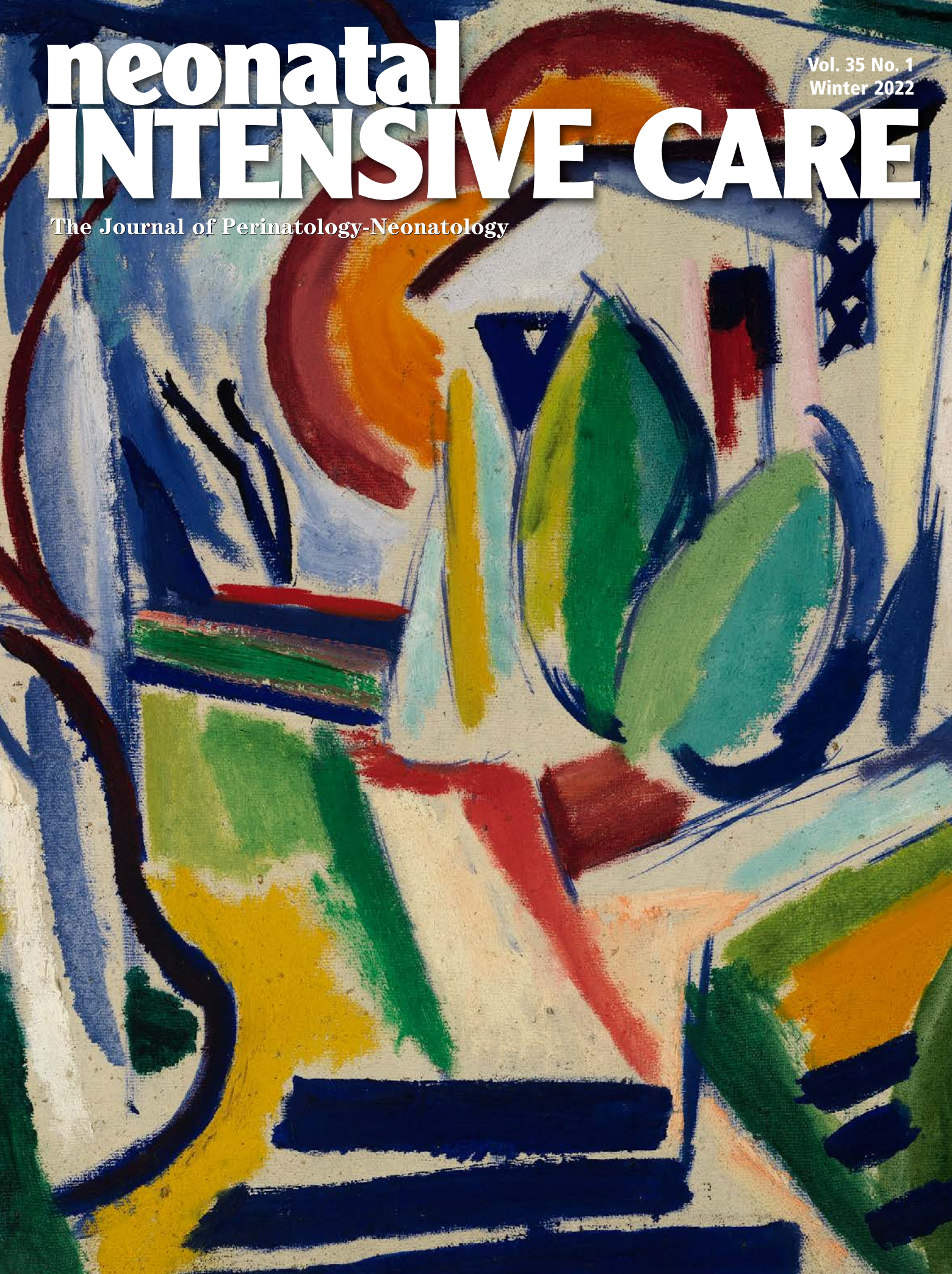


An abstract painting with bold, expressive brushstrokes in various colors including red, orange, yellow, green, blue, and black. The composition is dynamic and non-representational, with large, overlapping shapes and thick applications of paint.

neonatal INTENSIVE CARE

Vol. 35 No. 1
Winter 2022

The Journal of Perinatology-Neonatology



No Challenge Too Big. No Patient Too Small.

Discover the Masimo SET® Difference

For over 25 years, Masimo has been a trusted partner in neonatal and newborn care around the world—delivering innovative Masimo SET® Measure-through Motion and Low Perfusion™ pulse oximetry to enhance care even in challenging conditions.

Today, we remain committed to protecting your most delicate patients and strive to deliver a variety of specially tailored solutions that meet their needs and help you improve outcomes.

To learn more about how SET® is making a difference for neonates, visit [masimo.com/newborn-care](https://www.masimo.com/newborn-care)

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.

© 2021 Masimo. All rights reserved. PLCO-005107/PLMM-12056A-0621 PLLT-11507A



CLOSER TO THE HEART®

Full Line of Suction Tips

Made in the USA and Ready to Ship

**TRY THEM
FOR FREE!**

VISIT

neotech-neonatalic.com



N204



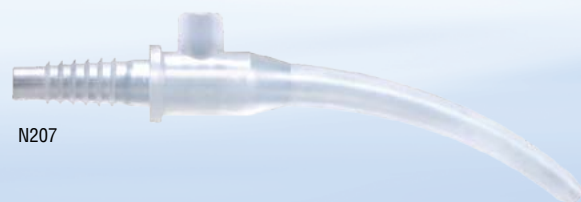
N205



N205C



N225



N207

Little Sucker[®]

ORAL AND NASAL SUCTION DEVICE

Little Sucker[®] Nasal Tip

NASAL SUCTION DEVICE

NeoSucker[®] Curved

ORAL AND NASAL SUCTION DEVICE

Neotech offers a family of oral and nasal suction devices. They are designed for single handed suctioning and feature a patented thumb port for intermittent suctioning. Each has a soft flexible tip, similar to a bulb syringe. The Little Sucker is made in the USA. Order your free sample today.

©2022 Neotech Products LLC. All rights reserved.



Made in USA

Request your free samples online at neotech-neonatalic.com



neonatal INTENSIVE CARE

Vol. 35 No. 1
Winter 2022

Table of Contents

DEPARTMENTS

- 5 News
- 6 Company Profile

ARTICLES

- 11 Non-invasive Blood Pressure Monitoring of Neonates
- 17 End-of-life Decision and Length of Stay in NICU
- 19 Blood Loss in the NICU
- 22 Are Flavonoids Effective For Perineal Pain And Safe?
- 24 NICU Noise: 50 Years of Worry
- 28 Got Milk? Increasing Mom's Milk Volumes
- 34 Utilizing Clinical Data to Enable Better Ventilation Management
- 38 How NICUs Are Tailoring Their Approach to Care for the Tiniest Babies
- 42 Electronic Alerts on the Social Determinants of Health
- 45 Leveraging Family Engagement Technology
- 49 Aquapheresis Offers Hope to Preterm Neonates
- 51 B. infantis EVC001 is Well-Tolerated
- 52 Pediatric Respiratory Stability
- 56 Cost-Effectiveness of Targeted Fortification Approach Versus Standard Fortification Approach
- 66 Examining the Impact of Early Fortification on Growth Rates
- 69 Respiratory Distress and Abnormal CT Scan in a Newborn Infant

Editorial Advisory Board

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

Leslie B. Altimier, DNP, MSN, BSN, RNC, NEA-BC
Senior Director of Clinical Innovation & Research, Masimo
Irvine, 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
Chairman 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-Neonatology, 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, Portland, 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
Kansas City, KS

William Meadow, MD
Professor of Pediatrics
Co-Section Chief, Neonatology
Cerner 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
Konya, Turkey

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. Battista 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 (NOHRT)
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
Neonatology Hospital Virgin del Consuelo
Valencia, Spain

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

New York First to Add G6PD Deficiency to Routine Screenings

New York State became the first state in the nation to add G6PD Deficiency to routine newborn screenings today, as New York State Governor Kathy Hochul signed the Brody James Bill into law. The bill, supported by The g6pd Deficiency Foundation, was named for two people whose lives were altered because G6PDd was not diagnosed until after it had caused severe health impacts. G6PDd (short for Glucose-6-Phosphate Dehydrogenase Deficiency) is the most common human enzyme disorder, affecting upwards of an estimated 400 million people worldwide and up to 6% of newborns in the US. G6PD Deficiency can have life-altering effects if it's not caught early and proactively controlled. "We are so grateful to Governor Hochul, as well as Senator Rivera and Assemblyman Gotfried, for helping us make New York State a safer place for newborns and their families through the Brody James Bill," said Keely Harris, Founder and President of The g6pd Deficiency Foundation. "I'm proud that this law will honor my grandson's journey and help prevent G6PDd from causing life-changing injuries to other children like him. New York State has once again proven itself to be a leader on children's health issues, and we hope to see other states follow its example so that families around the country might have some protection from the life-threatening crises caused by

G6PDd." The bill, introduced by State Senator Gustavo Rivera and Assemblyman Richard Gotfried, is the first of its kind in the United States, although many countries around the world include this screening for newborns, as does the US military as part of its routine medical assessment. It was inspired by the story of Keely's now 8-year-old grandson Brody and another individual, James, who recently passed at 20 years old, due to complications from brain damage, caused by undiagnosed G6PDd as a newborn. In Brody's case, after a harrowing experience with undiagnosed G6PD Deficiency that led to kernicterus, 1-week old Brody suffered brain damage that could have been avoided if he were screened at birth and diagnosed before he was discharged from the hospital. In response to the family's ordeal, and in honor of her grandson's ongoing battle, Keely founded The g6pd Deficiency Foundation which aims to raise awareness for the disease for both families and medical professionals and promotes newborn screenings as a life-saving tool. G6PD deficiency is an inherited genetic enzyme disorder that impacts the mechanism by which the body is able to process glucose. The majority of individuals who are G6PD deficient have no obvious clinical symptoms in the absence of "triggers" (such as primaquine or a reaction to fava beans) and are often unaware that they have this deficiency. G6PD deficiency has, however, the potential to cause attacks of acute hemolytic anemia, severe neonatal jaundice that can lead to kernicterus, and, more rarely, chronic anemia called Chronic Non-Spherocytic Hemolytic Anemia (CNSHA). A letter supporting the bill, written and signed by Dr. Richard O. Francis, Associate Professor, Department of Pathology & Cell Biology, Columbia University VP&S and Director of Special Hematology and Coagulation Laboratory at New York-Presbyterian Hospital-Columbia University Irving Medical Center stated, "Because testing for G6PD deficiency is not a part of New York State newborn screening, many times the infant who is not known to be G6PD-deficient is already at home while hyperbilirubinemia is developing and brain damage is occurring. Prior to the infant's discharge from the hospital, if the clinician knew that the newborn was G6PD deficient, proper treatment and parental education could occur, thereby preventing the development of kernicterus. A lifetime of unexplained sickness and unnecessary hospitalizations could be avoided for the infant and his or her family members if screening

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.

©2022 by Goldstein & Associates, Inc. All rights reserved. Reproduction in whole or in part without written permission is strictly prohibited.

Cover: H. Lyman Sayen, *Fugue*, 1915, oil on canvas, Smithsonian American Art Museum, Gift of H. Lyman Sayen to his nation, 1967.6.9

for G6PD deficiency is performed at birth.” G6PD Deficiency is more common in families with Mediterranean, Asian or African ancestry and disproportionately impacts minority communities. However, in the 21st century, ancestry is not always known or clear. In absence of a screening or parental blood tests specifically for this genetic mutation, it is impossible to identify a G6PD deficient person. Adding universal screenings for G6PD to the newborn screening list, along with Cystic Fibrosis and Sickle Cell Disease, would allow it to be diagnosed and treated early, saving lives, and sparing families unnecessary pain.

Fetal Gut May Have Insulin-Producing Cells That Shut Off at Birth

In addition to pancreatic beta cells that secrete insulin, researchers have found that fetal cells in the gut secrete insulin proteins, but neonatal cells do not, suggesting that this ability is turned off at birth.

The study findings are “plausible, because the pancreas and the small intestine originate from the same tissue in the growing fetus at about the fifth week of gestation,” said senior study author Shalev Itzkovitz, PhD, principal investigator, Weizmann Institute of Science, in Rehovot, Israel, in a news story in *The Jerusalem Post*. The study by Adi Egozi, a PhD student at the Weizmann Institute of Science and colleagues in Israel and in the United States, was recently published in *Nature Medicine*. The researchers speculated that if they could get cells in adults to secrete insulin proteins, this might lead to a new way to treat diabetes, but this research is very preliminary. “We found insulin-producing cells in fetuses, yet not in neonates,” Itzkovitz summarized in an email. “It would be exciting to uncover situations where the insulin-producing cells naturally re-appear, eg, in diabetes, gastric bypass, or other perturbations,” and to “identify molecules that could awaken the beta-like state we discovered,” Itzkovitz added. The study findings “highlight a potential extra-pancreatic source of beta cells and expose its molecular blueprint,” the researchers summarize. “The dream is to have a drug that could re-awaken the fetal insulin-expressing program,” Itzkovitz said. “Even though the insulin-producing cells are a minority, the gut surface is huge, and their numbers add up,” he noted. In addition, “gut cells are constantly replaced via divisions of stem cells.” “This means that the impact of autoimmune attack in type 1 diabetes might be less pronounced on intestinal insulin-producing cells,” according to Itzkovitz.

Delayed Umbilical Cord Clamping Improves Outcomes in Very Preterm Infants

Delayed umbilical cord clamping for at least 60 seconds after birth significantly reduced death or disability in infants of less than 30 weeks’ gestation, according to data from nearly 1,500 infants. The burden of disability and mortality for babies born before 30 weeks’ gestation remains high, especially in low- and middle-income countries, wrote Kristy P. Robledo, PhD, of the University of Sydney, Australia, and colleagues. Delayed clamping of the umbilical cord is a simple procedure that may improve mortality in this population, but more research is needed; recommended times to delayed clamping range from 30 seconds to 3 minutes, they noted. In a study published in *The Lancet Child & Adolescent Health*, the researchers randomized 767 very preterm infants to delayed clamping at least 60 seconds after birth and 764 to immediate clamping. Of these, 384 were multiple births (who were individually randomized), 862 were male, and 505 were born before 27 weeks’ gestation. The primary outcome was death or disability at 2 years of age. Major disability was defined as cerebral palsy, severe visual

loss, deafness requiring a hearing aid or cochlear implants, major language or speech problems, or cognitive delay at 2 years corrected age. The median time to clamping was 60 seconds in the delayed group and 5 seconds in the immediate group. Primary outcome data were available for 1,419 infants. Death or major disability occurred in 29% of infants assigned to delayed clamping compared to 34% of those assigned to immediate clamping (relative risk 0.83, $P = .010$). The infants were part of the APTS Childhood Follow-Up Study, an open-label *Continued on page 8...*

COMPANY PROFILE

NeoChild

Describe your product(s) and its unique features.

NeoChild offers various specialty neonatal/pediatric devices, including two safety enteral feeding systems, custom convenience kits, and various infusion sets. NeoChild’s SAFEkey™ System is our newest product offering and is the next generation for safety enteral feeding systems, providing clinical advantages, cost savings, and usability benefits.

Tell us about the latest advances in the area your product serves.

NeoChild has taken the steps to vertically integrate our manufacturing/capacity to alleviate supply chain issues and backorder situations. This decision will not only allow NeoChild to control our product quality but facilitate supply chain logistics. These advances also allow NeoChild to provide customized convenience kits to meet each hospital’s unique needs.

Discuss your R&D process, including clinical user input.

NeoChild closely works with clinicians in the specialized field of neonatal medicine and adheres to medical based evidence supporting all products. NeoChild is a pioneer in the development of enteral feeding devices that emphasize the continuum of care in newborns’ health. Research and development emphasizing efficacy, safety and improving clinical outcome are reviewed/advocated by global thought leaders in the neonatal space.

Discuss the educational services you offer for use of your product.

NeoChild offers training videos, literature, in-servicing, and various tutorials.

What new technology do you see as having the greatest impact on your area of expertise?

NeoChild’s SAFEkey™ System is the newest generation of safety enteral feeding systems and takes NeoChild’s Safe Child System™, the original and only patented legacy system, to the next generation of enteral feed safety. By eliminating misconnections, the SAFEkey™ System adds a locking design outside of the fluid pathway to not only eliminate disconnections, but also eliminate the dead space (moat) area associated with ENFit® connectors. Eliminating the moat area negates the need to brush clean potential bacteria growth concern. In addition, NeoChild’s SAFEkey™ System provides important operator benefit while extending a price savings advantage versus ENFit® device.

It's more than Tape, It's Baby Tape *PLUS*[™]!



New From B&B Medical Technologies!

Baby Tape *PLUS*[™] Hydrocolloid Infant Endotracheal Tube Holder

- Hydrocolloid adhesive is gentle on babies' delicate skin
- Pre-cut, pre-packaged Tapes reduce time to secure endotracheal tubes
- Versatile design fits a wide range of infants
- Can also be used to secure nasogastric / orogastric tubes & cannulas



For more information please contact us:

www.bandb-medical.com

+1.800.242.8778

+1.760.929.9972

B&B Products are also available through finer specialty distributors including: Tri-anim, Cardinal Health & Medline.

Follow us on **LinkedIn**

©2021 B&B Medical Technologies. All Rights Reserved.

B|B Medical Technologies®
BREATHING INNOVATION www.bandb-medical.com



News...continued from page 6

superiority trial conducted in Australia and New Zealand. By age 2 years, 8% of infants in the delayed group and 11% of those in the immediate group had died; 23% and 26%, respectively, met criteria for major disability. The impact of delayed clamping translates to a 30% reduction in relative risk of mortality at 2 years of age, but no significant impact on major disability, the researchers wrote. The findings were limited by several factors including the unblinded study design, lack of data on heart rate or time to first breath, and the clamping prior to 60 seconds in 26% of infants in the delayed group based on clinical concerns for these specific infants, the researchers noted. However, the results were strengthened by the large size, low risk of bias, and specific primary outcome, they said. The data support findings from recent systematic reviews and highlight the need for further trials to evaluate delayed clamping at different time points, with larger populations, inclusion of time to first breath and heart rate, and improved measures of disability, the researchers added.

Spreading Holiday Cheer: NICU Babies ‘Sleigh-ing It’ in Ugly Sweaters

Holiday merriment in a place often associated with trauma is part of the festivity of the winter season at Tallahassee Memorial HealthCare (TMH) in Tallahassee, Florida. As is their tradition, the nurses in the neonatal intensive care unit (NICU) at TMH dressed up their newborn patients in holiday attire. This year, they chose the “ugly sweater” look for the tiniest of hospital stayovers. About 20 baby photos grace the hospital’s Facebook page, starting with a Grinch baby and ending with one dressed as a candy cane. The photos are “live and full of just as much cuteness as ever,” marketing representative Morgan King said. The Facebook post, in keeping with custom, was full of puns to keep spirits high around an otherwise stressful environment. For starters: “There’s snow way we would miss our favorite holiday tradition! This year, our NICU babies are sleigh-ing it in their ugly Christmas sweaters.” An explanation beside the Grinch photo stated: “These NICU babies are so cute, they made our hearts grow three sizes.” Another photo joked: “What’s a snowman’s favorite hot drink? Frost-tea.” And aside a baby sporting a Christmas-tree costume: “We hope these babies really light up your day.” The post continued, “Thank you to our incredible NICU team who always go above and beyond to make the holidays special for our NICU families. The sweaters were hand-made by our NICU team to help these little cuties and their families get in the holiday spirit.” The parents of all babies pictured consented to their children being dressed up and photographed, the post further clarified. Earlier this year, NICU nurses took to Facebook with festive Halloween costumes for the babies under their care in a post that went viral, attracting national headlines. TMH has the only NICU and high-risk labor and delivery unit in the region, King said. “In addition to providing sick and premature babies the highest level of specialized care, our team works to make the NICU environment as comfortable as possible for our babies and families,” she said. “Having a baby in the NICU can be unexpected and challenging for families, making the holidays feel less merry. Bringing the festive fun to these little ones and their parents through this annual tradition is just one of the many ways our team works to normalize the NICU environment and make an uncertain time special for families. Our crafty NICU night team created the sweaters and our day team helped bring their visions to life.” Among the comments under the post, one visitor shared: “Praying for these special little ones and their families! They are rocking the sweaters!” The post ended with a disclaimer

to use caution with fragile little ones. “Please remember, you should always place your little ones on their backs to sleep, with nothing else in the crib. These NICU babies have special circumstances and are monitored 24/7 by our skilled nursing team.”

Program Assists Substance-Exposed Infants, Their Caregivers

Pregnant with her second child, Clarissa Collins was at her methadone clinic when a woman walked in with a box of doughnuts and a baby doll. The woman, Tara Sundem, was partway through a five-year effort to open Hushabye Nursery and launch a novel family-focused program that would treat substance-exposed infants and offer care and support to their caregivers. Hushabye Nursery recently celebrated one year in its current care facility in Phoenix and Collins now works there as a peer support specialist, helping others in recovery, the Arizona Capitol Times reported. The center houses a 12-room inpatient nursery for infants suffering from neonatal abstinence syndrome—newborns experiencing withdrawal from opioids they were exposed to in the womb, such as heroin and prescription painkillers. But on that day in 2019, Collins begrudgingly attended Sundem’s support group for pregnant women with opioid use disorder. By the second group meeting, she decided to come back every week. “I looked forward to it. I wanted to see the other girls; I wanted to hear their stories. I wanted to meet the baby,” Collins said. “And we became this little family. We became very close friends.” As the opioid epidemic worsens nationwide, neonatal abstinence syndrome (NAS) cases are increasing, too. Nationally, the number of babies born with the condition increased 82% from 2010 to 2017, according to the Centers for Disease Control and Prevention. The national trend in NAS cases holds true in Arizona and has worsened since the Covid pandemic began. Arizona’s NAS rate in 2020 was 9.1 per 1,000 newborn hospitalizations, up from 5.67 per 1,000 in 2015, according to Arizona Department of Health Services vital statistics reports. In 2010, that figure was 2.65 per 1,000. Some of the increase can be attributed to better reporting and other factors, not the opioid epidemic itself, said Sara Rumann, with the department’s Bureau of Women’s and Children’s Health. “But we can say overall the general trend is that it has increased over the last 10 years,” Rumann said.

Fertility Treatments Not Linked to Psychiatric Disorders in Offspring

Some reassuring findings for people pursuing assisted reproduction: babies born through the fertility procedures do not appear to be at increased risk of developing major psychiatric illnesses as they move through adolescence and into adulthood. The results, reported in *JAMA Psychiatry*, come from an analysis of more than 31,000 people conceived via assisted reproduction techniques (ART) in Sweden between 1994 and 2006. The researchers, from Sweden and the United States, found that in this group, rates of depression and suicidal behaviors were not elevated compared with the general population. “We welcome null findings in our study,” said Chen Wang, MPH, a doctoral student at the Karolinska Institutet (KI) in Stockholm, and the lead author on the study. “Overall we found no greater concern for poorer psychiatric health in adolescents conceived with ART compared with the general population, except for an elevated risk of OCD [obsessive-compulsive disorder] that may be explained by differences in parental characteristics.” “Couples and individuals undergoing or considering ART can indeed be reassured in the sense that our study found no indication that the

treatment per se could make children vulnerable to poor mental health later in life,” added Anna Sara Öberg, MD, PhD, the senior author of the paper, who holds appointments in epidemiology at the KI and the Harvard T.H. Chan School of Public Health, in Boston. ART has been linked to several potentially unwanted outcomes, including birth defects, preterm delivery, low birth weight, imprinting disorder, and possibly neurodevelopmental disorders. Previous research from Wang’s team showed that children conceived with ART do not appear to be more likely to have attention-deficit/hyperactivity disorder or poor school performance than children conceived spontaneously. The new study expands on that earlier work, which was published this year in the journal *Pediatrics*. From a Swedish database of more than 1.2 million people born between 1994 and 2006, Wang’s group identified 31,565 individuals born via ART —defined as in vitro fertilization with or without intracytoplasmic sperm injection and transfer of fresh or frozen-thawed embryos — during that period. At the time of final follow-up, in December 2018, participants in the study were between the ages of 12 and 25 years. To assess the risk of mental illness, the researchers looked for diagnoses in medical records from hospitals and outpatient clinics. They also included death certificates, to determine if suicide was the cause, and prescriptions of antidepressants to see if patients were being treated for depression.

Infant Milk Allergy Guidelines Promote Overdiagnosis, Study Says

International guidelines developed to help doctors diagnose cow’s milk allergy may lead to over-diagnosis, according to University of Bristol-led research published in the journal

Clinical and Experimental Allergy. The study found that three-quarters of infants have two or more symptoms at some point in the first year of life which guidelines say may be caused by cow’s milk allergy, yet the condition only affects one in 100. Cow’s milk allergy can present with either acute or delayed symptoms. Delayed symptoms are more varied and include gut and skin symptoms, such as possetting (bringing up milk) and vomiting, colic, loose stools or constipation, and flaring of eczema. Many of these symptoms are already known to be common in infants, making delayed cow’s milk allergy difficult to diagnose. Researchers found that one in four parents reported two or more possible “mild to moderate” symptoms every month. Symptoms were most numerous at three months of age, when all children were fully breastfed and not directly consuming cow’s milk. At six months of age, there was no difference in the number of children with two or more symptoms between those consuming and not consuming cow’s milk. Together, these findings suggest that the majority of symptoms listed in cow’s milk allergy guidelines are common, normal and not caused by cow’s milk allergy. Dr Rosie Vincent, Honorary Clinical Research Fellow at the Centre for Academic Primary Care, University of Bristol who led the research, said: “Guidelines, designed to help the non-specialist to diagnose cow’s milk allergy in infants may unintentionally medicalise normal infant symptoms and promote over-diagnosis of cow’s milk allergy.” Senior co-researcher and children’s allergy doctor, Dr Michael Perkin, from the Population Health Research Institute at St George’s, University of London, added: “Our findings come against a background of rising prescription rates for specialist formula for children with cow’s milk allergy, which is completely out of proportion to how common we know the condition is. Parents of young infants

NEOSCAN® II

LED TRANSILLUMINATOR

FINDING
VEINS & PNEUMO'S
FAST.



FREE TRIALS AVAILABLE.
SYLVAN FIBEROPTICS

WWW.SYLVANMED.COM ■ INFO@SYLVANMED.COM
1-800-628-3836



EARTurtle™

Easy ABR
newborn hearing
screening with the
EARTurtle™

Can be used
with various
equipment for
ABR testing

The EARTurtle™ is a new, soft, and easy-to-mount disposable ear coupler for ABR newborn hearing screening. You can use it with the RadioEar IP30 adapter and similar transducer couplers.

- ✓ Safe to apply on sensitive skin (complies with ISO 10993-1:2018)
- ✓ Consistent and reliable performance
- ✓ Durable and user-friendly design

Sanibel Supply A/S • info@sanibelsupply.com
www.sanibelsupply.com

Sanibel Supply

Sanibel Supply EARTurtle™ distributed by
Hearing Screening Associates info@teamhsa.com
www.hearingsscreeningassociates.com/EARTurtle



are often seen in clinics, worried about a medical cause for their infant's symptoms such as colic, bringing up milk or loose stools. However, our research confirms that these symptoms are extremely common. In an otherwise healthy infant, an underlying cause is unlikely. Incorrectly attributing these symptoms to cow's milk allergy is not only unhelpful, but it may also cause harm by discouraging breastfeeding." The researchers (from the University of Bristol, St George's, University of London, Imperial College London, King's College London, and St John's Institute of Dermatology), used data from the Enquiring About Tolerance study of 1,303 infants aged between three and twelve months, in which parents were asked to record any symptoms their child experienced on a monthly basis. They counted how many infants had cow's milk allergy symptoms each month, as defined in the international Milk Allergy in Primary Care (iMAP) guideline.

Negative Confirmatory Trial Did Little to Drive Down Use of Questionable Preterm Drug

Use of hydroxyprogesterone caproate injection (Makena) for recurrent preterm birth remained high in the US after a "confirmatory" clinical trial failed to show a benefit of the drug, a new analysis indicates.

"Despite the negative trial results and FDA (Food and Drug Administration) efforts to remove the drug from the market, use and spending continue, demonstrating a level of support for the drug among physicians, likely owing to conflicting evidence supporting the drug's use," researchers report in JAMA Internal Medicine. "The FDA has faced difficulties removing accelerated approval drugs from the market even when they fail to show a clinical benefit in their required confirmatory trials," first author Rachel E. Sachs, a professor of law at Washington University School of Law in St. Louis, said. "We wanted to look at whether the publication of negative trial results and statements by the agency or its advisory committees would be sufficient to drive down a drug's use and therefore its spending," she said. "We found that while use and spending did decline after these events, use has remained high, meaning that states may be spending their limited financial resources on products with weak or no clinical benefits," Sachs said. "In other words, issuing statements about the drug's clinical efficacy does not on its own significantly drive down use and spending - the agency does need to take steps to remove the drug from the market in order to have that effect," she added. Makena received accelerated approval in February 2011 based on a clinical trial demonstrating that it reduced the risk of preterm birth in women with previous spontaneous preterm birth. In March 2019, however, results of the FDA-required confirmatory trial failed to replicate the initial trial's reduction in recurrence preterm births. In October 2019, an FDA advisory committee narrowly voted to withdraw approval and a year later the FDA Center for Drug Evaluation and Research (CDER) proposed taking the drug off the market. But Makena's manufacturer requested a hearing, which FDA granted in August 2021. The proceedings remain ongoing. Sachs and colleagues used national Medicaid drug utilization and spending data to examine changes in hydroxyprogesterone caproate fills from 2010 to 2020. They found that use of the drug increased from less than 11,000 fills per quarter between 2010 and 2014 to more than 30,000 fills per quarter in the first quarter of 2019. In the second quarter 2019, after the failed the post-approval trial, there was no decline in use. Between the third and fourth quarters of 2019, use of the drug declined more than 8,000 fills per quarter, coinciding with formal publication of the negative trial and the FDA advisory committee recommendation to withdraw it from the market. A subsequent decline in use

was noted in quarter three of 2020, but use remained high at 19,554 fills per quarter (54.9% of the maximum volume reached in the second quarter of 2017). Since the second quarter of 2019, brand name Makena has maintained more than half of market share, despite availability of generic versions of the drug since 2018. Sachs and colleagues say low uptake of the generics may be driven by the newer branded autoinjector formulation of Makena that the FDA approved in February 2018. "The autoinjector has resulted in continued high spending on hydroxyprogesterone caproate, despite generic availability," they note. In the third quarter of 2020 alone, "state Medicaid programs reimbursed (before rebates) \$41,872,080 for all forms of hydroxyprogesterone caproate, 73.2% of which was for the Makena autoinjector," they report in their article.

Human Milk Introduced to Japanese Market

Prolacta Bioscience, the world's leading hospital provider of 100% human milk-based nutritional products for premature and critically ill infants, announced the enrollment of the first baby into a Japan-based clinical trial evaluating growth and safety associated with an Exclusive Human Milk Diet including Prolacta's 100% human milk-based fortifiers (Prolacta's EHMD). The Japan-based study — "JASMINE: A Randomized, Controlled Study to Assess Growth and Safety of the Exclusive Human Milk Diet (EHMD) in Very Low Birth Weight (VLBW) Infants" — began in October 2021. In Japan, Prolacta's human milk-based products will be registered as a drug. "Initiation of this study in Japan is another industry first, being led by Prolacta," said Scott Elster, CEO of Prolacta. "Japan's regulatory authorities have very strict requirements for conducting drug trials. Our industry-leading quality and safety standards meet Pharmaceuticals and Medical Devices Agency (PMDA) regulations, allowing us the opportunity to conduct this study and introduce an exceptional level of nutritional care for preterm babies in Japan." "We know that Prolacta's EHMD is the gold standard diet for premature infants," said principal investigator, senior professor of pediatrics Dr Katsumi Mizuno, MD, PhD, of the Showa University School of Medicine in Tokyo. "This study is necessary to bring a higher level of nutritional care to our very low birth weight babies in Japan." Mizuno-sensei, in association with a clinical research organization, will oversee the 10-site study taking place at Showa University Hospital, Showa University Koto Toyosu Hospital, Showa University Northern Yokohama Hospital, Nara Medical University Hospital, Saitama City Hospital, Fujita Health University, Tokyo Metropolitan Bokutoh Hospital, Nagano Children's Hospital, Takatsuki General Hospital, and Gifu Prefectural General Medical Center. The study will evaluate three of Prolacta's 100% human milk-based products.

UK Data Show Good Safety of COVID-19 Vaccines in Pregnancy

COVID-19 vaccination is safe for pregnant women and not associated with higher rates of complications, data released by the UK Health Security Agency showed, as officials urged pregnant women to take up the offer of shots. The real-world data from the rollout of COVID-19 vaccines in Britain support other studies around the world that the vaccines are safe to give at any stage of pregnancy, the UKHSA said. It found that there were not substantial differences in rates of stillbirths, rates of births of babies with low birthweight and the proportion of premature births between vaccinated women and unvaccinated women. Officials said the data were especially reassuring given that the first pregnant women to be offered the vaccine were

Continued on page 18...

Non-invasive Blood Pressure Monitoring of Neonates

Xina Quan, Junjun Liu, Thomas Roxlo, Siddharth Siddharth, Weyland Leong, Arthur Muir and Anoop Rao

Abstract

This paper reports results from preliminary studies on a device employing a novel algorithm-based blood pressure sensor which uses machine-learning techniques to extract blood pressure values from the shape of the pulse waveform in order to non-invasively monitor the blood pressure of neonates in critical care.

Introduction

Blood pressure is a vital sign widely used in the diagnosis and treatment of many medical conditions. Blood pressure monitoring and management is an essential part of medical care, particularly in the treatment of chronic hypertension, critical care monitoring and trauma care. The most commonly-used methods for blood pressure (BP) monitoring generally involve either non-invasive inflatable cuff-based oscillometric or invasive arterial line manometric measurement.

Inflatable BP cuffs take intermittent measurements, typically limited in frequency to no more than one measurement every five minutes, due to patient discomfort and the risk of skin and nerve damage. Automated systems similar to those used for ambulatory BP monitoring (ABPM) may be used, but can be expensive. Most importantly, intermittent measurements may not be sufficient for critical care where the status of a patient can change from minute to minute.

Invasive arterial lines (IALs) can provide continuous BP measurements and are typically used in intensive care unit (ICU) settings as they can be difficult to correctly place and maintain and require highly skilled medical staff and equipment. IALs can be difficult to use where patient transport is required, and they carry risks of complications due to their invasive nature.

BP monitoring is vital to the care of critically ill patients since episodes of both hypertension and hypotension have been linked to greater mortality and unfavorable non-mortality outcomes.¹⁻⁷

Adapted from Quan, Xina, et al. "Advances in Non-Invasive Blood Pressure Monitoring." *Sensors* 21.13 (2021): 4273. Xina Quan, Junjun Liu, Thomas Roxlo, Siddharth Siddharth, Weyland Leong, Arthur Muir are with PyrAmes Inc. Cupertino, CA 95014, USA; ljj@pyrameshealth.com (J.L.); troxlo@pyrameshealth.com (T.R.); sids@pyrameshealth.com (S.); wleong@pyrameshealth.com (W.L.); amuir@pyrameshealth.com (A.M.); Anoop Rao is with the Department of Pediatrics – Neonatology, Stanford University, Palo Alto, CA 94304, USA; anooprao@stanford.edu. Correspondence: xquan@pyrameshealth.com; Tel +408-216-0099.

Even short durations of hypotension may lead to traumatic brain injuries or complications due to a lack of perfusion.² However, it can be difficult to obtain accurate BP measurements, particularly from children and infants born prematurely who have fragile skin, extremely small blood vessels, and very low mean blood pressure values.⁸⁻¹²

Current Standard of Care for Blood Pressure Monitoring Invasive Arterial Catheters

Although cuff-based measurements are used today to guide most treatment decisions due to an abundance of literature and their ease of use, the "gold" standard for continuous BP monitoring is an invasive arterial line (IAL).^{6,13-14} This is a sensor inserted into the artery which directly measures changes in BP, generally after calibration with an inflatable cuff measurement. IALs are placed in up to 2% of all births.¹⁵ Each placement carries the risk of serious complications such as infection, bleeding, clots and nerve damage.¹⁶ IALs are generally used in ICUs due to the possibility of excessive bleeding and require maintenance to ensure patency. Costs can be high, over \$750 per adult patient and over \$2,000 for neonates, due to the need for highly skilled medical staff and equipment.¹⁷

While insertion of an IAL is considered essential for many critically ill patients and is generally benign for adults,^{7,13-14} it is more problematical for children who have smaller arteries and a greater tendency for vasospasm and must generally be sedated.^{6-7,10,16,18-23} Neonates are particularly at risk due to their fragile skin.²⁴ Insertion of a pediatric arterial line requires the services of highly trained personnel and may require multiple attempts.^{7,10,18} As many as half of pediatric arterial lines may be positioned non-optimally to such an extent that their accuracy in measuring BP may be insufficient to manage care.⁶ Short-term and long-term complications such as obstruction of blood flow and possible tissue or organ damage from arterial thrombosis or vasoconstriction,^{10,16,18-19,22} infection,^{10,21} bleeding complications,²² and nerve damage⁷ occur at a higher rate for children than adults, with younger, smaller children more likely to experience these issues.^{7,16,18,23} Thrombosis has been reported in 24%–66% of neonates with umbilical arterial lines in place.²⁵ In extreme cases, amputation may be required.²⁶

Despite the advantages to care management from continuous BP monitoring, the higher risk of complication leads many clinicians to avoid the use of IAL monitoring if possible, substituting intermittent cuff measurements or eschewing BP information entirely.

Inflatable Cuff Measurements

Cuff measurements can be time consuming if taken manually, and placement can be critical to the accuracy of the results. Frequent use of cuff devices is uncomfortable and carries risk of complications such as damage to the skin (e.g., petechiae, acute dermis capillary rupture, or skin necrosis) or peripheral nerves (e.g., compressive neuropathy, crush syndrome, or nerve ischemia).^{27–29} Cuffs are also less accurate at children's lower BP values.³⁰ Most importantly, intermittent measurements may not be sufficient for critical care where the status of a patient can change within minutes.

The Benefit of an Alternative Pediatric Solution

There is strong demand for a safer, non-invasive alternative which could be used for the majority of critically ill patients who do not require frequent blood gas sampling. More frequent BP monitoring could become ubiquitous during the 0.5 million pediatric surgeries in the US each year³¹ and ultimately could become routine in ICUs and step-down wards, particularly if the monitoring device is unobtrusive and does not interfere with the patient's sleep or activity. This could impact the care for 400 thousand critically ill neonatal patients (10%³² of four million live births³³) and 3.5 million pediatric admissions in the US each year.³¹

In the long-term, use of a comfortable, non-stressful, and easy-to-use BP monitor could spread to other applications as well. It potentially could be used to screen for some congenital heart defects such as patent ductus arteriosus, coarctation of the aorta, and aortic valve stenosis using BP and pulse waveform measurements at different body locations.^{34–42} With a low price point, it could be used for routine BP measurements during office visits. It could also be used to assist in the diagnosis and care management of hypertensive patients, both children and adults, given the use of ambulatory BP monitoring for children is now encouraged by the American Academy of Pediatrics.⁴³

There is a clear need for a convenient, continuous, and cost-effective device that can enable widespread BP monitoring with minimal risk, training and effort, particularly for neonatal patients in critical care. BP monitoring with IALs for this group is more difficult and poses greater risk due to the small size of neonatal arteries.⁷ It is also difficult to obtain cuff measurements on a frequent basis since neonates are prone to pressure ulcers from the pressure of medical devices,⁴⁴ and best practice is to avoid leaving cuffs in place for extended periods of time.⁴⁵

PyrAmes has developed a comfortable and easy-to-use wearable device (the “Boppli™”) for BP monitoring and management over

long periods of time. It uses capacitive sensors to capture pulse waveform data which can provide more detailed information about the health of the cardiovascular system. The Boppli has been used successfully on neonates.

Materials and Methods

PyrAmes' Solution

PyrAmes uses capacitive proximity sensing technology exclusively licensed from Stanford University to collect pulse waveform data used to derive continuous blood pressure measurements. The Boppli system consists of an array of sensors integrated into a soft foam band, which is worn on the wrist or foot (Figure 1), sending data wirelessly to a mobile device where continuous blood pressure values are displayed in real time.

How it Works

The Boppli is based on a very sensitive relative displacement sensor that sits with light contact against the skin over a palpable pulse point. When the heart beats, it pushes a pulse of blood through the arteries which locally expand and contract as the pressure wavefront caused by this pulse travels through them. This causes the surface of the skin to be displaced slightly which, in turn, results in motion of a movable surface within the PyrAmes sensor (Figure 2). The change in distance between the movable surface and a fixed electrode in the PyrAmes sensor is measured as a change in capacitance. The capacitance changes with time in a manner which correlates to the blood pressure changes or pulse waveforms that are measured with an IAL (Figure 3). The capacitance signal is digitized for wireless transmission to a mobile device via a Bluetooth connection.

An array of independent sensing elements spanning a 15 mm × 8 mm area is used to ensure that it is easy to locate the Boppli over a pulse point.

An application on the mobile device receives the sensor data and removes noise and artifacts from the data. The cleaned data is used to extract blood pressure values from the shape of the pulse waveform data with a series of convolutional neural networks (CNN), trained with data reflecting the similarity of the sensor signal to IAL data taken simultaneously.

Normalized waveform data are used to ensure the sensor is less affected by environmental effects such as placement pressure, sensor positioning, skin temperature, and skin hair density. Since it is not optically based (e.g., photoplethysmography or PPG), it is insensitive to ambient light and skin color. However, like many other wearable devices, it is sensitive to motion, and motion-affected data is detected and excluded. The premise that blood pressure can be derived from pulse waveform data is well supported in the literature.

Clinical data for this study were collected using protocols approved by the Institutional Review Boards at Stanford University and Aspire IRB. Details of the study are provided in Table 1.

Results

In this study, 16 patients ranging from 1 to 8 days old with umbilical IALs already in place were recruited from the Stanford Neonatal ICU (NICU) and Cardiovascular ICU (CVICU). Patients had gestational ages at birth of 25–40 weeks. They weighed 0.7–3.6 kg. The ratio of male to female patients was 11:5. Mean

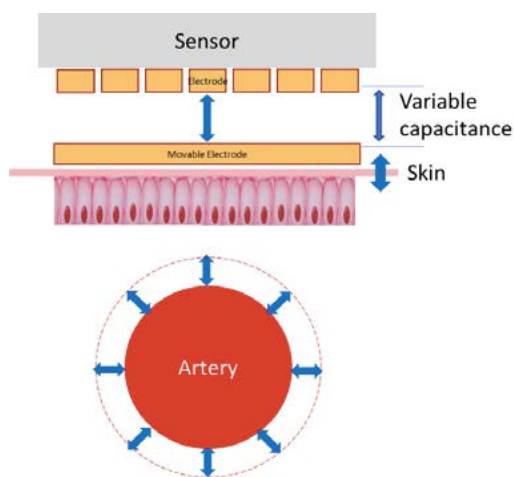


Figure 1. Boppli™ device to monitor the blood pressure of infants in critical care.

Table 1. Study details

Study participants	NICU Infants, n = 16, Age 1–8 days, 33%F, GA 25–40 wk, Weight 0.7kg–3.6 kg
Data duration	~10 hours per patient (360 h)
Device	Boppli Band
Sensor/Electronics size	Area of sensor array: 15 mm × 8 mm; Electronics: 2.0 cm × 2.5 cm, 12 g
PyrAmes device location	Wrist and/or foot
Source of invasive arterial line (IAL) training data	Stanford: n = 899, Age 1 day–53 year, Weight 0.83kg–114.8 kg, 45% F, ~9000 h total Children's National Hospital: n = 40, Age 1–2 day, Weight 0.5 kg–4.7 kg, 40% F, GA 23–40 wk
Outcome	Meets FDA accuracy criteria: MAE (sd) < ±5 (8) mmHg ⁴⁶ SBP: 2.8 (5.5) mmHg; DBP: –0.2 (4.6) mmHg; MAP: 0.1 (4.1) mmHg
Clinical collaborators	Drs. William Rhine, Anoop Rao
Stanford study site	Neonatal (ICU), CVICU

Abbreviations: M–Male; F–Female; GA–Gestational age; ICU–Intensive Care Unit; PICU–Pediatric ICU; CVICU–Cardiovascular ICU; NICU–Neonatal ICU; SBP, DBP and MAP–Systolic, Diastolic and Mean arterial pressure; IAL–invasive arterial line.

**Figure 2.** Schematic of operating principle of PyrAmes' capacitive sensors.

blood pressures and ranges were 54 (25–89), 66 (34–107), and 44 (17–81) mmHg for MAP, SBP, and DBP, respectively.

The Boppli was placed at the radial (N = 13) and/or *dorsalis pedis* pulse point (N = 5). In some cases, more than one sensor location was used for a patient. On average, 10 hours of data were collected per patient. Both IAL and sensor data were collected at a 125 Hz sampling rate (IAL data from Philips IntelliVue monitors, PIC/PIC iX, RDE/Data Warehouse Connect and Toolkits, Philips Healthcare, Cambridge, MA).

Blood pressure values were loosely anchored with initial BP values and patient age and weight. Table 2 shows how processing the resulting signal with the array of CNNs clearly meets the US Food and Drug Administration (FDA) guidelines for accuracy.

Table 2. Results of neonate BP-model-3 (N = 16).

MAP		SBP		DBP		FDA Guidelines ⁴⁶	
MAE	sd	MAE	sd	MAE	sd	MAE	sd
0.1	4.1	2.8	5.5	–0.2	4.6	< ± 5	< 8 mmHg

In Figure 4, mean average values of MAP, SBP, and DBP derived by the CNN models are compared against corresponding blood pressure values measured simultaneously with an arterial catheter. Each point represents the average value for all the

points taken for an individual. The color of the point indicates the age of the patient in days. The red line is a linear regression fit of the data. The derived BP values are well correlated with the ground truth values, with correlation coefficients of 0.91, 0.93, and 0.85 for MAP, SBP, and DBP respectively.

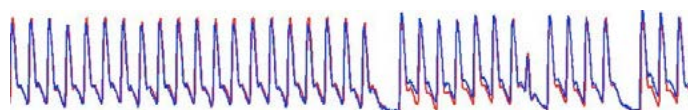
**Figure 3.** Comparison of normalized invasive arterial line data (red) taken simultaneously with normalized PyrAmes Boppli data (blue).

Figure 5 shows Bland-Altman plots for MAP, SBP, and DBP with the average of model and ground truth values for each individual on the *x*-axis and the average difference between model and ground truth values for each individual on the *y*-axis (model error or mean difference (MD)). The points are color-coded by the weight of the patient in kilograms. The solid red line shows the mean average error or bias. The green dotted lines indicate the FDA guidelines for the limit of acceptable error for the population of ±5 mmHg. The red dotted lines indicate the 95% confidence interval (1.96 × the standard deviation of the error in the measurement). The mean absolute error is 4.1, 5.5, and 4.7 mmHg for MAP, SBP, and DBP, respectively.

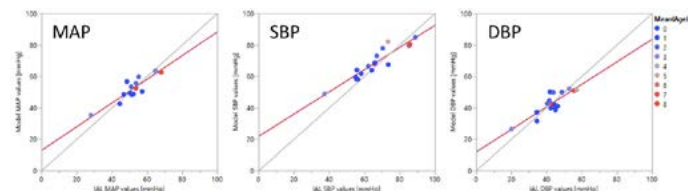
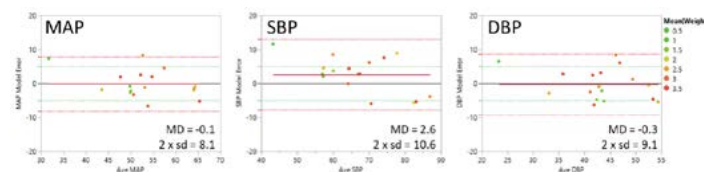
**Figure 4.** Plots of convolutional neural network model outputs vs. invasive arterial line ground truth values of mean arterial pressure (MAP), systolic (SBP), and diastolic (DBP) blood pressure values averaged over each individual. The points are color-coded for the patients' age in days.**Figure 5.** Bland-Altman plots of mean arterial (MAP), systolic (SBP), and diastolic (DBP) blood pressure values in mmHg averaged over each individual.

Figure 6 demonstrates how derived BP values (red curve) can track short term changes measured by the IAL (blue curve) over time. Data were collected for about six hours from an eight-day old infant boy (39-week, one day gestational age at birth, 2.68 kg) with an umbilical arterial catheter in place. The Boppli was placed on the left radial position. Both IAL and Boppli model values were averaged over 60-second intervals for this analysis, with trend curves fit to the individual values. Results for SBP and DBP exhibit similar correspondence to IAL data.

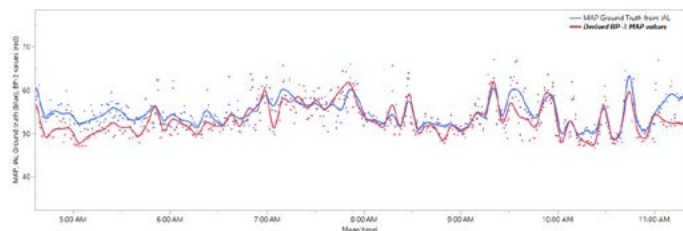


Figure 6. Comparison of invasive arterial line (blue) and derived (red) mean arterial pressure (MAP) values as a function of time. Each data point is averaged over a one-minute interval.

Summary

Continuous blood pressure monitoring is essential to the diagnosis and treatment of many medical conditions but the current standards of care, invasive arterial lines and inflatable cuffs, both have serious drawbacks which impede their use in many situations. There have been many attempts to develop non-invasive approaches which address the issues faced by the current standard of care which have not yet received widespread adoption due to cost or other considerations. The PyrAmes non-invasive approach utilizes capacitive sensing technology which shows promise in addressing some of the issues of the current alternatives. High sensitivity and a soft, smooth form-factor enable use with the fragile skin of newborns and elderly patients, two vulnerable patient populations where use of either invasive arterial lines or cuffs can be problematic. User feedback from usability studies indicates that the PyrAmes device is comfortable and easy to use, addressing issues that lead to a lack of compliance in many self-monitoring situations.

In feasibility studies, we have demonstrated capacitive sensing technology can collect pulse waveform data that can be used in conjunction with algorithms trained through machine learning to determine accurate blood pressure values which can be stable over long time periods without additional calibration. However, for models covering a wide population range, it appears that it will be challenging to obtain sufficient training data solely with cuff measurements, and we have found it necessary to augment our training sets with clinical data where sensor and arterial line data are taken simultaneously.

The bulk of this study focused on a somewhat homogeneous population of neonates under eight days old with an umbilical arterial catheter in place. The training set was further augmented with historical arterial line data for neonates and older children. The pulse waveform collected with the capacitive sensing technology showed strong correlation with blood pressure values obtained through the arterial catheter. It was thus possible to use an unanchored model (without using initial measurements from other tools) to directly predict the blood pressure for this population. However, the current unanchored model predictions are less accurate than those from anchored models and do not meet the guidelines for standard deviation

for all three BP parameters, SBP, DBP, and MAP, due to the limited clinical data. To fully meet the guidelines for accuracy for all three BP parameters, the model demonstrated here was developed to predict the blood pressure using pulse waveforms anchored with an initial blood pressure value, as well as the age and weight of the patient. We believe that with additional clinical data, it will be possible to train models to increase performance without requiring external calibration.

PyrAmes has conducted feasibility studies of different population groups ranging from infants to seniors, healthy to critically ill patients. Inclusion of different races and ethnicities and varying income levels will further provide robust clinical outcomes valuable for widespread use of blood pressure monitoring.

The use of wearable blood pressure sensors in the near future can be a significant stride toward improving public health. Measuring one's blood pressure easily and frequently is one of the best ways to prevent a multitude of major illnesses including heart attack, strokes, cerebral hemorrhage, cognitive impairment and other risk factors associated with hypertension. The latest progress in this field, therefore, is not only important to advance science but also to encourage preventive healthcare for a larger number of people.

Funding

This research was funded primarily by PyrAmes Inc., and in part by Stanford University and the National Institutes of Health - Small Business Innovation Research, grant number 1R43HD101175-01.

Institutional Review Board Statement

The studies were conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Stanford University (protocol codes 38071, August 3, 2016; 38320, December 9, 2016; 45892, September 23, 2019; 47185, June 9, 2019) and by the Institutional Review Board of Aspire IRB (protocol code PyrAmes-2018-01, September 11, 2018).

Informed Consent Statement

Written informed consent was obtained from all subjects involved in the study or their Legal Adult Representatives.

Acknowledgments

The authors are extremely grateful for the efforts and advice of our many collaborators including: Zhenan Bao, Amanda Nguyen, Andrei Afanasiev, Vivek Bhalla, Tara Chang, Sandra Tsai, Anita Honkanen, Chandra Ramamoorthy, Archana Verma, Alexandra Joseph, Eric Helfenbein, and Olga Afanasiev for working with us on the initial development of this technology and feasibility studies; William Rhine, Ya'el Weiner, Elle Billman, and Fatima Eskandar-Afshari for their collaboration on this work; and Lamia Soghier, Rathinaswamy Govindan, and Kevin Cleary, for the kind use of de-identified historical arterial line data from Children's National Hospital.

Conflicts of Interest

Xina Quan, Junjun Liu, Thomas Roxlo, Siddharth Siddharth, Weyland Leong and Arthur Muir are employees and shareholders of PyrAmes Inc. Anoop Rao declares no conflict of interest. Stanford University and NIH had no role in the design of the study; in the collection, analyses, or interpretation of data; in

the writing of the manuscript, or in the decision to publish the results.

References

- Zakaria, E.R.; Joseph, B. Traumatic brain injury: An update. *Surg. Res. Open J.* 2017, 4, e1–e5.
- De Wall, J. The ABCs of TBI. Evidence-based guidelines for adult traumatic brain injury care. *JEMS J. Emerg. Med. Serv.* 2010, 35, 54–61.
- Seamon, M.J.; Feather, C.; Smith, B.P.; Kulp, H.; Gaughan, J.P.; Goldberg, A.J. Just one drop: The significance of a single hypotensive blood pressure reading during trauma resuscitations. *J. Trauma Acute Care Surg.* 2010, 1, 1289–1295.
- Spaite, D.W., Hu, C., Bobrow, B.J., Chikani, V., Barnhart, B., Gaither, J.B., Denninghoff, K.R., Adelson, P.D., Keim, S.M., Viscusi, C. and Mullins, T. Association of out-of-hospital hypotension depth and duration with traumatic brain injury mortality. *Annals of emergency medicine*, 2017, 70(4), 522–530.
- Spaite, D.W., Hu, C., Bobrow, B.J., Chikani, V., Sherrill, D., Barnhart, B., Gaither, J.B., Denninghoff, K.R., Viscusi, C., Mullins, T. and Adelson, P.D. Mortality and prehospital blood pressure in patients with major traumatic brain injury: implications for the hypotension threshold. *JAMA surgery*, 2017, 152(4), 360–368.
- Joffe, R., Duff, J., Guerra, G. G., Pugh, J., & Joffe, A. R. (2016). The accuracy of blood pressure measured by arterial line and non-invasive cuff in critically ill children. *Critical Care*, 20(1), 1–9.
- Cuper, N. J., de Graaff, J. C., Hartman, B. J., Verdaasdonk, R. M., & Kalkman, C. J. (2012). Difficult arterial cannulation in children: is a near-infrared vascular imaging system the answer?. *British journal of anaesthesia*, 109(3), 420–426.
- Raising Children Network (Australia) Ltd. Your Premature Baby's Appearance. Available online: <https://raisingchildren.net.au/newborns/premature-babies/development/premature-appearance> (accessed on 21 May 2021).
- Aouad-Maroun, M.; Raphael, C.K.; Sayyid, S.K.; Farah, F.; Akl, E. Ultrasound-guided arterial cannulation for paediatrics. *Cochrane Database Syst. Rev.* 2016, 9, CD011364, doi:10.1002/14651858.cd011364.pub2.
- Schindler, E.; Kowald, B.; Suess, H.; Niehaus-Borquez, B.; Tausch, B.; Brecher, A. Catheterization of the radial or brachial artery in neonates and infants. *Pediatr. Anesth.* 2005, 15, 677–682, doi:10.1111/j.1460-9592.2004.01522.x.
- CDC. High Blood Pressure. Facts About Hypertension. 2020. Available online: <https://www.cdc.gov/bloodpressure/facts.htm> (accessed on 25 May 2021).
- Dempsey, E.M.; Al Hazzani, F.; Barrington, K.J.; Permissive hypotension in the extremely low birthweight infant with signs of good perfusion. *Arch. Dis. Child. Fetal Neonatal Ed.* 2009, 94, F241–F244.
- Weiner, R.E.; Yohannes-Tomicich, J. Arterial Line Monitoring and Placement. In: *Critical Care; Oropello, J.M., Pastores, S.M., Kvetan, V., Eds.; McGraw-Hill: New York, NY, USA, 2016.* Available online: <https://accessmedicine.mhmedical.com/content.aspx?bookid=1944§ionid=143522170> (accessed on 21 May 2021).
- Holt, T.; Davinia, R.; Withington, E.; Mitchell, E. Which pressure to believe? A comparison of direct arterial with indirect blood pressure measurement techniques in the pediatric intensive care unit. *Pediatric Crit. Care Med. Soc. Crit. Care Med.* 2011, 12, e391–e394.
- McAdams, R.M., Winter, V.T., McCurnin, D.C. and Coalson, J.J. Complications of umbilical artery catheterization in a model of extreme prematurity. *Journal of Perinatology* . 2009, 29, 685–692.
- Nuttall, G.; Burckhardt, J.; Hadley, A.; Kane, S.; Kor, D.; Marienau, M.S.; Schroeder, D.R.; Handlogten, K.; Wilson, G.; Oliver, W.C. Surgical and Patient Risk Factors for Severe Arterial Line Complications in Adults. *Anesthesiology* 2016, 124, 590–597, doi:10.1097/aln.0000000000000967.
- Froehler, M. T., Chitale, R., Magarik, J. A., & Fusco, M. R. Comparison of a pressure-sensing sheath and radial arterial line for intraoperative blood pressure monitoring in neurointerventional procedures. *Journal of neurointerventional surgery* 2018, 10, 784–787.
- Brotschi, B., Hug, M.I., Latal, B., Neuhaus, D., Buerki, C., Kroiss, S., Spoerri, C. and Albisetti, M. Incidence and predictors of indwelling arterial catheter-related thrombosis in children. *Journal of Thrombosis and Haemostasis* 2011, 9, 1157–1162, doi:10.1111/j.1538-7836.2011.04271.x.
- Vasquez, P., Burd, A., Mehta, R., Hiatt, M., & Hegyi, T. Resolution of Peripheral Artery Catheter-induced Ischemic Injury Following Prolonged Treatment with Topical Nitroglycerin Ointment in a Newborn: A Case Report. *Journal of Perinatology*. 2003, 23, 348–350, doi:10.1038/sj.jp.7210870.
- Gleich, S.J., Wong, A.V., Handlogten, K.S., Thum, D.E. and Nemergut, M.E. Major Short-term Complications of Arterial Cannulation for Monitoring in Children. *Anesthesiology* 2021, 134, 26–34, doi:10.1097/aln.0000000000003594.
- Furfaro, S., Gauthier, M., Lacroix, J., Nadeau, D., Lafleur, L., & Mathews, S. Arterial Catheter—Related Infections in Children A 1-Year Cohort Analysis: A 1-Year Cohort Analysis. *American journal of diseases of children* 1991, 145, 1037–1042.
- Veldman, A.; Nold, M.F.; Behnke, I.M. Thrombosis in the critically ill neonate: Incidence, diagnosis, and management. *Vasc. Health Risk Manag.* 2008, 4, 1337–1348.
- Cohen, M.M.; Cameron, C.B.; Duncan, P.G. Pediatric anesthesia morbidity and mortality in the perioperative period. *Anesth. Analg.* 1990, 70, 160–167.
- Blume-Peytavi, U., Tan, J., Tennstedt, D., Boralevi, F., Fabbrocini, G., Torrelo, A., Soares-Oliveira, R., Haftek, M., Rossi, A.B., Thouvenin, M.D. and Mangold, J. Fragility of epidermis in newborns, children and adolescents. *Journal of the European Academy of Dermatology and Venereology*. 2016, 30, 3–56.
- Rizzi, M., Goldenberg, N., Bonduel, M., Revel-Vilk, S., Amankwah, E., & Albisetti, M. Catheter-related arterial thrombosis in neonates and children: A systematic review. *Thrombosis and haemostasis* 2018, 118, 1058–1066.
- Mosalli, R.; Elbaz, M.; Paes, B. Topical Nitroglycerine for Neonatal Arterial Associated Peripheral Ischemia following Cannulation: A Case Report and Comprehensive Literature Review. *Case Rep. Pediatr.* 2013, 2013, 1–7, doi:10.1155/2013/608516.
- Tareerath, M.; Wongyingsinn, M. Comparison of the Incidences of Cuff-Related Trauma after Non-invasive Arterial Blood Pressure Measurement with and without Padding in Patients Undergoing Elective Surgery. *J. Med Assoc. Thail.* 2018, 101, 1.
- Jeon, Y.S., Kim, Y.S., Lee, J.A., Seo, K.H. and In, J.H. Rumpel-Leede phenomenon associated with noninvasive blood pressure monitoring-A case report. *Korean journal of anesthesiology*. 2010, 59, 203.
- Elmatite, W., Mangla, C., Upadhyay, S. and Yarmush, J. Perioperative Automated Noninvasive Blood Pressure-

- (NIBP-) Related Peripheral Nerve Injuries: An Anesthetist's Dilemma—A Case Report and Review of the Literature. *Case Reports in Anesthesiology* 2020, 2020, 1–6, doi:10.1155/2020/5653481.
- 30 Diprose, G. K., Evans, D. H., Archer, L. N., & Levene, M. I. Dinamap fails to detect hypotension in very low birthweight infants. *Archives of disease in childhood* 1986, 61, 771–773.
 - 31 Tzong, K. Y., Han, S., Roh, A., & Ing, C. Epidemiology of pediatric surgical admissions in US children: Data from the HCUP kids inpatient database. *Journal of neurosurgical anesthesiology* 2012, 24, 391–395.
 - 32 Schulman, J., Braun, D., Lee, H.C., Profit, J., Duenas, G., Bennett, M.V., Dimand, R.J., Jocson, M. and Gould, J.B. Association between neonatal intensive care unit admission rates and illness acuity. *JAMA Pediatrics* 2018, 172, 17–23.
 - 33 CDC National Center for Health Statistics. Births and Natality. 2021. Available online: <https://www.cdc.gov/nchs/fastats/births.htm> (accessed on 24 May 2021).
 - 34 Mohammadi, A.; Mehdizade, A.; Ghasemi-Rad, M. Bilateral Tardus-Parvus Waveforms in a Patient With Aortic Coarctation. *J. Ultrasound Med.* 2011, 30, 1030–1031, doi:10.7863/jum.2011.30.7.1030.
 - 35 Mayo Clinic. Coarctation of the Aorta. Available online: <https://www.mayoclinic.org/diseases-conditions/coarctation-of-the-aorta/diagnosis-treatment/drc-20352535> (accessed on 24 May 2021).
 - 36 Ahmed, M. Aortic Stenosis a Tight Aortic Valve—A Comprehensive Patient Guide. 2016. Available online: <https://myheart.net/articles/aortic-stenosis-a-tight-aortic-valve-a-comprehensive-patient-guide/> (accessed on 23 May 2021).
 - 37 Kutty, P.K.; Krishnaswamy, G. The Link: Pediatric History Taking and Physical Examination; Kutty, P.K., Krishnaswamy, G., Eds.; Jaypee Brothers: New Delhi, India, 2016.
 - 38 Dhandare, A. Cardiovascular System Examination. 2017. Available online: <https://www.slideshare.net/AshishDhandare2/cardiovascular-system-examination-75965094> (accessed on 23 May 2021).
 - 39 Fang, J.; O'Gara, P. The History and Physical Examination. An Evidence-Based Approach. 2016 Available online: <https://thoracickey.com/the-history-and-physical-examination/#s0060> (accessed on 23 May 2021).
 - 40 Gevers, M., Van Der Mooren, K., Stergiopoulos, N., Van Genderingen, H.R., Lafeber, H.N., Hack, W.W. and Westerhof, N. Bisferiens peaks in the radial artery pressure wave during patent ductus arteriosus in newborn infants: Relationship with ascending aortic flow. *Pediatric Res.* 1996, 40, 163–168.
 - 41 Moses, S. Arterial Pulse. 2021. Available online: <https://fpnotebook.com/CV/Exam/ArtrIPls.htm> (accessed on 23 May 2021).
 - 42 Giese, E. A., O'Connor, F. G., Brennan Jr, F. H., Depenbrock, P. J., & Oriscello, R. G. The Athlete Preparticipation Evaluation: Cardiovascular Assessment. *American Family Physician* 2007, 75, 1008–1014.
 - 43 Flynn, J.T., Kaelber, D.C., Baker-Smith, C.M., Blowey, D., Carroll, A.E., Daniels, S.R., de Ferranti, S.D., Dionne, J.M., Falkner, B., Flinn, S.K. and Gidding, S.S. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017, 140.
 - 44 Visscher, M.; Taylor, T. Pressure ulcers in the hospitalized neonate: Rates and risk factors. *Sci. Rep.* 2014, 4, 1–6.
 - 45 Seattle Children's Hospital. Improving Neonatal Skin Care. 2019. Available online: <https://www.seattlechildrens.org/globalassets/documents/healthcare-professionals/neonatal-briefs/neonatal-skin-care.pdf> (accessed on 26 May 2021).
 - 46 Association for the Advancement of Medical Instrumentation. American National Standard. Manual, Electronic or Automated Sphygmomanometers ANSI/AAMI SP10-2002. 3330 Washington Boulevard; AAMI: Arlington, VA, USA, 2003.

End-of-life Decision and Length of Stay in a Neonatal Intensive Care Unit

Shabih Manzar, MD, FAAP

Summary

Length of stay (LOS) is viewed as a quality indicator in hospitalized patients. However, in intensive care setup LOS is impacted by end-of-life decision. We present a case of a neonate who had severe encephalopathy with a prolonged stay in the neonatal intensive care unit (NICU). Due to social complications, involvement of Child Protection Services and legal custody issues, the end-of-life decision was delayed resulting in increased LOS. This increase LOS at one end resulted in increased cost and at the other resulted in poor quality performance indicator for the NICU (high-cost, low-value care). The case highlights on the interaction of early end-of-life decision and LOS in NICU with regards to healthcare quality.

Introduction

Length of stay (LOS) is viewed as a quality indicator in hospitalized neonates. In intensive care setup, LOS may be prolonged due to the severity of the illnesses. Further adding to this are cases requiring end-of-life decisions. Neonatal intensive care poses a different challenge in these terminally ill cases pertaining to the LOS. There are very limited facilities in our geographic location that can take care of neonates requiring palliative care. This non-availability of hospice care facilities further adds days to the total LOS in Neonatal intensive care (NICU). We encountered a situation where a neonate with severe encephalopathy stayed in the NICU for more than 90 days. The delay in end-of-life decision was secondary to social condition, involvement of child protection service (CPS) and legal custody issues due to two different states involved.

Case

This preterm infant was born at home, resuscitated by the EMS, and brought to the emergency room (ER). The gestational age was estimated to be 30-32 week by Ballard scoring. According to the EMS, they resuscitated the infant for 45 minutes including intubation, cardiac compressions, intraosseous line placement in the femur, and multiple doses of epinephrine. At the ER, the infant was re-intubated and umbilical lines were placed. Initial blood gas at ~75 minutes of life was pH 6.9/ pCO₂ 30/PO₂ 145/HCO₃ 8/ Base access – 22.4, lactate 20. Infant was then transferred to the NICU and placed on ventilator.

Shabih Manzar is with the Division of Neonatology at LSU School of Medicine, Ochsner LSU Health Science Center Shreveport, 1501 Kings Highway, Shreveport, LA 71103, Phone (318) 626-1622, Email: shabihman@hotmail.com. Web: www.neonatalogysolution.com.

Infant neurological examination was consistent with severe encephalopathy.

Hospital Course

Infant continued to require respiratory support, later had tracheostomy and gastrostomy placed for nutritional support. Due to the social circumstances and involvement of CPS, end-of-life decision was delayed. Finally, a DNR decision was obtained. At the time of this report infant is awaiting on placement to a medical facility, foster services or hospice care that can take care of this infant.

Discussion

The case presents a dilemma of tertiary care. Due to the family custody issue, the infant had to stay in the NICU for prolonged period. The infant required tracheostomy to help with the respiratory difficulty and gastrostomy for feeds. The prolonged stay resulted in increased resources utilization and cost. This case fits into the definition of high cost, low value care.

The value and impact of palliative care consultation in the ICU on length of stay has been discussed in a systematic review by Kyeremanteng, et al. ¹We were able to get palliative care consult, but it was delayed due to the above-mentioned custody issue. This brings us to the question that in such cases how LOS could be used as a worthwhile predictor in ICU, as posed by Kramer. ²

The LOS in NICU could depend upon many factors. ³ One of the factors that affects the LOS is a timely discharge from the hospital. The caveat with early discharge is the risk of re-admission with 30 days, which is also viewed as a poor quality indicator. To decrease LOS in the hospital, the trade-off strategy has been proposed by some authors between timely discharge and good follow up. ^{4,5}

In conclusion, when reviewing the LOS as a quality indicator in NICU, one must factor in the delayed end-of-life decisions. Early palliative care consultation and comfort care plan could potentially deter low-value high-cost care.

References

- 1 Kyeremanteng K, Gagnon LP, Thavorn K, Heyland D, D'Egidio G. The Impact of Palliative Care Consultation in the ICU on Length of Stay: A Systematic Review and Cost Evaluation. *J Intensive Care Med*. 2018;33(6):346-353. doi:10.1177/0885066616664329
- 2 Kramer AA. Are ICU Length of Stay Predictions

- Worthwhile?. Crit Care Med. 2017;45(2):379-380. doi:10.1097/CCM.0000000000002111
- 3 Seaton SE, Barker L, Jenkins D, Draper ES, Abrams KR, Manktelow BN. What factors predict length of stay in a neonatal unit: a systematic review. BMJ Open. 2016;6(10):e010466. Published 2016 Oct 18. doi:10.1136/bmjopen-2015-010466
 - 4 Williams G, Bada H, Chesnut L, Ferrell E, Mays GP. Examining the Trade-off Between NICU Length of Stay and Postdischarge Monitoring: An Instrumental Variables Approach. J Healthc Manag. 2018;63(5):301-311. doi:10.1097/JHM-D-16-00038
 - 5 Carey K. Measuring the hospital length of stay/readmission cost trade-off under a bundled payment mechanism. Health Econ. 2015;24(7):790-802. doi:10.1002/hec.3061

News...continued from page 10

those with underlying health conditions who would be expected to be at a higher risk of complications. "Every pregnant woman who has not yet been vaccinated should feel confident to go and get the jab, and that this will help to prevent the serious consequences of catching COVID-19 in pregnancy," said Dr Mary Ramsay, Head of Immunisation at UKHSA. The UKHSA data found that vaccinated women had a stillbirth rate of 3.35 per 1,000, slightly lower than the rate of 3.60 per 1,000 in unvaccinated women. The proportion of women giving birth prematurely was 6.51% for vaccinated people, slightly higher than 5.99% for unvaccinated women. The government is urging pregnant women who have not yet been vaccinated to get their shots. The health ministry said catching COVID-19 came with much bigger risks than having the vaccine, adding that only 22% of women who gave birth in August were vaccinated. It said that 98% of pregnant women in hospital with symptomatic COVID-19 were unvaccinated, and vaccine take-up was lower in deprived areas and some minority groups.

Enriched Infant Formula Offers No Academic Benefit Later: Study

Infants who are given nutrient- or supplement-enriched formula milk do not later have higher academic scores as adolescents than those fed with standard formula, a study published online in the BMJ suggests. One goal of modifying infant formula has been to make long-term cognitive outcomes similar to those for breast-fed infants, the authors noted. Rates for breastfeeding beyond 6 weeks are low in many parts of the world and more than 60% of babies worldwide under the age of 6 months are given formula to replace or supplement breast milk, the paper states. So far, research has been inconclusive on benefits, though enhancements continue to be added and claims have been made as to their benefits on cognition in advertising. Long-term trials are difficult as researchers move on and participants are lost to follow-up. In a new study, however, researchers led by Maximiliane L. Verfürden, MSc, with the University College of London's Great Ormond Street Institute of Child Health, linked data from seven dormant, randomized, controlled infant formula trials to participants' performance later as adolescents in the United Kingdom on mandatory national school math and English exams at ages 11 and 16 and found no difference in scores. They followed 1,763 adolescents who had been participants in the formula trials, which were conducted between 1993 and 2001, and were able to link 91.2% (1,607) to academic records. They found "no benefit of the infant formula modifications on cognitive outcomes." In this study, the researchers discuss three widely available types of modified infant formulas that have been promoted as benefiting cognitive development: formula enriched with nutrients; formula supplemented with long-chain polyunsaturated fatty acids (LCPUFAs); and follow-on formula fortified with iron.

Neonate Rewarming Tied to Increased Electrographic Seizure Risk, Poor 2-Year Outcomes

Neonates with hypoxic ischemic encephalopathy who are treated with hypothermia have an increased risk of seizures during rewarming, and those seizures are associated with greater death and disability at 2 years, a new study suggests. Researchers examined data on 120 newborns at a mean gestational age of 39 weeks who were randomized to receive either 72 hours (n=66) or 120 hours (n=54) of cooling as an intervention for hypoxic ischemic encephalopathy. The primary endpoint was

Continued on page 23...

Blood Loss in the NICU: The Difficulty and Tradeoffs of Caring for the Most Fragile Patients

Providing the best care for the most fragile NICU patients is full of challenges and tradeoffs. Sometimes the information doctors need to gather from their patients comes at a cost. When neonatal care teams need to assess how a patient is responding to the current level of ventilatory support, a blood draw is traditionally required. However, that blood draw can contribute to blood loss, pain, and infection risk for the infant.

Why do we need to ventilate NICU patients?

Caring for preterm infants requires 1) ventilating their underdeveloped lungs and 2) protecting their brains—which often have immature blood flow regulation—from intraventricular hemorrhage and other complications.

To determine whether or not the ventilation support that these patients are receiving is adequate, clinicians need to frequently measure and monitor the amount of indicative substances in the blood. One of the most critical is carbon dioxide (CO₂).

CO₂ levels can change quickly in neonates, and monitoring them is important because values too high (hypercarbia) or too low (hypocarbia), as well as fluctuations or sharp changes, have all been linked to intraventricular hemorrhage¹, which happens in as many as 25²-42%³ of neonates weighing less than 1500g at birth.

If ensuring CO₂ remains in a safe range helps support better outcomes for NICU patients, CO₂ levels must be measured and monitored closely.

How do we measure carbon dioxide levels in NICU patients' blood?

The gold standard for measuring CO₂ is through blood draws; Arterial Blood Gases (ABG) and capillary heel sticks are common in the NICU.

These blood samples, although accurate, offer only a point-in-time measurement and can miss periods of elevated or reduced levels of CO₂ in the blood. They also present an infection risk, cause pain and stimulation, and introduce iatrogenic blood loss: blood loss caused by medical examination or treatment.

Why is iatrogenic blood loss important?

We may not typically consider blood draws and heel sticks to be a large driver of patients losing blood, but the issue carries

greater significance with neonatal patients, who don't have much blood to give in the first place. One study found that 30% of the circulating blood volume of neonates was drawn for lab work each week in their first six weeks of life.⁴

The significance of this blood loss in the NICU cannot be understated. As another study noted, “to further place this in perspective, 6-7 mL of blood drawn from an infant weighing 1 kg is equivalent to a 450 mL blood loss in an adult.”⁵ 450 mL is roughly one pint.



In the first 6 weeks of life, up to **30% of the circulating blood volume** of neonates is drawn for lab work each week.

If blood loss is so important, why do we draw it so frequently?

The answer, as studies have shown, is often to determine blood gases and pH levels, as well as some electrolytes, all stemming from the desire to monitor how patients are responding to treatment and/or their current level of ventilatory support.

One analysis saw that Very Low Birth Weight (VLBW) infants receive an average of nearly 57 blood gas measurements over the course of, roughly, one week.⁶ The unfortunate reality of what happens next is that up to 63% of the blood lost by the infant is wasted.⁴



pH and Blood Gas measurements are the **highest driver of blood draws** in the NICU.

Transfusion, phlebotomy, and other issues with blood draws

Phlebotomy is well-established as the main nonphysiologic driver of anemia of prematurity,⁵ shown through the direct relationship and high correlation values between the volume of blood drawn and the volume of blood transfused.^{5,7}

We know that blood taken in these fragile patients must eventually be replaced. Transfusion, however, presents a wide variety of risks and complications in neonates, including infection, vascular overload, lung injury, and sensitization,⁸ and has even been linked to increased mortality in adult surgical patients.^{9,10}

Submitted by Sentec. For more information about transcutaneous monitoring, contact [sentec.com](https://www.sentec.com).

“ Decreasing the frequency and amount of phlebotomy loss is probably the area in the field of neonatology that can be changed the quickest. This will automatically **decrease the risk of neonatal anemia and save substantial transfusions and complications.** ”

Transfusion has a complex relationship to Necrotizing Enterocolitis (NEC), with one meta-analysis showing transfusion doubling the risk of developing the condition,¹¹ and another stating “incidence of Transfusion-associated Necrotizing Enterocolitis varies from 20-35% of NEC cases and reports suggest that infants with TANEC are more likely to develop more surgical NEC.”¹²

Patients with transfusion-associated NEC (TANEC) generally have higher mortality, longer hospital stays, and are more likely to require surgery than non-transfusion NEC patients.¹¹ Some evidence has even connected transfusions with worsening intraventricular hemorrhages.¹³

Care teams in the NICU need the information that blood draws can deliver, but the cost of iatrogenic blood loss and other risks associated with those draws needs to be fully understood and weighed by the clinician.

How can we reduce blood loss in the NICU?

While this may paint a bleak picture, there are options and strategies for better blood management in the NICU—and small changes can have a big impact for these fragile patients.

In a study in the *Journal of Maternal-Fetal and Neonatal Medicine*, Clare E Counsilman and colleagues at Leiden University Medical Centre share strategies they’ve implemented to reduce iatrogenic blood loss in their NICU, such as using placental and umbilical cord blood to decrease blood loss on Day 1 of life and adopting transcutaneous CO₂ monitoring to minimize the frequency of blood draws.

Their study concluded that “extreme preterm infants lose almost one-third of their total blood volume in the first month of life as a result of blood loss due to multiple blood draws for laboratory investigations and procedures.”

Additionally, Counsilman et al. determined that “in-line point-of-care testing through arterial catheters...or transcutaneous CO₂ measurement might help to reduce the high blood loss associated with mechanical ventilation.”

The role of transcutaneous CO₂

Transcutaneous monitors enable non-invasive measurement of patients’ CO₂ levels, lessening the need for frequent blood draws without sacrificing visibility to this critical parameter.¹⁴ Although blood draws provide crucial information and will likely never be eliminated from the NICU, efforts to reduce unnecessary blood loss are in the patient’s best interest and are already underway in NICUs around the world.

As Counsilman et al. stated in their study, “decreasing the frequency and amount of phlebotomy loss is probably the area in the field of neonatology that can be changed the quickest. This

will automatically decrease the risk of neonatal anemia and save substantial transfusions and complications.”

References

- 1 Hochwald O, Borenstein-Levin L, Dinur G, Jubran H, Ben-David S, Kugelman A. Continuous Noninvasive Carbon Dioxide Monitoring in Neonates: From Theory to Standard of Care. *Pediatrics*. 2019;144(1):e20183640. doi:10.1542/peds.2018-3640
- 2 Database of Very Low Birth Weight Infants Born in 2012. Burlington, VT: Vermont Oxford Network, 2013. Nightingale Internet Reporting System, accessed April 4, 2014.
- 3 Ahn SY, Shim SY, Sung IK. Intraventricular Hemorrhage and Post Hemorrhagic Hydrocephalus among Very-Low-Birth-Weight Infants in Korea. *J Korean Med Sci*. 2015;30 Suppl 1(Suppl 1):S52-S58. doi:10.3346/jkms.2015.30. S1.S52
- 4 Carroll PD, Widness JA. Nonpharmacological, blood conservation techniques for preventing neonatal anemia—effective and promising strategies for reducing transfusion. *Semin Perinatol*. 2012;36(4):232-243. doi:10.1053/j.semperi.2012.04.003
- 5 Widness JA. Pathophysiology of Anemia During the Neonatal Period, Including Anemia of Prematurity. *Neoreviews*. 2008;9(11):e520. doi:10.1542/neo.9-e5206.
- 6 Alves-Dunkerson JA, Hilsenrath PE, Cress GA, Widness JA. Cost analysis of a neonatal point-of-care monitor. *Am J Clin Pathol*. 2002;117(5):809-818. doi:10.1309/04WC-GFVE-M7T34MGY
- 7 Valieva OA, Strandjord TP, Mayock DE, Juul SE. Effects of transfusions in extremely low birth weight infants: a retrospective study. *J Pediatr*. 2009;155(3):331-37.e1. doi:10.1016/j.jpeds.2009.02.026
- 8 Whitehead, N.S., Williams, L.O., Meleth, S. et al. Interventions to prevent iatrogenic anemia: a Laboratory Medicine Best Practices systematic review. *Crit Care* 23, 278 (2019). <https://doi.org/10.1186/s13054-019-2511-9>
- 9 Wedel C, Møller CM, Budtz-Lilly J, Eldrup N. Red blood cell transfusion associated with increased morbidity and mortality in patients undergoing elective open abdominal aortic aneurysm repair. *PLoS One*. 2019;14(7):e0219263. Published 2019 Jul 11. doi:10.1371/journal.pone.0219263
- 10 Kertai MD, Tiszai-Szűcs T, Varga KS, Hermann C, Acsády G, Gal J. Intraoperative use of packed red blood cell transfusion and mortality in patients undergoing abdominal or thoracoabdominal aortic aneurysm surgery. *J Cardiovasc Surg (Torino)*. 2009;50(4):501-508.
- 11 Mohamed A, Shah PS. Transfusion associated necrotizing enterocolitis: a meta-analysis of observational data. *Pediatrics*. 2012;129(3):529-540. doi:10.1542/peds.2011-2872
- 12 Gephart SM. Transfusion-associated necrotizing enterocolitis: evidence and uncertainty. *Adv Neonatal Care*. 2012;12(4):232-236. doi:10.1097/ANC.0b013e31825e20ee
- 13 Baer VL, Lambert DK, Henry E, Snow GL, Christensen RD. Red blood cell transfusion of preterm neonates with a Grade 1 intraventricular hemorrhage is associated with extension to a Grade 3 or 4 hemorrhage. *Transfusion*. 2011;51(9):1933-1939. doi:10.1111/j.1537-2995.2011.03081.x
- 14 Mukhopadhyay S, Maurer R, Puopolo KM. Neonatal Transcutaneous Carbon Dioxide Monitoring—Effect on Clinical Management and Outcomes. *Respir Care*. 2016;61(1):90-97. doi:10.4187/respcare.04212



Protective, Proactive Neonatal Care

Sentec's safe and reliable transcutaneous tcPCO₂ monitoring system helps clinicians:

Protect the brain and lungs

Continuously monitored CO₂ levels are critically important in the NICU for both protecting the brain from intraventricular hemorrhage as well as properly implementing lung protective ventilatory strategies.

Reduce pain and blood loss

tcPCO₂ has been shown to reduce blood draws on ventilated neonates, while arterial blood gases and capillary heel sticks – the accepted standard for accurate PaCO₂ information – present important issues in the NICU such as blood loss, infection, and pain.

Prioritize NIV safely

tcPCO₂ provides accurate, continuous information where other monitoring technologies fail to deliver – including in high frequency and high flow ventilation methods, bubble CPAP, and spontaneous breathing.



Are Flavonoids Effective For Perineal Pain And Safe For Breastfeeding?

A Uryash MD, Ph D , BM Petrikovsky MD, Ph D , Y Garbie MD, J Nawshin MD, and J Schwob MD

Introduction

Post-episiotomy pain remains a common complaint in obstetrical patients. Novel drug formulations can be used to reduce post-episiotomy pain and promote an anti-inflammatory response. The goal of this report is to analyze the effectiveness and safety of flavonoids in addressing inflammation and pain caused by episiotomy. Flavonoids commonly consumed with food are xenobiotics. They possess antioxidant and anti-inflammatory properties. Flavonoids serve as inhibitors of lipid peroxidation in the biological membranes. They facilitate wound healing due to their antimicrobial, antioxidant, and anti-inflammatory properties.¹ Naringin (4,5,7-trihydroxyflavone 7-rhamnoglucoside) is a major flavanone glycoside.^{1,2} Previous studies have demonstrated that naringin promotes skin protection, wound repair, and tissue regeneration.^{3,4}

Materials and Methods

In this study we analyzed pain reducing effect of flavonoid-terpenoid naringin (Relivra) used as topical spray. The study was conducted in an outpatient setting in 46 women aged 18 to 39, who underwent a vaginal delivery with an episiotomy. Post-episiotomy pain was assessed according to the Visual Analog Scale (VAS)⁽⁵⁾. At the end of the treatment, healing progress was analyzed, based on wound healing, progress in the study, and placebo groups. To assess the safety of naringin-based preparation, we evaluated the presence of naringin and its concentrations in human milk after topical applications.

Results

The average pain score in patients of Relivra treatment group (35 ± 3 mm) was significantly lower compared to the placebo group (78 ± 5 mm). In Relivra treatment group pain was reduced by 42% ($P < 0.001$) (Fig 1).

In our study, topical application of 0.1 ml naringin in 9 lactating female volunteers resulted in naringin calculated maximum concentration (Cmax) for post-exposure 0.02 0.01 nmol/l ($P < 0.001$) or less than 0.1 ppm in individual milk samples. Naringin impregnated gel spray, applied over the skin, did not produce any skin irritation, erythema, or edema.

Conclusion

Treatments with plant-flavonoid peptide coupled with impregnated sol-gels caused a significant decrease in post-

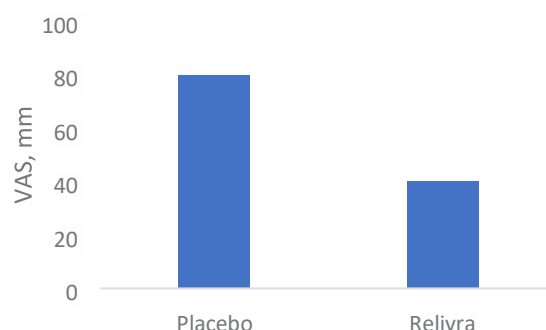


Figure 1. Pain score after treatment

episiotomy pain. The advanced biocatalyst topical formulation promotes wound healing. The proposed mechanism of action is the down-regulation of inflammatory, oxidant molecular factors and the up-regulation of protective cell signaling without diffusion to breast milk. Additionally, the effective delivery of protective and pro-regeneration molecules can modulate collagen and growth factor expression and induce angiogenesis and tissue regeneration. Naringin is commonly found in human milk in nmol/l concentrations without any documented adverse effects to the newborn. Our study has demonstrated that the topical application of naringin in Relivra sol-gel did not result in diffusion into the milk of breast-feeding women.

Based on the mechanisms of biosynthesis of human milk, diffusion of substances with a molecular weight exceeding 500 Da will be significantly lower compared to low molecular weight components, and naringin (580 Da) concentration in human milk will be lower than serum concentration.^{6,7} Naringin may increase the anti-oxidative and bacteriostatic properties of human milk without toxicity to infants, in comparison to synthetic pharmaceuticals.^{8,9}

Studies conducted to assess presence of flavonoids in human milk documented mean naringin concentration of 330.0 nmol/l in female volunteers ingesting 250 ml of red grapefruit juice, which corresponds to naturally occurring naringin in the regular diet of breastfeeding women.^{10,11} In summary, naringin-based spray is an effective and safe remedy for post-episiotomy pain and should be added to obstetrical armamentarium.

References

- 1 Uryash A, Mijares A, Flores V, et al. Cardioprotective effects of naringin in a rodent model of type 2 diabetes. *Front*

All authors are with Mount Sinai Medical Center, Miami, FL, New York Institute of Technology.

- Pharmacol 2021;12.
- 2 Uryash A, Adams J, Lopez JR. Cardioprotection in diabetic cardiomyopathy via upregulation of atp-sensitive K⁺ channels, *Circulation* 2019; 140: Suppl:1-11648
 - 3 Tripathi A, Awasthi H, Rokaya D, et al. Antimicrobial and Wound Healing Potential of Dietary Flavonoid Naringenin. *The Nat Prod.* 2019; 9(1)
 - 4 Kandhare A, Mithun J, Subhash A. Wound healing potential of naringin ointment formulation via regulating the expression of inflammatory, apoptotic and growth mediators. *Pharmaceut Biol.* 2015;54: 1-14
 - 5 Gould D, Kelly D, Goldstone L, Gammon J. Visual Analogue Scale (VAS). *J Clin Nurs* 2001; 10:697-706
 - 6 Rowe H, Baker T, Hale TW. Maternal medication, drug use, and breastfeeding. *Pediatr Clin North Am.* 2013;60(1):275-94
 - 7 Daly SE, Owens RA, Hartmann PE. The short-term synthesis and infant-regulated removal of milk in lactating women. *Exp Physiol.* 1993;78(2):209-20
 - 8 Tsopmo A. Phytochemicals in human milk and their potential antioxidative protection. *Antioxidants (Basel).* 2018 Feb 22;7(2):32
 - 9 Romaszko E, Marzec-Wróblewska U, Badura A, Bucinski A. Does consumption of red grapefruit juice alter naringenin concentration in milk produced by breastfeeding mothers? *PLoS One.* 2017 Oct 5;12(10):13
 - 10 Sawksin MJ, Saldin LT, Badylak SF, White LJ. Hydrogels for Regenerative Medicine; Extracellular Matrix for Tissue Engineering and Biomaterials, Stem Cell Biology and Regenerative Medicine, ed. Springer Nature 2018
 - 11 Song BJ, Jouni ZE, Ferruzzi MG. Assessment of phytochemical content in human milk during different stages of lactation. *Nutrition.* 2013;29(1):195-202.

News...continued from page 18

electrographic evidence of seizures during the 12 hours prior to rewarming compared with the first 12 hours of rewarming. Compared with the 12 hours prior to rewarming, infants had significantly greater seizure risk during the first 12 hours of treatment for both 72-hour rewarming (odds ratio 2.7) and 120-hour rewarming (OR 3.2). At ages 18-22 months, the infants who experienced seizures during rewarming had a significantly higher risk of mortality or severe disability (OR 1.7) in adjusted analysis that accounted for baseline clinical encephalopathy and seizures as well as treatment center. “The presence of higher odds of seizures during rewarming that are associated with death and disability at two years is a new and important finding,” said lead study author Dr Lina Chalak, a professor of pediatrics and psychiatry and director of the Neonatal Neurological Intensive Care and Fetal and Neonatal Neurology Fellowship Program at the University of Texas Southwestern Medical Center in Dallas. “The underlying mechanisms are likely related to impaired auto-regulation with hemodynamic mismatch between oxygen delivery and metabolic demands during rewarming which precipitates seizures,” Dr Chalak said by email. These results suggest that there’s a significantly elevated risk of seizures during the rewarming period, most of which typically go unnoticed if not monitored with EEG or amplitude compressed EEG, Dr. Chalak added. For infants randomized to a 72-hour rewarming period, 27% experienced seizures during the first 12 hours of rewarming, compared with 14% in the 12 hours prior to initiation of rewarming. For infants randomized to a 120-hour rewarming period, 21% experienced seizures during the first 12 hours of rewarming, compared with 10% in the 12 hours prior to treatment initiation.

Neonate Rewarming Tied to Increased Electrographic Seizure Risk, Poor 2-Year Outcomes

Hypothermia has been shown to improve long-term outcomes in neonatal hypoxic ischemic encephalopathy compared to normothermia. Despite this, there is room for optimization of care, as 29% of infants continue to have abnormal outcomes at age 18 to 22 months, where data on the risk of seizures during the rewarming phase is limited. This nested cohort study (SMART) assessed the likelihood of electrographic seizures during rewarming at 72 or 120 hours and their association with neurodevelopmental outcomes at 2 years, where it was hypothesized that seizures during rewarming were associated with higher odds of abnormal neurodevelopmental outcomes. The main endpoint was the occurrence of electrographic seizures during rewarming initiated at 72 or 120 hours compared with the preceding 12-hour epoch. Secondary endpoints included death or moderate or severe disability at age 18 to 22 months. Among 120 newborns, higher occurrence of electrographic seizure during the rewarming phase after hypothermia was associated with elevated relative risk of death or disability at 2-year follow-up. This association between seizure occurrence during rewarming and poor neurodevelopmental outcomes supported the American Clinical Neurophysiology Society’s Guidelines of continuous electroencephalography monitoring in neonates with suspected perinatal asphyxia at high risk. In addition to the standard 72-hour duration of hypothermia, it is recommended that monitoring be continued throughout rewarming until normothermia and seizure control has been achieved. A limitation of this study was the lack of hemodynamic evaluation to confirm the underlying mechanisms of electrographic seizures and rule out confounding causes of seizure in neonates.

Continued on page 33...

NICU Noise: 50 Years of Worry, and We're Finally Getting Somewhere!

Andrew Unger, MD, FAAP

A low profile, right-sized, easy to firmly apply and easy to remove, skin-friendly noise muffling device, engineered to provide significant acoustic protection against the majority of loud transient noises encountered by neonatal patients—whether the transient high frequency loud noises premature neonates typically experience in the NICU, or the broader frequency loud noises generated during infant transport or MR imaging—would represent a highly useful addition to current neonatal patient care.^{1,2} Such a device—quite simply “ earmuffs that actually work ”—could be a key part of a *data-driven*, holistic approach to reducing stressful infant noise exposure within the modern healthcare environment. To understand why, we first need to know a little history—and then review the modern data on NICU noise exposure.

In 1970, Richard Nixon founded the Environmental Protection Agency, the EPA. In 1974, two EPA researchers working on indoor office safety walked out alone into the middle of a rural tomato field in California's Central Valley on a still summer night and measured just how quiet it was.

It was very quiet. So quiet that two people could conduct a conversation with 100% comprehension standing ten feet apart without raising their voices. Ideal acoustics, in fact, for indoor office work.³ The average sound level in that otherwise deserted tomato field measured 45 dBA.

Meanwhile, also during the 1970's, neonatal intensive care units (NICU's) began proliferating throughout the United States—and more and more extremely premature newborns began surviving to hospital discharge. These new NICU's were noisy. Vital Sign monitors alarmed frequently, as did first generation transcutaneous oxygen saturation monitors of various designs. Doctors were shouting verbal orders, the portable X-ray machines made noise, the incubators made noise, the ventilators made noise—sometimes LOTS of noise—and they too had their own alarms. The telephones never stopped ringing.

It soon became obvious—most US NICU's were *too* noisy. NICU nurses could see that their patients weren't getting enough sleep. Not only that, quite a few NICU 'graduates' had permanent hearing disabilities. Some of that hearing loss might be due to excess noise exposure. After all, exposure to excess oxygen had helped cause an epidemic of blindness from Retinopathy of Prematurity, during the 1960's.

In 1997, the American Academy of Pediatrics decided that it needed to establish an acoustic standard for NICU's.⁴ At that time, good data on hearing impairment and long-term occupational exposure to factory noise was widely available, but little was known directly relevant to this novel environment—the NICU. Or to the response to noise of NICU patients—particularly premature infants.

Using the data that did exist, the Academy's focus was on preventing noise-related hearing loss. Noise-related sleep disturbance was recognized, but not directly addressed. Neither was vital sign instability—now commonly considered evidence of patient stress.

In the end, the Academy published a Position Paper that concluded that the best way to prevent even the slightest chance of NICU noise causing patient hearing loss was to adopt as a recommended Guideline for NICU Acoustics the EPA's 1974 recommended noise level for an ideally quiet business office. The 'tomato field' standard: an average sound level of 45dBA.

NICU's in the United States have struggled to achieve this degree of quiet ever since.

Indeed, the AAP standard for acceptable NICU noise level is nearly unattainable—and now is known to be irrelevant. Caregivers can state this with confidence because, since the 1970's, our understanding of normal fetal and newborn noise exposure, as well as the acoustic characteristics of NICU noise—has grown markedly. In addition, the clinical implications of NICU noise with respect to sleep and stress have now been reported in detail.



Photo by Brands&People on Unsplash.

Andrew Unger MD FAAP is one of the co-Founders of NEATCap Medical, LLC, and currently serves as its Medical Director

A brief summary of more modern findings related to fetal and NICU Noise Exposure and the Effects of Noise Exposure upon NICU patients follows:

1) The normal fetal acoustic environment has been well measured,⁵ as has the fetal and neonatal response to external noise. The gravid uterus is not quiet at all. In fact, it is much louder, on average than 45 dBA. Most of the sound that the fetus is exposed consists of low-frequency noise from maternal blood circulation, as well as bowel activity. The fetus also hears her mother's voice very well whenever she is talking—but the maternal uterus and anterior abdominal wall effectively filter out all but the loudest external noises, particularly noises of high frequency.

2) A gross motor response of the fetus and the neonate to loud external noises is almost always present by 32 weeks of gestation⁶ and may frequently be observed at earlier gestational ages. Typical fetal and neonatal 'non-auditory' responses to loud external noise besides body movements include tachycardia, apnea, and arousal.⁷ Collectively, these responses to loud noises are considered to be strong evidence of increased patient stress.

3) Most modern NICU's are quieter than those of past decades—with average dBA measurements in the 50's—quieter except when there are transient vital signs or ventilator function-related monitor alarms, or patient care interventions that involve the manipulation of respiratory tubing, infant feeding and cleaning, or the opening/closing of an incubator.⁸ These transient noises are associated with acute vital signs instability among NICU patients.



A Single Family Room NICU patient room.

4) The relatively quiet background noise level state of most modern NICU's has been achieved through various measures, including the wider adoption of Single Family Room (SFR) as opposed to open bay NICU design. In addition, numerous common-sense behavioral interventions directed at quieting caretakers and ancillary personnel have been widely implemented, and NICU patient monitoring equipment itself has improved, yielding fewer false-positive alarms.

Of note, SFR architecture has not been a panacea. The problem of transient loud noises that disrupt patient sleep and induce stress persists, even in SFR environments. There also is preliminary evidence to suggest that some SFR's may be *too quiet*, and delay speech acquisition.⁹ This negative outcome would be expected if adequate exposure to the human voice is not provided to the maturing neonatal patient cared for in a SFR environment.

5) An added complexity in the area of infant noise exposure during healthcare is the loud noise exposure that many neonatal patients encounter during both in-hospital and inter-hospital transport, and also during MR imaging.¹⁰ The loud noises experienced by infants during both ambulance and helicopter transport, as well as during MR imaging, tend to be more spread across the frequency spectrum than the primarily high frequency noises most common in the NICU.¹¹



Newborn Interfacility Transport - typical equipment

6) Evidence to support the hypothesis that exposure to background NICU noise levels above 45dB constitutes a significant or direct contributing cause of later hearing impairment in NICU patients is lacking. In contrast, exposure to loud noise transients is known to cause physiological instabilities in neonates including changes in cardiac activity, increases in respiratory rate, apneas, bradycardias and hypoxic episodes.^{12,13} Noise induces a pain-like stress response in neonates.¹⁴ Further, exposure to loud noises disrupts sleep.¹⁵ Since the amount of sleep *and* sleep-wake patterns may significantly affect neurodevelopment and long-term behavioral and cognitive outcomes,^{16,17,18} sleep disruption during care should be avoided.

In addition, infant MR imaging currently often is constrained in both image quality and study duration by motion-related artifact. Most neonatal patients undergoing prolonged MR imaging either are sedated, or great lengths are taken to muffle their exposure to procedural noise, which has been observed to have an arousing, non-auditory effect—even on recently fed and swaddled infants.

7) Finally, evidence that adequate early exposure to human voices is essential for proper infant speech development now is overwhelming.^{19,20}

Considering the above, a modern, holistic and *data-driven* approach to the problem of noise exposure among hospitalized neonates would primarily consist of an effort to reduce the frequency and intensity of patient exposures to arousing, stressful, loud transient noises—both low and high



frequency — while concurrently maintaining a reasonably quiet NICU. Ensuring adequate patient exposure to normal speech also would be necessary. A combination of 1) intelligent NICU design, 2) appropriate patient care-provider behavior, as well as 3) situation-specific on-patient interventions to physically muffle patient exposure to transient loud noises — would constitute the three mainstays of such a rational solution.



Types of neonatal ear muffs in current use.

Unfortunately, many hearing protection devices currently in use for neonates have significant limitations. Moldable ear canal plugs of various compositions represent an effective noise-muffling intervention, but rarely are employed due to fears of ear canal skin irritation and/or difficult plug removal. Adhesive foam ear coverings provide at most 7dB of noise protection, are not well-suited to the frequent application-removal-inspection-reapplication cycles characteristic of best-practice NICU care, detach easily in humid patient-care environments, and are not recommended for use during MR imaging. Adult-style semi-spherical ear muffs shrunk to term infant size can provide quite good acoustic muffling, but are bulky and difficult to secure snugly. They also are untested and unavailable in sizes suitable for the premature neonatal population. Of note, an improved design for MR and NICU safe neonatal ear muffs, appropriate for both premature and term infants, recently has become available.



After some 50 years of justifiable concern and confusion, clinicians finally have both the data and the tools to minimize the adverse effects of excessive noise exposure upon medically fragile newborns.

References

- 1 Chouery, N. Dunckley, K.T. Use of Hearing Protection in Neonatal Intensive Care Unit Patients: A Systematic Review of the Evidence. *J Early Hearing Detection and Intervention* (2018) 3, 37-46.
- 2 See: <https://www.neatcapmedical.com/>

- 3 Environmental Protection Agency, Office of Noise Abatement and Control. *Information on Levels of Environmental Noise Requisite to Protect Public Health and Welfare With an Adequate Margin of Safety*. Washington, DC: Government Printing Office (1974).
- 4 American Academy of Pediatrics Committee on Environmental Health. Noise: A hazard for the fetus and newborn. *Pediatrics*. (1997) 100, 724-727.
- 5 R.M. Abrams, K.J. Gerhardt. The acoustic environment and physiological responses of the fetus. *J. Perinatol.* (2000) 20, 31-36.
- 6 P.G. Hepper, B.S. Shahidullah Development of fetal hearing. *Arch Dis Child Fetal Neonatal Ed.* (1994) 71, 81-87.
- 7 L.K. Zahr, S. Balian. Responses of premature infants to routine nursing interventions and noise in the NICU. *Nurs Res.* (1995) 44,179-185.
- 8 S.W. Smith, A.J. Ortmann, W.W. Clark, Noise in the Neonatal Intensive Care Unit: A New Approach to Examining Acoustic Events. *Noise Health.* (2018) 20, 121-130.
- 9 B.M. Lester, A.L. Salisbury, K. Hawes, L.M. Dansereau, R. Bigsby, A. Laptook, M. Taub, L.L. Lagasse, B.R. Vohr, J.F.Padbury. 18-Month Follow-Up of Infants Cared for in a Single-Family Room Neonatal Intensive Care Unit. *J Pediatr.* (2016) 177, 84-89.
- 10 B.M. Karlsson, M. Lindkvist, W. Karlsson, R. Lundstrom, S. Hakansson, U. Wiklund, J. van den Berg. Sound and Vibration: effects on infants' heart rate and heart rate variability during neonatal transport. *Acta Paediatrica.* (2012) 101, 148-154.
- 11 J.A. Tkach, Y. Li, R.G. Pratt, K.A. Baroch, W. Loew, B.R. Daniels, R.O. Giaquinto, S.L. Merhar, B.M. Kline-Fath, C.L. Dumoulin. Characterization of acoustic Noise in a neonatal intensive care unit MRI system. *Pediatr. Radiol.* (2014) 44, 1011-1019.
- 12 E.M. Wachman, A. Lahav. Effects of noise on preterm infants in the NICU, *Arch. Dis. Child. Fetal Neonatal Ed.* (2011) 96, 305-310.
- 13 Bremner P, Byers JF, Kiehl E. Noise and the premature infant: Physiological effects and practice implications. *J Obstet Gynecol Neonatal Nurs.* (2003) 32, 447-54.
- 14 A. Salavitarab, K.K. Haidet, C.S. Adkins, E.J. Susman, C. Palmer, H. Storm. Preterm infants' sympathetic arousal and associated behavioral responses to sound stimuli in the NICU, *Adv. Neonatal Care.* (2010) 10, 158-166.
- 15 M.G. Monsén, U.M. Edéll-Gustafsson. Noise and sleep disturbance factors before and after implementation of a behavioural modification programme, *Intensive Crit. Care Nurs.* (2005) 21, 208-219.
- 16 S. Gertner, C.W. Greenbaum, A. Sadeh, Z. Dolfin, L. Sirota, Y. Ben-Nun. Sleep-wake patterns in preterm infants and 6 month's home environment: Implications for early cognitive development. *Early Hum. Devel.* (2002) 68, 93-102.
- 17 I.F. Borghese, K.L. Minard, E.B. Thoman. Sleep rhythmicity in premature infants: implications for developmental status. *Sleep.* (1995) 18, 523-530.
- 18 S. Graven. Sleep and brain development. *Clin. Perinatol.* (2006) 33, 693-706.
- 19 V.A. Marchman, K.A. Adams, E.C. Loi, A. Fernald, H.M. Feldman. Language processing efficiency predicts later receptive vocabulary outcomes in children born preterm. *Child Neuropsychol.* (2015) 22, 649-665.
- 20 E. McMahon, P. Wintermark, A. Lahav. Auditory brain development in premature infants: the importance of early experience. *Ann. N.Y. Acad. Sci.* (2012) 1252, 17-24.

DREAMIES® & DREAMIES® T-M

Advanced Hearing Protection for Neonatal Intensive Care

NICU, Transport or MRI...
we have you covered
no matter where you are!

DREAMIES

- 18 dB overall sound attenuation
- Closely simulates mother's natural noise protection
- Blocks NICU alarm sounds; allows some voice transmission



DREAMIES T-M

- 25 dB overall sound attenuation
- Blocks low-frequency Transport noise
- MR Safe
- Blocks broad-spectrum MRI noise



Features:

- **Progressive sizing** (XS, S, M, LG)
23-39 cm head circumference
- **Transparent ear cups**
 - Low profile; contoured shape
 - Soft foam seal
- **Adjustable band** for securing ear cups and ensuring proper fit
- **Ease of use** - easily integrated into patient care



Rx only



301 Broadway, Suite 203
Bethlehem, PA 18015-1559
Phone: 888-403-6328

www.neatcapmedical.com

Got Milk? Increasing Mom's Milk Volumes by Overcoming Pumping Barriers

Lori Wood, MSN, CNS, RNC-NIC, IBCLC

Mothers of infants in the Neonatal Intensive Care Unit (NICU) face daily challenges to the initiation of lactation (the provision of human milk), continued pumping, increasing the volume of milk to meet the increasing needs of a growing baby, and the transition of feedings by gavage to breastfeeding. The provision of human milk by pumping is reliant on several factors. Moms must be motivated to pump which is often driven by education on the necessity and value of mom's own human milk (MOM). Many physical factors can influence mom's milk volume. Timing and diligence of pumping affect coming to volume (CTV) as well. In addition to the barriers all moms face, significant and continuing data points to the struggles faced by black women as well as moms suffering from postpartum depression. Education, continued communication, support, and standardized and consistent practices will help at-risk moms to improve outcomes.

Mothers of infants delivered preterm are at risk for failure to progress to lactogenesis II following the birth of their baby. Many interventions and best practices can influence mom's production and increase the chances of meeting breastfeeding goals. Preterm delivery is often complicated by additional risk factors such as: overweight and obesity (body mass index ≥ 25), preeclampsia, cesarean section delivery, prolonged bed rest and postpartum hemorrhage (described as total blood loss ≥ 500 milliliters). These complications and conditions can result in reduced levels of prolactin; the hormone needed to begin lactogenesis II resulting in high volumes of milk. RNs and lactation staff working with moms in the NICU should be aware of these issues. Following daily outputs and number of pumpings should be a priority, especially in the first two weeks. This very important time in the initiation of lactation sets the stage for future volumes of milk which dictates the ability of mom to provide the amounts needed as the infant grows and consumption increases.¹

A negative correlation with obese and overweight moms and the ability to meet breastfeeding goals and provide MOM have been established for over a decade. First time overweight or obese moms have been noted to be less successful at establishing sufficient milk volumes and continuing milk expression. Overweight mothers are 50% more likely to need a cesarean section, considered to be a risk factor for delayed onset of



lactogenesis II. Moms with a high body mass index (BMI) are noted to be at risk for early cessation of pumping and providing milk for their infants.² Addressing the special needs of the overweight mother who has delivered a preterm infant early and consistently may prove to increase milk production and meet the breast feeding goals of these moms.²⁻⁵

Mapping out a plan inclusive of timing and equipment is also imperative to setting up the behavioral needs of the pumping mom. Critical factors to initiation include: effective breast pumps that completely empty the breast, timely pumping intervals both frequent and in longevity, proper fitting of breast shields, and suction pressures that are individualized to mom and not too low.⁵ Once CTV is established, daily pumping and continued dedication often wane. While the endorsement of The American Academy of Pediatrics for exclusive provision of human milk in the first six months of life has greatly increased support in the NICU for pumping moms, the continuation of pumping for infants with extended stays often declines.⁶ Pumping long term is often described as inconvenient and time consuming which results in decreased number of pumpings over long months and a reduced milk volume.⁷ Stress related to the wellbeing of the baby coupled with travel between home and the hospital and possibly the care of other children at home can be overwhelming. Coping with pump dependency for the mother, as well as continued stress, often prove too much and mothers may experience a decrease in volume. As the infant grows and gains weight, requiring more milk, mom can often feel defeated when she can't keep up with the amount of milk needed by her baby. These feelings may result in giving up pumping. Multiple articles of support for moms who decide to no longer pump can be found

Lori Wood is a Neonatal Clinical Nurse Specialist at Desert Regional Medical Center, Palm Springs, CA. Lori is certified as a RNC-NIC in Neonatal Intensive Care Nursing and is an International Board Certified Lactation Consultant. She is also a consultant for Medela, LLC.

online.¹⁰ Hospital lactation staff and nurses should be aware of these feelings and provide support and evidence-based strategies early to reduce these situations.⁷ While many moms initiate pumping upon admission to the NICU with 60-80% of moms providing milk to their infants, only 44-49% of babies are still receiving some mother's own milk at discharge.^{8,9}

Diversity in educational and cultural beliefs among certain populations can also affect desire and decision to breastfeed as well as continued success. Initiation and the continuation of pumping to provide milk for baby can be hinged to best practices with these populations.¹ Understanding disparities and differences may help healthcare workers in the NICU to encourage mothers to choose human milk for many reasons.

Black mothers, especially those living in low socioeconomic conditions, remain less likely to breastfeed or provide human milk to their babies than white women. Low income hispanic mothers were more likely than black women to provide milk for their infants.¹ Black women in the United States are 2.6 times more likely than white (non-hispanic) women to give birth to a very low birth weight (VLBW) infant weighing less than 1500 grams.¹¹ We know from years of study, that an exclusively human milk diet greatly reduces the incidence of morbidities associated with preterm birth. Problems such as necrotizing enterocolitis, chronic lung disease, retinopathy of prematurity, neurodevelopmental delays and sepsis can be reduced.^{6,12-14} These benefits of a human milk diet are noted in correlation with the amount of human milk, especially MOM, received by the infant.^{1,6} Therefore, if we as healthcare providers are able to influence the decision of black mothers to begin and continue pumping, we can increase the amount of MOM received by the infant and improve neonatal outcomes.

Benefits of breastfeeding extend to the mother providing milk for her infant as well. The lifelong health of the mother can be improved in many ways including a reduced risk of hypertension, myocardial infarction, ovarian and breast cancer and complications of diabetes.¹⁵⁻¹⁷ These maternal health benefits are increased by the longevity of breastfeeding or pumping milk. The longer a mother provides milk for her infant, the greater the potential of the health benefits for mom. Encouraging mom to begin pumping for her VLBW infant and continuing support to increase the time pumping and the amount of milk received reduces these racial disparities and improves the health and quality of life for moms and babies.

Multiple studies point to the fact that black American mothers are less likely to pump and provide milk for their VLBW babies.¹⁸⁻²³ Some reported barriers include: initial plan to breastfeed during the pregnancy, education at the time of a preterm birth on the benefits of MOM to the infant, age and education of the mother, eligibility to receive aid (formula), and surprisingly the advice and influence of the maternal grandmother.¹⁸ In favor of reducing stress and improving quality of life, some moms will decrease or discontinue pumping before baby is discharged. Lack of support is another reason moms may choose not to pump, or pump for a limited time. Lack of support of the maternal grandmother, especially in black teen moms who live at home with their mother, was commonly cited as a reason to stop pumping. Young mothers living at home were often encouraged to continue their schooling or work to develop life skills; time spent pumping may be seen as a barrier to these priorities.²⁴ These living situations are reportedly



Hollie Santos, unsplash.com

associated with stress and dysfunction as related to parenting and result in less time providing milk for baby.²³⁻²⁶ Receipt of aid for nutritional support is another common factor in the decision not to breastfeed or pump especially among black mothers. Using formula may still be seen as a sign of wealth and a higher status by black mothers and especially black maternal grandmothers, influencing their daughter's decisions. Education and information, prior to delivery, may change this decision.^{27,28} Effect on breastfeeding and pregnancy outcomes with mothers who lack access to a car, and neighborhood influences such as crime, economic disadvantage, and deprivation remain in question. While black families disproportionately live in lower socio economic neighborhoods, studies and statistics show varied reports of negative versus no impact on duration of lactation in particular. This may be due to the increasing education and provision of services, guidance, and equipment such as pumps and breast shields. This is encouraging for caregivers in NICU settings. This data should be fuel for leaders in the NICU to continue to advocate for educational support, lactation consultants, and the provision of equipment to lower income moms.^{21,29-32} Postpartum Depression (PPD), especially during this COVID-19 Pandemic, has reached new heights. NICU moms with premature babies are at-risk of developing postpartum depression. PPD affects about 11% of all new mothers in the first three months following birth, but NICU moms experience PPD in greater numbers with 28-40% of all moms showing signs.^{33,34} Many studies show an increase in PPD to 28.6-44% during the COVID-19 Pandemic.³⁵⁻³⁷ Studies also point



Medela Symphony® Pump

to an increase in maternal depression with lower gestational age deliveries.³⁸ It is well known that breastfeeding decreases PPD. Oxytocin is released during milk ejection which enhances feelings of maternal competence, well being, reduces anxiety, and promotes mother infant bonding. Skin to skin care promotes many of these same feelings and increases maternal milk production by increasing prolactin levels. Mothers who provide milk for their NICU babies also report feelings of control and a greater participation in the care of their infant.³⁹ In a small study by Hollen, et al, a relationship between the lack of pumping and greater PPD was noted. A call for more studies will provide important information to push for continued support for mothers pumping in the NICU for yet another reason, a reduction in depression. Initiation of pumping is a key intervention for the wellbeing of both babies and mothers.³⁸

Lastly, difficulties in transitioning to feeding at the breast remains difficult for NICU moms. As already noted, many moms initiate pumping soon after delivery, but only 44% of infants are still receiving breast milk at the time of discharge. Moms of VLBW infants provide milk when the baby requires small amounts via gavage feedings, but as baby grows and requires more, moms may become discouraged at the inability to keep up. Best practices with regards to promoting early breastfeeding and a transition from small trophic gavage feedings to actual feeding at the breast can improve outcomes and support mom's early intent to breastfeed.¹

With many identified barriers to the initiation of lactation and continued pumping, how can hospital staff help moms? In addition to education and counsel, many best practices exist. First and most important is to establish pumping with a hospital-grade pump. Early pumping is best using a golden hour approach. The golden hour following delivery in term infants calls for placing the baby on the mother's breast, providing skin to skin care, and allowing breast feeding to occur. When mom and baby are separated, the pump now takes the place of baby; pumping should ideally occur in the first hour following birth. The mother's birth support person can easily be taught how to set up the pump and can assist mom. This can improve time spent pumping and can relieve the labor nurse from trying to incorporate this into cares, which is often a barrier to pumping. A few minutes spent educating the support person on pump set up empowers that person to help and provides consistent time pumping. Educating labor and delivery nurses on the importance of early pumping can improve CTV and positively affect mom's initiation.⁴²

Another best practice is using an evidence-based pump. The Medela Symphony® pump is an evidence-based choice providing

a researched pattern which closely mimics early infant sucking patterns. The Symphony pump is shown to increase the volume of milk expressed. Initiate program is used first.

Encouraging mom to pump approximately eight times a day in this mode brings an increase in volume. Once mom reaches three consecutive pumpings of 20 milliliters (mls) from both breasts, mom can switch to the maintain program. Moms starting with the initiate program see approximately 200 mls more per day, a significant amount needed by the NICU nurses to provide feedings and oral care. Using this pump and its Initiation Technology™ provide a significant improvement milk volume.⁴⁷

Reducing tension and stress during the COVID-19 Pandemic proves to be difficult. Healthcare staff, parents and family suffer the effects of lock down, isolation, and reduced support from family and friends. Incorporating music therapy has proved beneficial for babies, families, and hospital staff during these difficult times. A music program at the University of California San Francisco's Benioff Hospital has proved helpful for children of all ages, including infants, to reduce stress, pain, anxiety, and improve developmental support.^{43,44} Listening to music is shown to provide support. Music therapy can prove useful in reducing the stressors of moms and may promote relaxation and concentration in mothers focusing on pumping and providing milk for their babies. Several studies have effectively used music to reduce maternal anxiety, improve breastfeeding and increase milk volumes.^{45,46} Using music in pumping rooms, at the baby's bedside, and anywhere mom may be pumping can be a useful aid in improving milk production.

The paradigm of breastfeeding for prematurely delivered infants must change. Instead of breastfeeding solely referring to baby at the breast, we as caregivers must begin to see multiple practices as breastfeeding for preterm infants. Early skin to skin care (STS) with ventilated infants should be seen as breastfeeding for VLBW babies. By using a standing transfer method of placing baby skin to skin while still on a ventilator or other respiratory modalities of care, the mother or father can easily transfer the baby to the chest with minimal disruption supporting developmental care.⁴⁰ By starting baby and mom in early STS holding this becomes the first step in the transition from gavage feeds to feeding at the breast.^{1,42,48}

Oral Care with colostrum is another step in transitioning the infant to feeding at the breast. Oral care has many evidence-based benefits. Colostrum triggers the mucosa and gastric associated lymph tissue (MALT and GALT) which help to protect the newly born infant.^{41,42} These systems help to protect the infant from morbidities such as necrotizing enterocolitis and ventilator associated events such as pneumonia. Oral care with colostrum also begins the gustatory development of the VLBW infant. By placing a small amount of mom's colostrum in the infant's mouth, both taste and smell are stimulated and the infant begins to develop this important sense which is integral to successful and competent oral feedings. Oral care with colostrum should be viewed as breastfeeding in the small, preterm infant.⁴⁸

The next step in transitioning to breastfeeding is promoting non nutritive suck (NNS) at the breast. Infants begin NNS at about 28 weeks gestation. By continuing daily STS care and progressing to NNS at a pumped breast, NICU staff can continue the progression to feeding at the breast. Mom can pump just prior

to baby's feeding time and then during the gavage feed, place baby to the breast and begin the association of becoming full and suckling at the breast. By pumping prior to the feed, the infant who is not yet gestationally ready to suck, swallow and breath, but who is gaining competence in sucking can "practice" prior to the next step. NNS at a pumped, "dry" breast is breastfeeding in these preterm babies.⁴⁸

The last stage of transition is actually placing baby at the breast, ready for a feeding. The concept of infant driven feedings, or cue based feedings, should be used when beginning oral feeds. Cue-based feedings rely on assessing the baby's current status and readiness to feed. Infants are usually ready to begin oral feedings at approximately 32-34 weeks gestation. Each facility should research and develop its own protocol for progressing baby through oral feedings. A validated scoring system to assess baby's current status should be used to determine if the baby is showing signs or engagement, wakefulness, and physiologic stability needed to feed. Many NICUs may choose to begin feeding with a bottle, however if a mother is interested in feeding at the breast, the infant can safely start by breastfeeding. By placing baby to the breast, instead of a bottle, and continuing to assess during the feed, the infant can begin transitioning to the breast instead of bottle feedings. If the baby continues to show engagement and stability, the feeding can continue until the baby tires or is done feeding. Feeding at the breast following a cue based strategy is supporting continued comfort and competence at the breast.^{49,50}

A continued model of progression serves to get baby to the breast much earlier and more consistently than the usual afterthought of placing baby at the breast a week or two prior to discharge home. By consistently providing the baby with increasing encounters and experience at the breast, this becomes a safe and comfortable place for baby. Mom becomes encouraged and comfortable with each step. The transition is gradual and paced leading to better success. The more time mom has with baby at the breast, the more competent the pair becomes. This leads to better success prior to discharge, leaving mom and baby better suited to continue at home.⁴⁸

An important part of feeding progression in VLBW infants includes competence at oral feedings and progression from gavage feeds to feeding at the breast. This important facet of feeding care is often overlooked by NICU staff. A steady progression and early immersion are part of nurturing the infant who's successful gestation rests in the hands of the provider. We must change our paradigm of breastfeeding.

Understanding that each part, STS, oral care with colostrum, NNS at an empty breast, cue-based feeding, and finally full feeds at the breast are all breastfeeding at that gestational age, makes us better suited to meet the needs of the mother/infant pair.

The initiation of lactation is the first crucial step. Early and consistent attention must be given every day to mom and her pumping regime. Pumping logs, follow up with a lactation consultant or nursing staff are the beginning steps. Careful attention to volume produced, time spent pumping, suction pressures, and proper fitting of breast shields is integral to the outcome. Time educating NICU staff on this importance and changing the hierarchy of skills and priorities to include a strong focus on early breastfeeding and initiation of lactation will

produce more of the greatest gift that mom can give her baby.

The more we embody the concept that without mom's own milk, we as caregivers are unable to provide the best care, the better we will become at supporting lactation and all its needs. By focusing on some of the unique barriers such as social and racial disparities and depression in moms, we can identify the individual needs of each mom and create a specific plan geared to pump up the volume and show us the milk.

References

- 1 Meier, P., Johnson, T., Patel, A. & Rossman, B. (2017). Evidence-based methods that promote human milk feedings of preterm infants: an expert review. *Clinical Perinatology* 44(1). Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5328421/>
- 2 Wood, L. (2014). Increased Maternal Body Mass Index and Overweight: Impacts of Breastfeeding Outcomes and Implications for NICU Staff. *Neonatal Intensive Care Magazine* 27(3). Retrieved from nicmag.ca/pdf/NIC-27-3-MJ14-R7-web.pdf
- 3 Leonard, S., Labiner-Wolfe, J., Geraghty, S & Rasmussen, K (2011). Associations between high prepregnancy body mass index, breast-milk expression, and breast-milk production and feeding. *The American Journal of Clinical Nutrition* 93(30). Retrieved from <http://ajcn.nutrition.org/content/93/3/556.long>
- 4 Nomssen-Rivers, L., Chantry, C., Pearson, J., Cohen, R. & Dewey, K (2011). Delayed onset of lactogenesis among first-time mothers. *The American Journal of Clinical Nutrition* 92(3). Retrieved from <https://academic.oup.com/ajcn/article/92/3/574/4597439>
- 5 Meier, P. Patel, A., Hoban, R. & Engstrom, J (2016). Which breast pump for mother: An evidence based approach to individualizing breast pump technology. *Journal of Perinatology* 36(7).
- 6 American Academy of Pediatrics (2021). Promoting Human Milk and Breastfeeding for the Very Low Birth Weight Infant. *Pediatrics* 148(5).
- 7 Rossman, B., Meier, P. & Spatz, D. (2018). A wake-up call: Persistent barriers to the Provision of evidence-based lactation support and education in the NICU. *Journal of Perinatology* 38.
- 8 Casavant, S., Judge, M. & McGrath, J. (2017). Influence of anthropometric parameters on breastmilk provision in preterm infants. *Applied Nursing Research* 38.
- 9 Pineda, R. (2011). Predictors of breastfeeding and breastmilk feeding among very low birth weight infants. *Breastfeeding Medicine* 6(1).
- 10 Hand to Hold.org (2013). Letting go of the guilt when pumping doesn't work. Retrieved from <https://handtohold.org/letting-go-of-the-guilt-when-pumping-doesnt-work/>
- 11 March of Dimes ((2017). Very low birthweight by race/ethnicity: United States, 2012-2014 average.
- 12 Patel, A., Johnson, T. & Engstrom J. (2013). Impact of early human milk on sepsis and health care costs in very low birth weight infants. *Journal of Perinatology* 33.
- 13 Patel, A., et al (2017). Influence of mother's own milk on bronchopulmonary dysplasia and costs. *Archives of Disease in Children. Fetal and Neonatal Edition* 102.
- 14 Lechner, B. & Vohr, B (2017). Neurodevelopmental outcomes of preterm infants fed human milk: a systematic review. *Clinical Perinatology* 44.
- 15 Steube, A.(2009). The risk of not breastfeeding for mothers

- and infants. *Reviews in Obstetrics and Gynecology* 2.
- 16 Steube, A. & Schwarz, M. (2010). The risks and benefits of infant feeding practices for women and their children. *Journal of Perinatology* 30.
 - 17 Victoria, C., Bahl, R. & Barros, A., et al (2016). Breastfeeding In the 21st Century: Epidemiology, mechanisms and life long effects. *Lancet* 387.
 - 18 Fleurant, E., Schoeny, M., Hoban, R., Asiodu, I., Riley, B., Meier, P., Bigger, H. & Patel, A. (2016). Barriers to human milk feeding at discharge of very low birth weight infants: maternal goal setting as a key social factor. *Breastfeeding Medicine* 12(1).
 - 19 Hoban R., et al (2015). Goals for human milk feedings in mothers of very low birth weight infants: How do goals change and are they achieved during the NICU hospitalization? *Breastfeeding Medicine* 10.
 - 20 Patel, A., Schoeny, M., Hoban, r., Johnson, T., Bigger, H., Engstrom, J., Fleurant, E., Riley, B. & Meier, P. (2019). Mediators of racial and ethnic disparity in mother's own milk feeding in very low birth weight infants. *Pediatric Research* 85.
 - 21 Riley, B., Schoeny, M., Rogers, L., Asiodu, I., Bigger, H., Meier, P. & Patel, A. Barriers to Human milk feedings at discharge of low-birthweight infants: evaluation of neighborhood structural factors. *Breastfeeding Medicine* 11(7).
 - 22 Kim, J., Fiese, B. & Donova, S. (2017). Breastfeeding is natural, but not the cultural norm: a mixed-methods study of first time breastfeeding, African American mothers participating in WIC. *Journal of Nutrition, Education and Behavior* 49.
 - 23 Asiodu, L., Water, V., Daily, C. & Lyndon, A. (2017). Infant feeding decision making and the influences of social support persons among first time African American Mothers. *Maternal Child Health Journal* 21.
 - 24 Black, M. & Nitz, K. (1996). Grandmother co-residence, parenting and child development among low income, urban teen mothers. *Journal of Adolescent Health* 18.
 - 25 Arnold, A., Lewsi, J. & Maximovich, A. (2011). Antecedents and consequences of caregiving structure on young mothers and their infants. *Maternal Child Health* 15.
 - 26 Gaskin-Butler, V., Engert, T., Markievitz, M., et al. (2012). Prenatal representations of co-parenting among unmarried, first-time African American mothers. *Family Process* 51.
 - 27 Asiodu, L. & Flaskerud, J (2011). Got milk? A look at breastfeeding from an African American perspective. *Issues in Mental Health Nursing* 32.
 - 28 Gross, T., Powell, R., Andersen, A, et al (2015). WIC peer counselors' perceptions of breastfeeding in African American women with lower incomes. *Journal of Human Lactation* 31.
 - 29 Anthopolos, R., Kaufman, J., Messer, L., et al (2014). Racial residential segregation and preterm birth: Built environment as mediator. *Epidemiology* 25 pp. 397-405.
 - 30 Brody, G., Lei, M., Chen, E., et al (2014). Neighborhood poverty and allostatic load in African American youth. *Pediatrics* 134pp. e1362-1368.
 - 31 Burdette, A. (2013). Neighborhood context and breastfeeding behaviors among urban mothers. *Journal of Human Lactation* 26 pp. 597-604.
 - 32 Cubbin, C., Marchi, K., Lin, M., et al (2008). Is neighborhood deprivation independently associated with maternal and infant health? Evidence from Florida and Washington. *Maternal Child Health* 12 pp. 61-74.
 - 33 Hawes, K., McGowan, E., O'Donnell, M., Tucker, R. & Vohr, B. (2016). Social emotional factors increase risk of postpartum depression in mothers of preterm infants. *Journal of Pediatrics* 179 pp. 61-67.
 - 34 Knights, J., Salvatore, M., Simpkins, G., Hunter, K. & Khandelwal, M. (2016). In search of best practice for postpartum depression screening: Is once enough? *European Journal of Obstetrics, Gynecology and Reproductive Biology* 206 pp. 99-104. Retrieved from <https://www.ejog.org/action/showPdf?pii=S0301-2115%2816%2930878-8>
 - 35 Davenport, M., Meyer, S., Meah, V., Strynadka, M. & Khurana, R. (2020). Moms are not OK: COVID-19 and maternal mental health. *Frontiers in Global Women's Health* 1. Retrieved from <https://www.frontiersin.org/articles/10.3389/fghw.2020.00001/full>
 - 36 Vatcheva, T., Mostaert, A., Inglegem, V., Henrion, E. & Legors, L. (2021). Impact of COVID-19 on postpartum depression among mothers of extreme and early preterm infants. *International Journal of Gynecology and Obstetrics* 155 pp.490-495. Retrieved from <https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.13859>
 - 37 Ostacoli, L., Cosma, S., Bevilacqua, F., et al (2020). Psychosocial factors associated with postpartum psychological stress during the COVID-19 pandemic: a cross-sectional study. *BMC Pregnancy and Childbirth*. Retrieved from <https://bmcpregnancychildbirth.biomedcentral.com/track/pdf/10.1186/S12884-020-03399-5.pdf>
 - 38 Hollen, R., Smith, A. & Smith-Gagen, J. (2019). Breastmilk pumping for the mental health of the NICU mother. *Clinical Lactation* 10(2). Retrieved from <https://connect.springerpub.com/content/sgrcl/10/2/60.full.pdf>
 - 39 Flaherman, V., Hicks, K., Huynh, J., Cabana, M. & Lee, K. (2016). Positive and negative experiences of breast pumping during the first 6 months. *Maternal and Child Nutrition* 12(2). Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6860131/pdf/MCN-12-291.pdf>
 - 40 UCSF Benioff Children's Hospital (2018). How To Do a Standing Transfer When Your Baby is on a Respirator. Retrieved from <https://www.youtube.com/watch?v=WD2lCM8arok>
 - 41 Rodriguez, N, Meier, P., Groer, M & Zeller, J. (2009). Oropharyngeal administration of Colostrum to extremely low birth weight infants: Theoretical perspectives. *Journal of Perinatology* 29(1).
 - 42 Wood, L. (2013). Decreasing ventilator associated pneumonia in the neonatal intensive care unit. *neonatal Intensive Care Magazine* Human Milk Edition.
 - 43 Negrete, B. (2020). Meeting the Challenges of the COVID-19 Pandemic: Virtual Developmental Music Therapy Class for Infants in the Neonatal Intensive Care Unit. *Pediatric Nursing* 46(4) pp.198-201.
 - 44 Wood, R. (2021). Singing the COVID Blues: The Intersection of Music Therapy and a Global Pandemic. Manuscript in preparation Regis College.
 - 45 Jayamal, A., Lackshmanagowda, P., Predeep, G. & Goturu J. (2015). Impact of music therapy on breast milk secretion in mothers of premature newborns. *Journal of Clinical Diagnostic Research* 9(4). Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4437063/>
 - 46 Nguyen, H & Aduna, S. (2020). Effects of Music Therapy on Relaxation and Breastfeeding Anxiety. *Journal of Obstetrics Gynecology and Neonatal Nursing* 49(6). Retrieved from [https://www.jognn.org/article/S0884-2175\(20\)30261-6/fulltext](https://www.jognn.org/article/S0884-2175(20)30261-6/fulltext)
 - 47 Meier, P., Engstrom, J., Janes, J., Jegier, B. & Loera, F. (2010). Breast pump suction patterns that mimic the human infant

during breastfeeding: Greater milk output in less time spent pumping for breast pump-dependent mothers with premature infants. *Journal of Perinatology* 32.

- 48 Wood, L. (2021). Hitting the target-Transitioning the NICU baby from trophic feeds to feeding at the breast. Retrieved from <https://www.youtube.com/watch?v=2LxhcvXEO10>
- 49 Ludwig, S. & Waitzman, K. (2007). Changing feeding documentation to reflect infant-driven feeding. *Newborn and Infant Nursing Reviews* 7(3). Retrieved from <http://www.redesignhealthcare.org/wp-content/uploads/2018/09/dSchool-Ludwig-and-Waitzman-2007.pdf>
- 50 Nyquist, K. (2013). Lack of knowledge persists about early breastfeeding competence in very preterm infants. *Journal of Human Lactation* 29 pp. 296-299.

News...continued from page 23

Enriched Infant Formula Offers No Academic Benefit Later: Study

Infants who are given nutrient- or supplement-enriched formula milk do not later have higher academic scores as adolescents than those fed with standard formula, a study published online in the BMJ suggests. One goal of modifying infant formula has been to make long-term cognitive outcomes similar to those for breast-fed infants, the authors noted. Rates for breastfeeding beyond 6 weeks are low in many parts of the world and more than 60% of babies worldwide under the age of 6 months are given formula to replace or supplement breast milk, the paper states. So far, research has been inconclusive on benefits, though enhancements continue to be added and claims have been made as to their benefits on cognition in advertising. Long-term trials are difficult as researchers move on and participants are lost to follow-up. In a new study, however, researchers led by Maximiliane L. Verfürden, MsC, with the University College of London's Great Ormond Street Institute of Child Health, linked data from seven dormant, randomized, controlled infant formula trials to participants' performance later as adolescents in the United Kingdom on mandatory national school math and English exams at ages 11 and 16 and found no difference in scores. They followed 1,763 adolescents who had been participants in the formula trials, which were conducted between 1993 and 2001, and were able to link 91.2% (1,607) to academic records. They found "no benefit of the infant formula modifications on cognitive outcomes." In this study, the researchers discuss three widely available types of modified infant formulas that have been promoted as benefiting cognitive development: formula enriched with nutrients; formula supplemented with long-chain polyunsaturated fatty acids (LCPUFAs); and follow-on formula fortified with iron. In one supplement group the academic results were worse than for those given standard formula. At age 11, children who had been given the LCPUFA-enhanced formula scored lower in both English and math. "Given the potential associations between the source of LCPUFAs and adverse cognitive outcomes, long-term follow-up of trials testing infant formulas from other sources of LCPUFAs is recommended," the authors wrote.

Drug Used to Prolong Gestation Linked to Increased Cancer Risk in Offspring

Children exposed in utero to 17 alpha-hydroxyprogesterone caproate (17-OHPC) may be at increased risk for cancer, a new study suggests. In an analysis of data from more than 18,000 mother-child pairs, researchers found that, overall, offspring of women who were injected with the synthetic progesterone during pregnancy had nearly double the risk of any cancer compared with those not exposed to the hormone. Exposure during the first trimester carried some of the highest risks for cancers later in life, including for pediatric brain cancer (adjusted hazard ratio 34.72), prostate cancer (aHR 5.10), and colorectal cancer (aHR 5.51), according to the report published in the American Journal of Obstetrics & Gynecology. "Exposure in the womb to a drug used to prevent miscarriage in the 1950s and 60s increases the offspring's risk of cancer many decades later, especially for prostate, colorectal, and pediatric brain cancer," said the study's first author, Caitlin Murphy, an associate professor at the School of Public Health at the University of Texas Health Sciences Center in Houston. "This drug is still available in the United States for pregnant women to prevent preterm birth," Murphy noted. "We were surprised

Continued on page 35...

Utilizing Clinical Data to Enable Better Ventilation Management

Howard Brick

For more than a century, neonates have received respiratory support in various modes, including oxygen therapy and ventilation. Since its inception, clinicians have learned a lot from neonates' response to oxygen treatment—both positive and negative. Despite its long tenure in the NICU, it remains a point of contention.¹ Unlike most drugs, oxygen does not have clear guidelines for use, making it difficult to administer therapeutically, especially in the treatment of one of the most fragile and vulnerable patient populations.² Mechanical ventilation (MV) can be a lifesaving intervention, but when not closely monitored, there is a risk for injury to the lungs, brain, and other organ systems.³

If properly managed, we believe the benefits of ventilation in neonates far outweigh the risks.

The use of oxygen treatment is vital for neonates with various respiratory issues, including Chronic Lung Disease (CLD)/Bronchopulmonary Dysplasia (BPD), Respiratory Distress Syndrome (RDS), and Persistent Pulmonary Hypertension of the Newborn (PPHN). When proper ventilation is used and closely monitored, neonates may benefit from decreased time on a ventilator, resulting in a shorter stay in the NICU.

At Etiometry, we are acutely aware of the complex nature of neonatal oxygen therapy. And we sympathize with NICU clinicians who need to achieve a flawless balance between reaching adequate tissue oxygenation and avoiding oxygen toxicity—quite a complex and dangerous challenge. Not to mention, each patient is unique, with individual needs and responsive ranges, so there is no one-size-fits-all solution. For these reasons, the Etiometry R&D team has extensively studied how we can apply our analytics-driven clinical decision-support software to ventilation management in the NICU. Our comprehensive, data-based solution can help clinicians fine-tune ventilation management, analyze risks, and make near real-time decisions to improve outcomes for their patients.

Our platform is an end-to-end data management software solution for the collection, analysis, visualization, and archiving of ICU clinical data. When applied to ventilation management in the NICU, it could facilitate the use of all available data to support the anticipation and management of respiratory disease in neonates. In addition, we can implement our Clinical Management Applications (Clinical MAPs) that guide clinicians



through each step of the appropriate protocol process and provides continuous visibility into patients' progress. From identifying eligible patients to assessing protocol performance, these Clinical MAPs automate a hospital's guidelines to improve efficiency and compliance.

As a leader in clinical decision-support software, the Etiometry platform is already utilized in more than 20 of the top children's hospitals nationwide. Clinicians utilizing the platform are able to better manage patient data to discern actionable information in intensive care settings. We look forward to helping a current or future partner empower their clinicians with the proper technology, process, and protocols for better ventilation outcomes.

About Etiometry

Etiometry Inc. is the leader in clinical decision-support software for the intensive care environment. Our technologies provide valuable clinical insight and analysis to support early recognition of subtle changes in patient condition to avoid complications and speed recovery. Etiometry is committed to improving patient outcomes, increasing clinical efficiency, and lowering costs of care through the more effective use of all available data.

References

1. <https://pubmed.ncbi.nlm.nih.gov/23402990/>
2. <https://www.seattlechildrens.org/globalassets/documents/healthcare-professionals/neonatal-briefs/managing-oxygen-neonatal-brief.pdf>
3. <https://www.uptodate.com/contents/overview-of-mechanical-ventilation-in-neonates>

Howard Brick is the Chief Strategy Officer at Etiometry.

News...continued from page 33

by the strength of our findings,” Murphy said in an email. “This is newsworthy because rates of several cancers are increasing across generations, starting with persons born in the 1960s or Generation X. Increasing rates of cancer across generations implicate exposures in very early periods of life as risk factors. This is consistent with our finding that earlier and more frequent injections of 17-OHPC in pregnancy was associated with higher risk of cancer in offspring. We need to know if risk of these cancers begins before birth, so that we can better weigh the pros and cons of medications in pregnancy.” While it isn’t known exactly how the drug may raise cancer risk, Murphy says it may be because the drug isn’t an exact duplicate of progesterone. “Synthetic hormones, or drugs made to act like natural hormones, disrupt the way natural hormones work, especially during the vulnerable time of fetal development,” she said. “The potential for synthetic hormones to disrupt development and increase risk of cancer is well-established by studies of diethylstilbestrol, a synthetic estrogen that was commonly prescribed to pregnant women to prevent miscarriage in the 1950s and 60s. 17-OHPC is a synthetic progestogen and may similarly contribute to risk of cancer.” To look at possible impacts of the medication on fetuses, Murphy and her colleagues turned to data from Child Health and Development Studies (CHDS), a population-based cohort of more than 18,000 mother-child dyads receiving prenatal care in the Kaiser Foundation Health Plan (Oakland, CA) between 1959 and 1966, and followed for 60 years. CHDS monitors participants by annual linkage to the California Department of Motor Vehicles, the California Department of Vital Statistics and the California Cancer Registry.

Stillborn Birth Linked to Maternal SARS-CoV-2 Infection

Clinicians in Ireland are warning about a spate of stillbirths in the first few months of 2021 that they have linked to SARS-CoV-2 infections. There were six women in the country who suffered stillbirths and one who experienced a miscarriage, each a few weeks after she had COVID-19. Five of the cases so far involved the variant B.1.1.7, which has now come to dominate cases in Ireland, the UK, much of Europe, and the US. In all instances, the placenta was extensively damaged. “The placentas look completely burnt out, just incredibly necrotic and damaged,” says Keelin O’Donoghue, an obstetrician at Cork University Maternal Hospital in Ireland who is part of team preparing a manuscript on the cases. “They all have suffered acute injury, which is why you have an acute effect in terms of fetal compromise or death.” In addition to the stillbirths and miscarriage, there have also been three instances so far this year in Ireland in which expectant mothers diagnosed with COVID-19 had emergency deliveries and severely degraded placentas. The babies survived. “There’s a very abnormal appearance” to the surface of the placenta when it is cut for examination, says Brendan Fitzgerald, a pathologist at Cork University Hospital who has examined five of the affected placentas, “with white streaks and nodules occupying large portions of the placental disk. It is a very uncommon finding that we would rarely see in routine practice.”

Masimo Launches Dual SET Pulse Oximetry

Masimo announced Dual SET Pulse Oximetry for Root, a highly versatile patient monitoring and connectivity hub. The first application of Dual SET Oximetry is a significant
Continued on page 44...



How do you measure
peace of mind?

When caring for fragile patients in critical condition, there are no obvious care decisions.

Etiometry's monitoring and data aggregation technology helps clinicians in the NICU bolster their expertise and intuition, by providing a well-informed picture of the patient's condition at a glance.

Stay ahead of critical inflection points in your patients' care. [Etiometry.com/NICU](https://etiometry.com/NICU)



Making our world more productive



Comprehensive Solution For Nitric Oxide Inhalation Therapy

Complete with 24/7/365 support – peace of mind for critical care providers.

National Reach, Local Service

NOXIVENT® (nitric oxide) gas for inhalation, along with the NOxBOXi® delivery system, offered with customizable, consumption-based billing, is backed by Linde's national network, responsive support and reputation for medical gas distribution.

The NOxBOXi nitric oxide gas delivery system is reliable, accurate and easy to use. System features include:

- Real-time, closed-loop monitoring with auto-adjusting alarms
- Pre-packaged, configured circuits ready for use with validated ventilators
- Disposable circuits, including the NOxFLOW module, for easy clean up
- Auto-cylinder changeover with alerts, helping you avoid therapy interruptions

Our Commitment

- Integrated gas delivery system for inhaled nitric oxide therapy
- 24/7/365 service and support
- Simplified billing process
- Reliable and responsive distribution network
- Established reputation for quality and customer satisfaction

A summary of the prescribing information, including indication and other important safety information, is on the adjacent page. For the full prescribing information, visit www.noxiventus.com.

Call 1-844-445-4633 today for a complimentary requirements evaluation.
www.noxiventus.com



NOXIVENT[®] Indication and Important Safety Information

Indication

Noxivent[®] is a vasodilator indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

Important Safety Information

Contraindications

Noxivent is contraindicated in neonates dependent on right-to-left shunting of blood.

Warnings and Precautions

Rebound: Abrupt discontinuation of Noxivent may lead to worsening oxygenation and increasing pulmonary artery pressure.

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

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

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

Adverse Reactions

The most common adverse reaction of Noxivent is hypotension.

Drug Interactions

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

Administration

Use only with a calibrated, FDA-cleared NOxBOXi[®] Nitric Oxide Delivery System (NODS). Refer to the NODS labeling for needed information on training and technical support for users of this drug product with the NODS.

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

How NICUs Are Tailoring Their Approach to Care for the Tiniest Babies

Part One: Small Baby Neonatal Intensive Care Units (NICUs)

Sandra Carroll, OTR, CLC, C-ELBW, CNT

Introduction

Neonatal intensive care unit (NICU) clinicians are tasked with caring for the smallest, most vulnerable patients. Recognizing how these infants have very special needs, such as temperature control requirements, respiratory care, and noise and light protection, NICU teams have evolved their strategies, unit designs and equipment over the decades to improve patient care and outcomes.

As NICU teams find themselves caring for increasingly smaller and younger pre-term babies they are further adapting their approaches based on the unique needs of extremely low birth weight (ELBW) infants. Because these babies' bodies and brains are developing outside of their mothers' wombs, NICU clinicians must do everything they can to protect them from environmental elements that can cause lasting damage.

Hospitals across the US have been establishing small baby units (SBU) separate from their main NICUs to care for infants younger than 28 weeks in the womb weighing less than 1,250 grams. These special spaces have been carefully designed based on clinical evidence, and staffed by a dedicated, multidisciplinary team of clinicians with expertise in all aspects of ELBW babies' physical and neurological care, development and growth.

In this first article in a two-part series, I describe the specialized needs of ELBW infants, define the ideal small baby NICU based on the Engage, Grow, Thrive Small Baby Care Specialist program, and explore the critical importance of neuroprotective care and family-centered care to support

Sandra Carroll, OTR, CLC, C-ELBW, CNT, has nearly 30 years of experience in the neonatal intensive care unit (NICU). She is a Registered Occupational Therapist (OTR), Certified Neonatal Therapist (CNT), a Certified Lactation Counselor (CLC), Certified in the care of Extremely Low Birth Weight infants (C-ELBW), and is a NICU Trauma Informed Professional. With a deep interest and passion for providing care for infants with specialized needs, Carroll has been instrumental in contributing to the international growth of the highly specialized field of Neonatal Therapy. Carroll currently serves as NICU Supervisor of Therapy Services for Baylor University Medical Center in Dallas, Texas, where she helped establish the facility's Small Baby Unit (SBU) - "The Tiniest Texans". Sandra and Dräger worked in collaboration to develop this article as part of Dräger's continuing efforts to advance neonatal care through the sharing of insights, knowledge and best practices within the neonatal community.



improved outcomes. I have also included results from research published by two pioneering small baby units at CHOC Children's Hospital and OSU Wexner Medical Center.

Tiny Babies Have Special Needs

Traditionally ELBW infants would be placed in a general NICU along with babies who have had more time to develop in the womb, whether they are older, larger preemies or full-term babies with significant medical conditions. But research has shown that the youngest and tiniest NICU patients require specialized care to help them face the challenges of the world at such an early stage.¹

Nature intends them to be protected within a quiet, dark and peaceful womb, sheltered from noise and light, shielded from movement by a cushion of water while hearing the muffled voice of mom at this stage. However early arrival into the world bombards these babies with external stimuli their tiny brains and bodies are not ready to process.

Even something as simple as a diaper change in a traditional NICU environment can be traumatic and damaging. Within the first moments after birth, preemie babies are exposed to an exorbitant amount of toxic stimuli that can impact their growth and development. This includes clinicians handling fragile, thin skin never intended to be touched, exposure to lights shining on pupils unable to constrict, and the beeps of monitors and voices impacting an auditory system that cannot defend against the assault.

Defining the Ideal Small Baby NICU

Based on scientific research on the impact of the NICU environment on babies born under 28 weeks' gestation, and



their own experiences and intuition, NICU clinicians recognize that the environment and interventions that are appropriate for older babies are often harmful to the youngest ones. While younger and smaller babies are surviving, many suffer neurodevelopmental delays and/or chronic medical problems.² This has prompted change in the culture of the NICU with a greater focus on the baby's and family's needs.

One of the most influential movements in small baby NICU care has been driven by the Engage, Grow, Thrive Small Baby Care Specialist program. It is an evidence-based curriculum presented by small baby experts designed to provide the neonatal interdisciplinary clinician an opportunity to learn current evidence and best practices as a Small Baby Care Specialist® (SBCS). The program is directed at reducing variation in practice and making it more consistent with an interdisciplinary team-based approach.³

Engage, Grow, Thrive is led by Mindy Morris and Liz Drake, two advanced practice nurses (APN) who have over 60 years combined neonatal nursing experience. Based on the program's criteria, Morris helped to establish a Small Baby Unit (SBU) at Children's Hospital of Orange County (CHOC) for ELBW infants born at 28 weeks or less and weighing less than 1,000 g at birth.

Key elements of a small baby NICU

A tiny baby who is born very early is very high risk for lung injuries, brain injuries and skin injuries that can increase their risk of infection. An adult in this condition would be cared for in an intensive care unit (ICU).

In adult medicine we have a Neuro ICU, Cardiac ICU and Medical Surgical Units with specialized teams to care for specific patient conditions. But in a traditional NICU, it is not uncommon for a NICU a nurse to have an assignment with a 500 g baby and a 10 pound baby- each with individualized needs. That nurse is expected to switch gears and have skills in her care toolbox to provide the same standard of care and expertise despite her patients' very different clinical requirements. The goal of an SBU is to create a standardized, protective, multi-disciplinary space that will foster growth and development of ELBW babies.

Small baby unit (SBU) requirements

- Physically separate, environmentally-controlled location

from general NICU

- Dedicated multidisciplinary team providing specialized care
- Standardized care pathways developed according to evidence-based guidelines, protocols and checklists
- Ongoing educational and process improvement collaboration
- A true team approach to care delivery

Protecting Mind and Body: The Importance of Neuroprotective Care

Pre-term birth interrupts the precise process of fetal maturation, forcing critical neurologic growth to continue within the NICU.⁴ Pre-term babies' brains develop right in front of the clinicians' eyes in the NICU for the many months they are in the hospital.

The brain is most active in the last trimester of pregnancy—at 24 to 40 weeks of fetal development. It grows rapidly in size and builds millions of nerve cells, which develop synaptic connections. When sensory pathways that are intended to develop in a sequential order are all attacked by external stimuli at the same time, damage is likely to occur. For example, assault on the auditory system at the time when the visual system is supposed to be developing can interrupt how those two sensory systems interact. Therefore, providing a neuroprotective environment in the NICU is critical to outcomes.

Signs of overstimulation in the premature infant

Too much sound, touch, movement or light can result in examples of the following physical reactions:

- A drop in blood oxygen levels (oxygen desaturation)
- An increase in apnea and bradycardia
- A rapid heart rate (tachycardia)
- Disrupted sleep cycles
- Delayed growth
- Twisting, arching or scowling⁵

The impact of light

High noise levels, bright lights, sleep deprivation and long-term sedation all affect the processes of early visual development.⁶ The more premature the baby, the more sensitive to light they are. A baby under 30 weeks doesn't have pupillary constriction—the reflex to constrict their pupils. With no regulation of light coming into their brain, babies exposed to bright lights experience pain and the risk for eye injury.

On the other hand, a supportive light environment helps to reduce levels of cortisol, extends sleep duration, stimulates the release of growth hormones and encourages the early development of a circadian rhythm.^{7,8} Cycled lighting, imitating the circadian rhythm, has been shown to be the most beneficial approach. Babies exposed to this form of lighting show better growth and hormone regulation, and they are less anxious, cry less, sleep better and are more active during the day.^{9,10}

The impact of sound

With regards to sound, most people believe loud noises impact only a baby's hearing, but toxic noise levels can have much broader implications. A baby's auditory system becomes functional at around 25 weeks' gestation, with the cochlea of the middle ear and the auditory cortex in the temporal lobe being the important structures in the development of the auditory system.¹¹ Exposure to noise and other environmental in the NICU may result in not only structural damage, but also disrupt normal growth and development of premature infants.¹²

A baby in an incubator processes sounds at a much higher level. For example, if someone puts a glass bottle on top of an incubator, the sound could be anywhere between 85-90 decibels. For a pre-term infant, that is the equivalent to a gunshot next to the ear. While noise can impact babies of any age, research has shown that noise events result in a significant increase in heart and respiratory rates in pre-term neonates as compared to full-term infants.¹³ The impact of loud noise in the NICU can be long-term, increasing the risk for hearing damage, developmental delays, periventricular leukomalacia and bleeding.¹⁴

The American Academy of Pediatrics recommends that noise levels in the NICU be lowered to an operating level of 45 dBA, and 55 dBA for transient sound levels, as proposed by the US Environmental Protection Agency, and that pediatricians monitor sound in the NICU and within incubators.¹⁵ The goal is to reduce stress on the babies' cardiovascular breathing, neurological and endocrine systems, thus promoting growth and improving outcomes.

Parents as Part of the Team: The Importance of Family-Centered Care

If a pre-term baby remained in the womb, he or she would be in constant maternal contact, feeling her body and hearing her voice. When delivered at a young gestational age, babies are deprived of these sensations. Rather, they are housed in incubators, attached to life supporting devices and monitors and separated from the maternal body's embrace.

While a pre-term baby in the NICU can't have 24-hour body-to-body maternal contact, there are ways to integrate family into care. For example, Kangaroo Care, where the baby has frequent skin-to-skin contact with his or her mother or another caregiver, has been shown to significantly improve outcomes both short and long-term.

Kangaroo Care has been proven to reduce cortisol and increases oxytocin levels in pre-term infants, stabilize infant physiological functions (e.g., respiration rate), promote early initiation of breastfeeding, improve baby's weight gain, increase maternal-infant attachment and reduce maternal stress.^{16,17,18,19}

Key to the success of family-centered care is educating the parents and other family members on the important role they play in their baby's development. Help them understand how they are vital members of their baby's care team, and how their touch, voices and closeness to the baby are as valuable as any medical intervention.

It Takes Two: A New Approach in NICUs

Historically, a nurse in the NICU would work alone to care for a tiny patient, changing a diaper, taking a temperature, performing other required interventions all as quickly as possible so the baby could again rest and sleep.

In recent years there has been growing recognition of the positive and negative impacts of touch on pre-term babies. Whereas in the womb their delicate bodies and fragile skin would be shielded, in the NICU they are subjected to direct human contact. In essence, every touch to them is somewhat traumatic because it is not supposed to be happening.

The new standard is two-person care of pre-term babies in the NICU, where one clinical staff member performs the

required task (e.g., diaper change, blood draw) and a second supports the baby and calms him/her (e.g., holding the pacifier in the baby's mouth), thereby serving as a buffer from the intervention. Any member of the NICU team can serve as the second person, such as a nurse, doctor, therapist or even a parent.

Long-term Success Across the US

The implementation of SBUs across the US is growing as NICU teams see how this unique environment helps tiny babies survive and thrive. Here are results from two pioneers in this unique approach to care: CHOC Children's Hospital and OSU Wexner Medical Center.

CHOC Children's Hospital

CHOC Children's Hospital's SBU, which cares for ELBW infants born at 28 weeks or less and weighing less than 1,000 g at birth, documented data from the two years prior to establishment of its SBU and four years after this new unit was opened. It found:

- A reduction in chronic lung disease from 47.5% to 35.4%
- A reduction in hospital-acquired infection from 39.3% to 19.4%
- A reduction in infants being discharged with growth restriction (combined weight and head circumference, 10th percentile) from 62.3% to 37.3%
- A reduction in resource utilization, with the mean number per patient of laboratory tests decreasing from 224 to 82 and radiographs decreasing from 45 to 22

OSU Wexner Medical Center

The NICU team at OSU Wexner Medical Center published a review article on SBUs in the March 2021 edition of the *Journal of Perinatology*, describing the elements of their small baby program, which align with the Engage, Grow, Thrive program criteria: Multi-disciplinary collaboration, specialized and standardized care based on evidence-based practice, focus on parent-centered care and removing noxious stimuli to improve neurodevelopmental outcomes.²⁰

Since establishing their SBU in 2004, the NICU team at OSU Wexner Medical Center has achieved:

- A dramatic decline in mortality rates of extremely premature (EP) infants admitted to the small baby program, from 30% in 2004 to nearly 10% in 2017
- Relatively low rates of cerebral palsy, with the majority having average Bayley scores as corrected for age at 18 months despite significant vulnerability related to extreme prematurity
- A reduction in bronchopulmonary dysplasia (BPD) rates from 68% to 50%



Conclusion

It is a tremendous responsibility and honor to be tasked with nurturing the development of ELBW babies. The challenges of these tiny, fragile patients are numerous but working together as a community of NICU clinicians we can share best practices and learnings to give them the healthy start they need.

The second article in this series focuses specifically on the work I have led to establish a small baby unit at Baylor, Scott & White Health's flagship hospital, Baylor University Medical Center in Dallas, Texas. In this article, I describe in detail our team and culture, practice standardization methodologies, unit design and supporting equipment.

References

- 1 Children's Hospital of Philadelphia, Low Birthweight, <https://www.chop.edu/conditions-diseases/low-birthweight#:~:text=Nearly%20all%20low%20birthweight%20babies%20need%20specialized%20care,babies%20%28%3C500%20grams%29%20having%20the%20lowest%20survival%20rate.>
- 2 Morris M, Cleary JP, Soliman A. Small Baby Unit Improves Quality and Outcomes in Extremely Low Birth Weight Infants. *Pediatrics*. 2015 Oct;136(4):e1007-15. doi: 10.1542/peds.2014-3918. Epub 2015 Sep 7. PMID: 26347427. <https://pubmed.ncbi.nlm.nih.gov/26347427/#:~:text=Small%20Baby%20Unit%20Improves%20Quality%20and%20Outcomes%20in,and%20development%20are%20required%20to%20sustain%20improved%20outcomes.>
- 3 Engage, Grow, Thrive Small Baby Care Specialist program, <https://engagegrowthrive.com/small-baby-care-specialist-program/>
- 4 Lockridge T. Neonatal Neuroprotection: Bringing Best Practice to the Bedside in the NICU. *MCN Am J Matern Child Nurs*. 2018 Mar/Apr;43(2):66-76. doi: 10.1097/NMC.0000000000000411. PMID: 29261516 <https://pubmed.ncbi.nlm.nih.gov/29261516/>
- 5 Premature Infant: Signs of Overstimulation, Kaiser Permanente, <https://wa.kaiserpermanente.org/kbase/topic.jhtml?docId=tn7258>
- 6 Graven, Stanley. (2004). Early neurosensory visual development of the fetus and newborn. *Clinics in perinatology*. 31. 199-216, v. 10.1016/j.clp.2004.04.010.
- 7 Graven SN. Early neurosensory visual development of the fetus and newborn. *Clin Perinatol*. 2004;31(2):99-216
- 8 Rivkees SA. Emergence and influences of circadian rhythmicity in infants. *Clin Perinatol*. 2004 Jun;31(2):217-28
- 9 Guyer C, Huber R, Fontijn J et al. Very preterm infants show earlier emergence of 24-hour sleep-wake rhythms compared to term infants. *Early Hum Dev*. 2015 Jan;91(1):37-42
- 10 Borniger JC, McHenry ZD, Abi Salloum BA, et al. Exposure to dim light at night during early development increases adult anxiety-like responses. *Physiol Behav*. 2014 Jun 22;133:99-106
- 11 Graven S, Browne J, Auditory Development in the Fetus and Infant, *Newborn and Infant Nursing Reviews* Volume 8, Issue 4, December 2008, Pages 187-193.
- 12 Noise: a hazard for the fetus and newborn. American Academy of Pediatrics. Committee on Environmental Health. *Pediatrics*. 1997 Oct;100(4):724-7. PMID: 9836852.
- 13 Hassanein SM, El Raggal NM, Shalaby AA. Neonatal nursery noise: practice-based learning and improvement. *J Matern Fetal Neonatal Med*. 2013 Mar;26(4):392-5. doi: 10.3109/14767058.2012.733759. Epub 2012 Dec 12. PMID: 23190305.
- 14 S. Swathi S, Ramesh A, Nagapooranima M et al. Sustaining a "culture of silence" in the neonatal intensive care unit during nonemergency situations: A grounded theory on ensuring adherence to behavioral modification to reduce noise levels. *Int J Qual Stud Health Well-being*. 2014;9:10.3402/qhw.v9.22523.
- 15 Noise: a hazard for the fetus and newborn. American Academy of Pediatrics. Committee on Environmental Health. *Pediatrics*. 1997 Oct;100(4):724-7. PMID: 9836852.
- 16 Pados, Britt Frisk PhD, RN, NNP-BC; Hess, Francis Systematic Review of the Effects of Skin-to-Skin Care on Short-Term Physiologic Stress Outcomes in Preterm Infants in the Neonatal Intensive Care Unit, *Advances in Neonatal Care*: February 2020 - Volume 20 - Issue 1 - p 48-58 doi: 10.1097/ANC.0000000000000596 https://journals.lww.com/advancesinneonatalcare/Abstract/2020/02000/Systematic_Review_of_the_Effects_of_Skin_to_Skin.7.aspx
- 17 Cho ES, Kim SJ, Kwon MS, Cho H, Kim EH, Jun EM, Lee S. The Effects of Kangaroo Care in the Neonatal Intensive Care Unit on the Physiological Functions of Preterm Infants, Maternal-Infant Attachment, and Maternal Stress. *J Pediatr Nurs*. 2016 Jul-Aug;31(4):430-8. doi: 10.1016/j.pedn.2016.02.007. Epub 2016 Mar 11. PMID: 26975461 <https://pubmed.ncbi.nlm.nih.gov/26975461/>
- 18 Mekonnen AG, Yehualashet SS, Bayleyegn AD. The effects of kangaroo mother care on the time to breastfeeding initiation among preterm and LBW infants: a meta-analysis of published studies. *Int Breastfeed J*. 2019 Feb 19;14:12. doi: 10.1186/s13006-019-0206-0. PMID: 30820239; PMCID: PMC6379962 <https://pubmed.ncbi.nlm.nih.gov/30820239/>
- 19 Evereklian M, Posmontier B. The Impact of Kangaroo Care on Premature Infant Weight Gain. *J Pediatr Nurs*. 2017 May-Jun;34:e10-e16. doi: 10.1016/j.pedn.2017.02.006. Epub 2017 Mar 11. PMID: 28292543 <https://pubmed.ncbi.nlm.nih.gov/28292543/>
- 20 Fathi, O., Nelin, L.D., Shepherd, E.G. et al. Development of a small baby unit to improve outcomes for the extremely premature infant. *J Perinatol* (2021). <https://doi.org/10.1038/s41372-021-00984-0> <https://www.nature.com/articles/s41372-021-00984-0#citeas>

Electronic Alerts on the Social Determinants of Health

Ariana Bolumen, MD and Shabih Manzar, MD

Abstract

Introduction: Social determinants of health (SDoH) are the non-medical factors that influence one's health causing an impact in their medical outcomes. These factors include financial condition, food availability, insecurity, transport facility, physical activity, stress, social connections, housing stability, depression, tobacco, and alcohol use. SDoH have been associated with adverse maternal and birth effects. With the advent of electronic charting and documentation, SDoH are now incorporated into electronic health records. This pilot study was performed to determine the utility of this incorporation and how it can contribute to improvements in healthcare.

Methods: On admission to the labor unit of the hospital, all pregnant women completed the SDoH questionnaire. Upon completion of the questionnaire, a color-coded wheel was created by the electronic record system. Based on the color, Green: 0, Yellow: 1, and Red: 2, the system then generates an alert response labeled as 'concern present'.

Results: Incorporation of SDoH in the electronic health record system is useful in detecting potential cases that need additional medical attention.

Conclusion: Our observation demonstrated the successful use of electronic SDoH score and alert notification. A collaborative team, involving the primary health provider, family, community, and public health worker, should be developed to further establish an action plan for these SDoH alerts among pregnant women.

Keywords: Social Determinants of Health (SDoH), Electronic records, Clinical Decision Support, Alerts, Notification

Introduction

Social determinants of health (SDoH), as defined by World Health Organization,¹ are the non-medical factors that influence the health outcomes. SDoH may include conditions in which people are born, grow, work, live, and age. These factors include financial condition, food availability, insecurity, transport facility, physical activity, stress, social connections, housing stability, depression, tobacco, and alcohol use.

Previous studies have shown the effect of SDoH and adverse maternal and birth outcomes. Amjad et al² in their meta-

analysis evaluated SDoH and found race and rural residence as predictors of preterm birth (PTB) while low maternal socio-economic status and illiteracy are risk factors for maternal mortality and low birth weight infants. Maness and Buhi³ in their systematic review of seventeen studies reported poverty and family structure as the most important SDoH in pregnancy. Earlier, Palacio et al⁴ developed the SDoH score by using survey questionnaire and showed an association of SDoH score and risk of cardiovascular disease.

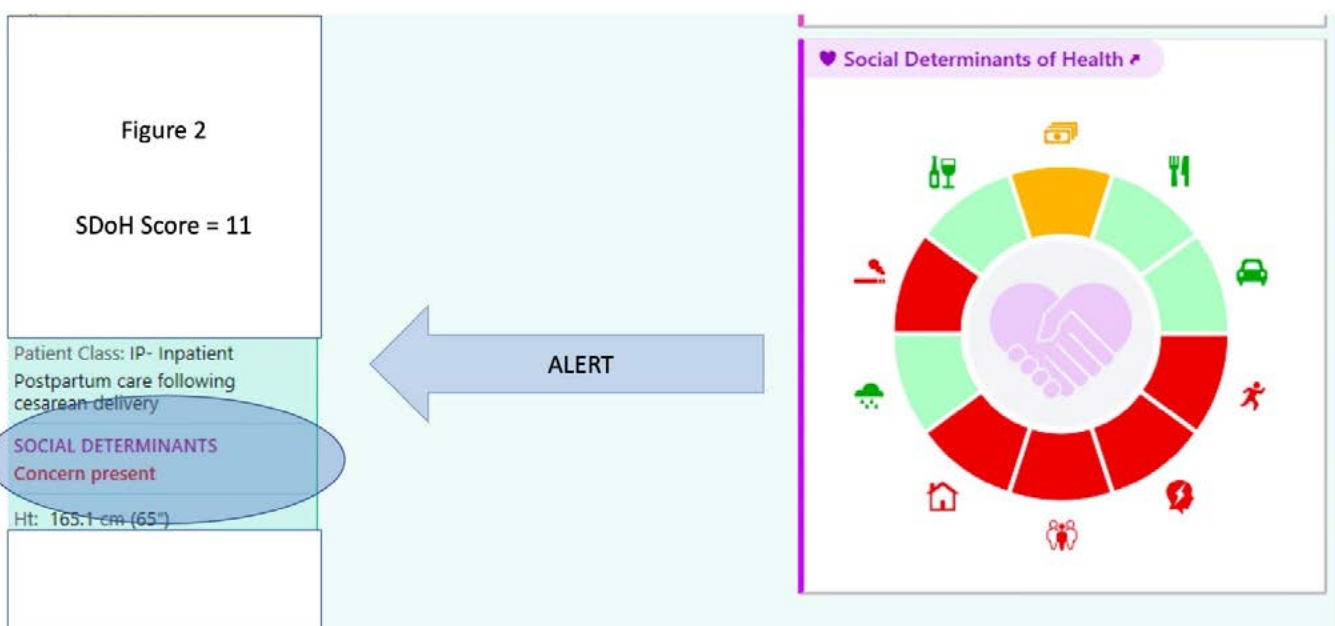
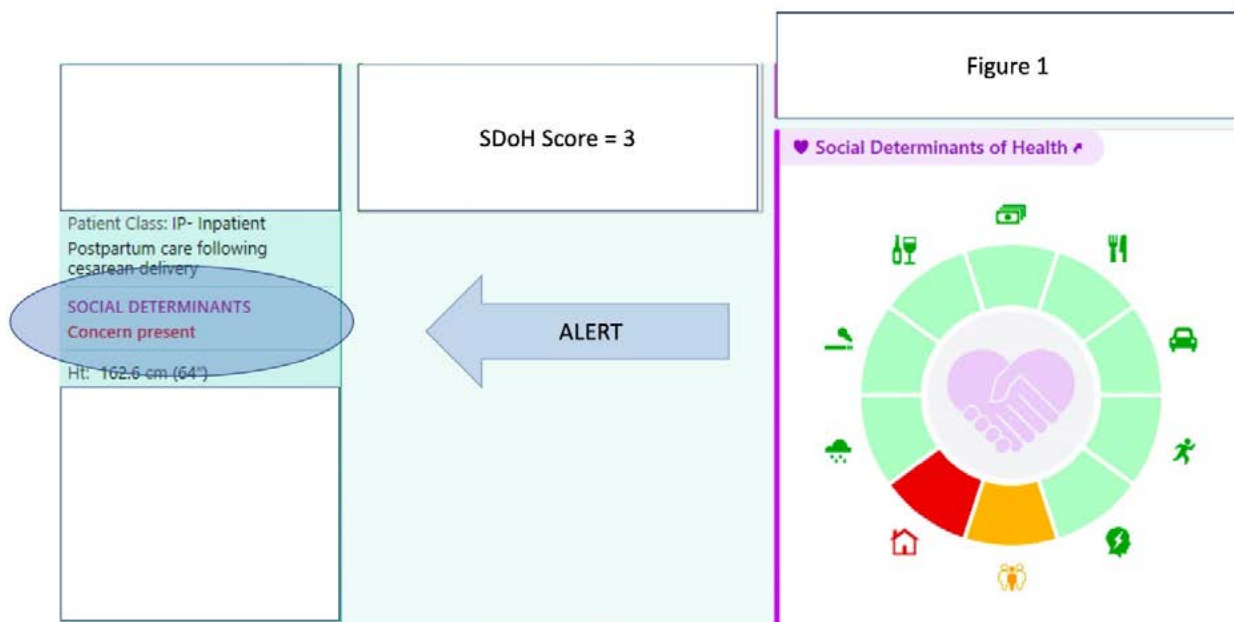
United States has the highest rate of preterm birth (PTB). Social determinants of health (SDoH) including race, poverty, homelessness, and substance use have been negatively associated with birth outcomes.⁵ Maternal medication abuse and mental stress during pregnancy have been reported as risk factors for low birth weight.⁶ One important factor in SDoH is housing instability. DiTosto et al⁷ have shown that housing instability and homelessness during pregnancy were significantly associated with preterm birth, low birthweight neonates, neonatal intensive care unit admission, and delivery complications. Another important factor in SDoH is the psychosocial vulnerability of pregnant women. Pregnant women with high psychosocial vulnerability face a higher risk of preterm birth.⁸ Healthy environments include neighborhood with low crime rate. Higher exposure to violent crimes in the close vicinity of pregnant women's residence has shown to be associated with substantial increases in the odds of low birth weight and prematurity.⁹

The Centers for Disease Control and Prevention (CDC)¹⁰ has developed a Social Vulnerability Index (SVI). SVI is an online database tool that integrates 15 different community characteristics and groups them into 4 different themes to identify "at-risk" communities. Higher indices indicate high vulnerability. Given et al¹¹ have recently shown SVI as a valuable tool in identifying preterm births. This pilot study was performed to investigate the utility of SDoH incorporation into electronic health records. We formulated a SDoH scoring system, based on maternal responses to the questions, using the electronic charting system. An alert labeled as 'concern present' was generated based on the severity of SDoH.

Methods

An IRB approval was obtained for the study. Recently the information on SDoH is made available as a built-in tool in our hospital electronic health records system (Epic®).¹²

Ariana Bolumen is an Intern, Department of Pediatrics, Louisiana State University Health Sciences Center, Shreveport, LA. Shabih Manzar is with Section of Neonatology, Department of Pediatrics, Louisiana State University Health Sciences Center, Shreveport, LA.



All pregnant women on admission to the labor unit of the hospital, completed the SDoH questionnaire, assisted by the nurse assigned to the patient. The SDoH items included:

1. Financial Resource Strain
2. Food Insecurity
3. Transport Needs
4. Physical Activity
5. Stress
6. Social connections
7. Housing stability
8. Depression
9. Tobacco use
10. Alcohol use

Upon completion of these questionnaires, a color-coded wheel was generated by the electronic record system. Based on the color, Green: 0, Yellow: 1, and Red: 2, the system then generates an alert 'concern present'.

Results

Incorporation of SDoH in the electronic health record system is a useful tool. It could be used in generating a SDoH score and alerts; thereby detecting potential cases that need extra medical attention. Figure 1 and 2 depicts two examples.

Discussion

Maternal health during pregnancy and the first 1,000 days of life are important aspects of maternal and child health. SDoH affect both. With the advent of electronic charting, it has now become possible to collect and store information more efficiently. Machine learning and clinical decision support are important tools used in current practice.¹³ These could be used in generating alerts for health practitioner. In our preliminary study we demonstrated the successful use of electronic SDoH calculation and alert generation.

For public health providers these findings could be used as a guide to identify pregnant women at high risk for poor outcomes. A collaborative team, involving the primary health provider, family, community, and public health worker should be developed to further establish an action plan for these SDoH alerts among pregnant women.

References

1. https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1
2. Amjad S, MacDonald I, Chambers T, et al. Social determinants of health and adverse maternal and birth outcomes in adolescent pregnancies: A systematic review and meta-analysis. *Paediatr Perinat Epidemiol*. 2019;33(1):88-99. doi:10.1111/ppe.12529
3. Maness SB, Buhi ER. Associations Between Social Determinants of Health and Pregnancy Among Young People: A Systematic Review of Research Published During the Past 25 Years. *Public Health Rep*. 2016;131(1):86-99. doi:10.1177/003335491613100115
4. Palacio A, Mansi R, Seo D, et al. Social determinants of health score: does it help identify those at higher cardiovascular risk?. *Am J Manag Care*. 2020;26(10):e312-e318. Published 2020 Oct 1. doi:10.37765/ajmc.2020.88504
5. Abatemarco DJ, Gannon M, Short VL, et al. Mindfulness in Pregnancy: A Brief Intervention for Women at Risk. *Matern Child Health J*. 2021;25(12):1875-1883. doi:10.1007/s10995-021-03243-y
6. Moradi G, Zokaei M, Goodarzi E, Khazaei Z. Maternal risk factors for low birth weight infants: A nested case-control study of rural areas in Kurdistan (western of Iran). *J Prev Med Hyg*. 2021;62(2):E399-E406. Published 2021 Jul 30. doi:10.15167/2421-4248/jpmh2021.62.2.1635
7. DiTosto JD, Holder K, Soyemi E, Beestrum M, Yee LM. Housing instability and adverse perinatal outcomes: a systematic review. *Am J Obstet Gynecol MFM*. 2021;3(6):100477. doi:10.1016/j.ajogmf.2021.100477
8. Pedersen JF, Kallesøe SB, Langergaard S, Overgaard C. Interventions to reduce preterm birth in pregnant women with psychosocial vulnerability factors-A systematic review. *Midwifery*. 2021;100:103018. doi:10.1016/j.midw.2021.103018
9. Dos Santos AC, Brentani A, Fink G. Associations between neighborhood violence during pregnancy and birth outcomes: evidence from São Paulo's Western Region Birth Cohort. *BMC Public Health*. 2021;21(1):865. Published 2021 May 5. doi:10.1186/s12889-021-10900-y
10. https://www.atsdr.cdc.gov/placeandhealth/svi/data_documentation_download.html
11. Givens M, Teal EN, Patel V, Manuck TA. Preterm birth among pregnant women living in areas with high social vulnerability. *Am J Obstet Gynecol MFM*. 2021;3(5):100414. doi:10.1016/j.ajogmf.2021.100414
12. <https://www.epic.com/>
13. Saqib K, Khan AF, Butt ZA. Machine Learning Methods for Predicting Postpartum Depression: Scoping Review. *JMIR Ment Health*. 2021;8(11):e29838. Published 2021 Nov 24. doi:10.2196/29838

News...continued from page 35

advancement to Masimo SET-guided critical congenital heart disease (CCHD) screening, with the CE marking and European launch of the Masimo SET MOC-9 module and the addition of the Eve CCHD Newborn Screening Application for Root. Together, this combined solution enhances the automation of newborn screenings using Dual SET Oximetry: two simultaneous measurements of oxygen saturation (SpO₂) at pre- and post-ductal sites by the intuitive Eve application, customized to align with a hospital's CCHD screening protocol. CCHD affects approximately 2.5 to 3 newborns per 1000 live births and requires intervention soon after birth to prevent significant morbidity or mortality; later detection in infants also increases the risk of brain damage. Traditionally, newborns were observed for evidence of CCHD by physical assessment and monitoring for common symptoms, but studies have shown that physical assessment of newborns alone can be unreliable and may fail to detect some infants with CCHD before discharge. Adding screening with pulse oximetry can help clinicians identify CCHD before an infant becomes symptomatic. Clinically proven Masimo SET Measure-through Motion and Low Perfusion pulse oximetry has been shown in more than 10 CCHD screening studies—representing over 300,000 babies—to increase the effectiveness of screening newborns for CCHD. For example, in a study of almost 40,000 infants, CCHD screening sensitivity increased from 63% with physical exam alone to 83% with physical exam and SET. In another study of more than 120,000 infants—the largest CCHD screening study to date—combined use of clinical assessment and SET increased screening sensitivity from 77% to 93%. Evidence from CCHD studies using SET has even been used to help establish CCHD screening guidelines used around the world. Powered by Masimo SET pulse oximetry, the Eve CCHD Newborn Screening Application is designed to simplify the CCHD screening process by providing step-by-step visual instructions, animations, and a detailed, easy-to-interpret display of screening results—standardizing and enhancing clinical workflows, improving consistency in screening practices among clinicians, and reducing the possibility of calculation errors. Eve also allows clinicians to incorporate perfusion index into screening, which has been shown to increase sensitivity to the detection of CCHD. Already available for Radical-7 and Rad-97 Pulse CO-Oximeters, Eve is particularly well suited for display on Root's large, high-resolution screen. With its built-in barcode scanner, Root can automatically associate patients with their screening results, and with its integration into the Masimo Hospital Automation platform, Root automates the transfer of those results to electronic medical records (EMRs)—eliminating the need for manual charting. Now, with the addition of the new Masimo SET MOC-9 module for Root—made possible by another key differentiator of the hub, its advanced, flexible connectivity capabilities—CCHD screening guided by Eve is even more streamlined and efficient: one pulse oximetry sensor can be connected to Root via Radical-7, and a second via the MOC-9 module, allowing for the pre- and post-ductal SpO₂ readings needed for screening to be taken simultaneously rather than sequentially, with results conveniently displayed on one screen. This Dual SET Oximetry technique streamlines the CCHD screening process, improving clinical workflows. Gerard R. Martin, MD, C.R. Beyda Professor of Cardiology at Children's National Hospital, said, "As an advocate for congenital heart disease efforts nationally and internationally, I believe Masimo SET pulse oximetry is an excellent tool for pulse oximetry CCHD

Continued on page 50...

Leveraging Family Engagement Technology To Support Your Quadruple Aim Objectives For Neonatal And Pediatric Departments

Christopher Rand, Chief Executive Officer and
Jaylee Hilliard, MSN, RN, NEA-BC, CPXP, Senior Director of Clinical Strategy

The Quadruple Aim is a well-known concept derived from the Institute of Healthcare Improvement that provides a framework for reducing costs, improving population health, patient experience, and team well-being. Today's healthcare executives and providers must be dedicated to simultaneously improving health system performance and the clinical outcomes of the patients they serve. In an increasingly competitive healthcare climate, utilizing the framework of the Quadruple Aim to enhance efficiency and quality is more critical than ever. The goals are clear but the path to achieving them isn't so cut and dry. Today's providers remain focused on finding the best way forward to successfully navigate how they address current challenges, provide quality care, and set the organization's direction. Organizations can be well-positioned to deliver on these goals with an eye towards the future and the explosion of technology throughout the healthcare ecosystem.

Leveraging Innovative Family Engagement Solutions to Meet Clinical and Operational Aspirations

The acceptance of family engagement technology in hospital settings has been growing. This presents neonatal and pediatric units with additional opportunities to support families during their child's time in the hospital and fosters a lasting bond between the child, family members, and the care team. In addition, with the onset of the COVID-19 pandemic and reduced visitation in many hospital units, the ability to view one's child via remote-access cameras became more valuable and more necessary than ever before.

Due to the stressful nature of NICU and pediatric admissions, it's no surprise that parents are at increased risk for anxiety during their child's hospital stay. However, by expanding the use of web camera and video conferencing capabilities, families are empowered to connect with their child through remote viewing and remain in communication with the care team via clinical updates, both of which can contribute to a more satisfactory hospital stay.⁵

Family engagement technology also supports family-centered care and engagement in the hospital. It can serve as an essential element in ensuring a successful experience from admission to discharge and beyond. Additionally, integrating family engagement solutions into the workflow can lead to significant,

Christopher Rand, Chief Executive Officer of AngelEye Health.
Jaylee Hilliard, MSN, RN, NEA-BC, Senior Director of Clinical Strategy,
AngelEye Health.



realized cost savings due to an improved family and patient experience. Several studies have been performed looking at the success of virtual visits and the use of telehealth to support this conclusion. Metrics such as a decreased length of stay, fewer readmissions, and fewer NICU follow-ups^{2,4,5} result in more satisfied families, which can positively impact HCAHPS scores, and the organization becoming a facility of choice for future patients and families.

Delivering a Proven, Positive Impact—The AngelEye Commitment

AngelEye understands the essential role that family-integrated care plays in all aspects of neonatal and pediatric care. Our HIPAA-compliant Family Engagement Platform integrates parents simply and seamlessly into the child's care team. Delivering a proven, positive impact on the family experience, care delivery workflows, and patient outcomes, AngelEye Solutions support the specialized needs of neonatal and pediatric units, including a successful transition home, and make a measurable impact on the Quadruple Aim.

Enhancing the Patient and Family Experience

Communication plays a pivotal role in both patient and family experience, making or breaking the trust between the healthcare provider and the patient and/or family. A disjointed exchange of critical health information can potentially contribute to feelings of loneliness, abandonment, and unwanted responsibility, which only adds to the burden of an already difficult situation. A recent publication by Sigurdson et al.⁷ clearly delineated this dynamic, especially among families of low socioeconomic status and families of color.

Interventions and new models of care are increasingly focused on improving collaboration among healthcare professionals, integrating parents into their child's care plan as early as possible, increasing staff support to help parents better cope, and optimizing the management of a patient's discharge process. Central to the success of each of these initiatives are effective and consistent communication between clinicians and a patient's family.

AngelEye's Family Engagement Solutions were purpose-built to elevate the hospital experience for patients and their families. This includes:

- Supporting family-integrated care
- Building trust with the care team as a result of ongoing virtual communication with families
- Improving parent satisfaction as families feel more supported in their child's journey towards improved health

Improving Provider Work/Life Balance

When it comes to incorporating families into the child's care plan and through their path to discharge, early educational and emotional support for parents can significantly decrease their stress. Critical time spent locating, distributing, and confirming families review and comprehend required education prior to discharge can quickly add up. The result can be staff burn-out and dissatisfaction due to being distracted from direct patient care.

Educating neonatal and pediatric parents and families during their child's hospitalization and before discharge is an essential task for staff from the moment a child is admitted to the unit. The care team is responsible for providing parents with a myriad of education regarding the hospital environment and information concerning their child's medical condition. In a 2019 study, Richardson et al.¹⁷ performed an evaluation that revealed that less than half of the available apps (at that time) targeting NICU parents should be considered acceptable educational material. Over two-thirds of the apps were found to have issues regarding credibility and just over a quarter were considered good quality.

AngelEye's team of clinicians have vetted professionally-curated digital education materials offered through AngelEye's OnlineEducation Solution to ensure education effectively empowers parents to be more involved in their child's care while allowing clinicians to focus on the most immediate health needs of patients. A recent article (February 2021) in the *Journal of Neonatal Nursing* explored the development and use of digital education with NICU parents and staff. Although it was a small study, participants considered the digital educational program presented relevant and complete. They believed the digital educational program should be available as soon as possible for parents, at admission or even before.⁸

AngelEye's OnlineEducation Solution increases the ease of access to family education resources required for discharge, all from a mobile app. When utilizing AngelEye's solution, a family is more likely to engage with the OnlineEducation tools since they are already immersed in the remote camera viewing experience. A simple-to-read dashboard provides clinicians with a list of materials assigned to a patient's family and data regarding the completion of specific lessons or tasks. Utilizing digital education materials improves clinical efficiency, reduces discharge delays, and eliminates room for error or missed critical



lessons. In addition, families are even more likely to complete assigned education as these tasks are incorporated into the frequently accessed camera system.

AngelEye is dedicated to improving the provider work/life balance by:

- Saving valuable time and clinical resources
- Improving care team efficiency
- Eliminating professional risk

Enriching Population Health

From a population health improvement perspective, integrating web camera technology into the pediatric (and NICU specifically) environment has demonstrated its benefits to health care providers and rural or remote patients and their families in particular. Web cameras provide families with a unique opportunity to connect with their hospitalized child(ren). Studies performed over the last six years have shown the majority of parents have positive attitudes toward the implementation of a webcam system in the NICU;^{9,10,11} thus, a cost-efficient neonatal/pediatric webcam program like AngelEye's CameraSystem™ has the potential to improve the quality of life for participating families by relieving anxiety and cultivating a distance bonding experience.

From a nutrition perspective, camera technology also promotes breast milk production due to an increased maternal bond with the child. While "fed is best" in all circumstances, increasing access to lactation care and providing education and services related to breastfeeding in communities where these services may be scant helps overcome breastfeeding barriers for many parents.

With AngelEye, today's pediatric patients and their families are benefitting from:

- Stronger parent-child bonding opportunities and decreased anxiety
- Elevated breast milk production rates
- Ongoing family educational support

Reducing Costs Through Decreased Length of Stay

The economics of neonatal and pediatric hospital stays can be staggering, with the average daily costs estimated between \$3,000 to \$10,000. A baby weighing less than 1500 grams, known as a Very Low Birth Weight (VLBW), is a very expensive patient. The "typical" or average VLBW infant costs \$131,472 and stays 55.5 days, based on data from the Agency for Healthcare Research and Quality, more than ten times the cost of the



average hospitalized patient.¹² In fact, reducing the NICU Length of Stay (LOS) by as little as one day can, on average, reduce healthcare expenses by as much as \$5,000. As such, finding ways to decrease LOS and reduce patient readmissions remains a top-of-mind priority for hospital and clinical leaders nationwide.

Over the years, AngelEye has expanded its portfolio of Family Engagement Solutions to offer a range of capabilities for addressing the high costs of neonatal and pediatric care by reducing LOS. It's been widely reported that breastfed babies often leave the hospital sooner. The AngelEye MilkTracker™ Application supports breast milk production by offering accessible lactation resources while providing better milk inventory management and visibility capabilities and reducing the need for donor milk usage, all of which can directly impact time and resource savings for clinical staff.¹⁴ Another aspect of feeding in Neonatal and Pediatric departments that can be overlooked is patient safety. Despite recommendations from regulatory agencies and the significant efforts by healthcare systems and organizations, milk mix-ups can and do occur. The Center for Disease Control has guidelines on its website for what to do when a mix-up happens.¹⁵ Nurses spend thousands of hours every year managing milk for hospitalized babies. These efforts include feeding and monitoring, labeling, printing, and logging infant-specific nutrition data. Is it any wonder that milk mix-ups occur? The MilkTracker Solution was purpose-built to address these resource challenges by offering a simplified way to manage milk inventory while ensuring that the right feed (prepared specifically according to physician orders) matches the right patient every time, ultimately mitigating risk and enhancing safety throughout the feeding process.

In addition, AngelEye's technology offerings are also well-suited to help address discharge readiness. According to Smith (2021), "Neonatal intensive care unit (NICU) discharge readiness is the primary caregivers' masterful attainment of technical care skills and knowledge, emotional comfort, and confidence with infant care by the time of discharge," and "NICU discharge preparation is the process of facilitating discharge readiness." This helps explain why families who spend more time with a hospitalized child tend to leave the hospital sooner, which makes the family

engagement opportunities offered by the CameraSystem™ and PatientConnect™ Solutions so important to the process. AngelEye's OnlineEducation™ ensures that families have received the proper guidance when it comes to transitioning their child home, supporting both a timely patient discharge as well as reduced future readmissions.

AngelEye is poised to reduce costs related to pediatric hospital stays by:

- Supporting breast milk production and reducing donor milk costs
- Reducing the lengths of stay
- Ensuring a more timely discharge process
- Decreasing readmissions
- Reducing operational expenses

Multiple Family Engagement Solutions From A Single Platform

Lack of interoperability and reliance on multiple technology vendors can be costly and resource intensive. The AngelEye Solutions (CameraSystem, PatientConnect, OnlineEducation, and MilkTracker) are available on a single platform to both clinicians and parents. These solutions integrate into any EHR, removing interoperability issues and eliminating dependence on multiple vendors.

Clinicians are adopting innovative approaches to family engagement as parents increasingly use mobile technology to search for information about their hospitalized child. AngelEye's Solutions provide a credible, evidence-based, easy-to-use platform for families and clinicians.

Interested in learning more about how AngelEye's comprehensive suite of technology solutions can position your hospital to achieve strategic goals in pursuit of the Quadruple Aim? Connect with us at info@angeleyehealth.com.

References

- 1 Arnetz BB, Goetz CM, Arnetz JE, et al. Enhancing healthcare efficiency to achieve the Quadruple Aim: an exploratory study. *BMC Res Notes*. 2020;13(1):362. Published 2020 Jul 31. doi:10.1186/s13104-020-05199-8
- 2 Cena L, Biban P, Janos J, et al. The Collateral Impact of COVID-19 Emergency on Neonatal Intensive Care Units and Family-Centered Care: Challenges and Opportunities. *Front Psychol*. 2021;12:630594. Published 2021 Feb 24. doi:10.3389/fpsyg.2021.630594
- 3 Craig JW, Glick C, Phillips R, Hall SL, Smith J, Browne J. Recommendations for involving the family in developmental care of the NICU baby. *J Perinatol*. 2015;35 Suppl 1(Suppl 1): S5-S8. doi:10.1038/jp.2015.142
- 4 Feeley, D. (2017 28 November Tuesday). *The Triple Aim or the Quadruple Aim? Four Points to Help Set Your Strategy*. retrieved from <http://www.ihl.org/communities/blogs/the-triple-aim-or-the-quadruple-aim-four-points-to-help-set-your-strategy>
- 5 Ranu, J., Sauers-Ford, H., Hoffman, K. (2021) Engaging and supporting families in the Neonatal intensive care unit with telehealth platforms. *Seminars in Perinatology*, 45(5) <https://doi.org/10.1016/j.semperi.2021.151426>.
- 6 Yeo, C., Ho, S. K., Khong, K., & Lau, Y. (2011). Virtual visitation in neonatal intensive care: experience with the use of internet and telemedicine in a tertiary neonatal unit. *The Permanente journal*, 15(3), 32–36.

- 7 Sigurdson K, Profit J, Dhurjati R, et al. Former NICU Families Describe Gaps in Family-Centered Care. *Qual Health Res*. 2020;30(12):1861-1875. doi:10.1177/1049732320932897
- 8 Lebel,V., Héon,M., Juneau,A.L., Collette,K., Feeley,N.(2021) The development of a digital educational program with parents of preterm infants and neonatal nurses to meet parents' educational needs, *Journal of Neonatal Nursing*,27(1), 52-57, <https://doi.org/10.1016/j.jnn.2020.06.004>.
- 9 Hawkes, G. A., Livingstone, V., Ryan, C. A., & Dempsey, E. M. (2015). Perceptions of webcams in the neonatal intensive care unit: here's looking at you kid!. *American Journal of Perinatology*, 30(2), 131–136. <https://doi.org/10.1055/s-0034-1376388>
- 10 Reimer A, Mause L, Hoffmann J, et al. Webcam use in German neonatological intensive care units: an interview study on parental expectations and experiences. *BMC Health Serv Res*. 2021;21(1):970. Published 2021 Sep 15. doi:10.1186/s12913-021-06901-7
- 11 Kubicka, Z., Zahr, E., Clark, P. et al. Use of an internet camera system in the neonatal intensive care unit: parental and nursing perspectives and its effects on stress. *J Perinatol* 41, 2048–2056 (2021). <https://doi.org/10.1038/s41372-021-00934-w>
- 12 Johnson, T. (2015 August) Unraveling the Cost of Very Low Birth Weight Infants, Neonatal Perspectives Blog retrieved from <https://www.medela.us/breastfeeding-professionals/blog/unraveling-the-cost-of-very-low-birth-weight-infants>
- 13 Johnson TJ, Patel AL, Bigger HR, Engstrom JL, Meier PP. Cost savings of human milk as a strategy to reduce the incidence of necrotizing enterocolitis in very low birth weight infants. *Neonatology* 2015;107:271-6.
- 14 Meier PP, Johnson TJ, Patel AL, Rossman B. Evidence-Based Methods That Promote Human Milk Feeding of Preterm Infants: An Expert Review. *Clin Perinatol*. 2017;44(1):1-22. doi:10.1016/j.clp.2016.11.005
- 15 Centers for Disease Control and Prevention: Guidelines and recommendations for Breastfeeding, retrieved from <https://www.cdc.gov/breastfeeding/recommendations/index.htm>
- 16 Smith VC. Discharge planning considerations for the neonatal intensive care unit. *Arch Dis Child Fetal Neonatal Ed*. 2021;106(4):442-445. doi:10.1136/archdischild-2019-318021
- 17 Richardson B, Dol J, Rutledge K, et al. Evaluation of Mobile Apps Targeted to Parents of Infants in the Neonatal Intensive Care Unit: Systematic App Review. *JMIR Mhealth Uhealth*. 2019;7(4):e11620. Published 2019 Apr 15. doi:10.2196/11620

Jaylee Hilliard, MSN, RN, NEA-BC, Senior Director of Clinical Strategy, AngelEye Health, has more than 10 years of nursing and leadership experience. Starting as a bedside nurse in the NICU, she then advanced to Manager of House Supervisors and Supplemental Pool, Director of Patient/Family Support Services, and Director of Neonatal Services and the Neonatal and Pediatric ECMO Program at McLane Children's Hospital Baylor Scott & White Health. Jaylee chaired the Physician Nurse Advisory Council with system-wide responsibilities for 12 NICUs. She has also served as a Neonatal Care Surveyor for Test EMS Trauma & Acute Care Foundation (TETAF) and as chair of the pediatric and neonatal value analysis team.

Christopher Rand, Chief Executive Officer of AngelEye Health. Since assuming the leadership role in 2019, Rand has built a team and created a culture that is based on both collaboration and innovation and focused on empowering neonatal and pediatric intensive care units with the most advanced family engagement technologies available today. In addition to his role at AngelEye Health, Rand has advised over 50 healthcare companies including Tri-Star Health Partners, Carrot Medical, InvisionHeart, WorkMeln, Satchel Health, and Evermind. He also serves as a partner for a venture investment firm, Tristar Health Partners.

Family Engagement Solutions

IMPROVE NICU OUTCOMES





Download Solutions eBook





Live-Stream Video



Family Resources



Text, Photo, Video Messaging



Feeding Management

angeleyehealth.com • info@angeleyehealth.com

Aquapheresis Offers Hope to Preterm Neonates < 3 kg with Renal Failure

Laura Hedli

Lucile Packard Children's Hospital Stanford, the core of the Stanford Children's Health network, has successfully begun delivering extracorporeal kidney replacement therapy (KRT) to the smallest neonates using a modified ultrafiltration device called aquapheresis. The device and method are FDA-approved to treat adults with heart failure when other medical management strategies have failed. Building on recent work at other pediatric institutions,^{1,2} the Stanford Children's Health team utilizes a novel, off-label modification of aquapheresis in the neonatal population to provide fluid removal and clearance. Early evidence indicates that KRT can be successful even in babies weighing < 2–3 kg.

Kidney replacement therapy can be crucial for treating infants with developmental defects impacting the kidneys or acute kidney injury (AKI). Full-term infants with conditions such as hypoxic-ischemic encephalopathy or requiring extracorporeal membrane oxygenation are at risk for AKI. Preterm infants are also vulnerable, since approximately 50% of babies born at 22–29 weeks of gestation will experience AKI.

At Packard Children's Hospital, which operates a Level IV Neonatal Intensive Care Unit, a sudden cluster of small, preterm infants with renal failure in the summer and fall of 2020 prompted the introduction of aquapheresis into clinical use. Some of these babies were born with bilateral renal agenesis, and some had developed congenital renal failure due to other causes. Because other organ systems were not affected, the clinical teams felt compelled to try something different, even if it meant pushing the boundaries of typical intensive care. The aquapheresis initiative was led by Stanford Children's Health nephrologists Scott Sutherland, MD, clinical professor of pediatrics and systems medicine, and Cynthia Wong, MD, clinical professor of pediatrics and medical director of dialysis, and neonatologist Alexis Davis, MD, clinical associate professor of pediatrics and medical director of the NICU. "Peritoneal dialysis is widely accepted to be the standard of care in neonates with kidney failure," said Sutherland. "But this new therapy offers a number of advantages, and in some of the smallest neonates it is really the only option available."

Packard Children's Hospital has been known as a pioneer in providing peritoneal dialysis in neonates; however, in babies < 3 kg, this approach can be fraught with complications,



including catheter leaks and infection. With aquapheresis, fluid delivery and nutritional support can be significantly liberalized while maintaining adequate dialysis support. The overall approach in the smallest babies is to dialyze these infants using aquapheresis until they are large enough—usually at least 3–3.5 kg—to safely start peritoneal dialysis. Once older, these patients can become candidates for kidney transplant.

Today, Lucile Packard Children's Hospital Stanford is a noted referral center for aquapheresis and dialysis of small neonates. A multidisciplinary team composed of neonatology, nephrology, nursing, anesthesiology, and interventional radiology (IR) collaborates to provide an individualized approach for each patient. Packard Children's Hospital is the first institution in the San Francisco Bay Area with a dedicated pediatric interventional radiology team, led by Shellie Josephs, MD, clinical professor of radiology. The team is highly specialized—with each member having completed training in adult interventional radiology, pediatric radiology, and pediatric interventional radiology.

Vessel preservation is paramount in any pediatric patient requiring long-term KRT, and the neonatal population is no exception. Catheters that are typically used for hemodialysis are too big for the preterm population, so the Stanford Children's Health interventional radiology team has adapted alternative vascular access devices in order for aquapheresis to be successfully performed. "It takes a lot of creativity to be able to take things that are not necessarily designed specifically for a given purpose, but are available to us, and modify them so that we can use them safely, especially in these very small, premature

Laura Hedli is a science writer with the Division of Neonatal and Developmental Medicine at the Stanford University School of Medicine.

infants,” said Josephs. “We are uniquely situated to be able to do this vascular access in these little ones.”

Traditionally, most dialysis catheters contain two lumens and are placed within a single access point. Because these preterm neonates are too tiny to fit a single line capable of tolerating the pressures of a dialysis device, the approach developed by the Stanford Children’s Health team uses two separate, smaller lumens at the neck and groin. One draws out blood and runs it through the circuit, and another delivers the blood back to the baby; tailoring catheter length for each individual baby is critical. Josephs and her pediatric interventional radiology colleagues use ultrasound to place the catheters and then x-ray to ensure that the catheter tip is the right length within the vein. The team continues to evaluate patients to understand if the two-catheter approach effectively circulates blood and preserves long-term patency of the veins at the access sites.

“There’s no one institution that’s going to have enough of these patients that we can really state with certainty what is safe,” said Josephs. Collectively, between 5,000 and 6,000 children require kidney dialysis or transplant in the United States each year.³ “We all have to work together to look at these patients based on size and determine what is best for them.”

So far, the results from Stanford Children’s Health are promising. For several babies, aquapheresis has been a bridge to peritoneal dialysis. These babies are thriving, working on growing big enough that they are eligible to receive a kidney transplant.

References

- 1 Askenazi D, Ingram D, White S, Cramer M, Borasino S, Coghill C, Dill L, Tenney F, Feig D, Fathallah-Shaykh S: Smaller circuits for smaller patients: improving renal support therapy with Aquadex™. *Pediatr Nephrol*, 31:853–60, 2016.
- 2 Menon S, Broderick J, Munshi R, Dill L, DePaoli B, Fathallah-Shaykh S, Claes D, Goldstein SL, Askenazi DJ: Kidney Support in Children Using an Ultrafiltration Device: A Multicenter, Retrospective Study. *Clin J Am Soc Nephrol*, 14:1432–40, 2019.
- 3 United States Renal Data System. 2021 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2021.

News...continued from page 44

screening. Having access to accurate simultaneous pre-ductal and post-ductal measurements helps simplify the process of screening and allows for rapid recognition of discrepancies, ultimately improving newborn care.” Root is a powerful, expandable hub that integrates an array of technologies, devices, and systems to provide centralized, multimodal monitoring and connectivity solutions. Root’s plug-and-play expansion capabilities allow clinicians to simultaneously monitor with numerous measurements in addition to dual oximetry Masimo SET, such as advanced rainbow Pulse CO-Oximetry measurements, O3 regional oximetry, and SedLine brain function monitoring, for expanded visibility of patient status. Using Root in combination with the Hospital Automation platform, monitoring data from all connected devices can be automatically charted in EMRs. Augusto Sola, MD, Vice President of Medical Affairs at Masimo, commented, “As a neonatologist who has worked nationally and internationally in the early diagnosis and treatment of hypoxemic and hyperoxemic conditions that affect neonates in order to improve neonatal survival and quality of life for these fragile infants, I know that Masimo SET measure-through motion technology’s accuracy and reliability have not only enabled CCHD screening with pulse oximetry, but have helped dramatically reduce retinopathy of prematurity (ROP). SET provides reliable, high-quality monitoring to prevent serious long-term morbidities and is now the standard of care for CCHD newborn screenings and ROP. With the availability of the SET MOC-9 Module, clinicians can now obtain simultaneous, dual oximetry pre- and post- ductal measurements, using one display, and increase efficiency of CCHD newborn screenings with Root. Furthermore, the Eve application on Root is automated and therefore simplifies and systematizes the screening process. Millions of newborn babies and their families throughout the world will be greatly benefited by this unique solution.”

New Ceiling Supply Units Add Flexibility in Hospitals

Dräger’s new Ambia and Ponta ceiling supply systems offer hospitals substantial flexibility in creating customized workstations that supports specific clinical needs in the operating room (OR), intensive care unit (ICU) and neonatal intensive care unit (NICU). The ceiling supply systems provide the ability to mount medical equipment and accessories on all four sides of the frame rail. This optimizes space, and allows equipment and accessories to be placed exactly where they are needed. Free positioning of a mix of electrical and gas outlets on all panels make it possible to place more outlets on a media column or head. The result, Ambia helps streamline workflow with the goal of increasing the satisfaction and safety of staff and patients—now and in the future. And with coordinated frame color selections and drawer decor variants, Ambia and Ponta can be easily integrated into any room concept, creating a patient-friendly environment. In addition, lighting options featuring warm, glare-free light, along with the ability to select from a range of RGB colors, helping to contribute to a calming and soothing atmosphere. Ambia and Ponta feature intuitive user interfaces that support quick and easy operation. The arm brake handles feature touch-sensitive sensors that automatically release the brakes, allowing rapid positioning of the media heads or columns. The brake handle locations on the units can also be adapted to suit individual staff or workflow requirements for ideal ergonomics. The handles communicate using wireless technology, allowing them to be located almost anywhere on the system. For infection protection, rounded profiles and smooth

Continued on page 55...

***B. infantis* EVC001 is Well-Tolerated and Improves Human Milk Oligosaccharide Utilization in Preterm Infants in the NICU**

Sarah Bajorek, DO

Human Milk Oligosaccharide Utilization

Colonization with beneficial bifidobacteria is delayed in preterm infants.¹ Instead, preterm infants in the neonatal intensive care unit (NICU) are colonized by potential pathogens linked to adverse outcomes, including high-mortality conditions such as late onset sepsis (LOS) and necrotizing enterocolitis (NEC).² Thus, strategies to promote overall gut health by increasing populations of beneficial *Bifidobacterium* in the preterm gut warrant attention.

Prior studies showed that activated *B. infantis* EVC001 has profound effects on the gut microbiome of term and preterm infants, specifically by increasing the abundance of beneficial bifidobacteria and reducing taxa capable of eliciting pathogenicity.³

The formation of a *Bifidobacterium*-dominant gut microbiome in neonates is attributed to the presence of human milk oligosaccharides (HMOs) in the diet.³ *B. infantis* is an infant gut symbiont uniquely equipped to utilize these HMOs.⁴

A small prospective, open-label study was conducted at Orlando Health Winnie Palmer Hospital for Women and Babies to evaluate the tolerability, HMO utilization, and effects on the fecal microbiota of feeding activated *B. infantis* EVC001, an infant-adapted microbe, to preterm infants in the NICU.

B. infantis EVC001 feeding resulted in significantly higher relative abundance of *Bifidobacterium* in the gut microbiome due to a significant improvement in HMO utilization. The Control infants excreted significant quantities of unutilized HMO, which would otherwise support growth and development of the infant. Higher levels of *Bifidobacterium* in infants fed *B. infantis* EVC001 was also significantly associated with reduced *Enterobacteriaceae*, a family that includes species such as *E. coli* and *Klebsiella*, often implicated with NEC and LOS.

Safety and Tolerability

This study adds to a growing body of evidence supporting the use of *B. infantis* EVC001 as a high-quality nutritional product to preterm infants in the NICU. In this study, feeding *B. infantis* EVC001 was safely fed and well-tolerated in this population.

Health care providers seeking to reduce risk associated with the neonatal gut should consider increasing *Bifidobacterium* and improving HMO utilization by adding *B. infantis* EVC001 to standard feeding protocols in the NICU.

References

- 1 Henderickx JGE, Zwittink RD, Lingen RA van, Knol J, Belzer C. The Preterm Gut Microbiota: An Inconspicuous Challenge in Nutritional Neonatal Care. *Front Cell Infect Mi* 2019;9:85.
- 2 Masi AC, Stewart CJ. The role of the preterm intestinal microbiome in sepsis and necrotising enterocolitis. *Early Hum Dev* 2019;138:104854.
- 3 Frese SA, Hutton AA, Contreras LN, Shaw CA, Palumbo MC, Casaburi G, Xu G, Davis JCC, Lebrilla CB, Henrick BM, et al. Persistence of Supplemented *Bifidobacterium longum* subsp. *infantis* EVC001 in Breastfed Infants. *Mosphere* 2017;2:e00501-17
- 4 Sela DA, Chapman J, Adeuya A, Kim JH, Chen F, Whitehead TR, Lapidus A, Rokhsar DS, Lebrilla CB, German JB, et al. The genome sequence of *Bifidobacterium longum* subsp. *infantis* reveals adaptations for milk utilization within the infant microbiome. *Proc National Acad Sci* 2008;105:18964–9.

Dr. Sarah Bajorek is a board-certified neonatologist at St. Mary's Hospital in Grand Junction, CO.

Pediatric Respiratory Stability: What Follows The Acute Care Setting?

Gabriela Ortiz, BSRT, RCP

Children born with medically complex conditions comprise 3% of the US pediatric population.¹ Children, who are medically complex, may be born with conditions that are congenital, progressive, or caused by a traumatic event. Any may be severe enough to require care and attention at an acute care hospital, some for extended times involving weeks or even months. The care provided may become very costly for the facility, patients, and their families. Once the patient has recovered from their acute state, the medical staff plans and coordinates the discharge to a step-down level of care or to home. When children are born with medical complications, it places them on the path to receive many medical interventions, which also may affect the emotional and psychological well-being. Because of the needs of a medically complex child, they frequently require a high level of unique medical care to meet their special medical needs.²

These needs involve interventions with high levels of expertise in specialty areas, such as:

- Specialized doctors.
- Individualized, regular checkups and follow-up by specialists.
- Extensive care at home or at a sub-acute level of care.

Following Graduation from Acute Care

So, what happens when the child graduates from the acute care setting, once they are stable respiratory-wise? The discharge plan begins once they can maintain body temperature (36.4°C – 37.5°C), indicative of nervous system function; demonstrate infrequent apneic or bradycardia episodes; exhibit weight increases to an appropriate scale per protocol; maintain oxygen saturation (>90%) within normal range; and effectively ventilate with secretions managed. Defining stability also may include maintaining an appropriate nutrition status and a stabilized medication regimen that is managing overall symptoms, such as seizures. These may be some indicators that the patient is now a good candidate for discharge from the acute care hospital. The care and monitoring of sick children require a team approach, whether in an acute care hospital, a sub-acute facility, or a home setting.

Gabriela has been in the field of respiratory care since 2006. She has worked in various roles, both clinically and professionally, where she gained extensive knowledge about mechanical ventilation as it relates to use within acute and subacute care hospitals. She combines this with her clinical experiences to provide support to others through education and clinical publications. She is currently a prn clinical consultant with Passy-Muir, Inc.

Initial Acute Care Assessment

The customary APGAR scoring (1 to 10 scale), which is completed at birth, is an assessment tool to indicate levels of deficiency in appearance, pulse, grimace, activity, and respirations.³ If the child presents with an APGAR score of less than seven, clinicians will continue therapies to improve the infant's medical status, which will increase the score. If no success with initial interventions, a continuation of further assessment occurs. Another consideration is that a baby may present with a normal to midrange score at first but decline rapidly with presentation of shallow breathing, apnea, duskiness, or oxygen saturation between 70 and 80%, thus requiring non-invasive or invasive support. The potential causes for a decline are variable.

Invasive Interventions

Due to improvements in non-invasive interventions, the need for invasive therapies in term and preterm infants have changed over time. While some interventions may seem simple, they still require close monitoring. For example, oxygen and systems that aid in secretion management must be set up to accommodate precise liter flows and pressures so not to cause lung injury. Positive pressure machines, such as invasive or non-invasive ventilators, will require the attention of a medical professional to adjust as needed for patient comfort and the best efficacy.

In certain situations, intubation and ventilation are crucial for survival. With the difficulty of tiny airways, special skills are required for successful placement of the endotracheal tube. The identification of infections, anatomical abnormalities, or neurological diseases affecting the integrity of the airway helps the clinical team determine the intubation process. In pediatrics, intubation usually occurs for no more than a couple weeks but may be variable as it is dependent on facility protocol and team management. If weaning from mechanical ventilation is unsuccessful, the decision to tracheostomize is considered.

Many fears come with the decision of a tracheotomy, but at times it is the only alternative as a lifesaving modality.⁴ De Jesus-Rojas et al. (2018) compared outcomes of technology-dependent infants discharged from the NICU with tracheostomy tubes with care defined as Usual Care (UC) versus Comprehensive Care (CC).⁵ Because the needs of patients with tracheostomy tubes are complex, this study investigated the use of a comprehensive care model that involved the use of extended medical visits, a multidisciplinary team approach, phone calls between visits, and a 24/7 telephone access for the caregiver. Findings indicated



Using a Passy Muir Valve in-line with mechanical ventilation while at home.

that a CC approach mitigated the many challenges and barriers that medical complexity may cause and improved outcomes as compared to UC. The CC group showed significantly lower mortality (3.4%) versus UC (35.7%) and less readmissions, 21% for those under CC compared to those infants under UC at 36%. The implications of a tracheostomy tube in the NICU are often misunderstood. Advancements in specialty procedures and technology has allowed the survival rate of infants to increase, thus the care of specialists and parents with extensive training and education is essential.

Tracheostomy tubes alter airflow and pressures; therefore, when a tracheostomy tube is used, consideration is given to the possible negative effects on neurological and respiratory status. A reduction or loss of airflow to the upper airway decreases sensation in the airway, which may negatively impact the normal coordination of the suck, swallow, breathe pattern. A change in this pattern may negatively affect feeding, secretion management, and vocalization.⁶ The inability to engage in positive airway pressures may also have an impact on positive end-expiratory pressure (PEEP), affecting ventilation; intrathoracic pressures, affecting body core strength and posture; and subglottic pressure, potentially affecting swallowing and reducing protection of the airway. Loss of airflow and pressures may delay children from reaching developmental milestones in physical development and speech and language. With these potential effects on development, it is imperative that a multidisciplinary approach occur, allowing for closer monitoring and implementation of interventions for enhanced development.

Following Acute Care

Different approaches to care are required once a child has recovered from their acute state. Members of a multidisciplinary team, such as a nurse case manager (NCM) or social worker (SW), will prepare and plan the discharge—either to a lower level of care, such as a sub-acute facility, or to the patient's home. The discharge planner (DC-planner) identifies specialists, such as Home Health Nursing (HHN) and durable medical equipment (DME) providers, who are then contracted with the patient's insurance company.

Most hospitals also employ a specialty team to manage children who go home on ventilatory support, whether invasive or noninvasive. However, there are instances when situations may not meet the home care criteria.

Garber and Guertin (2012) reported several contraindications for homecare, including:⁷

- The presence of a physiologically unstable medical condition, requiring higher level of care or resources not available in the home.
- Lack of an appropriate discharge plan.
- Unsafe physical environment.
 - Presence of safety hazards.
 - Inadequate basic utilities.
- Inadequate resources for care in the home.
 - Financial resources.
 - Caregiver availability.
 - Access to medical follow-up.

When considering home placement, Sterni et al. (2016) reported that an awake and attentive trained caregiver should be in the home and available, especially if a child always requires chronic invasive ventilation.⁸ Homecare also may help reduce exposure to hospital-borne infections and help free hospital ICU beds for other acutely ill patients, thus, also benefitting the financial side.⁹

Example of Considerations for One Diagnosis

The prognosis of each child determines the level of support needed. One example would be the considerations to make when working with a child who has Congenital Central Hypoventilation Syndrome (CCHS). This child may discharge home, after residing in acute care facility for months. CCHS, also known as Ondine's curse, is a rare disorder of decreased respiratory function and impaired autonomic regulation. It is a lifelong and life-threatening disease, typically occurring in newborns, and with a milder, later-onset presentation in children and adults.¹⁰ Typically, this disorder causes the child to need mechanical ventilation on a long-term basis.¹¹

A discharge planner will coordinate resources, home health nursing, educate parents, and allocate medical equipment. The parents prepare the home and the care room to accommodate medical size cribs or beds, furniture, and storage to house equipment and supplies. Most DME companies provide equipment, meeting the needs for tracheostomy care, and may provide clinicians who monitor breathing and secretion management. HHN agencies may provide physical therapy (PT), occupational therapy (OT), or speech-language pathology (SLP) services to evaluate and treat the child's fine and gross motor skills, cognitive functioning, and speech-language needs as appropriate for either developmental delays or changes in typical development due to the disorder.

In home care circumstances, a child may be eligible for up to 18-20 hours of home health nursing, leaving any remaining hours for the parents or caregivers to manage the child's care. All caregivers for the child should be trained on the use and care of the medical equipment, including how to change out the soft supplies, such as ventilator circuitry, oxygen tubing, suction catheters, and pulse-oximeter probes. A typical day in the care of a child with a tracheostomy tube may involve medication, which is given on a schedule; pulmonary hygiene, conducted as the child needs; feedings via G-tube or by mouth; daily trach and stoma care; and social and parental bonding.

In many cases PT, OT, and SLP may also be authorized by insurance. The number of visits by these therapies are dependent on the needs of the child and matched with the insurance or other payment source. If the child has a tracheostomy tube, then the speech-language pathologist will collaborate with the home care respiratory therapist for speaking Valve assessment. Brooks et al. (2019) investigated predictors of success for speaking Valve use in infants. They discussed the benefits of early intervention and restoring a more normal physiology in infants with a tracheostomy.¹² Following discharge to home, the child also may have outpatient, multidisciplinary team appointments, with frequency changing based on the child's diagnosis and needs. While the home environment is a safe and comfortable place for children who are recovering or have complex medical conditions, the busy, round-the-clock medical intervention schedule may put a strain on family life. Support groups and counseling may be something that a family seeks or to which they should be referred to assist with the impact that occurs secondary to these changes in their family dynamics and daily life.

What if home is not a good option?

Another child, even with the same diagnosis, may not meet the discharge requirements due to factors such as:

- Unsafe home environment.
- Poor accessibility.
- Lack of home health caregivers.
- Language barriers.
- Lack of a durable equipment provider within a reasonable distance to the home.

A child who is not a good candidate for home care may be discharged to a sub-acute facility for children. In this setting, they also would be cared for by skilled, licensed clinicians following close instruction from the child's specialists. Ventilation and oxygenation needs would be met through the care plans, which would be followed closely and adjusted to the patient's needs. Care plans may consist of ventilator protocols, which may include management of oxygen saturation (SpO₂) or end-tidal carbon dioxide by (EtCO₂); secretion management modalities for the prevention of respiratory infections; tracheostomy care; and speaking Valve use. Use of a speaking Valve will provide an opportunity to promote vocal communication and restore a more normal physiology for the child. Development is supported by engaging the child in activities that are age appropriate. Social services advocate for the child's wellbeing, with the primary plan often being for discharge home.

During a stay in a subacute facility, parents and family members have visitation, but in some cases, visitation is impacted by other factors, such as other children already in the home, financial

situations, or location. Pediatric facilities are limited, often leaving a child residing hours away from their families.

Conclusion

Once a child has recovered from their acute state, the complexity of care may vary dependent on their case and various scenarios related to their discharge environment and caregivers. While a home environment is the goal for discharge, Akanguire et al. (2017) investigated factors affecting rehospitalization. They reported that infants with tracheostomy and mechanical ventilation must both be closely monitored by a multidisciplinary team throughout the first 1.5 years of life as this is a critical period for identifying risk factors, such as viral illness.¹³ Whether the parents or caregivers are new or seasoned, having a medically complex child is very different than a child with a typical birth without complications. This complexity may cause feelings of both fear and excitement. Though there will be many obstacles, having resources to provide necessary specialty care to keep their child as healthy as possible, despite their comorbidities, is critical. The clinical professionals involved in the child's care are a great resource to provide the education and support needed to the families and caregivers, no matter the setting.

References

- 1 Mooney-Doyle, K., & Lindley, L.C. (2020). Family and child characteristics associated with caregiver challenges for medically complex children. *Family Community Health*, 43(1), 74-81. <https://doi.org/10.1097/FCH.0000000000000245>
- 2 Children First Healthcare System. (2020). Medically complex child: More than special needs. Retrieved on 11/21/2021 from <https://childrenfirst.com/medically-complex-child-more-than-special-needs/>
- 3 John Hopkin's All Children Hospital. (2021). What is the apgar score? <https://www.hopkinsallchildrens.org/Patients-Families/Health-Library/HealthDocNew/What-Is-the-Apgar-Score>
- 4 Abraham, S. (2003). Babies with tracheostomies: The challenge of providing specialized clinical care. *The ASHA Leader*, 8(5). <https://doi.org/10.1044/leader.FTR2.08052003.4>
- 5 De Jesus-Rojas, W., Mosquera, A. R., Samuels, C., Eapen, J., Gonzales, T., Harris, T., McKay, S., Boricha, F., Pedroza, C., Aneji, C., Khan, A., Jon, C., McBeth, K., Stark, J., Yadav, A., & Tyson, E. J. (2018). The effect of comprehensive medical care on the long-term outcomes of children discharged from the NICU with tracheostomy. *The Open Respiratory Medicine Journal*, 12:39-49. <https://doi.org/10.2174/1874306401812010039>
- 6 da Cunha de Lima, J. A., Collet, N., Baggio, A., & de Almeida, A. M. (2021). Breastfeeding based on the experience of mothers of tracheostomized children and the use of the Passy-Muir valve. *Anna Nery School Journal of Nursing*, 25(3), 1 - 7. <https://doi.org/10.1590/2177-9465-EAN-2020-0290>
- 7 Garber, K., & Guertin, M. (2012). Home mechanical ventilation: Bringing patients home with improved ventilation options. *Respiratory Therapy Magazine*. <https://rtmagazine.com/disorders-diseases/critical-care/ards/home-mechanical-ventilation-bringing-patients-home-with-improved-ventilation-options/>
- 8 Sterni, L. M., Collaco, J. M., Baker, C. D., Carroll, J. L., Sharma, G. D., Brozek, J. L., Finder, J. D., Ackerman, V. L., Arens, R., Boroughs, D. S., Carter, J., Daigle, K. L., Dougherty, J., Gozal, D., Kevill, K., Kravitz, R. M., Kriseman, T., MacLusky, I., Rivera-Spoljaric, K., Tori, A. J., Ferkol, T., &

- Halbower, A. C. (2016). An official American Thoracic Society clinical practice guideline: Pediatric chronic home invasive ventilation. *American Journal of Respiratory and Critical Care Medicine*, 193 (8). e16 – e35. <https://doi.org/10.1164/rccm.201602-0276ST>
- 9 King, A. (2012). Long-term home mechanical ventilation in the United States. *Respiratory Care*, 57(6), 921-932. <https://doi.org/10.4187/respcare.01741>
 - 10 Weese-Mayer, D. E., Marazita, M. L., Rand, C. M., & Berry-Kravis, E. M. (2004). Congenital Central Hypoventilation Syndrome. *Gene Reviews*. <https://www.ncbi.nlm.nih.gov/books/NBK1427/>
 - 11 Ortiz, G. (2021). Congenital central hypoventilation syndrome: Not just a respiratory disorder. *Neonatal Intensive Care*, 34 (1).
 - 12 Brooks, L., Figueroa, J., Edwards, T., Reeder, W., McBrayer, S., & Landry, A. (2019). Passy Muir Valve tolerance in medically complex infants and children: Are there predictors for success? *Laryngoscope*, 130(11), e632 – e639. <https://doi.org/10.1002/lary.28440>
 - 13 Akangire, G., Manintim, W., Nyp, M., Townley, N., Dai, H., Norberg, M., & Taylor, J. B. (2017). Factors leading to rehospitalization for tracheostomized and ventilator-dependent infants through 2 years of age. *Journal of Perinatology*, 37, 857 – 863. <https://doi.org/10.1038/jp.2017.54>

News...continued from page 50

materials that are compatible with a wide range of disinfection products help make the Ambia and Ponta easy and fast to clean and disinfect. A range of cable management options help eliminate cord clutter and assist with reducing exposed surface area and the accumulation of dirt. A touchless user control for operating ceiling and floor lights further supports infection prevention efforts. Dräger has more than 60 years of consulting experience in the design of medical workplaces, including the analysis of work processes and space requirements, consulting for optimized workflows and digitally supported room concept creation, and on-site equipment implementation.

COVID-19 Vaccines in Pregnancy May Protect Baby, Too

Women who receive COVID-19 vaccines during pregnancy pass antibodies to their babies, which could protect newborns from the disease, research has shown. In a new study that examines umbilical cord blood from 36 deliveries, researchers provide additional evidence that vaccines—and not COVID-19 infections—elicited the antibodies detected in this cohort. Researchers with New York University Langone Health conducted a study that included pregnant women who had received at least one dose of an mRNA COVID-19 vaccine (Pfizer/BioNTech or Moderna). All neonates had antibodies to the spike protein at high titers, the researchers found. Unlike similar prior studies, the researchers also looked for antibodies to the nucleocapsid protein, which would have indicated the presence of antibodies from natural COVID-19 infection. They did not detect antibodies to the nucleocapsid protein, and the lack of these antibodies suggests that the antibodies to the spike protein resulted from vaccination and not from prior infection, the researchers said. The participants had a median time from completion of the vaccine series to delivery of 13 weeks. The study was published online in the *American Journal of Obstetrics & Gynecology* MFM. “The presence of these anti-spike antibodies in the cord blood should, at least in theory, offer these newborns some degree of protection,” said study investigator Ashley S. Roman, MD, director of the division of maternal-fetal medicine at NYU Langone Health. “While the primary rationale for vaccination during pregnancy is to keep moms healthy and keep moms out of the hospital, the outstanding question to us was whether there is any fetal or neonatal benefit conferred by receiving the vaccine during pregnancy.” Questions remain about the degree and durability of protection for newborns from these antibodies. An ongoing study, MOMI-VAX, aims to systematically measure antibody levels in mothers who receive COVID-19 vaccines during pregnancy and in their babies over time.

Cost-Effectiveness of Targeted Fortification Approach Versus Standard Fortification Approach for Very Low Birth Weight Infants

Isabel Hoffmann, Diogo Barros and Paolo Satta

Background: Very Low Birth Weight infants (VLBW, < 1,500g at birth) require extended neonatal care via fortification of breast milk to meet their nutritional needs. Targeted Fortification (TFO) is based on measuring macronutrients in human milk to tailor infants' feeding, while Standard Fortification (SF) assumes average macronutrient values in milk. TFO is becoming the preferred method in Neonatal Intensive Care Units (NICUs), but there is a lack of studies about its cost-effectiveness. This study analyses the cost-effectiveness of TFO, by quantifying the total costs versus the economic benefits of TFO over SF.

Methodology: Various use case scenarios were analyzed, considering different frequency of milk analysis (every day to three times per week) and sizes of the NICU (on average 10, 50 and 100 VLBW infants fed TFO every day). The costs of TFO were calculated considering costs for purchasing and operating one of two different systems for human milk analysis, and include the cost for the device to analyze human milk, recurring costs such as consumables, and operating costs such as the increased workload for nurses and dieticians. The economic benefits were calculated by quantifying the health outcomes resulting from TFO as reported in literature, namely the reduction in the prevalence of key neonatal diseases—Necrotizing Enterocolitis (NEC), Sepsis, and Bronchopulmonary Dysplasia (BPD).

Results: TFO generates significant savings in all the scenarios. In a 50-bed unit, annual savings can reach up to \$1,549,888, entirely covering TFO costs for 10 years (\$1,058,903). A sensitivity analysis was performed to quantify the reduction rate for each disease that would cover all the TFO related cost for 10 years. In a 50-bed unit performing human milk analysis every day, 10-year costs of TFO would be covered by reducing NEC by 21.4 cases in 10 years (0.65% net reduction), sepsis by 87.3 cases (2.6% reduction), and BPD by 27.8 cases (0.84% reduction), over the same 10-year period.

Conclusion: We concluded that TFO is a more cost-effective

Isabel Hoffmann, CEO and founder of Tellspec, is a deep-tech entrepreneur who has successfully founded eight companies over the last 28 years in the fields of analytical vibrational spectroscopy, medical devices and more recently in AI-based data analysis. Diogo Barros is data scientist at Tellspec, the company that is developing the Preemie System for human milk analysis. Paolo Satta, Tellspec's Chief Operating Officer, is leading the operations for developing the Preemie Systems. More about the authors' bios at the end of this article.

fortification approach, since initial set-up costs and operating costs are recovered within 1-2 years, depending on the scenario, due to the reduction in the prevalence of key diseases. Furthermore, the economic benefits achieved with TFO are expected to be higher than the ones reported, due to the medium- and long-term health benefits achieved in the life of VLBW infants.

Background

Very Low Birth Weight infants (VLBW, birth weight < 1,500 g) have specific nutritional needs that can be adequately addressed by fortifying human milk, so as to achieve growth similar to intrauterine growth.

The Standard Fortification (SF) approach is widely adopted in the majority of Neonatal Intensive Care Units (NICUs). This approach assumes that human milk has an average content of macronutrients (proteins, lipids, and carbohydrates), and fortifiers are added in fixed doses irrespective of the unique composition of the milk administered (see Rochow 2015a). The approach does not take into account that the content of macronutrients in human milk is subject to significant variation, depending on donor's age, diet and even on the time of the day, and therefore poses infants at risk of not getting the recommended intake (see Ehrenkranz 2014, and Henriksen 2009).

Targeted Fortification (TFO) is an individualized approach based on the actual measurement of the macronutrients in milk through human milk analysis, and is gaining wide recognition as the most indicated fortification procedure based on the actual nutritional content in breast milk. Macronutrients in milk change their concentration throughout time, particularly protein, whose content decreases as the stages of lactation evolve. TFO tailors the fortification to the specific nutritional intake of preterm infants, thus increasing infants' growth rates (see Rochow 2015b).

Several studies have been carried out to assess the health outcomes of TFO when compared to SF. It has been evidenced that infants fed with TFO experience higher macronutrient intakes, higher weight gain and improved growth velocities for what concerns weight, length, and head circumference (see Rochow 2013, Rochow 2020). TFO prevents infants to get constantly changing amounts of macronutrients, which exposes them to a continuous regime of over- and under-nourishment on a daily basis. Since the macronutrient intake

is constant over-time, infants receive a balanced diet, and avoid getting higher or lower amount of macronutrients than those required. This poses less stress on their premature gut and metabolism, and a less frequent feeding intolerance has been evidenced. Such outcomes have been also associated to reduced neonatal morbidity, in particular for what concerns the occurrence of Necrotizing Enterocolitis (NEC), Sepsis, and Bronchopulmonary Dysplasia (BPD)—see Rochow 2020 and Sánchez Luna 2020.

Achieving robust evidence of the health outcomes generated by TFO and also quantifying the extent and impact of its outcomes is a necessary step towards the wide adoption of such an approach. As a matter of fact, TFO is a much more expensive option than SF, since it requires the purchase and maintenance of equipment for analyzing human milk, as well as trained staff for both operating the device and for calculating the fortification needed. An average of 10-15 minutes of increased workload per patient per day has been estimated for applying this approach (Rochow 2013), which clearly raises the overall operational costs of the nursery. In order to contain such costs and make TFO sustainable in all nurseries, studies have been performed to assess the most cost-effective frequency of human milk analysis, trying to reach an optimal trade-off to minimize as much as possible the macronutrient variation in infants' feeding from day to day, but also to contain the workload for operators. It has been suggested to perform human milk analysis "at least twice a week" as an optimal trade-off (Rochow 2015), while other studies perform three milk analysis per week (Rochow 2020).

To date, the overall costs associated to the adoption of TFO have not been analyzed in detail, and no publication exists with an estimation of the potential economic benefits that could be generated as a result of the health outcomes evidenced when applying TFO. The lack of this analysis is due to the need to provide more robust evidence of such health outcomes through specifically designed clinical trials, and above all to quantify their impact (see Fabrizio 2020 for a recent review, which highlights the need to carry out further studies on the impact of TFO).

The aim of this paper is to leverage the evidence acquired so far to estimate whether TFO is a cost-effective approach, by quantifying the costs to be borne for applying such an approach and comparing them to the expected economic benefits that could be generated thanks to the health outcomes evidenced so far in the available literature.

Methodology

Our approach is based on retrieving and analyzing data related to the costs to be borne to implement TFO in a NICU, to the health outcomes that can be generated by implementing TFO and the extent of such outcomes, and to the quantification of the economic benefits generated thanks to the above-mentioned health outcomes, namely the reduction of BPD, Sepsis and NEC incidence.

All the costs and the benefits are expressed in 2020 US dollars. This is due to the fact that the reference health economic studies related to the health benefits associated to TFO have been performed in the US, leveraging larger availability of data. In order to build reliable use case scenarios, we therefore opted for considering costs and benefits as they would be experienced by US NICUs.

In order to perform a reliable cost analysis, we need to consider specific use case scenarios, since the overall TFO cost varies depending on the amount of analyses to be performed, which in turn depends on the number of infants fed with TFO, and also the weekly frequency of human milk analyses performed for each infant. We therefore defined the following use case scenarios: two scenarios based on frequency of analysis (every day, which is the most appropriate way to reduce variations in macronutrients intake; and three times per week, which has been reported as an optimal trade-off between optimal nutrition and sustainable workload, see Rochow 2020); then three scenarios based on the average number of VLBW infants hospitalized in the NICU and fed with TFO (10, 50, and 100). Combining the two frequencies of analysis with the three scenarios for the average number of VLBW infants hospitalized, we have 6 reference scenarios. They can be used as a reference by NICUs wishing to quantify the expected costs and benefits when adopting TFO, based on the average number of infants they intend to feed with TFO, and on the frequency of human milk analyses they intend to perform.

Cost Analysis

The first step is assessing the costs to be borne to implement TFO in a NICU. To this purpose, we used several sources, including publications, interactions with manufacturers of human milk analysers, tests with nurses and neonatologists to assess the workload and related costs required to implement and use TFO.

The analysis is directed to identify all the cost items linked to the adoption and actual usage of Systems for human milk analysis which enable TFO. In this analysis, we consider two reference Systems for using the TFO approach: System 1 is already distributed and adopted by several NICUs, while System 2 is currently in development phase and claims to significantly reduce the costs for implementing and running TFO. We do not disclose here the brands for confidentiality issues. The two Systems have been selected since they provide a reliable quantification of the cost range in which the adoption of TFO falls into. The currently available System 1 represents a reference benchmark of the actual costs for adopting such an approach, while System 2, which is expected to be marketed in 2022, could reduce such costs.

The following cost items have been identified, which apply to whatever system is being adopted and used:

1. Equipment costs

The costs have been defined by considering quotes from manufacturers of analyzers. While System 1 equipment is sold at a price of **\$45,000**, the start-up costs for System 2 are in the order of **\$25,000**. These are the costs needed to purchase just the equipment, including the human milk analyzer. System 2 also includes in the price a tablet for running the software, while both the Systems include homogenizer, bead baths and other accessories for starting-up human milk analysis.

2. Operating costs

Those costs are the result of the increased workload for nurses and clinical dieticians for operating the Systems. In this case, we consider the increased costs with respect to the current methodology in place for managing fortification, that is the SF approach, which represents the baseline cost for managing preterm feeding. Therefore, we only consider the operations

that are needed on top of the current operations performed for managing SF. As an example, we do not consider the time needed to fortify human milk bags, since this operation is standardly performed whatever approach is followed. We do not consider either the costs for the fortifiers used, since they can vary depending on the type of fortifiers. It has to be noted that studies also reported that TFO could reduce the overall costs of fortifiers, since it would optimize their use—see, for instance, de Halleux 2013, where it is reported a significantly lower mean use of fortifier with individualized fortification compared to SF (3.6 compared with 4.0 packets/dL).

In order to quantify the operating costs, we analyzed in detail the whole process for using the two Systems when carrying out the analyses. The workload for using the two Systems has been quantified by both performing analysis sessions with personnel working at NICUs, and by analyzing the instruction for use provided in the manuals.

Operating costs can be divided in 2 main groups of activity: the first one is the increased workload for the nurse to carry out human milk analyses by using the Systems; the second one is the increased workload for the clinical dietician (in certain cases, the nurse or the doctor) to calculate the fortification based on human milk analysis. We assume that the time for the doctor to finalize the prescription does not increase, since the clinical considerations when prescribing the feeding do not substantially change when SF or TFO is applied.

Starting from the increased workload for the nurse, the following section briefly describes the various operations and the rationale behind the time quantification.

The operations for System 1 are quite complex, and require the preparation and warm up of various consumable solutions. Before each scanning session, the System has to undergo a check operation for ensuring its functionality, and a calibration session by using specific consumables to check it is correctly calibrated. After 10 analyses, a cleaning procedure has to be followed, which also implies to re-use cleaning solutions, so each 10 analyses some time has to be dedicated to cleaning and preparing the System. The human milk samples need to be warmed up before the analysis, then each sample has to be prepared, homogenized, and finally analyzed by the System. The session ends with a specific cleaning procedure for the System, and data export by using a pen drive or connection to a PC.

The operations for System 2 are more straightforward: after an automatized device warm-up, and calibration activity (just an empty scan is needed to calibrate the device), each sample need to be prepared for analysis and then scanned, and the results are directly provided into the software, without the need to export them in other software to calculate the fortification, since this function is provided in the software. After each analysis, and at the end of the session, the cuvette needs to be cleaned. Therefore, based on our testing, the fixed time to start-up each analysis session is around 140 seconds, while each analysis requires around 130 seconds (including sample preparation and homogenization, sample analysis, and System cleaning). The final cleaning requires 20 seconds.

Table 1 summarizes the time required (in seconds) for each activity needed to operate the two Systems, and carry out human milk analysis.

Table 1. Time needed to operate the two Systems for human milk analysis

Activity	Time unit	System 1	System 2
Solution warm-up time	seconds	1200	0
Operation for warm-up	seconds	240	0
Check time	seconds	180	0
Sensor warm up	seconds	0	120
Sensor Calibration	seconds	240	20
Cleaning time	seconds	180	20
Cleaning time end of session	seconds	240	20
Sample preparation time (warmup)	seconds	600	0
Sample preparation time (homogenization)	seconds	60	60
Analysis time	seconds	80	50
Data export	seconds	60	0

When comparing the workload required by the 2 systems, we did not consider the solution warm-up time for System 1, since after the solution preparation, nurses can perform other work during the warm-up. It is worth mentioning that considering the solution warm-up time, the average time for the analysis of one sample that considering solution warm-up time, the average time for the analysis of one sample with System 1 is around 5 minutes, in line with what has been reported in Rochow 2015: “Implementing target fortification adds additional workload to the neonatal intensive care unit team. The total time required to analyse breast milk composition is approximately 5 to 7 min per sample.” System 2 claims to significantly reduce this time, thanks to the reduction of preparation time (no warm-up of solutions nor of samples), set-up time (faster calibration), and cleaning (just the cuvette has to be cleaned when after each analysis).

We can finally compare the workload for the nurse in the use-case scenario identified based on the number of analyses per session (10, 50 and 100), as illustrated in Table 2.

The workload is then economically quantified for both the Systems. The associated costs are calculated considering the average annual salary of a registered nurse in the US, which accounts for \$77,460, making on average an hourly salary of \$40.34 (considering 1,920 working hours per year). This allowed us to calculate the annual increased costs for nurse workload in each of the six use-case scenarios (varying number of analyses per analysis session and varying frequency of the analysis during the week). Results for both the Systems are illustrated in Table 3.

Then, we need to consider the increased work of the clinical dietician for calculating the quantity of fortifiers to be added to the measured human milk, and the associated costs. Rochow 2015 reports that by optimizing the operations for human milk analysis, and by using a “predefined Excel sheet” to perform the calculation of fortification, “the additional workload on days with breast milk measurements to fortify a 24-h batch was less than 10

Table 2. Time for each scanning session in the 3 scenarios

Total time per analysis session	Time unit	System 1	System 2
Scenario 1 - 10 analyses	seconds	2,360	1,460
Scenario 2 - 50 analyses	seconds	10,180	6,660
Scenario 3 - 100 analyses	seconds	19,580	13,160

Table 3. Annual increased costs for human milk analysis

Annual Nurse Increased Costs	System 1		System 2	
	Every day	3 times per week	Every day	3 times per week
10 analyses	\$ 9,652	\$ 4,125	\$ 5,971	\$ 2,552
50 analyses	\$ 41,636	\$ 17,795	\$ 27,240	\$ 11,642
100 analyses	\$ 80,083	\$ 34,227	\$ 53,825	\$ 23,005

min, compared to 1–2 min on days without measurements”. The additional workload, starting from human milk analysis till the final prescription, would therefore be in the order of 8 minutes per sample. Considering that the very same paper reports that the analysis of human milk takes on average 5–7 minutes, we can state that the work for calculating the fortification and making the prescription in an optimized setting takes around 3–4 minutes. Time savings are clearly dependent also on the specific tools used in the hospital, which usually vary from one hospital to the other (hand calculations, Excel files, built-in software applications, etc.).

The most time-consuming operation in TFO with respect to SF is calculating the quantity of fortifiers needed based on the macronutrient content measured in human milk. The other activities (milk fortification, documentation and printing of the prescription) need to be performed also when SF is followed. At the same time, each feeding prescription is different, and can take less or more time depending on various factors not related to the tools used, starting from the specific health status of the infant, the presence of comorbidities and the clinical analysis performed by the doctor. System 2 provides a software which is able to automatically store the results of the milk analyses, match the milk to a specific infant, and then support the dietitian in the activity by providing automatic calculation and suggestion of the fortification needed. The dietitian has just to input either the targeted values to be administered (volume of fluid, quantity of macronutrients and energy), and the System automatically calculates the amount of fortifiers needed. Considering the functionality that System 2 offers for speeding up the calculation process, we estimate that an average additional workload of 2 minutes is needed to calculate the fortification and make the prescription with respect to SF. System 1 does not provide such functionality, meaning that the results of human milk analysis need to be exported or entered by hand, and then the calculation has to be done using other tools. We therefore estimate an average additional workload of 4 minutes in these cases.

The associated costs for the calculation are quantified considering an average annual salary of \$65,000 for the NICU dietitian performing the calculation of fortification, which makes a \$33.85 hourly salary considering 1,920 working hours per year. This leads to the annual increased costs illustrated in Table 4 for the six use-case scenarios.

Table 4. Annual increased costs for calculating the fortification

Annual Dietician Increased Costs	System 1		System 2	
	Every day	3 times per week	Every day	3 times per week
10 analyses	\$ 8,237	\$ 3,520	\$ 4,118	\$ 1,760
50 analyses	\$ 41,184	\$ 17,602	\$ 20,592	\$ 8,801
100 analyses	\$ 82,368	\$ 35,204	\$ 41,184	\$ 17,602

3. Recurring direct costs

These costs include consumables, fees, and maintenance costs. To precisely estimate the recurring direct costs, we analyse in detail the costs associated to the use of the two Systems over time. The operators are required to use additional products or services, which are listed in Table 5.

Some of the direct costs are just fixed annual costs needed to operate the System. In particular, maintenance costs include the factory calibration of the device, which requires the device to be either sent back to the factory or specialized personnel to calibrate the device on-site (Item #6). Then System 2, which does not require consumables to be operated, provides a software solution for operating the System through a tablet, and the revenues model is based on an annual subscription fee at \$4,750, which customers are required to pay from the second year onwards (Item #5).

The only recurring costs that do depend on the number of analyses performed are those linked to the usage of consumables. System 1 requires the purchase of a set of consumables for operating the System (items #2, 3, and 4), which clearly vary depending on the number of analyses performed per year. This is the reason why the definition of reference use-case scenarios was needed beforehand in order to precisely identify the costs to be borne when using System 1.

In the case of System 1, we calculate the costs considering the specific use-case scenarios we identified as reference. The recurring costs based on the number of analyses depend on the actual usage of the consumable solutions, which follow a specific procedure. Based on the procedures described in System 1 manual, we assumed that 10 mL of Check solution are used every 20 analyses (since around 5–6mL for a check session are used, and after 10 analyses the System has to be cleaned and checked again); cleaning requires 15 mL before and after usage, as well as every 10 analyses; calibration has to be performed before every session, and uses 1 kit out of the 10 in a box. The annual costs for the consumables in the six reference use-case scenarios are illustrated in Table 6.

All the costs related to System 2 are fixed, meaning that they do not vary based on the number of analyses performed. The annual fixed costs to operate the device are at \$5,750 (\$4,750

Table 5. Cost of the products and services needed to operate the two Systems for human milk analysis

Item#	Cost Item	Reference for Calculation	System 1	System 2
1	Main Unit price	One time	\$ 45,000	\$ 25,000
2	Cleaning solutions	unit (5 bottles)	\$ 172	
3	Calibrating solutions	unit (10 kits)	\$ 198	
4	Check solutions	unit (5 bottles 10mL)	\$ 190	
5	Software costs (from 2nd year)	Annual subscription		\$ 4,750
6	Maintenance cost per year	Average per year	\$ 500	\$ 1,000

Table 6. Annual costs for consumables when using System 1

		Every-day analysis			3-times per week analysis		
Scenarios	unit	10 analyses	50 analyses	100 analyses	10 analyses	50 analyses	100 analyses
Usage per analysis session							
Check	ml	10	30	50	10	30	50
Cleaning	ml	30	90	165	30	90	165
Calibrations	kits	1	1	1	1	1	1
Annual quantity required							
Check	ml	3,650	10,950	18,250	1,560	4,680	7,800
Cleaning	ml	10,950	32,850	60,225	4,680	14,040	25,740
Calibrations	kits	365	365	365	156	156	156
Total Annual Costs							
Check		\$ 1,387	\$ 4,161	\$ 6,935	\$ 593	\$ 1,778	\$ 2,964
Cleaning		\$ 377	\$ 1,130	\$ 2,072	\$ 161	\$ 483	\$ 885
Calibrations		\$ 7,227	\$ 7,227	\$ 7,227	\$ 3,089	\$ 3,089	\$ 3,089
Total Costs		\$ 8,991	\$ 12,518	\$ 16,234	\$ 3,843	\$ 5,350	\$ 6,938

for the software subscription fee from the second year on, and \$1,000 for the annual calibration service).

4. Human milk costs

Human milk is quite precious, and each milliliter of milk wasted represents a loss for the nutrition of the infant and can be economically quantified. In order to quantify savings related to this cost item, we considered the value of the milk as referenced in different studies and also through interactions.

System 1 requires 3 mL of milk for performing the scan, while System 2 claims to require just 0.04 mL, the quantity needed to fill in the cuvette (and a pre-set syringe comes with the System 2 package to support in extracting the right quantity of milk). System 2 needs 2 mL to be homogenized before the scan, and then the user has to take the quantity needed for the analysis (0.04 mL). The remaining quantity can be re-used for feeding the infant, since homogenization is not an issue for human milk, and, on the contrary, there are studies that suggest that homogenization of pasteurized milk could be beneficial for the infant (see de S.C. Oliveira 2017).

The value of the milk was set at \$3 per ounce (American academy of Paediatrics), which makes the cost of \$101.40 per liter, leading to the annual costs highlighted in Table 7.

Total costs

After having identified the various cost items, final calculations have been made for quantifying the overall annual costs for operating the Systems in the selected scenarios, as illustrated in Table 8, where all the cost items described in the previous section are summed up providing the final costs.

Figure 1 illustrates the cumulative increased costs that a NICU would bear when shifting from SF to the TFO approach, considering a 10-year period. The graphs consider the cumulative costs for the 6 selected scenarios when using the 2 Systems, without considering potential malfunctioning, need for repair or substitutions.

Table 7. Annual increased costs due to the waste of human milk

Annual Milk Costs	System 1		System 2	
	Every day	3 times per week	Every day	3 times per week
10 analyses	\$ 1,110	\$ 475	\$ 15	\$ 6
50 analyses	\$ 5,552	\$ 2,373	\$ 74	\$ 32
100 analyses	\$ 11,103	\$ 4,746	\$ 148	\$ 63

Benefit Analysis

In order to identify and quantify the benefits that can be generated when adopting TFO, we started by analyzing the health outcomes associated to TFO which could generate economic savings. Several benefits have been reported in various studies, even if such evidence suffers from two main issues for the purpose of our analysis:

- Evidence of important in-hospital and post-discharge clinical outcomes generated by TFO is still considered sparse, due to the limited size of the studies as well as to the different approaches followed in the various studies, which generate biases in the comparison between TFO and SF (see Fabrizio 2020).
- As a consequence, the second issue is to quantify the extent of such clinical outcomes, since the quantification is clearly affected by the above-mentioned biases.

Table 8. Annual costs for operating the 2 Systems, not including equipment costs

Scenarios	SYSTEM 1		SYSTEM 2 (first year)		SYSTEM 2 (from second year on)	
	Every day	3 times per week	Every day	3 times per week	Every day	3 times per week
Total Annual Costs						
10 analyses	\$ 28,490	\$ 12,463	\$ 11,105	\$ 5,319	\$ 15,855	\$ 10,069
50 analyses	\$ 101,390	\$ 43,620	\$ 48,906	\$ 21,475	\$ 53,656	\$ 26,225
100 analyses	\$ 190,288	\$ 81,615	\$ 96,157	\$ 41,670	\$ 100,907	\$ 46,420

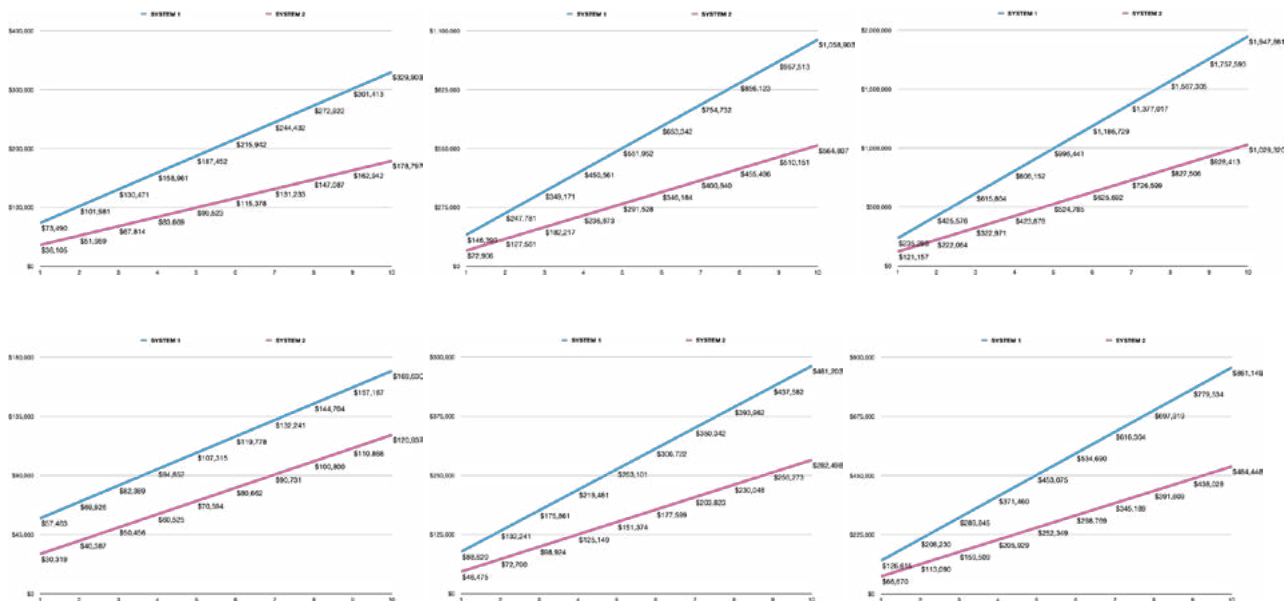


Figure 1. Cumulative 10-year costs for operating the 2 Systems in the 6 use case scenarios. The above plots illustrate the costs to be borne for daily analysis (10, 50, and 100 infants per day from left to right). Plots below depict the costs to be borne for three-time per week analysis (10, 50, and 100 infants per day from left to right)

Amongst the most promising health outcomes evidenced so far, infants fed with TFO experience higher macronutrient intakes, higher weight gain and in general improved growth velocities for what concerns weight, length, and head circumference. They also show higher fat-free mass and less frequent feeding intolerance. Such results are due to a limited variation of macronutrient intake, which allows for a more balanced and constant diet. Such outcomes have been recently linked to a reduced neonatal morbidity, in particular for what concerns the occurrence of NEC, sepsis and BPD (see Rochow 2020 and Sánchez Luna 2020), and are being studied in upcoming clinical trials (see Seliga-Siwecka 2020). Therefore, we decided to consider in this study the reduction in the prevalence of such diseases during hospitalization.

Next step has been retrieving in literature the costs associated with the occurrence of those diseases, which have been calculated in terms of marginal increased cost per infant.

- **NEC:** Johnson 2015 reported an average total NICU hospitalization cost (in 2012 dollars) of \$180,163 per infants with NEC and \$134,494 for infants without NEC. NEC was associated with a marginal increase in costs of \$43,818, which means **\$49,394** in 2020 dollars.
- **Sepsis:** Johnson 2013 reported a \$10,055 increase in direct costs due to the occurrence of late-onset sepsis (in 2009 dollars), which accounts for **\$12,130** in 2020 dollars.
- **BPD:** Johnson 2013 associated the presence of BPD with a \$31,565 increase in direct costs (in 2009 dollars), which accounts for **\$38,115** in 2020 dollars.

After having selected the health outcomes, and determined the associated costs, in order to turn them into benefits we need to identify the impact or extent of such outcomes as reported in the reference studies, and then use them as reference for our model.

Our reference study was Rochow 2020. This prospective, single-center, double-blind RCT in a Level III NICU, compared the health outcomes in 89 and 90 infants randomized to SF control and TFO intervention groups, respectively. At the end of the 21-day intervention period, besides other useful data, also the

prevalence of key morbidities has been reported in the 2 groups, highlighting a reduction at **4% in NEC prevalence** (net reduction from 6% to 2%) from the SF group to the TFO group, at **4% for BPD** (net reduction from 35% to 31%), and at **10% for sepsis** (net reduction from 37% to 27%).

Based on the data collected, as a first approach we quantify the economic savings that would be generated in the case evidence from Rochow 2020 is confirmed. In order to do so, the first step is to quantify the range of occurrence of such diseases in each of the 6 scenarios. The rationale behind this calculation is the need to determine how many infants are hospitalized in each scenario, so as to precisely calculate how much savings the reduction rate of each economic impact would generate. As an example, a 100-bed NICU is expected to experience a higher number of infants with a specific disease compared to a 50-bed unit, and therefore it is mandatory to define the average prevalence rates for each disease to precisely calculate the number of infants expected to get such disease, and the economic savings that would be generated by reducing this number thanks to TFO. Since we are using prevalence rate reductions coming from Rochow 2020, we decided to also use the prevalence rate reported in the same study as a benchmark, that is 6% for NEC, 35% for BPD and 37% for sepsis. Such prevalence rates are in line with what is reported in other analyses and studies.

After having defined the prevalence range, we defined for each scenario both the overall number of days of hospitalization within each NICU size (assuming all beds are occupied), and the average number of infants who are expected to develop the diseases every year. As illustrated in Table 9, the NICUs, based on their size, can accommodate up to a maximum number of infants per year (for instance 329 in a 50-bed unit), considering an average Length of Stay of 55.5 days. This allows us to infer, based on the reported average prevalence for each disease, how many infants are expected to develop each disease in the course of one year (for instance, out of the 329 infants treated, the 50-bed NICU is expected to have 20 infants with NEC, 115 with BPD, and 122 with sepsis).

Table 9. Number of infants expected to develop the three target diseases in one year for the 3 NICU size scenarios (the numbers of infants are rounded to the nearest integer).

NICU size	Annual # bed days	Annual # infants	Infants with NEC (6%)	Infants with BPD (35%)	Infants with Sepsis (37%)
10	3,650	66	4	23	24
50	18,250	329	20	115	122
100	36,500	658	39	230	243

By knowing the incremental costs for each case of the diseases, and applying the benchmark reduction rates evidenced in Rochow 2020, we are therefore able to quantify the expected savings generated each year by applying TFO. Table 10 illustrates the savings in number of infants who will not develop each disease thanks to TFO, and the economic savings associated to such outcomes.

Results

After collecting all data required, we compared the costs to be borne for implementing TFO and the economic benefits expected to be generated in the various scenarios. Due to the lack of robustness of the evidence reported in relation to the health outcomes generated by TFO in the available literature, we used two different approaches to the cost-benefit analysis.

The first approach consists of simply comparing the costs and the economic benefits as we have calculated them in the previous sections, assuming that such benefits are obtained in both the frequency of analyses hypothesized—daily analyses and 3-time per week analyses. As illustrated in Table 11, the annual savings due to the reduction of the target diseases entirely cover the costs for 10-year TFO adoption within 1 or 2 years.

Even if we consider just one disease alone, for instance NEC, the annual savings would cover the entire 10-year TFO costs within 3 years (10-bed unit), 2 years (50-bed unit), and 2 years (100-bed unit) for System 1, and within 2 years (10-bed unit), 1 year (50-bed unit), and 1 year (100-bed unit) for System 2. The 10-year overall savings would be huge in all the hypothesized scenarios.

Finally, we performed a sensitivity analysis to calculate the extent of each health outcomes which is needed in order to make TFO cost-effective. The objective of this analysis is basically to determine which is the minimum impact that each benefit, that is each disease's reduction, should have in order to entirely cover the costs for TFO adoption over a period of 10 years. To do so, we will assume that each single clinical outcome evidenced in Rochow 2020 is the only one generated by TFO, and then quantify the impact that such an outcome shall have in order to cover the costs of TFO over a 10-year period.

Figure 2 illustrates the results in just one reference scenario, that is a 50-bed unit where analyses are performed every day. The values are quantified for both System 1 (pink line) and System 2 (blue line). As illustrated in the Table, since the costs for System 2 are lower, the numbers of infants who are needed to not develop each disease in order to cover TFO costs are clearly lower than those for System 1, and so is the net reduction needed with respect to the overall number of infants expected to develop the disease.

In the case that just NEC reduction occurs thanks to the adoption of TFO, considering the reference scenario of a 50-bed unit (analyses performed every day), in 10 years just 11.4 to 21.4 NEC cases avoided would cover the costs for adopting TFO, respectively for System 2 and 1. Considering the expected range of prevalence of such disease in the NICU (20 infants per year at a 6% prevalence, as in Rochow 2020), an overall net **reduction rate of NEC prevalence at 0.34%** (when adopting System 2) **to 0.65%** (when adopting System 1) would cover TFO costs (11.4 to 21.4 over 3,290 infants hospitalized), which in both cases is a small portion of the one reported in Rochow 2020 (4%).

In the case that just sepsis reduction, in 10 years 46.6 to 87.3 sepsis cases avoided would cover the costs for adopting TFO. Considering the expected range of prevalence of such disease in the NICU (122 infants per year at a 37% prevalence as in Rochow 2020), an overall net **reduction rate of sepsis prevalence at 1.41% to 2.6%** would cover TFO costs (46.6 to 87.3 over 3,290 infants hospitalized), which is a small portion of the one reported in Rochow 2020 (10%).

In the case that just BPD reduction, in 10 years 14.8 to 27.8 sepsis cases avoided would cover the costs for adopting TFO. Considering the expected range of prevalence of such disease in the NICU (115 infants per year at a 35% prevalence as in Rochow 2020), an overall net **reduction rate of BPD prevalence at 0.45% to 0.84%** would cover TFO costs (14.8 to 27.8 over 3,290 infants hospitalized), which is a small portion of the one reported in Rochow 2020 (4%).

Similar results are obtained also by considering the other scenarios taken as reference based on NICU sizes and frequency

Table 10. Benefits in terms of number of infants avoiding the diseases and related economic savings in the three NICU sizes scenarios (the numbers of infants are rounded to the nearest decimal).

NICU size		NEC Savings	Sepsis Savings	BPD Savings	Total Savings
10	# infants	2.6	6.6	2.6	11.8
	Economic Savings	\$ 129,937	\$ 79,774	\$ 100,266	\$ 309,997
50	# infants	13.2	32.9	13.2	59.3
	Economic Savings	\$ 649,687	\$ 398,867	\$ 501,332	\$ 1,549,888
100	# infants	26.3	65.8	26.3	118.4
	Economic Savings	\$ 1,299,374	\$ 797,739	\$ 1,002,665	\$ 3,099,778

Table 11. Comparison between the 10-year cumulative costs of TFO and the expected annual savings

Scenarios	10-years TFO costs System 1	10-years TFO costs System 2	Annual Total Savings	Annual NEC Savings	Annual Sepsis Savings	Annual BPD Savings
10 beds – every day analyses	\$ 329,903	\$ 178,797	\$ 309,977	\$ 129,937	\$ 79,774	\$ 100,266
10 beds – 3-times a week analyses	\$ 169,630	\$ 120,937	\$ 309,977	\$ 129,937	\$ 79,774	\$ 100,266
50 beds – every day analyses	\$ 1,058,903	\$ 564,807	\$ 1,549,888	\$ 649,687	\$ 398,869	\$ 501,332
50 beds – 3-times a week analyses	\$ 481,203	\$ 282,498	\$ 1,549,888	\$ 649,687	\$ 398,869	\$ 501,332
100 beds – every day analyses	\$ 1,947,881	\$ 1,029,320	\$ 3,099,778	\$ 1,299,374	\$ 797,739	\$ 1,002,665
100 beds – 3-times a week analyses	\$ 861,149	\$ 484,448	\$ 3,099,778	\$ 1,299,374	\$ 797,739	\$ 1,002,665

of analyses, even if we do not report the results here due to space constraints.

Conclusions

This study represents the first attempt to demonstrate the cost-effectiveness of TFO based on data available to date, or at least to show the conditions which need to be met in order to ensure that TFO is cost-effective.

While we cannot infer that TFO is cost-beneficial due to the need for more robust studies demonstrating the clinical outcomes evidenced in a few studies performed so far, with the present analysis we can conclude that TFO becomes cost-beneficial in the case that even small improvements in the hypothesized clinical outcomes are achieved.

As a result of this study, we concluded that the adoption of TFO as fortification approach, by using the currently available Systems to perform TFO, is cost-beneficial. In the case the health outcomes and their impact as reported in available literature are confirmed, the costs of 10-year TFO will be entirely covered within 1 to 2 years of adoption, with huge savings over the 10-year lifecycle of the product. Break-even in 1 to 3 years and huge savings can be reached even in the case that only one of the health outcomes evidenced so far is confirmed by other scientific studies on TFO.

The limits of this study are linked to the need for more robust evidence that TFO generates the selected clinical outcomes, and for extensive, unbiased studies which provide clear evidence

about the “improvement” rate generated by TFO for each of those outcomes.

Besides the quantification of short-term benefits that occur during the hospitalization period, which are the most tangible ones for running a cost-benefit analysis, we can also make some reasonings about the long-term benefits that can be obtained by adopting TFO.

Savings in this area are hard to be demonstrated and quantified, since they require the quantification of savings on clinical complications after hospitalization and on potential life-long morbidities. One focus of the analysis could be related to the long-term benefits (and related savings) due to avoiding under- and over-nourishment caused by SF. Another example is related to avoiding neurological or physical impairment, due to optimal growth and to the reduction of infants’ morbidities during the hospitalization period. This is the outcome we want to briefly explore here in order to provide just a feeling of the potential outcomes and related savings.

A key point is related to the “quality” of the weight gained during the hospitalization period. Parat 2020 showed that “targeted fortification of milk can influence the quality of weight gain through promoting fat-free mass in infants”. At the very same time, early gain in fat-free mass has been demonstrated to generate positive long-term effects, unlike fat mass. Ramel 2016 demonstrated the association of fat-free mass at discharge with improved neurodevelopment in VLBW preterm infant at 12 months. Scheurer 2018 showed that high percentage of fat

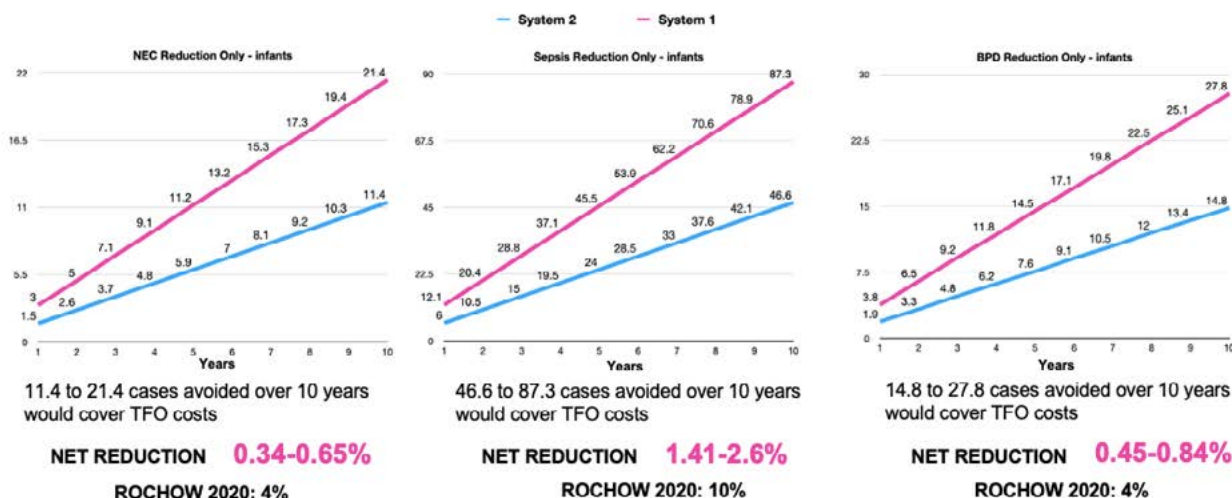


Figure 2. Cumulative number of infants who are required to not develop the three diseases for covering 10-year TFO costs, and related net reduction rates (numbers of infants are rounded to the nearest decimal)

mass is associated with lower-working memory performance in pre-school age (4 years). Another study (Fronidas-Chauty 2018) demonstrated that a deficit of fat-free mass at discharge is associated with neurological impairment at two years of age. Neurodevelopment impairment has also been demonstrated to more likely occur in infants who had NEC or sepsis than in preterm infants without such morbidities (see Rees 2006 and Cai 2019). NEC and sepsis are diseases whose prevalence, as we have seen in this study, TFO is expected to reduce. Conditions such as cerebral palsy, vision impairment or hearing impairment could be reduced thanks to the optimal growth promoted through TFO, or indirectly by reducing the occurrence of diseases that make such impairment more likely in a later age. And their costs are not negligible. Honeycutt 2015 showed that lifetime costs per person for cerebral palsy are around \$804,000 (in US\$ 2000), for hearing loss are around \$325,000 and for vision impairment are around \$469,000. This gives us a sense of how large the life-long savings could be both for the society and for the patients.

We expect that such long-term clinical outcomes will be explored further by large and focused trials, so as to correlate the adoption of TFO more closely with potential reduction in prevalence of diseases which can affect patients during the entire life.

The results of this study are in line with what has been evidenced in several studies (for instance Rochow 2020, Sánchez Luna 2020), which stated the feasibility and the cost-effectiveness of TFO, even without providing detailed economic analysis. While waiting for large and robust clinical studies, the present study

shows that TFO becomes cost-effective even with a minimal impact on the health outcomes, which have been shown to be less than negligible by several studies. We therefore conclude by saying that TFO is the most cost beneficial approach in the immediate future for feeding preterm infants in hospitals' NICUs.

Disclaimer

The authors declare that they are employees of Telspec LTD, the company that is developing the Preemie System for human milk analysis, which has been considered as the reference System 2 in the context of the present article.

This article is part of a project that has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 879228.

References

- Cai 2019 – Shirley Cai, Deanne K. Thompson, Peter J. Anderson, and Joseph Yuan-Mou Yang. Short- and Long-Term Neurodevelopmental Outcomes of Very Preterm Infants with Neonatal Sepsis: A Systematic Review and Meta-Analysis. *Children* (Basel). 2019 Dec; 6(12): 131. doi: 10.3390/children6120131.
- de Halleux 2013 – Virginie de Halleux and Jacques Rigo. Variability in human milk composition: benefit of individualized fortification in very-low-birth-weight infants. *Am J Clin Nutr* 2013;98(suppl):529S–35S. 2013 American Society for Nutrition.
- Ehrenkranz 2014 – Ehrenkranz RA. Nutrition, growth and clinical outcomes. In: Koletzko B, Poindexter B, Uauy R, editors. *Nutritional care of preterm infants*. Karger; 2014. pp.

PREEMIE
Preterm Feeding Management System

NiCU AI
AI Decision Support System

The first clinical AI platform to deliver optimal infant-centric feeding and care

PreemieSensor.com | NiCU-AI.com | Info@PreemieSensor.com

- Fabrizio 2020 – Fabrizio V, Trzaski JM, Brownell EA, Esposito P, Lainwala S, Lussier MM, Hagadorn JI. Individualized versus standard diet fortification for growth and development in preterm infants receiving human milk. *Cochrane Database of Systematic Reviews* 2020, Issue 11. Art. No.: CD013465. DOI: 10.1002/14651858.CD013465.pub2.
- Frondas-Chauty 2018 – Anne Frondas-Chauty, Laure Simon, Cyril Flamant, Matthieu Hanf, Dominique Darmaun, and Jean-Christophe Rozé. Deficit of Fat Free Mass in Very Preterm Infants at Discharge is Associated with Neurological Impairment at Age 2 Years. *J Pediatr*. 2018 May; 196: 301-304. doi: 10.1016/j.jpeds.2017.12.017.
- Henriksen 2009 – Henriksen C, Westerberg AC, Rønnestad A, Nakstad B, Veierød MB, Drevon CA, et al. Growth and nutrient intake among very-low-birth-weight infants fed fortified human milk during hospitalisation. *Br J Nutr* 2009; 102: 1179-86.
- Honeycutt 2015 – Amanda A Honeycutt, Scott D Grosse, Laura J Dunlap, Diana E Schendel, Hong Chen, Edward Brann, Ghada al Homsy. “Economic Costs Of Mental Retardation, Cerebral Palsy, Hearing Loss, And Vision Impairment” In Using Survey Data to Study Disability: Results from the National Health Survey on Disability. Published online: 10 Mar 2015; 207-228.
- Johnson 2013 – Tricia J. Johnson, Aloka L. Patel, Briana J. Jegier, Janet L. Engstrom, and Paula P. Meier. Cost of Morbidities in Very Low Birth Weight Infants. *The Journal of Pediatrics*, Vol. 162, No. 2, 2012. doi: <https://doi.org/10.1016/j.jpeds.2012.07.013>.
- Johnson 2014 – Tricia J. Johnson, Aloka L. Patel, Harold R. Bigger, Janet L. Engstrom, and Paula P. Meier. Economic Benefits and Costs of Human Milk Feedings: A Strategy to Reduce the Risk of Prematurity-Related Morbidities in Very-Low- Birth-Weight Infants. *Adv Nutr*. 2014 Mar; 5(2): 207–212. Published online 2014 Jan 6. doi: 10.3945/an.113.004788
- Johnson 2015 – Tricia J. Johnson, Aloka L. Patel, Harold R. Bigger, Janet L. Engstrom, and Paula P. Meier. Cost Savings of Human Milk as a Strategy to Reduce the Incidence of Necrotizing Enterocolitis in Very Low Birth Weight Infants. *Neonatology*. 2015 ; 107(4): 271–276. doi:10.1159/000370058.
- Parat 2020 – Sumesh Parat, Praneeta Raza, May Kamleh, Dennis Super and Sharon Groh-Wargo. Targeted Breast Milk Fortification for Very Low Birth Weight (VLBW) Infants: Nutritional Intake, Growth Outcome and Body Composition. *Nutrients*. 2020 Apr 21;12(4):1156. Doi: 10.3390/nu12041156.
- Ramel 2016 – Sara E. Ramel, Heather L. Gray, Ellen Christiansen, Christopher Boys, Michael K. Georgieff, and Ellen W. Demerath. Greater Early Gains in Fat-Free Mass, but Not Fat Mass, Are Associated with Improved Neurodevelopment at 1 Year Corrected Age for Prematurity in Very Low Birth Weight Preterm Infants. *J Pediatr*. 2016 Jun;173:108-15. doi: 10.1016/j.jpeds.2016.03.003. Epub 2016 Apr 4.
- Rees 2006 – Clare M Rees, Agostino Pierro, Simon Eaton. Neurodevelopmental outcomes of neonates with medically and surgically treated necrotizing enterocolitis. *Arch Dis Child Fetal Neonatal Ed* 2007;92:F193–F198. doi: 10.1136/adc.2006.099929.
- Rochow 2013 – Niels Rochow, Gerhard Fusch, Arum Choi, Lorraine Chessell, LouAnn Elliott, Kimberley McDonald, Elizabeth Kuiper, Margaret Purcha, Steve Turner, Emily Chan, Meng Yang Xia, and Christoph Fusch. Target Fortification of Breast Milk with Fat, Protein, and Carbohydrates for Preterm Infants. *J Pediatr*. 2013 Oct;163(4):1001-7. Doi: 10.1016/j.jpeds.2013.04.052. Epub 2013 Jun 12.
- Rochow 2015a – Rochow N, Landau-Crangle E, Fusch C. Challenges in breast milk fortification for preterm infants. *Curr Opin Clin Nutr Metab Care* 2015; 18:276-84.
- Rochow 2015b – Niels Rochow, Gerhard Fusch, Bianca Zapanta, Anaam Ali, Sandip Barui and Christoph Fusch. Target Fortification of Breast Milk: How Often Should Milk Analysis Be Done?, *Nutrients* 2015, 7, 2297-2310; doi:10.3390/nu7042297
- Rochow 2020 – Niels Rochow, Gerhard Fusch, Anaam Ali, Akshdeep Bhatia, Hon Yiu So, Renata Iskander, Lorraine Chessell, Salhab el Helou, Christoph Fusch. Individualized target fortification of breast milk with protein, carbohydrates, and fat for preterm infants: A double-blind randomized controlled trial. Published by Elsevier Ltd. 2020, <https://doi.org/10.1016/j.clnu.2020.04.031>.
- Sánchez Luna 2020 – Manuel Sánchez Luna, Sylvia Caballero Martin, Carmen Sánchez Gómez-de-Ortiz. Human milk bank and personalized nutrition in the NICU: a narrative review, *European Journal of Pediatrics*, 2020, <https://doi.org/10.1007/s00431-020-03887-y>
- Scheurer 2018 – Johannah M. Scheurer, Lei Zhang, Erin Plummer, Solveig Hultgren, Ellen W. Demerath, Sara E. Ramel. Body Composition Changes from Infancy to 4 Years and Associations with Early Childhood Cognition in Preterm and Full-Term Children. *Neonatology* 2018; 114: 169–176. Doi: 10.1159/000487915
- Seliga-Siwecka 2020 – Joanna Seliga-Siwecka, Anna Chmielewska and Katarzyna Jasińska. Effect of targeted vs standard fortification of breast milk on growth and development of preterm infants (≤ 32 weeks): study protocol for a randomized controlled trial. *Trials* (2020) 21:946 <https://doi.org/10.1186/s13063-020-04841-x>

Isabel Hoffmann is a mathematician with extensive business experience and a natural ability to lead and inspire. She is the recipient of numerous awards and honors including the 2018 Women in Innovation Award, given by the European Institute of Innovation and Technology (EIT). She is a sought-after keynote speaker, she's presented at conferences around the world, her presentations include a talk at TED Global 2014 in Rio de Janeiro, Brazil, and TEDx Zwolle 2015, Holland.

Diogo Barros is an analytical chemist and chemometrician with a passion for data and with experience in solving industry-related problems by applying a variety of analytical techniques ranging from chromatography and mass spectrometry to, more recently, vibrational spectroscopy coupled to machine learning methods. Prior to joining Telspec Diogo was conducting research in the interface of analytical chemistry and machine learning, particularly, data augmentation methods and its application in the electronic industry.

Paolo Satta is a specialist in deep-tech innovation, business development, and fundraising, with particular focus on the healthcare sector. He coordinated several multinational innovation projects, including top-notch research centers, large companies, and start-ups as partners. He is currently leading the operations for developing the Premie System for human milk analysis.

Examining the Impact of Early Fortification on Growth Rates in Preterm Infants Fed an Exclusive Human Milk Diet: Timing Matters

Jenelle Ferry, MD

Introduction

In the past decade, a growing body of evidence has continued to demonstrate that human milk remains the ideal nutrition for all infants, particularly those born prematurely. The American Academy of Pediatrics reaffirmed this principle in its most recent breastfeeding guideline: “The potent benefits of human milk are such that all preterm infants should receive human milk. Mother’s own milk, fresh or frozen, should be the primary diet and it should be fortified appropriately for the infant born weighing less than 1.5 kg.”¹

Since then, data from a variety of studies in which infants born extremely prematurely were fed an Exclusive Human Milk Diet (EHMD), including early use of Prolacta Bioscience’s human milk-based fortifiers mixed with either mother’s own milk or pasteurized donor breast milk, have shown that an EHMD supports adequate growth.²⁻⁵ Additionally, premature infants who receive an EHMD experience reduced morbidity^{3,5-9} and better long-term outcomes¹⁰ than those who received various feeding regimens that included cow milk-based nutrition. Importantly, an EHMD uses only human milk to deliver essential macronutrients like protein, fat, and carbohydrates, and does so without the addition of any cow milk-based components. This is significant because studies have shown that, unlike cow milk, human milk is a complex bioactive fluid with a myriad of compounds that contribute to optimal growth and development in infants, particularly those born prematurely. Notably, the wide spectrum of bioactive prebiotics, known as human milk oligosaccharides, are not easily manufactured and thus are missing from cow milk-based nutritional products.¹¹ Among the bioactive components most closely associated with growth and development are arachidonic acid¹² and linoleic acid/alpha-linolenic acid, two of several vital long-chain fatty acids contained in human milk.^{13,14}

Dr. Ferry has been a neonatologist with Mednax Tampa Regional Practices since 2011. She received a B.A. in Dance and B.S. in Neurobiology and Physiology from the University of Maryland, College Park. She attended medical school at the University of Oklahoma, where she also completed her intern year in Pediatrics. She completed residency at Louisiana State University in New Orleans and then remained at LSU for her Neonatology fellowship. After training she joined the Mednax practice in Tampa, where she spends most of her time at St. Joseph Women’s Hospital. She has been the Director of Feeding, Nutrition, and Infant Development for her group 14 Neonatologists since 2014. She has particular interest in human milk nutrition for all infants.

But what implications does an EHMD have on growth in extremely premature infants?

An emerging body of evidence indicates that growth metrics may be improved among premature infants fed an EHMD. In this context, an EHMD is particularly beneficial because it allows for earlier initiation of feeding with a lower risk of feeding intolerance,^{5,15} and potentially life-threatening complications, such as necrotizing enterocolitis (NEC),^{5,7,9} as well as fewer days of parenteral nutrition and lower risk of late-onset sepsis.^{3,8}

Additionally, a recent independent study from Osmanova et al¹⁶ found significant clinical benefits to feeding very low birth weight infants an EHMD with human milk-based fortifier versus cow milk-based fortifier. The infants who received an EHMD had fewer comorbidities and shorter stays in the neonatal intensive care unit (NICU), which helped offset the therapeutic cost of the human milk-based fortifiers. This study enrolled preterm infants of < 32 weeks gestational age who weighed less than 1000 g at birth at a single institution in Germany, with 10 infants receiving an EHMD and 13 infants receiving cow milk-based fortifiers. Just one-third of the infants in the EHMD group experienced “typical morbidities” like bronchopulmonary dysplasia (BPD) or NEC, while three-fourths of those in the cow milk-based fortifier group experienced at least one adverse event. Osmanova et al concluded that, “[N]eonates treated with human milk-based fortifier showed positive effects in cost-effectiveness justified in a shorter hospital stay and reduced complication rate in contrast to preterms fed with bovine fortifier.”

In O’Connor et al’s small randomized clinical trial that compared outcomes among very low birth weight infants fed with human milk-based fortifier versus cow milk-based fortifier, outcomes trended in favor of human milk-based fortifier, while growth was the same between the two groups.¹⁷ These findings lend credence to the EHMD providing for adequate growth, even when fortification is started later than typically recommended. Infants in the human milk-based fortifier group had sepsis rates that were half those seen in the cow milk-based fortifier group, and infants in the human milk group also saw a statistically significant reduction in severe retinopathy of prematurity (ROP) compared to infants in the cow milk group. Among 127 infants, fortification began at 100 mL/kg per day of human milk-based fortifier (0.81 kcal/mL) or cow milk-based fortifier (0.72 kcal/mL) and advanced at 140 mL/kg per day to 0.88 and 0.78 kcal/mL, respectively. Interestingly, this study employed a nontraditional feeding protocol with a slow feeding approach at a target feeding volume of 150 mL/kg/day, which meant that infants did

not receive fortification until day 16 of life and did not attain full feeds until day 23. O'Connor et al expected the delayed feeding protocol to give infants the best chance of tolerating fortifiers without complications; this was perhaps justified given the known risk of cow milk-based fortifiers. As a result, the delayed feeding practice resulted in no improvement in tolerance between the fortifiers and suggests that late fortification may compromise clinical outcomes.

Impact of Earlier Fortification With EHMD

Huston et al recently published a multicenter retrospective cohort study, which found that early fortification—within the very first days of life—with 100% human milk-based fortifiers is safe and appears to enhance neonatal growth in the NICU. A total of 394 infants with a birth weight of 500 to 1250 g were fed Prolacta's EHMD. The investigators compared early fortification, starting at < 60 mL/kg/day of enteral feeding volume, with late fortification, which they started at > 60 mL/kg/day of enteral feeding volume. The infants who received early fortification had better growth metrics, including the co-primary outcome of greater weight gain velocity (13.3 ± 2.6 vs 12.9 ± 2.6 g/kg/day; $P = 0.03$). 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 chronic lung disease (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. The early fortification group also showed reduced morbidity, including a reduction in BPD/CLD (42.6% vs 27.6%; $P = 0.008$).¹⁵

This study should nullify concerns about growth and outcomes that may be impacting optimal feeding with an EHMD. An EHMD without cow milk-based nutrition does not hinder weight gain, and early fortification with a human-milk based fortifier does not place extremely premature infants at increased risk of the life-threatening complications observed in the past with cow milk-based nutrition. Rather, early adoption of an EHMD that includes human milk-based fortifiers promotes healthy weight gain while at the same time minimizing the risk of potentially life-threatening complications that can result from using cow milk-based nutrition.

Other Evidence Correlating an EHMD with Healthy Growth

Huston's work supports prior research demonstrating positive growth outcomes with an EHMD that includes Prolacta's fortifiers. Hair et al conducted a single-center, prospective observational cohort study that hypothesized that an EHMD, including human milk-based fortification, would meet growth standards in infants with a birth weight of 1250 g or less. Investigators fed 104 preterm infants weighing ≤ 1250 g at birth an EHMD until 34 weeks postmenstrual age. A total of 22 infants (21%) were small for gestational age at birth. However, when excluding those infants who were small for gestational age at birth, only 22% of appropriate for gestational age infants had extrauterine growth restriction at discharge. The investigators started fortification with donor human milk-derived fortifier at 60 mL/kg/d and advanced to provide 6 to 8 additional kilocalories per ounce. The authors then compared the infants' growth to historical growth standards and previous human milk-fed cohorts. This cohort had a mean gestational age of 27.6 weeks and birth weight of 913 g. Weight gain was 24.8 g/kg/day with length increases of 0.99 cm/week and head circumference

increases of 0.72 cm/week. The authors concluded that an EHMD with early fortification enables premature infants to meet targeted growth standards. Additionally, they concluded that this diet leads to a low rate of extrauterine growth restriction.⁴

Shortly after Hair et al's study published, Abrams et al reanalyzed the data from two key studies: Sullivan et al 2010 and Cristofalo et al 2013. Sullivan et al's study, known for establishing the link between cow milk-based fortification and increased rates of NEC, randomized premature infants into study groups based on whether their diet of mother's own milk included fortification with human milk-based or cow milk-based fortifiers (some infants in the cow milk-based group received formula when there was a shortfall in mother's milk). Cristofalo et al conducted a randomized clinical trial of premature infants fed Exclusive Human Milk Diets versus preterm formula diets in infants whose mothers could not provide milk (donor milk was not universally available at the time of this study).

Abrams' post-hoc analysis included a total of 260 infants born extremely prematurely with a birth weight < 1250 g. Of these infants, 167 received an EHMD that included a human milk-based fortifier, and the remaining 93 received variable amounts of cow milk-based protein. They did not find any overall effect on length of time for parenteral nutrition, but a subgroup analysis of infants who received < 10% of their diet as formula ($n = 182$) had 21 days of parenteral nutrition. This compared to 29 days of parenteral nutrition for infants who received > 10% of their diet as formula ($n = 78$, $P = 0.02$).

In 2020, Lucas et al published a subgroup analysis of the Sullivan data set. They included only the 114 infants who received solely mother's own milk as a base diet plus fortification, thus excluding any infants who received formula in the original trial. The only difference between subgroups was whether the fortifier was derived from cow milk or human milk. In this analysis, infant growth rates were secondary outcomes. Head circumference gain, reflecting brain growth, was 13% higher in the EHMD group, with a median growth of 0.78 cm/week compared to 0.68 cm/week among infants whose fortifier contained cow milk ($P = 0.04$). There was no significant difference between groups in other growth metrics.²

Conclusion

With a growing body of clinical evidence, the value of an EHMD for preterm infants becomes clearer in terms of reduced morbidity and mortality, especially in the smallest and most fragile preterm infants. The American Academy of Pediatrics' unequivocal support for human milk for all infants ushered in a growing acceptance of human milk for extremely premature infants a decade ago, yet many guidelines still do not address the ideal composition of milk fortifiers nor the ideal time to give them. Nevertheless, these two issues—composition and timing—can have significant effects on growth and other outcomes for premature infants.

As an EHMD becomes more widely available, an important piece of the clinical puzzle is still missing. While an EHMD provides the best building blocks for good outcomes, the common practice of delaying fortification due to concerns about complications that occurred with cow milk-based fortifiers interferes with the goal of achieving the best possible growth and clinical outcomes. These concerns are causing clinicians to delay fortification rather than starting with an early and standardized feeding

regimen such as described in Huston 2020, which showed that an EHMD works optimally and produces the best growth outcomes when fortification takes place in the first days of life. An EHMD including fortification with a human milk-based fortifier makes early fortification possible and significantly improves the overall health of premature infants. Neonatal intensive care teams should adopt guidelines using early fortification when using human milk-based products for optimum results.

References

- 1 American Academy of Pediatrics [AAP]. Breastfeeding and the use of human milk. Section on Breastfeeding. *Pediatrics*. 2012;129(3):e827-e841. doi:10.1542/peds.2011-3552
- 2 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). Published online May 8, 2020. doi.org/10.1089/bfm.2019.0133
- 3 Abrams SA, Schanler RJ, Lee ML et al. 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
- 4 Hair AB, Hawthorne KM, Chetta KE & Abrams SA. Human milk feeding supports adequate growth in infants $\leq$ 1250 grams birth weight. *BMC Research Notes*. 2013;6:459 <http://www.biomedcentral.com/1756-0500/6/459>
- 5 Assad M, Elliott MJ, Abraham JH. Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. *J Perinatol*. 2016 Mar;36(3):216-20. doi: 10.1038/jp.2015.168. Epub 2015 Nov 12.
- 6 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.0000000000000676
- 7 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
- 8 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
- 9 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 milk-based products. *J Pediatr*. 2010;156(4):562-567.e1. doi:10.1016/j.jpeds.2009.10.040
- 10 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
- 11 Ballard et al. Human milk composition: nutrients and bioactive factors. *Pediatr Clin North Am*. Feb. 2013; 60(1):49-74. doi: 10.1016/j.pcl.2012.10.002.
- 12 Hadley KB, Ryan AS, Forsyth S, Gautier S, Salem N Jr. The essentiality of arachidonic acid in infant development. *Nutrients*. 2016;8(4):216. doi:10.3390/nu8040216
- 13 Fleig LN, Unger JP, Cluette-Brown JE, et al. Longitudinal fatty acid levels in preterm infants fed; 2018
- 14 Gleason CA, Juul SE, eds. *Avery's diseases of the newborn*. 10th ed. Elsevier:Philadelphia, PA;2018:1009-1022.e4.
- 15 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
- 16 Osmanova M, Müller MJ, Habisch B, Hippe A, Seeliger S. Nutrition of infants with very low birth weight using human and bovine based milk fortifier: benefits and costs. *Neonatal Pediatr Med*. 2021;S10:003.
- 17 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. Published corrections appear in *Am J Clin Nutr*. 2019;110(2):529. doi:10.1093/ajcn/nqz091 and *Am J Clin Nutr*. 2020;111(5):1112. doi:10.1093/ajcn/nqaa042

Respiratory Distress and Abnormal CT Scan in a Newborn Infant

Ellen Foster, MD and Shabih Manzar, MD

Summary

We present here an infant born at 34 weeks with abnormal chest CT scan of unknown etiology. At the time of this report, infant remains on 60% oxygen and 1.5 liter per minute of flow to keep the oxygen saturations in the target range of 92-95%. The genetic workup including Surfactant Protein B (SFTP-B) deficiency, Surfactant Protein C (SFTP-C) deficiency, ATP binding cassette protein (ABCA-3) dysfunction and NKX2-1 mutation are pending.

Case

A late preterm 34-2/7 weeks black male infant was delivered via emergency C-section at an outside facility due of fetal decelerations and breech presentation. APGARS were 7 and 9 at 1 and 5 minutes. Maternal prenatal history was significant for drug use (THC, opiates), *E. coli* UTI, trichomonas infection, and poor prenatal care. Perinatal labs were unremarkable. At delivery infant required positive pressure ventilation (PPV) followed by blow-by oxygen. On day 2 of life, patient had spontaneous desaturations while crying. Patient was transferred to the NICU and started on high flow nasal canula. The chest X-ray (CXR) at this time showed minimal bilateral perihilar streaky lung edema. Sepsis workup was collected to rule out infection and patient was started on ampicillin and gentamicin.



Figure 1. Chest X-ray compatible with RDS

Ellen Foster is Resident and Shabih Manzar is Attending Neonatologist at Department of Pediatrics, School of Medicine, Louisiana State University Health Sciences Center. 1501 Kings Highway, Shreveport, LA 71103. Address correspondence to: shabih.manzar@lsuhs.edu.

Sepsis workup remained negative and blood cultures showed no growth, so antibiotics were discontinued after 48 hours. Repeat CXR showed improvements in perihilar markings. However, multiple attempts to wean on high flow nasal cannula failed as patient continued to experience spontaneous desaturations. The blood gas showed pO₂ of 50 and then 57 even after FiO₂ was increased to 100%; pH remained normal. Echocardiogram showed PFO vs. ASD. Pre- and post-ductal SpO₂ difference noted to be >3%. On day 7 of life, patient was transferred to our NICU for further evaluation and higher level of care.

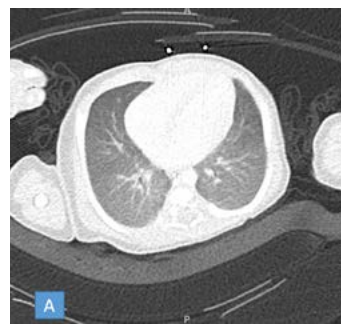


Figure 2 A. Chest CT axial view showing bilateral infiltrates



Figure 2 B. Chest CT coronal view showing bilateral infiltrates

Investigation into the cause of patient's hypoxia began with a repeat CXR, which now revealed a fine diffuse granular appearance of the lungs without evidence of consolidation, pneumothorax, or effusion (Figure 1). Repeat echocardiogram was obtained and revealed peripheral branch PAS and PFO. CT chest revealed diffuse ground-glass opacities in both lungs (Figure 2 A and B). Upper airway evaluation revealed excessive nasal secretions and mild laryngomalacia, which was not obstructing the airway and not contributory to patient's symptoms. Upper GI series notable for significant reflux to the lower neck level (Figure 3); modified swallow study was normal with no evidence of aspiration. This points to the possibility of RDS with subsequent chronic lung disease or interstitial lung disease as the cause of this patient's symptoms.

Case Progression

An intensive search for etiology of abnormal chest CT remains unrevealing. Repeat echocardiogram and modified swallow study were normal. Upper GI series showed gastroesophageal reflux. Treatment attempts including furosemide, chlorothiazide, and prednisolone have had little to no effect on the patient's oxygen requirements or respiratory status to date. The genetic workup

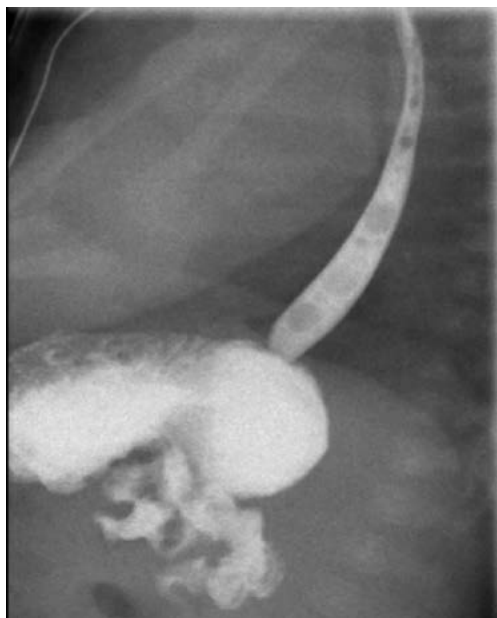


Figure 3. Upper GI showing reflux

including Surfactant Protein B (SFTP-B) deficiency, Surfactant Protein C (SFTP-C) deficiency, ATP binding cassette protein (ABCA-3) dysfunction and NKX2-1 mutation is pending.

The case remains a mystery for now. We are waiting on the results from genetic workup. We plan to send the infant home on oxygen and follow up with pediatric pulmonology.

Discussion

Respiratory distress is a common finding in premature infants and remains the most common cause of admission to the NICU.¹ However, this case presents an interesting challenge in both diagnosis and management. On initial evaluation, the patient exhibited signs of classic respiratory distress syndrome (RDS) on both physical exam and CXR. He was placed on high flow nasal cannula on day 2 of life. While RDS is much more common in patients born < 34 weeks of age, this patient's C-section delivery placed him at higher risk of this common disorder, making this the most likely diagnosis at the time. RDS typically improves by day 4 or 5 of life as surfactant production and diuresis improve.² In the case of this patient, he began to clinically deteriorate around day 7 of life with worsening appearance of CXR and continuous need for respiratory support. Increases in FiO₂ to 100% produced minimal changes in observed pO₂ and multiple attempts to wean support were unsuccessful, prompting workup for causes other than RDS. Evaluation for cardiac, infectious, or aspiration-related causes of symptoms was unrevealing, and the patient's newborn screening was negative for CF, thyroid, or other autoimmune disorders. Ultimately, chest CT was performed and revealed diffuse bilateral ground glass opacities.

While ground glass opacity is nonspecific and not diagnostic of any particular disorder, it is a common finding seen in interstitial lung disease.³ These disorders are rare in the pediatric population with an estimated prevalence of 0.13-16 cases/100,000 children per year; the incidence in neonates is not known.⁴ According to the guidelines devised by the American Thoracic Society, diagnosis is considered in a patient that has 3 of the 4 following criteria—respiratory symptoms, respiratory signs, hypoxemia, and diffuse abnormalities on chest radiography;⁵ this patient fits all 4 criteria. As with this patient, initial CXR

may appear unremarkable and progressively worsen over time. Beyond the general diagnosis of interstitial lung disease (ILD), the identification of the specific disorder present presents another challenge as radiography is not diagnostic of the specific ILD at hand. In fact, a survey of the European Respiratory Society Pediatric Assembly found that in 10.6% of cases, no specific cause of ILD was found.⁶ In preterm infants like this patient, congenital disorders of surfactant production are often the culprit and require genetic testing of surfactant protein B (SFTP-B), surfactant protein C (SFTP-C), ATP binding cassette protein (ABCA-3), and NKX2-1 mutation. While the sensitivity and specificity of these genetic tests is not known, the results are positive for SFTP-C in ~17% and ABCA-3 in ~5-22% in patients with signs and symptoms of ILD beyond 4 weeks of life.⁵ Identification of the underlying cause of ILD is essential to tailor the patient's therapy as well as guide parental counseling on the patient's prognosis. If this patient's genetic testing is unrevealing, lung biopsy will be the next step in diagnosis.

As the prevalence of these diseases in the neonatal population is low, there are few current guidelines to the management of these patients. Previous cases report success with immunosuppressives such as corticosteroids and hydroxychloroquine,⁵ but management currently relies on case studies/series and clinical judgment. Our patient remains stable on VTH and is growing appropriately. Corticosteroids had little effect on the patient's respiratory status, and he continues to require high flow nasal cannula at 1.5 LPM with FiO₂ of 60%. We will continue to adjust nutrition and respiratory support as clinically indicated until genetic testing results become available.

In conclusion, interstitial lung disease is a rare but present disorder in the neonatal population. Diagnosis and management guidelines are limited due to the lack of controlled trials and low disease incidence in the pediatric population. More research is needed in this field of study to better manage newborn infants with signs and symptoms of interstitial lung disease.

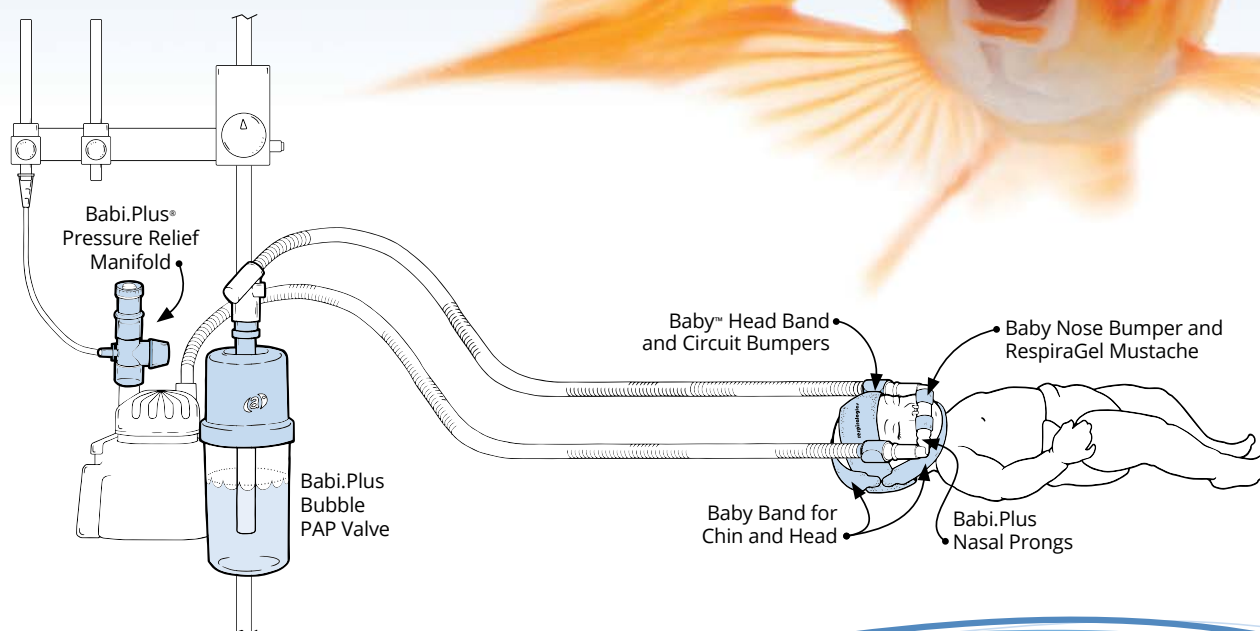
References

- 1 Jain SN, Modi T, Varma RU. Decoding the neonatal chest radiograph: An insight into neonatal respiratory distress. *Indian J Radiol Imaging*. 2020;30(4):482-492. doi:10.4103/ijri.LJRI_281_20
- 2 Yadav S, Lee B, Kamity R. Neonatal Respiratory Distress Syndrome. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; January 5, 2021.
- 3 Guillermin RP. Imaging of Childhood Interstitial Lung Disease. *Pediatr Allergy Immunol Pulmonol*. 2010;23(1):43-68. doi:10.1089/ped.2010.0010
- 4 Noguee LM. Interstitial lung disease in newborns. *Semin Fetal Neonatal Med*. 2017;22(4):227-233. doi:10.1016/j.siny.2017.03.003
- 5 Kurland G, Deterding RR, Hagood JS, et al. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Respir Crit Care Med*. 2013;188(3):376-394. doi:10.1164/rccm.201305-0923ST
- 6 Clement A, Nathan N, Epaul R, Fauroux B, Corvol H. Interstitial lung diseases in children. *Orphanet J Rare Dis*. 2010;5:22. Published 2010 Aug 20. doi:10.1186/1750-1172-5-22

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
4info@respiralogics.com



respiralogics™

3545 Airway Drive, Suite 104 • Reno, NV 89511
775 954 0160 • www.respiralogics.com

© 2019 Respiralogics, GaleMed. All rights reserved.



Bioactivity Matters

for Immunity, Development, Growth, and
the Long-Term Health of Premature Infants

Learn more at Prolacta.com/Bioactivity

Gila-Diaz A, Arribas SM, Algara A, et al. A review of bioactive factors in human breastmilk: a focus on prematurity. *Nutrients*. 2019;11(6):1307. doi:10.3390/nu11061307

©2022 Prolacta Bioscience, Inc. All rights reserved.
MKT-0754 Rev-0 01/22

 **Prolacta**[®]
BIOSCIENCE
Advancing the Science of Human Milk[®]