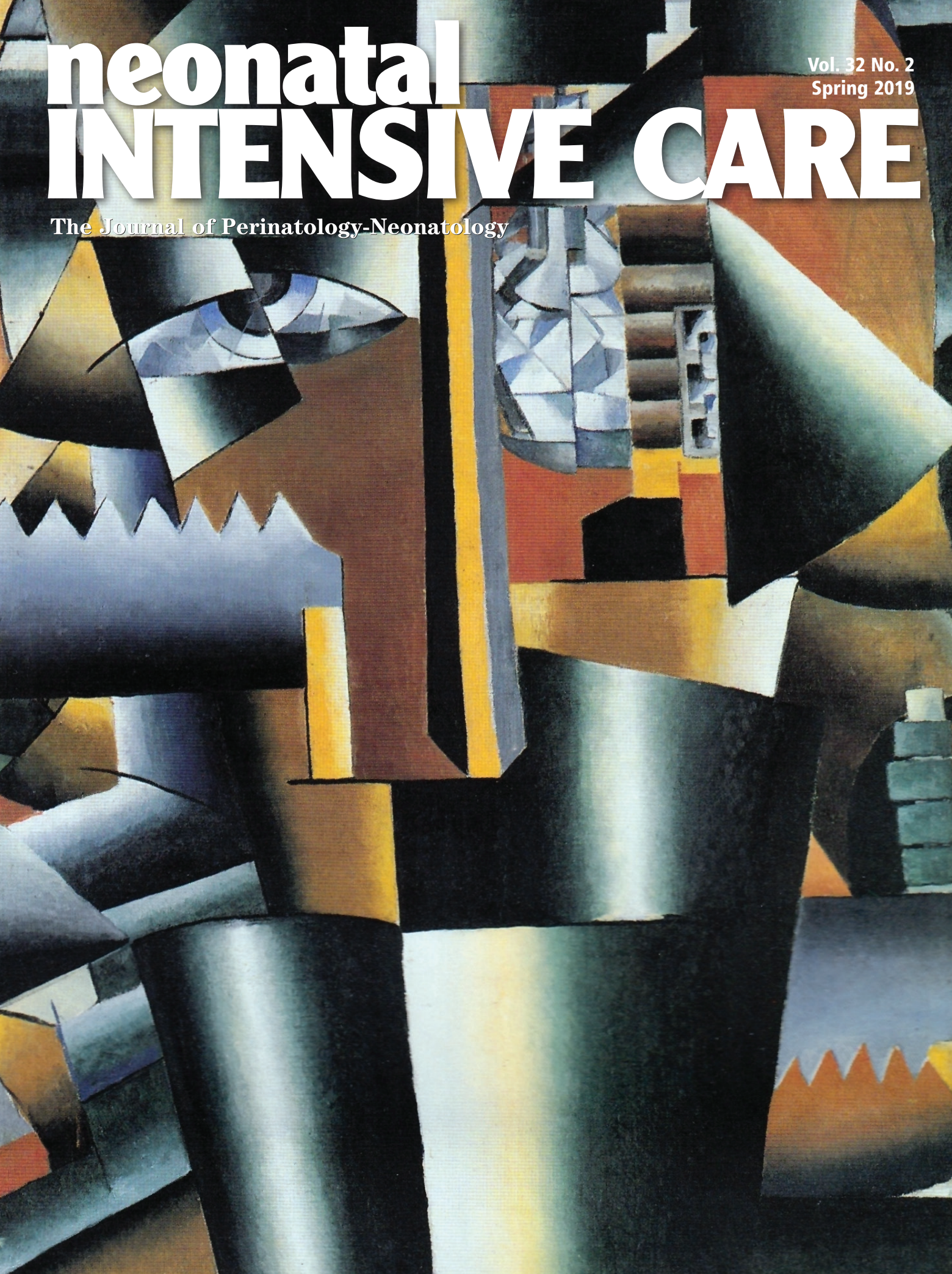
Vol. 32 No. 2
Spring 2019

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology



NEOTECH®
Making a Difference

GET YOUR FREE BOX!
NeotechNeoShades.com

Phototherapy with Style!

NeoShades®
Phototherapy Eye Shields

Available with skin friendly NeoFoam® headstrap or NeoBond® Hydrocolloid tabs. Available in three sizes with a cute sunglasses design.

Order Your Free Box While Supplies Last!

Supplies limited: request your free box at neotechneoshades.com

neonatal INTENSIVE CARE

Vol. 32 No. 2
Spring 2019

Table of Contents

DEPARTMENTS

ARTICLES

Editorial Advisory Board

News

☐ Spring 2019

Fetal Movement Awareness Effort Doesn't Reduce Stillbirth

An intervention to increase pregnant women's awareness of reduced fetal movement does not have the desired effect of reducing rates of stillbirth delivery, and in fact, is associated with an increased risk of cesarean section, induced labor, and prolonged time in the neonatal unit, according to new research said to represent the largest study of fetal movement awareness to date. "This study will re-ignite the controversy about the efficacy of reduced fetal movement awareness to reduce stillbirth and the underlying mechanisms linking reduced fetal movement and stillbirth," say Jane E Norman, MD, director of the Edinburgh Tommy's Centre for Maternal and Fetal Health, University of Edinburgh, UK, and colleagues in their study. "With a population of more than 400,000 women, we showed that reduced fetal movement awareness did not significantly reduce the risk of stillbirth." In an accompanying commentary, Kate F. Walker, PhD, and Jim G. Thornton, MD, of the Division of Child Health, Obstetrics, and Gynaecology, School of Medicine, at the University of Nottingham, UK, note that the advice to pregnant women in the study "was that they should monitor changes in [fetal] movements from 24 weeks and that they should refer themselves immediately if they detected altered movement after 28 weeks." "With hindsight, the recommendation to encourage mothers to report changes from as early as 28 weeks might have been misguided," they add. "Although overall deaths were not stratified by duration of gestation, it is plausible that limiting awareness campaigns to beyond 37 weeks would be safer."

Breastfeeding Might Benefit Babies by Reducing Stress

Mothers have long been told that "breast is best" when it comes to feeding newborn babies, but a small experiment suggests at least some of the benefits may have nothing to do with the milk itself. Pediatricians recommend that mothers exclusively breastfeed infants until they're at least 6 months old because it can bolster babies' immune systems and reduce their risk of ear and respiratory infections, sudden infant death syndrome, allergies, obesity and diabetes. While there's plenty of research documenting these benefits, less is known about exactly how breastfeeding might cause these improvements in babies' health, researchers note in a report. For the current study, researchers studied levels of the stress hormone cortisol in 21 babies who were exclusively breastfed for their first five months and another 21 babies who were not. When infants were exposed to a stressful situation — their mothers ignoring them — researchers found less evidence of a "fight-or-flight" stress response in the babies who had nursed. "Breastfeeding was associated with decreased DNA methylation of the glucocorticoid receptor promoter and decreased cortisol reactivity in 5-month-old infants. Decreased DNA methylation occurred in the promoter region involved in regulation of the hypothalamic-pituitary-adrenal and immune system responses," they report. "Nurturing behavior controls a specific gene that regulates the infant's physiological response to stress," said lead study author Dr Barry Lester, director of the Center for the Study of Children at Risk at the Warren Alpert Medical School of Brown University in Providence, Rhode Island. The study was inspired by previous studies in rats, which linked maternal care or nurturing behavior by mothers to changes in the rat pups' physiologic response to stress, Lester said.

Neonatal Phototherapy Tied to Small Increased Risk of Seizures in Boys

Phototherapy in newborn boys is associated with an increased risk of childhood seizures, but the risk is weaker than previously thought, researchers say. A recent Danish cohort study found that boys who had received phototherapy

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.

for neonatal jaundice had approximately double the risk of subsequent epilepsy. The current study confirmed the association in a larger cohort, but found the risk was lower than in the Danish study. Nonetheless, Dr Thomas Newman of the University of California, San Francisco, said, "These results and others…have led the UCSF Northern California Neonatology Consortium to raise jaundice treatment thresholds in anticipation of similar changes expected in guidelines currently being updated by the American Academy of Pediatrics." The current guidelines are online at http://www.phototherapyguidelines.com/. Dr Newman and colleagues studied 37,683 infants born at 35 weeks' gestation or later from 1995 to 2011 in Northern California. The mean follow-up time was 8.1 years, and the primary outcome was at least one seizure diagnosis plus at least one prescription for an antiepileptic drug. The authors conclude, "Phototherapy in newborns is associated with a small increased risk of childhood seizures, even after adjusting for bilirubin values, and the risk is more significant in boys."

Probing Congenital Nasolacrimal Obstruction May Be OK in 9- to 15-month-Olds

The optimal time window to probe the tear duct of a child with congenital nasolacrimal duct obstruction (CNLDO) may be earlier and narrower than previously thought, researchers suggest. "Probing between age 9 and 15 months may be reasonable given that the rate of spontaneous resolution plateaued after 9 months and initial probing success declined after 15 months. This time frame supports an earlier and narrower range of ages for intervention compared with the current practice of probing after age 1 year," researchers from Mayo Clinic, in Rochester, Minnesota, write. "CNLDO affects about 11% of newborns," senior author Dr Brian G. Mohny added. "Our study showed that pediatricians and primary care physicians can refer babies to an ophthalmologist sooner for the five-minute procedure. I think families will be relieved that their babies don't need to live with the gooey discharge so long." Dr Mohny and his co-authors reviewed ten years' worth of medical records for nearly 2,000 consecutive infants in the Rochester Epidemiology Project (REP) database who had been diagnosed with CNLDO symptoms early in their first year of life while they lived in Olmsted County, Minnesota. Almost all the babies were white, about half were female, and the children had been diagnosed at a median age of 1.2 months. Of the 1,958 infants not lost to follow-up, CNLDO had resolved without treatment by age 3 months in 47.3%, by 6 months in 66.4%, by 9 months in 75.7% and by 1 year in 78.4%. The rate of CNLDO resolution slowed significantly over time: It was 35% faster in infants younger than 1 month vs those 3 months of age, 43% faster at 3 months vs 6 months and 39% faster at 6 months vs 9 months. The difference was no longer significant between 9 months and 1 year, however. Obstruction in one eye resolved 0.2 months more quickly than in both eyes (P=0.002). Children probed at 15 months of age or later were less likely to have the procedure fix the problem than were children probed between 12 and 14 months of age (odds ratio, 0.11; P=0.04).

Morbidities More Common in Black, Hispanic Preemies

Neonatal morbidities are much more common among black and Hispanic very-preterm infants, compared with their white peers, researchers report. "Clinicians should be aware of the sizeable increased risk of these important very-preterm morbidities among black and Hispanic women and strive for optimal prevention and treatment strategies to reduce the burden on black and Hispanic infants and their families," Dr Teresa Janevic from Icahn School of Medicine at Mount Sinai, in New York City, said. Previous research on racial/ethnic disparities in severe morbidities among preterm infants has yielded inconsistent findings. This may result from bias created when infants are stratified on birthweight or gestational age. Dr Janevic and colleagues estimated racial/ethnic differences in four severe neonatal morbidities: necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD). They used both a conventional approach and the fetuses-at-risk (FAR) approach designed to address biased paradoxical associations. In fully adjusted conventional models, among very-preterm infants, black infants compared with white infants had a significantly increased risk of BPD and a borderline increased risk of NEC; Hispanic infants had a borderline increased risk of NEC; and Asian infants had a significantly increased risk of ROP, the team reports. Results were considerably different using FAR denominators. In fully adjusted FAR models, black infants compared with white infants had a 4.4-fold increased risk of NEC, a 2.73-fold increased risk of IVH, a 4.43-fold increased risk of BPD and a 2.98-fold increased risk of ROP. Similarly, Hispanic infants compared with white infants had a 2.52-fold increased risk of NEC, a 2.12-fold increased risk of IVH, a 2.18-fold increased risk of BPD and and 99% increased risk of ROP. Very-preterm Asian infants were 2.43-fold more likely to have ROP. All these risk increases were statistically significant. "Reports on racial/ethnic disparities from select populations of very preterm births are misleading and can lead to the erroneous belief that black and Hispanic infants are at a lower or similar risk

of severe morbidities, which detracts from the magnitude of the problem," Dr Janevic said. "We hope in future research to pinpoint specific points of intervention to reduce disparities, as well as conduct further investigation how these very preterm birth morbidity disparities contribute to inequalities in health and development in childhood and beyond," she said.

Hydrocortisone Does Not Reduce BPD in Preemies

Systemic hydrocortisone (HC) does not reduce the risk for bronchopulmonary dysplasia (BPD) or for a composite endpoint of BPD or death in very preterm infants receiving mechanical ventilation, a randomized trial shows. However, a planned secondary analysis suggests that HC may reduce the risk for death when analyzed as an endpoint on its own. "Our study shows that HC does not reduce BPD. Our finding that it does reduce death is somewhat surprising, although trials on prophylactic HC use indicated that this might be a benefit from HC," senior author Anton H. van Kaam, MD, PhD, from the department of neonatology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, the Netherlands, said. Wes Onland, MD, PhD, from the department of neonatology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, the Netherlands, and colleagues published their findings online January 29 in JAMA for the Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants (SToP-BPD) Study Group. Dexamethasone is effective at reducing the risk for death or BPD in this patient population. "However, this benefit may be outweighed by an increased risk of neurodevelopmental impairment. As a result, clinicians started using dexamethasone less frequently, in lower doses, and at later postnatal ages. Furthermore, international guidelines recommended investigating whether hydrocortisone would be an effective and safe alternative to dexamethasone," the authors write. The researchers conducted a double-blind, placebo-controlled randomized trial to determine whether systemic hydrocortisone treatment started between 7 and 14 days after birth decreased the incidence of death or BPD at 36 weeks' postmenstrual age in ventilator-dependent very preterm infants. The study included 372 infants (mean gestational age, 26 weeks; 55% male) in 19 neonatal intensive care units with a gestational age of less than 30 weeks and/or birth weight below 1250 g. The infants were randomly assigned to receive systemic hydrocortisone (cumulative dose, 72.5mg/kg; n = 182) or placebo (n = 190) for 22 days. One infant treated with hydrocortisone was withdrawn from the study by the parents. The study's primary composite endpoint was death or BPD at 36 weeks' postmenstrual age. Overall, 73 infants (20%) died and 195 survivors (53%) were diagnosed with BPD. Death or BPD occurred in 128 infants (70.7%) in the hydrocortisone group and in 140 infants (73.7%) in the placebo group (adjusted risk difference, −3.6%; [95% confidence interval (CI), −12.7% to 5.4%]; adjusted odds ratio [OR], 0.87 [95% CI, 0.54 - 1.38]; P = .54), after adjustment for the stratification variables of gestational age and study center. Eight of 29 secondary outcomes were significantly different between the two groups. Death at 36 weeks' postmenstrual age was less likely among infants in the hydrocortisone group (15.5% with hydrocortisone vs 23.7% with placebo; risk difference, −8.2% [95% CI, −16.2% to −0.1%]; OR, 0.59 [95% CI, 0.35 - 0.995]; P = .048).

Circassia Acquires US and Chinese Commercialization Rights to Novel Nitric Oxide Product AirNOvent

Circassia Pharmaceuticals announced that it is acquiring exclusive commercialization rights from AIT Therapeutics Inc. to its ventilator compatible nitric oxide product, AirNOvent, in the United States and China. The rights cover all potential indications in the hospital setting for the administration of inhaled nitric oxide, which includes hypoxic respiratory failure associated with persistent pulmonary hypertension of the newborn (PPHN). PPHN is a life-threatening circulatory and respiratory condition in newborns that results in decreased blood flow and oxygen to the lungs and extreme difficulty breathing. Estimates of PPHN in the US vary widely, from 1,500-26,200 newborns annually; approximately 10% of babies with PPHN die. Inhaled nitric oxide is a pulmonary vasodilator which is approved in the

United States for use as part of a regimen in the treatment of hypoxic respiratory failure associated with PPHN.AirNOvent is a portable system that utilizes an electric voltage to produce precise quantities of nitric oxide from the nitrogen and oxygen in air. It uses disposable smart filters to remove unwanted NO2 produced during the process. In the United States, only one inhaled nitric oxide product is currently available, INOMAX®. It is used in neonatal intensive care units (NICUs) and its delivery system administers nitric oxide from pressurized cylinders in conjunction with ventilator systems. The product generated estimated US revenues of over $400 million in 2017. Unlike INOMAX, AIT's AirNOvent is cylinder-free and is smaller, significantly lighter and more convenient than the INOMAX system. It is designed for compatibility with current ventilators, and does not require special storage and handling. These features will make this essential and life-saving treatment more accessible to NICUs and smaller clinics without the facilities required to manage nitric oxide cylinders. AIT anticipates applying to the FDA for Premarket Approval for AirNOvent in Q2 2019 for use in the treatment of PPHN, and Circassia anticipates launching the product in the first half of 2020, once approved.

Skip Pulse Oximetry in Bronchiolitis, Experts Say

Healthcare providers should avoid pulse oximetry in young children with bronchiolitis, according to a research analysis. "Pulse oximetry as a technology represents a major and significant advance in medicine.… However, its increasing and widespread use in stable infants and young children with bronchiolitis, a self-limited disease with a generally benign course, has led to technology driven overdiagnosis of hypoxaemia — fueling uncertainty, increased use of resources, and patient harm," write Ricardo Quinonez, MD, from Baylor College of Medicine in Houston, Texas, and colleagues. The American Board of Internal Medicine Foundation (ABIM) recognizes this problem in its Choosing Wisely campaign, which is aimed at decreasing overuse of unnecessary medical practices. In 2013, the Society of Hospital Medicine published a list of five tests and treatments to avoid in hospitalized children as part of that effort. That list includes avoiding continuous pulse oximetry in children admitted for respiratory illness who are not receiving supplemental oxygen. Updated American Academy of Pediatrics (AAP) clinical practice guidelines also advise against use of continuous pulse oximetry in bronchiolitis. At the same time, guidelines and clinical practice differ on standard definitions for hypoxemia. The AAP has set lower thresholds for hypoxemia, at 90%, on the basis of research suggesting that this level is safe and may have better outcomes than higher thresholds. The UK National Institute for Health and Care Excellence guidelines recommend a higher threshold, at 92%. However, the evidence from three randomized controlled trials suggests that "exposing children to lower probabilities of diagnosis of hypoxaemia seems to be safe and could also lead to improved outcomes," the authors write. Most studies have been too small to find a measurable benefit of increased pulse oximetry in short- to medium-term outcomes such as mortality, rehospitalization, or need for increased care, the authors explain. Some studies have suggested reduced mortality rates or possible cognitive benefits, but these have been done in developing countries, in critically ill children, or in children with chronic disease; therefore, the results may not apply to those in developed countries or otherwise healthy children. Aside from live births, bronchiolitis represents the leading cause of hospital admission in US infants during the first year of life. Bronchiolitis is a viral infection of the lower respiratory tract that mostly affects children up to age 2. Treatment is mostly supportive. Admissions for bronchiolitis have almost tripled during the last 30 years, mirroring the increased use of pulse oximetry for measuring blood oxygen saturation. As bronchiolitis-related disease severity and mortality have not decreased during that time, some experts suggest that borderline low oxygen levels, likely detected by increased use of pulse oximetry, have led to overdiagnosis of hypoxemia. The best-documented harms of such overdiagnosis are unnecessary hospitalization and increased length of hospital stay, the authors write. Both can increase the risk for hospital-acquired infections and other adverse events. Unnecessary admission and overly aggressive care also increase healthcare costs. At least one study estimates the cost of bronchiolitis at approximately $652 million per year. An economic analysis of data from one trial found lowering oxygen saturation thresholds may decrease costs by $377 per patient; those savings increase after factoring in other variables including travel and missed work. "The cost savings from preventing overdiagnosis could prove significant, both for individual patients and at a societal level," the authors explain. "The current body of evidence suggests that we should challenge assumptions regarding the detection and aggressive management of borderline hypoxaemia in non-critically ill infants with bronchiolitis," they stress. "The most impactful intervention may be to decrease overdependence on pulse oximetry as a major decision point in admission of children with bronchiolitis," the authors conclude.

Less Retinopathy of Prematurity Seen With Biphasic Oxygen Targets

In prematurely-born infants, compared to static oxygen standards, biphasic oxygen targets are associated with reduced rates of retinopathy of prematurity (ROP), without increased mortality, according to a new study. "Although premature infants require oxygen supplementation to prevent mortality, excess oxygen can be simultaneously harmful to premature developing tissues such as the retina, leading to ROP," Dr Jonathan E. Sears of the Cleveland Clinic Cole Eye Institute, in Ohio, said. "Early in premature life, in phase 1 of ROP, hyperoxia attenuates retinal growth, which provides the substrate for abnormal angiogenesis in phase 2 of ROP," he added. "Using a biphasic approach," Dr Sears continued, "phase 1 and phase 2 can be 'flipped' so that early physiologic hypoxia induces normal retinal growth to remove the substrate for ROP. Later in the course of prematurity, oxygen standards are increased to support increased metabolic demands and prevent tissue hypoxia." To compare oxygenation approaches, Sears and colleagues examined retrospective data on 260 infants who underwent the biphasic approach and a further 302 who were treated with static standards in accordance with guidelines in the 2010 SUPPORT study. All infants were treated at the same level III neonatal intensive care unit, were born at a corrected gestational age (CGA) of 31 weeks or less or had a birth weight of no more than 1,500 g. The pre-SUPPORT group underwent biphasic protocol target saturations of 85% to 92% at less than 34 weeks of CGA and greater than 95% at 34 weeks of CGA or more; the post-SUPPORT group underwent a constant 91% to 95% target.

There was a significant increase in any ROP overall from 20% pre-SUPPORT to 28% post-SUPPORT (P=0.03), the researchers report. Infants in the post-SUPPORT group also had significantly more treatment-requiring ROP (6% vs

Delivering **uninterrupted bubble CPAP** in neonatal critical care environments

B&B Bubbler™ Water Seal CPAP Valve

Convenient, cost-effective, and versatile

- Patented dual-chambered design allows fluid level to be observed without disrupting therapy
- Internal, drainable overflow chamber limits fluid to desired CPAP level
- Clearly marked CPAP settings
- Adjustable from 1 – 10 cm H_2O

ALSO AVAILABLE

12.5 cm H_2O Pressure Relief Manifold and Pole Clamps for Bubble CPAP systems

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

B|B BREATHING INNOVATION

Medical Technologies
www.bandb-medical.com

2%) and more-frequent vascularization delays (6% vs 2%). However, there were no significant between-group differences in mortality (5% in the pre-SUPPORT group vs 6%, P=0.81). The researchers hypothesize "that biphasic oxygen saturation targets might be different than static oxygen targets." Concluded Dr Sears: "one approach to balancing the pros and cons of oxygen is to consider a biphasic approach." In an accompanying editorial, Dr Lois E. H. Smith of Harvard Medical School, in Boston, and colleagues note that the study "is an important first step in defining the use of oxygen while considering the timing of oxygen supplementation as well as the saturation targets. The use of lower SpO2 targets early and higher during a later period has the potential to become a preventive strategy for ROP." Dr Alex R. Kemper, division chief of Ambulatory Pediatrics at Nationwide Children's Hospital, in Columbus, Ohio, noted, "One of the important challenges in taking care of prematurely born infants is knowing how best to administer oxygen, which really should be considered a drug with both benefits and harms. If the levels of oxygen are too low, there is an increased risk of death but if too high, retinopathy of prematurity, potentially leading to blindness, can develop."

Cannabis Exposure Linked to Harm in Newborns

In utero exposure to cannabis can lead to significantly higher rates of adverse outcomes, including low birth weight and preterm delivery, new research shows, and increasing numbers of pregnant women are using cannabis as legalization laws sweep the country. "As marijuana has been legalized" in an increasing number of states, "become more potent, and gained acceptance, we have many women using it who do not necessarily engage in other negative health behaviors, such as tobacco, alcohol, and other drug use," said Beth Bailey, PhD, from the University of Colorado Denver Anschutz Medical Campus in Aurora. "As a result, newer studies are identifying clear links between in utero marijuana exposure and adverse outcomes in exposed children," she said at the Society for Maternal-Fetal Medicine 2019 Annual Pregnancy Meeting in Las Vegas. Bailey and her colleagues conducted a retrospective chart review of 1062 newborns delivered at one of six delivery hospitals in the University of Colorado Health System or one of five delivery hospitals in Tennessee and Virginia from July 2011 to June 2016. In utero exposure to cannabis during late pregnancy was confirmed with a positive urine drug screen at delivery in 531 mothers of the newborns. The exposed infants were rigorously matched for background and other prenatal exposures with an equal number of control infants whose mothers had a negative drug screen.

Antenatal Betamethasone Does Not Impair Neurocognitive Function

Repeated antenatal doses of betamethasone does not impair neurocognitive function in elementary-school-aged children born with fetal growth restriction, according to a secondary analysis from the ACTORDS clinical trial. "We were a little surprised by the results, as animal studies have repeatedly raised concerns about exposing fetuses with growth restriction to increasing amounts of corticosteroids," said Dr Christopher J D McKinlay of the University of Auckland, New Zealand. "But our study clearly shows that treatment with repeated doses of betamethasone for preterm birth is safe in the long term, even in the presence of fetal growth restriction. This is an important finding, as growth restriction is common in cases where repeat doses are indicated (27% in our study)," he said. The Australasian Collaborative Trial of Repeat Doses of Corticosteroids (ACTORDS) showed that repeated antenatal doses of corticosteroids are not associated with adverse effects on neurocognitive function, learning, behavior, growth, lung function and cardiometabolic function in offspring at mid-childhood. In their secondary analysis of ACTORDS data, McKinlay's team investigated whether the presence of fetal growth restriction influenced the effects of repeated antenatal doses of betamethasone on neurocognitive function and behavior in 988 children (mean age at follow-up, 7.5 years). About a quarter of the children (28.2% of the betamethasone group and 24.6% of the placebo group) had been born with fetal growth restriction. At corrected ages of 6 to 8 years, the rates of survival free of any disability and of death or moderate to severe disability, the primary outcomes, were similar between treatment groups in the subgroups with and without fetal growth restriction, respectvely, with no evidence of an interaction effect, the team reports in JAMA Network Open, online February 1.

Regardless of the presence or absence of fetal growth restriction, repeated betamethasone treatment was associated with significantly greater survival free of any disability and significantly reduced death or moderate to severe disability.

Among children born with fetal growth restriction, repeated-dose betamethasone therapy reduced the incidence of respiratory distress syndrome, the severity of neonatal lung disease and serious neonatal morbidity, as well as the need for mechanical ventilation, oxygen and surfactant therapy. Regardless of treatment exposure, however, children with fetal growth restriction fared worse than those without fetal growth restriction, with an increased risks of death or moderate to severe disability and motor impairment, lower IQs and lower scores for measures of attention, executive function and reading. "It is sometimes mistakenly assumed that growth-restricted fetuses don't need repeat dose treatment due to higher endogenous corticosteroid levels," McKinlay said. "However, our study has shown that growth-restricted fetuses not only have higher rates of respiratory and other morbidities but also are more likely to benefit from repeated doses therapy."

Intrapartum Group-B-Streptococcus Molecular Screening Cost-Effective

Point-of-care intrapartum group B streptococcus (GBS) PCR testing cost-effectively reduces disease rates and antibiotic use in newborns, researchers from France report. "Point-of-care GBS PCR screening is more reliable than antenatal culture to detect GBS colonization of the mothers at the time of delivery," Dr Najoua El Helali from Groupe Hospitalier Paris Saint-Joseph, in Paris, said. "PCR screening is easy to implement. Since 2010, the midwives in our institution perform intrapartum PCR GBS screening at the point-of-care in the delivery suite." Preventing early-onset GBS disease in newborns relies on reducing or eliminating mother-to-child transmission by administering intrapartum antibiotic prophylaxis to GBS-colonized mothers. Most cases now occur in newborns whose mothers had negative results of culture screening for GBS colonization at 35-37 weeks of gestation. Antenatal culture screening has only 58.3% positive predictive value compared with intrapartum PCR screening. Dr El Helali and colleagues assessed outcomes and costs associated with around-the-clock point-of-care intrapartum GBS PCR screening in the delivery suite versus antenatal screening by culture of a vaginal swab at 35-37 weeks of gestation. Significantly

more term deliveries screened positive during the intrapartum PCR screening period (14.5%) than during the antenatal culture period (12.2%). But there was no significant difference in the percentages of women who received intrapartum antibiotic prophylaxis after screening positive (91.8% vs 89%, respectively). The rate of proven and probable early-onset GBS disease in newborns was much lower in the intrapartum PCR period (0.9/1,000 births) than in the antenatal culture period (3.8/1,000 births), the team reports. Total days of hospitalization for early-onset GBS disease declined by 64%, and antibiotic therapy for early-onset GBS disease declined by 60% with the use of intrapartum PCR. The mean yearly cost of delivery and treatment of newborns with GBS infection decreased from $41,875 during the antenatal-culture period to $11,945 after implementation of intrapartum PCR screening. Compared with antenatal culture, the estimated extra cost of PCR to avoid one additional case of early-onset GBS disease was $5,819.

Newborn Screening Identifies SCID and T-Cell Lymphopenia

Newborn screening of DNA from dried blood spots identifies infants with severe combined immunodeficiency (SCID) and clinically important non-SCID T-cell lymphopenia, researchers report. Population-based newborn screening is the only strategy for identifying all infants with SCID early enough to provide treatment before infectious complications ensue. California instituted population-wide screening for SCID in 2010, and currently all 50 states in the US, plus the District of Columbia and Puerto Rico, and an increasing number of countries have adopted universal newborn screening for SCID.

The SCID newborn screening test is based on the detection of T-cell receptor excision circles (TRECs), DNA markers of normal T lymphopoiesis that can be measured by PCR using dried blood spots routinely obtained from newborns by heel stick. Dr Jennifer M. Puck from University of California, San Francisco and Benioff Children's Hospital and colleagues report the experience and outcomes of the first 6.5 years of screening >3.25 million newborns for SCID in California. During this time, TREC screening identified 50 cases of SCID (1 per 65,000 births). Among the cases of non-SCID T-cell lymphopenia, there were 72 categorized as congenital syndromes (most commonly DiGeorge syndrome, in 47 infants), 25 resulting from another condition and resolving once that condition was corrected, 33 related to preterm birth alone and resolving if the infant survived, and 33 idiopathic cases. Of the 50 infants with SCID, 49 were immediately hospitalized for treatment with allogeneic hematopoietic cell transplant from a suitably matched healthy donor, autologous corrected cell gene therapy, or enzyme replacement therapy. The other infant born to a foreign visitor left the US before receiving further evaluation or treatment. Survival of patients with SCID was 94% at 1 to 8 years of age, and 31 of the 46 surviving children (67%) had fully reconstituted B- as well as T-cell immunity and no longer required IgG supplementation. Screening missed no known cases of typical SCID, but two infants with delayed-onset leaky SCID resulting from missense defects in the ADA and IL2RG genes had normal TREC newborn screening and did not come to clinical attention until 7 and 23 months of age.

Tiniest Preemies Still Have Low Survival Odds

Although extremely preterm birth is no longer the death sentence it once was, the tiniest preemies still have low survival odds and are likely to have severe impairments if they live, a research review suggests. The team examined data from 65 studies focused on the most vulnerable preemies - those born between 22 and 27 weeks gestation - to see how many survived and how many had severe physical or mental impairments at 18 to 36 months. As a proportion of all deliveries including stillbirths, virtually no babies born at 22 weeks survive. And among only the live births at this very

early stage, just 7.3% of babies survive. But survival rates surge to 24% for the subset of these babies who can be admitted to neonatal intensive care units (NICUs). In contrast, 82% of all babies delivered at 27 weeks live, with the survival odds rising to 90% for those admitted to NICUs, the study team reported. Longer gestation also increases the odds of survival without severe impairments: at 22 weeks, just 1.2% of babies born alive are free of major impairments, but this rises to 64% of infants who arrive at 27 weeks. "Except for infants approaching the limit of viability around 22-24 weeks, most of them survive without major impairments," said senior study author Dr Trond Markestad of the University of Bergen in Norway. "Most major impairments, i.e. cerebral palsy, severe sensory (vision, hearing) impairment and mental retardation are discovered at 3 years of age," Markestad said by email. "But we know that less severe mental and physical impairments, such as significant learning, behavioral and attention difficulties and clumsiness that are not detected at 3 years are common among school children born very and extremely preterm, and again, in particular when approaching the limit of viability." The study only focused on babies born in high-income countries where more mothers might have access to prenatal care and more infants might have access to NICUs and advanced medical technology. Pregnancy normally lasts about 40 weeks, and babies born after 37 weeks are considered full-term. In the weeks after birth, preemies often have difficulty breathing and digesting food, and their survival odds can depend very much on the availability of effective lung treatments, intravenous nutrition and pumped breast milk. For the study, researchers focused on babies born between 2000 and 2017. Most advances in breathing and nutrition support happened before this time period.

Limited Evidence Supports Buprenorphine for Neonatal Abstinence Syndrome

Buprenorphine might be the best pharmacological treatment for neonatal abstinence syndrome, based on limited evidence, according to a systematic review and network meta-analysis. "Our findings would suggest that buprenorphine is likely the most favorable pharmacological treatment for this population with respect to the overall treatment exposure and length of hospital stay without evidence for immediate harm," Dr Marcia Campbell-Yeo from Dalhousie University School of Nursing, Halifax, Nova Scotia, said. "However, given limitations of the number, size, and quality of the studies available to be included, we would caution an immediate large-scale practice pharmacological treatment change at this time."

The incidence of neonatal abstinence syndrome (NAS) in the US has increased more than 5-fold since 2004, to 8.0 per 1000 live births, but the choice of first-line treatment remains variable. An estimated 53% of neonates with NAS receive morphine, 36% receive phenobarbital, and the rest receive methadone or other treatments. Campbell-Yeo's team sought to identify which treatment is the most effective at reducing the duration of pharmacotherapy in their systematic review and network meta-analysis of 18 studies involving 1072 neonates. "It was surprising how few clinical trials there were, as well as their size, without much promise for conclusive trials in our registry search," co-author and PhD candidate Timothy Disher said. "Considering the increased incidence of NAS and strong consensus regarding treatment, we expected to see a stronger evidence base." Few included studies were considered to be at low risk of bias, with 11 trials making no effort to mask treatments or not providing sufficient information to judge the risk of bias related to blinding. For the primary outcome, the network meta-analysis estimated that with buprenorphine, treatment was 2.19 days shorter than with clonidine and 12.75 days shorter than with morphine, according to the January 22nd JAMA Pediatrics online report. Secondary analyses found buprenorphine to be associated with a reduced length of hospital stay (5.35 days fewer than with clonidine and 11.43 days fewer than with morphine), but there were no significant differences in the number of infants who required adjuvant treatment.

USPSTF Reaffirms Advice on Prevention of Gonococcal Eye Infections in Newborns

The US Preventive Services Task Force (USPSTF) continues to recommend that all newborns be treated with a topical antibiotic ointment to prevent gonococcal eye infections. This "A" recommendation, meaning there is high certainty that the net benefit is substantial, matches the task force's recommendation put forth in 2011. In the United States, the rate of gonococcal ophthalmia neonatorum was estimated to be 0.4 cases per 100,000 live births per year from 2013 to 2017. However, this is likely an underestimate, the task force notes. Gonococcal ophthalmia neonatorum can cause corneal scarring, ocular perforation, and blindness as soon as 24 hours after birth. Without ocular prophylaxis, transmission rates of gonococcal infection from mother to newborn range from 30% to 50%. The task force commissioned a "reaffirmation evidence update" to identify any new evidence sufficient enough to change their 2011 recommendation. There wasn't any, and so the recommendation remains that all newborns receive topical ocular prophylaxis to guard against gonococcal eye infections. The Centers for Disease Control and Prevention, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, and the World Health Organization all recommend universal topical ocular prophylaxis to prevent gonococcal ophthalmia neonatorum. Currently, 0.5% erythromycin ophthalmic ointment is the only drug approved by the US Food and Drug Administration for this purpose, and it's not known whether Neisseria gonorrhoeae has developed resistance to erythromycin ointment in the US.

Optimal Oxygen Use Differs for Preterm, Term Newborn Resuscitation

Room-air resuscitation reduces short-term mortality in term newborns compared with pure oxygen, while the optimal oxygen concentration for preterm newborn resuscitation remains unclear, according to two systematic reviews. "Oxygen can cause harm, and it should be used judiciously," Dr Michelle Welsford from McMaster University, in Hamilton, Canada, said. "Do not start resuscitation in term neonates with oxygen. Almost all preterm newborns <=32 weeks' gestation will require oxygen supplementation within the first five minutes after delivery. Start low and titrate using oxygen saturation targets, avoiding hyperoxia." Welsford and colleagues on the International Liaison Committee on Resuscitation Neonatal Life Support Task Force undertook two systematic reviews with meta-analyses in an effort to ascertain the optimal initial fraction of inspired oxygen (FIO2) for preterm- and term-newborn resuscitation. For preterm neonates (<35 weeks' gestation), short-term mortality and long-term mortality did not differ between starting respiratory support with lower FIO2 (0.5 or lower) or with higher FIO2 (above 0.5), the team reports. Similarly, there was no difference in long-term neurodevelopmental impairment (NDI) rates

between preterm newborns receiving respiratory support starting with lower compared with higher FIO2. Moreover, there were no significant differences in any of the additional secondary outcomes that were deemed important markers of morbidity, and subgroup analyses by gestational age (32 weeks and earlier and 28 weeks and earlier) revealed no significant differences when comparing lower with higher FIO2. For term neonates, however, the use of room air for resuscitation led to a 27% reduction in short-term mortality compared with 100% oxygen (an absolute survival benefit of 4.6 percentage points). The number needed to treat with room air to have one additional survivor was 22. Long-term moderate-to-severe neurodevelopmental impairment did not differ by initial FIO2, and there were no differences between low and high FIO2 in the rates of hypoxic-ischemic encephalopathy (HIE). All studies of term neonates compared room-air oxygen levels with 100% oxygen levels, making it impossible to undertake subgroup analysis according to different oxygen concentrations.

Cord Blood Test May Flag Neonatal Hypoxia Risk

MicroRNA in umbilical cord blood may signal risk for imminent hypoxic-ischemic encephalopathy (HIE) in neonates, offering potential advantages over current diagnostic methods, new research suggests. In a study of 160 full-term infants, two specific microRNAs (miR-374a-5p and miR-376c-3p) distinguished both infants with perinatal asphyxia (PA) and infants with HIE from healthy neonates. To increase the clinical application of the findings, the researchers also identified a third microRNA (mir-181b-5p) that may help determine which neonates would benefit from therapeutic hypothermia.

The need for a better measure of HIE following PA prompted the investigators to search for a test that is quantifiable, robust, and available early enough to guide decision making in the first few hours after birth. "Apgar score is still our best current measure, but it is subjective," study investigator Deirdre M. Murray, MD, PhD, professor in the Department of Pediatrics and Child Health, University College Cork, Ireland, said. "Clinicians find it hard to rely on the Apgar score assigned by someone else, especially from another center," she added.

Delaying Newborn Baths Boosts Breastfeeding Rates

Delaying the bathing of newborns for at least 12 hours after birth is associated with significant improvements in exclusive breastfeeding while in hospital and with mothers being more likely to have feeding plans on discharge that include human milk (exclusively or in addition to formula). "Our results provide new information on the benefits of delayed bathing after hospital discharge," say the authors of the study. "Although our findings need to be replicated in other studies, they reinforce the connection between delayed bathing and greater likelihood of newborn breastfeeding that may extend into the post-discharge feeding plan and practice," note nursing specialist Heather Condo DiCioccio, DNP, RNC-MNN, and colleagues at the Cleveland Clinic Hillcrest Hospital, in Mayfield, Ohio, and colleagues, in their article. Skin-to-skin contact between the newborn and mother immediately after birth has well-known benefits and is urged as part of usual care, but the rationale for delayed bathing, recommended by the World Health Organization (WHO) and other organizations, has been less clear. Theories surround the idea that newborns

Continued on page 40…

Patent Ductus Arteriosus (PDA) and its Treatment with the Amplatzer Piccolo Occluder Device

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Dr Mark Weems, Associate Professor at the University of Tennessee Health Science Center and the Associate Medical Director of the NICU at Le Bonheur Children's Hospital in Memphis, TN, about patent ductus arteriosus (PDA) and use of the Amplatzer Piccolo Occluder device for its treatment.

Neonatal Intensive Care: How often do you come across patent ductus arteriosus (PDA) in your practice?
Dr Mark Weems: The ductus arteriosus is critical to the fetus so nearly all babies are born with patent ductus. Fortunately, most spontaneously resolve in the first few days before they lead to symptoms. Infants born at younger gestational ages are more likely to have a persistent PDA that is associated with complications. At Le Bonheur, all of our patients are referred from other birthing centers, and about 30% of our VLBW infants (birthweight <1500g) have a diagnosis of PDA at admission. Many more get their first echocardiogram after they are admitted revealing a PDA. Of course, not all PDAs need treatment, but infants born at 27 weeks or less are likely to have a hemodynamically significant PDA that persists long enough to cause complications.

NIC: What are some of the symptoms of a PDA that help you diagnose it?
MW: The classic clinical signs of PDA include a heart murmur, wide pulse pressure, and pulmonary edema. But the signs of a hemodynamically significant PDA in extremely premature neonates can be variable depending on the infant's ability to compensate for pulmonary overcirculation and decreased organ perfusion during diastole. Now, we look for an infant who requires prolonged mechanical ventilation and has signs of a hemodynamically significant PDA on echocardiogram. Echocardiography signs include large PDA size with unrestrictive flow pattern, increased size of the left atrium, and decreased or reversal of diastolic flow in large arteries.

NIC: Which newborns generally develop a PDA that requires urgent treatment and how many babies does it affect?
MW: Knowing which babies will benefit from PDA treatment is very difficult. We know that neonates have better outcomes if the PDA closes naturally in the first few days after birth, but many PDA treatment studies have been unable to demonstrate improved outcomes due to treatment. There is evidence to suggest that long-standing PDA is associated with increased risk of bronchopulmonary dysplasia (BPD), decreased brain growth, and increased mortality in the NICU. On the other hand, PDA treatment carries risks that may offset benefits gained from routine PDA treatment, especially in infants born >28 weeks. Most infants born <26 weeks will have PDA longer than 2 months, and they are at the highest risk for BPD and other complications during this time. A selective treatment approach for preterm infants <28 weeks may allow us to identify and close the high-risk PDAs before long-term complications develop,

NIC: Before the FDA approval of Abbott's Amplatzer Piccolo Occluder, what types of treatment options were available to patients with a PDA and how effective were they?
MW: Before the FDA approval of the Abbott Piccolo Occluder, the only available treatment for premature infants who have failed medical therapy for PDA was surgical ligation. This procedure is effective at closing the PDA, but it is associated with significant morbidity. About 30% suffer from cardiovascular compromise after ligation, 30-40% have left vocal cord paralysis, and most studies do not show improved outcomes after ligation.

NIC: Who is a candidate for treatment with the Abbott Piccolo device?
MW: The Piccolo PDA Occluder is approved for infants weighing more than 700g who are at least 3 days old. The ideal candidate seems to be a premature infant with a hemodynamically significant PDA about 3 weeks after birth. This timing allows enough time for spontaneous closure or medical treatment but ensures the PDA is closed before the infant develops pulmonary hypertension and other complications of prolonged PDA.

NIC: Can you describe the procedure for patients receiving treatment with the Abbott Piccolo device?
MW: At Le Bonheur, we put a great deal of effort into ensuring safe transport to the cardiac catheterization lab and maintaining normothermia throughout the procedure. Once in the cath lab, the infant is placed under general anesthesia, and careful transthoracic echocardiography measurements are obtained. The Piccolo Occluder is delivered through the femoral vein, and appropriate position is confirmed by echocardiography and fluoroscopy. The venous approach decreases the risk of limb ischemia compared to the arterial approach common in larger patients. Once the device position is determined, it is released from the delivery wire, and the catheter is removed. The patient is carefully transported back to the NICU where a chest radiograph and blood gas are used to adjust respiratory support. Several hours later, a follow-up echocardiogram is performed to confirm device placement and to guide further cardiac management.

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

NIC: What is the recovery and prognosis following treatment with the Piccolo device?
MW: The short recovery time is the most remarkable benefit of the Piccolo Occluder. After surgical ligation, about 30% of patients suffer from post-ligation syndrome requiring increased respiratory support and blood pressure support, and up to 40% suffer from left recurrent laryngeal nerve injury. In our experience, neonates who had transcatheter PDA closure returned to the pre-procedure respiratory status faster and were extubated sooner compared to neonates who had surgical ligation. Transcatheter closure in infants <2kg is a relatively new procedure so long-term outcomes are still unknown.

NIC: What types of results can patients and their families expect following treatment with the Abbott Piccolo device?
MW: Immediately after transcatheter PDA closure, the family is not likely to notice any differences. Most babies return to the NICU with the same respiratory support they had prior to closure. In the days after closure, however, the family will notice the baby is more stable, may tolerate feeding better, and will begin to require decreased respiratory support. The timing of this improvement depends on the age of the patient; babies whose PDAs are closed after 6-8 weeks tend to have a longer recovery time than those whose PDAs are closed at 3-4 weeks of age.

NIC: What kind of follow-up do babies who are treated with the Piccolo device need?
MW: Because transcatheter PDA closure is a new procedure for neonates <2kg, we do not yet know the long term outcomes. To help answer this question, our patients are followed in our neurodevelopmental clinic; this is standard for all preterm infants. We have also created a PDA clinic to assess cardiac function, device placement, and complications over time.

NIC: In your opinion, how do medical advancements like the Piccolo device enable important advances in treatment for patients?
MW: The Abbott Piccolo has the potential to significantly improve outcomes in the NICU for the highest risk premature infants. Preliminary reports suggest it is safer than surgical ligation and more effective than medical therapy. If we find the Piccolo can safely be used to reliably close the PDA before the baby develops complications, it may reduce the burden of BPD and other long-term morbidities in the NICU.

Finding Comfort and Functionality With Infant CPAP

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. this interview is with Jessica Sexton, MS, RRT-NPS, an Education Specialist II, Respiratory Care at Cincinnati Children's, Cincinnati, OH.

NeoPAP® is a sophisticated respiratory support system that boasts patient comfort, high functionality, and ease of use. NeoPAP is a major departure from the traditional time-intensive approach to infant CPAP therapy that demands continuous monitoring.

1. The Circadiance NeoPAP System is intended to provide continuous positive airway pressure (CPAP) for use in hospitals to treat newborns and infants with respiratory distress syndrome (RDS) or recovering from RDS. The system is intended for use on patients less than 5kg in weight. Stable airway pressure is important in the development of premature infants because they often lack the lung infrastructure to maintain an adequate lung volume following exhalation.

When following these guidelines, what has been your overall success with the NeoPAP system?
Our overall success is that the NeoPAP system provides effective CPAP with variable flow, utilizing their Baby-Trak technology, with appropriate alarms for safety. As the system measures parameters at the interface, we can be assured that the readings at the machine are more accurate and better informed decisions regarding the patient's care can be made.

2. NeoPAP offers the versatility of three therapy modes: CPAP mode, flow mode, and resuscitation mode. FiO2 concentration can be set between 21% and 100% while operating in any mode. It also incorporates a standby mode that allows clinicians to set up the unit in anticipation of admitting a baby needing CPAP or when an interruption of Therapy is required.

What are the advantages of having all of these therapies and features available in one system instead of having to use multiple systems?
Being able to utilize one machine for multiple therapies benefits the neonatal patient, the clinician, as well as the facility. The clinician can prepare for the patient prior to their arrival by putting the machine in stand-by. The patient interface does not need to be switched out when changing between CPAP and flow mode. This reduces the clinician's time needed to switch out equipment and changing circuits/interfaces. The amount of resources in equipment and disposables can also decrease, benefitting the facility.

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

3. NeoPAP offers set parameters and measured parameters visually on the screen allowing for real-time confirmation of settings and changes to settings as they happen.

How does having real time accurate pressure measurements taken from the patient interface benefit the patient?
The system's adjustments are going to be based on accurate pressure measurements and alarms are more reliable.

What are the benefits of being able to visually see the pressure measurement on the screen in real-time?
The clinician is able to make recommendations and changes based on accurate measurements taken closest to the patient, rather than estimated values measured from the machine.

4. NeoPAP incorporates Baby-Trak leak compensation technology in CPAP mode to create a dynamic variable flow system that increases or decreases the flow to manage the CPAP pressure set by the clinician. The Baby-Trak leak compensation technology algorithm quickly responds to patients' changing respiratory requirements related to breathing patterns. During exhalation, the CPAP level is maintained, but the flow level is automatically reduced to decrease the resistance on exhalation to the baby. During inspiration, if there is a reduction in pressure as the infant inhales, NeoPAP increases flow to maintain the set pressure. This allows the device to provide the patient with constant measured pressure support despite minor leaks that may be present at the patient interface or elsewhere in the patient circuit. When the device recognizes a pressure drop from a leak, it will provide additional flow to compensate for the leak and maintain the pressure level set by the clinician.

How has Baby-Trak technology given you peace of mind that your patient will always get the proper measured CPAP therapy?
I know with the Baby-Trak technology that the flow is going to adjust to ensure my patient is given the set pressure.

5. Because of accurate measurements at the patient interface, NeoPAP robust alarm settings can be adjusted to minimize false alarms.

What are the advantages of having NeoPAP alarms vs CPAP systems that don't have any alarms?
So many times myself or other clinicians have walked up to a patient's bedside only to find that the water is no longer bubbling with bubble CPAP systems and is therefore not providing

adequate therapy. Having alarms helps to ensure effective therapy is being delivered before it begins to negatively affect the patient clinically.

How can you tell with other CPAP systems if the baby is getting the proper therapy without an alarm system? Can you explain?
In my experience, you often do not know the patient is not getting proper therapy until it affects them clinically, meaning physiologic changes are happening such as the patient begins to desaturate and a vital sign monitor alarms.

6. Many NICUs across the country are concerned with ambient noise within their unit. NeoPAP has 3 adjustable alarm volume settings as well as a visual alarm indicator. At the lowest volume, it is the quietest CPAP or High Flow device with an alarm available.

How does your NICU feel about ambient noise?
Our NICU aims to reduce any extraneous noises when possible, providing a healing environment that promotes growth and development for the smallest of patients.

How does NeoPAP's adjustable alarm volume help with this issue?
Adjustable alarms allow for the most appropriate alarm for the setting it is being used in, setting it the lowest we can that is safe for the situation.

7. NeoPAP is the only respiratory device available where a cannula or mask can be used in Hi Flow mode. This allows you to switch from CPAP mode to Hi Flow mode without having to change the patient interface or to a separate Hi flow machine. Many NICU's have stated that it takes between 25-40 minutes to switch from one therapy to another.

What is your main concern for the patient during the switch from one therapy to another?
My concern is that some of the therapeutic value you have gained is lost in the transition between two different therapies, or that it may take too long to escalate therapy if needed. The transition for the neonatal patient may be distressing both clinically and developmentally.

What are the advantages of not having to change interfaces or machines to go from CPAP therapy to Hi Flow therapy as the baby is weaned off CPAP therapy?
Advantages include it being less stressful for the baby, less clinician time spent switching devices, and less equipment/ circuits used. There are positives from a clinical perspective as well as from a financial perspective.

Now that you have NeoPAP, what are your thoughts about having to switch between therapies?
Anytime we can avoid switching therapies, especially if it's the same or similar we are going to try to avoid it.

How long does it take now?
If staying on the NeoPAP, it is only as long as it takes to make a few changes on the device.

8. Most CPAP therapies available today cover up the baby's face and make it difficult for the parent or caregiver to make eye contact. The NeoPAP patient interface system was designed to be developmental friendly. It allows for constant eye contact. It also allows for skin to skin contact during kangaroo care without having to discontinue the therapy.

As a caregiver, what are your thoughts about having a system that is developmentally friendly?
This is so important, and has been challenging with other devices. The NeoPAP's design sits more like a traditional nasal cannula, rather than going up and over the nose and forehead. The baby's view is not obstructed and it allows for skin-to-skin, which we know is so important for bonding, growth and healing.

10. The NeoPAP's innovative bonnet is made with Fabrifoam* lining to help minimize torsional stress placed on the patient interface. This unique design virtually eliminate the need to tighten the interface to the patient. When properly placed on the baby, it allows the clinician or caregiver to open up the bonnet to do an hourly head/skin check, Scalp IV check, or cranial ultrasound without having to remove the bonnet or discontinue therapy.

How does this help with clinician workflow efficiency?
There can be a great deal of time spent trying to properly place a neonatal patient on non-invasive CPAP therapy. Any time you can avoid having to re-do all of that work improves workflow efficiency, and of course is beneficial to the patient.

What are the clinicians and parents thoughts about the softness of the Fabrifoam* lining?
Clinicians are impressed with the softness and quality of the Fabrifoam lining. With the delicate nature of the neonatal patient's skin, we are always looking for material that is going to be developmentally appropriate that also does not cause the patient to incur skin breakdown.

11. NeoPAP has a two hour battery and can be used for transport on an oxygen cylinder within the hospital.

What are the advantages of being able to continue therapy during transport verses having to unhook the baby and discontinue therapy?
Being able to continue therapy, especially without having to change interfaces unnecessarily is so beneficial to the neonatal population. Not only is it more developmentally appropriate, but it also avoids potential loss of lung volumes due to less effective therapy during the transport.

12. The NeoPAP Infant Respiratory Support system is manufactured, marketed, and clinically supported by Circadiance.

Please share your overall experience with Circadiance as a partner to deliver the best education for your staff and care for your patients.
Circadiance has been receptive via email, phone and in-person. They have provided in-services as well as educational materials. We have been able to troubleshoot over the phone with a challenging patient.

NICU physicians and caregivers from a growing number of prominent healthcare facilities in the United States have discovered that NeoPAP is the ideal solution for infant CPAP therapy. NeoPAP allows the medical staff to spend more time caring for patients and less time tending to the device.

Circadiance develops, manufacturers and markets remote patient monitoring and respiratory therapy products. Circadiance products deliver superior patient comfort in the home care and acute care settings, ultimately resulting in reduced cost of care and improved patient outcomes.

Eliminating Device-Related Hospital-Acquired Pressure Injuries in the Neonatal Intensive Care Unit Through Quality Improvement Methods

Anne Geistkemper, Sara Murphy, Kellianne Fleming, Christie Lawrence, Jean Silvestri and Laura Hernandez

Abstract

Background: CPAP is used as a method to support ventilation and oxygenation in pre-term infants. In addition to having an immature respiratory system, pre-term infants also have very immature and fragile skin. The interfaces most commonly used with CPAP devices are known to cause pressure injuries in this patient population. The aim of this quality improvement project was to develop a multidisciplinary team to reduce the incidence of device related hospital-acquired pressure injuries (HAPI) in the NICU due to Q3 of 2014 presenting with an increased Stage II rate.

Methods: A multidisciplinary team formed and evaluated risk factors for pressure injuries. A key driver diagram (see Figure 1) was created with the following primary drivers: 1. Skin integrity by providing education to identify pressure injury, applying skin protectant, and introducing an RT/RN coordinated skin assessments. 2. Evaluation of interface by alternating the interfaces of mask and prongs, adopting Bubble CPAP (BCPAP), encouraged a decreased usage of mask (due to fixation limitations), changing interfaces only as needed due to skin protectant. 3. Developed the team by creating a core RT/RN group, encouraged collaboration with wound service, and provided re-education on the usage of BCPAP and skin protectant. 4. Event review, communication, and awareness by implementing reporting process for skin concerns, reviewed events at multidisciplinary meetings, and displayed 'I'm bubbling' sign outside of patient's room. The outcome measure is the rate of HAPI per NICU patient census. Plan-Do-Study-Act (PDSA) cycles to test and learn from change were utilized. After the first PDSA cycle was complete HAPIs were continued to be noted. Upon completion on the second PDSA cycle HAPIs were eliminated; therefore, the team maintained the current assessment and patient care routine.

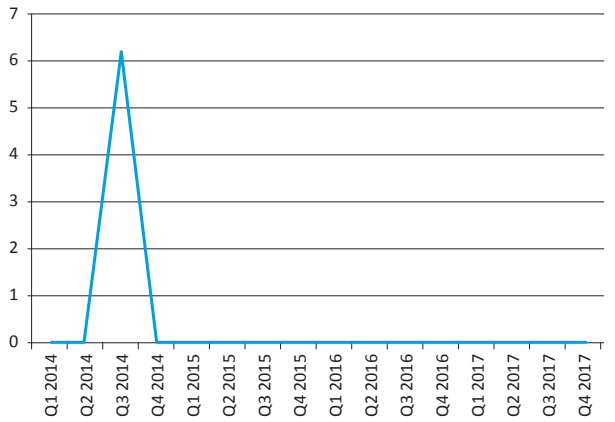


Figure 1. Stage II HAPI Rate

Results: Quarter 3 of 2014 had an increase in device related HAPI in the NICU with a rate of 6.12. All subsequent quarters have maintained a HAPI rate of zero. It was noted that with over 3,100 BCPAP days per year, there was no increase in HAPI.

Conclusions: Based on the above mentioned interventions our team has eliminated device related HAPI. We continue to monitor skin integrity with RT and RN simultaneously; assessing includes in and around nares, behind and in ears, and entire head. We continue to review literature and develop a best practice guideline for the utilization of BCPAP in premature infants.

Submitted by Respiralogics, A Global Respiratory Solutions, Inc Company, 3545 Airway Drive, Suite 104, Reno, Nevada, USA.

Does Prenatal Exercise Affect the Fetus?

Daniel Plotkin, BS, and Esther Petrikovsky, BS

For much of relatively recent human history, pregnancy was considered a state much too fragile to risk exercise that could potentially cause injury to the mother or fetus. However, in the last 25 years, attitudes have dramatically shifted. The safety and potential benefits of exercise to mother and fetus have been validated by a sufficient body of literature. However, the majority of pregnant women still do not exercise as much as the American College of Obstetricians and Gynecologists (ACOG) recommends.[1]

Recommended Guidelines

The ACOG publishes committee opinions on exercise for pregnant women and has updated its stance several times in the last few decades. The most recently published opinion is from 2015, where it was determined that physical activity during pregnancy has minimal risks and has been shown to be beneficial for most pregnant women. Additionally, women who were inactive prior to pregnancy may begin an exercise program during pregnancy, but should progress gradually. Women who were highly active prior to pregnancy may continue exercise at their previous levels of intensity.[2]

Addressing Main Fetal Safety Concerns

Exercise has shown to be very well-tolerated by the fetus, however, individuals must be informed of potential concerns and make an informed decision about their participatory capacity. One common concern is the effect of aerobic exercise (AE) on uterine blood flow and the potential for fetal hypoxia. During maternal exercise, observed responses in fetal heart rate exhibit a modest increase followed by a reduction. However, while uncommon, post-exercise fetal bradycardia has been observed.[3] The cause of the response is unknown, but it may be due to a vagal reflex, cord compression, fetal head malposition, or a combination of these factors. However, this observation isn't accompanied by any increased risk on the fetus.[3] Studies which analyze umbilical blood flow with Doppler velocimetry report similar safety outcomes. The preponderance of data, as evidenced by a recent meta-analysis points toward a nonsignificant change in hemodynamics, related to placental perfusion during maternal exercise.[4] The difficulty in using Doppler velocimetry is that measurements can only be feasibly taken before and after exercise. This means that intra-exercise responses may be missed and, therefore, results are interpreted with a critical lens. Nonetheless, current evidence gives reassurance that there is a margin of safety embedded within maternal/fetal physiology as it relates to fetal perfusion.

Another cause for concern is maternal hyperthermia during exercise, which could potentially cause harm to the fetus. Studies in the animal model have observed that maternal hyperthermia can be teratogenic, especially when exposure occurs during the first trimester.[5] Research has indicated that exercise can result in core temperatures above the recommended 38.9°C (102°F).[6] However, current data does not suggest that the average woman exercises to a level of exertion that causes significant hyperthermia.[5,7] Additionally, human data from retrospective studies and sauna bath exposure studies are not conclusive.[5] Consequently, due to mechanistic plausibility and animal data, it may be prudent that exercising mothers be mindful of not engaging in activities that would exceed the specified body temperature threshold.

Supine exercise is another common concern for the safety of the fetus of an exercising mother. While uterine blood flow does decrease during supine exercise, evidence suggests the fetus is able to tolerate it well.[8] Vasoconstriction during supine rest is largely responsible for a decrease in uterine blood flow. However, supine exercise increases cardiac output, blood pressure, and venous return, which increases uterine blood flow to a level significantly above that observed at supine rest in healthy, fit, late-pregnant women. Consequently, supine rest has been shown to decrease uterine blood flow at twice the amount as supine exercise and is not recommended.[8] There seems to be insufficient evidence for recommending against supine exercise of the duration in which recreational exercisers would participate. However, while the topic remains contentious, the ACOG recommends avoiding the supine position as much as possible.[2]

Potential Benefits

It has been shown that AE leads to better controlled gestational diabetes and potentially reduces its incidence.[9,10] While significant increases in glucose tolerance have been observed, along with a lower requirement of insulin in those that are insulin dependent,[10] several previous review articles have concluded that there is insufficient evidence to support physical activity during pregnancy as an effective intervention to decrease the risk of developing gestational diabetes.[11-13] While the most recent review article did find significant reductions in the development of gestational diabetes, controversy still exists.[9] Nonetheless,

Daniel Plotkin, BS in Family, Nutrition and Exercise Sciences, Queens College. Esther Petrikovsky, BS in Family, Nutrition and Exercise Sciences, Queens College.

more successful glycemic management, even below thresholds diagnostic of diabetes, may mitigate risk of increased birth weight, neonatal hypoglycemia, and elevated cord-blood serum c-peptide.[14]

Other potential benefits relate to hypertension and preeclampsia. Observational data has shown an inverse relationship between physical activity and blood pressure in pregnant women,[15] and preeclampsia risk is inversely associated with maternal physical activity before and/or during pregnancy.[16,17] However, while randomized controlled trials have shown significant reductions in blood pressure, they have not consistently shown that preeclampsia risk is reduced with exercise during pregnancy.[18]

Several studies have found that exercise during pregnancy may also have psychological benefits. Recreational physical activity has also been linked to improvements in emotional well-being and reductions in depression, stress, and anxiety.[19,20]

Resistance training (RT) or weight training is understudied in pregnancy, but has its own potential benefits. A common complaint during pregnancy, especially in the susceptible, is low back pain, which has been shown to decrease with RT during pregnancy.[21] RT increases muscular strength, endurance, and flexibility in pregnant women safely and efficiently.[22] RT is also known to be effective in increasing glycemic control and can even reduce insulin requirements in women who have gestational diabetes.[23]

Based on the research, as well as the current recommended guidelines, exercise is safe and beneficial for the mother and the fetus. However, as contraindications do exist, it is important for pregnant women to consult their physicians before partaking in an exercise regimen.

References

1 Borodulin KM, Evenson KR, Wen F, Herring AH, Benson AM. Physical Activity Patterns During Pregnancy. Med Sci Sports Exerc. 2008; 40(11): 1901-8.

2 Physical Activity and Exercise During Pregnancy and the Postpartum Period. Committee Opinion No. 650. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2015; 126:e135-42.

3 Carpenter MW, Sady SP, Hoegsberg, B, et al. Fetal heart rate response to maternal exercise. JAMA. 1998; 259(20): 3006-9.

4 Skow RJ, Davenport MH, Mottola MF, Davies GA, Poitras VJ. Effects of prenatal exercise on fetal heart rate, umbilical and uterine blood flow: a systemic review and meta-analysis. Br J Sports Med. 2018; doi: 10.1136/bjsports-2018-099822.

5 McMurray RG, Katz VL. Thermoregulation in Pregnancy. Implications for Exercise. Sports Med. 1990;10(3): 146-58.

6 Gleeson M. Temperature regulation during exercise. Int J Sports Med. 1998; 19:S96-S99.

7 Jones RL, Botti JJ, Anderson WM, Bennett NL. Thermoregulation during aerobic exercise in pregnancy. Obstet Gynecol. 1985;65(3):340-345.

8 Jeffreys RM, Stepanchak W, Lopez B, Hardis J, Clapp JF 3rd. Uterine blood flow during supine rest and exercise after 28 weeks of gestation. BJOG. 2006; 113(11):1239-47.

9 Yu Y, Xie R, Shen C, Shu L. Effect of exercise during pregnancy to prevent gestational diabetes mellitus: a systematic review and meta-analysis. The Journal of Maternal-Fetal & Neonatal Medicine. 2018; 31(12):1632-1637.

10 Deierlein AL, Siega-Riz AM, Evenson KR. Physical activity during pregnancy and the risk of hyperglycemia. J Womens Health (Larchmt). 2012;21:769-75

11 Han S, Middleton P, Crowther CA. Exercise for pregnant women for preventing gestational diabetes mellitus. Cochrane Databases Syst Rev. 2012; 7:CD009021

12 Ruchat SM, Mottola MF. The important role of physical activity in the prevention and management of gestational diabetes mellitus. Diabetes Metab Res Rev. 2013; 29: 334-46.

13 Yin YN, Li XL, Tao TJ, Luo BR, Liao SJ. Physical activity during pregnancy and the risk of gestational diabetes mellitus: a systemic review and meta-analysis of randomized controlled trials. Br J Sports Med. 2014; 48:290-5.

14 The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358:1991-2002.

15 Yeo S, Steele NM, Chang MC, Leclaire SM, Ronis DL, Hayashi R. Effect of exercise on blood pressure in pregnant women with a high risk of gestational hypertensive disorders. J. Reprod. Med. 2000; 45:293-298.

16 Saftlas AF, Logsden-Sackett N, Wang W, Woolson R, Bracken MB. Work, leisure-time physical activity, and risk of preeclampsia and gestational hypertension. Am. J. Epidemiol. 2004; 160:758-765.

17 Sorensen TK, Williams MA, Lee IM, Dashow EE, Thompson ML, Luthy DA. Recreational physical activity during pregnancy and risk of preeclampsia. Hypertension. 2003; 41(6):1273-80.

18 Magro-Malosso ER, Saccone G, Di Tommaso M, Roman A, Berghella V. Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2017; 96(8):921-931.

19 Marquez-Sterling S, Perry AC, Kaplan TA, Halberstein RA, Signorile JF. Physical and psychological changes with vigorous exercise in sedentary primigravidae. Med. Sci. Sports Exerc. 2000; 32:58-62.

20 Gaston A, Prapavessis H. Tired, moody and pregnant? Exercise may be the answer. Psychol Health. 2013; 28:1353-1369.

21 Garshasbi A, Faghih Zadeh S. The effect of exercise on the intensity of low back pain in pregnant women. Int J Gynaecol Obstet. 2005; 88(3): 271-5.

22 O'Connor PJ, Poudevigne MS, Cress ME, Motl RW, Clapp JF 3rd. Safety and efficacy of supervised strength training adopted in pregnancy. J Phys Act Health. 2011; 8(3): 309-320.

23 de Barros MC, Lopes MA, Francisco RP, Sapienza AD, Zugaib M. Resistance exercise and glycemic control in women with gestational diabetes mellitus. Am J Obstet Gynecol. 2010; 203(6):556e1-556e6.

High Versus Low-Value Care in Neonatal Intensive Care Unit

Shabih Manzar, MD

Recently Basset and Rowinsky [1] describe how certain decisions taken by the physician results in low-value care. They describe a 5 day old infant who had one investigation followed by other resulted in unnecessary medical intervention. Septic work up included urinary tract infection (UTI) screen was performed and phototherapy was instituted at a level of 19.8 mg/dl that resulted in unwarranted hospital admission. Similar tendency has been observed in neonatal intensive care unit (NICU). We present a case on a premature infant that highlights on the need for critical thinking and high-value care.

Case

Infant was Twin B, female, born to a 34-year old gravida 7, para 2 mother. All antenatal labs including HIV, Hepatitis B, and rapid plasma reagin were negative. There was no history of sexually transmitted diseases. Pregnancy was complicated by poor fetal growth. Twin A, male has normal intrauterine growth. Cesarean section was done at 34 weeks of gestation. Apgar scores were 8 and 9 at one and five minutes respectively for twin B. Infant's birth weight was 1500 grams (2.56%, Z= -1.95 on Olsen Growth Chart), head circumference 27.5 centimeters (2.56%, Z= -2.24 on Olsen Growth Chart) and length of 37.5 centimeters (0.37%, Z= -2.68 on Olsen Growth Chart). As infant was symmetrical growth restricted in these measurements the on-call practitioner sent the TORCH titer test (further including urine and PCR test for Cytomegalovirus).

Next morning on careful review of the maternal chart, it was noted that fetal Doppler study was abnormal on twin B (S/D ratio 4.03, RI 0.73 and PI 1.25) indicating utero-placental insufficiency. Placental pathology was also suggestive of insufficiency (low placental weight of 520 grams, < 10th percentile for 34 weeks gestational age). No chorioamnionitis or funisitis were noted.

After reviewing these two reports, it is inferred that the growth restriction observed in twin B was most likely due to placental insufficiency rather than congenital infection. Also as twin A has normal growth it will be less likely to be a hematogenous CMV or Toxoplasmosis infection while he shared the same maternal blood.

The phenomenon of value care is well described by Dewan et al.[2] They highlighted on the need for training high-value care. They pointed out that this training should occur in pediatric residency. Once good, high-value, evidence based practice is incorporated during training it will become the part of day to day management plan resulting in quality care.

In summary, training and education are needed at all levels of medical practice to make sure we don't end up with the domino effect of low-value care, especially in NICU.

Contributed by Shabih Manzar, MD, Children's Hospital at Erlanger, 910 Blackford St, Chattanooga, TN 37403. Email : shabihman@hotmail.com.

References

1 Bassett HK, Rowinsky P. The snowball effect of low-value care. Hospital Pediatrics 2018; 793-795; DOI: 10.1542/hpeds.2018-0050

2 Dewan M, Herrmann LE, Tchou MJ, et al. Development and evaluation of high-value Pediatrics: A high-value care pediatric resident curriculum. Hospital Pediatrics 2018; 785-792; DOI: 10.1542/hpeds.2018-0115

Suggested reading

1 Johnson KE. Overview of TORCH infection. UpToDate, Sep 19, 2017

2 Boom JA. Microcephaly in infants and children: Etiology and evaluation. UpToDate, Nov 9, 2018

3 Resnik R. Fetal growth restriction: Evaluation and management . UpToDate, Oct 10, 2018

Cultural Influences in Infant Feeding

Sandra Sundquist Beauman, MSN, RNC-NIC, CNS

Introduction

Infant feeding practices can impact diet and health for the remainder of one's life. The evidence that supports the health benefits of providing human milk is plentiful. In addition to the scientific evidence, there are many things that may influence a mother or family's decision to supplement human milk with formula. In some cases, the scientific evidence is not well-communicated. In addition, we find that the practice of supplementing breastfeeding often varies by culture. Many cultures also supplement the infant feeding with solid foods very early in life. These practices will be reviewed by cultural group in this article as well as the effect this has on the mother's and infant's health later in life.

Benefits of providing human milk

Many scientific studies demonstrate that breastfeeding and human milk provide not only optimal nutrition, but also protect infants from infection and disease and play an important role in brain development with improved cognitive ability related to length of exclusive breastfeeding.[1] Infants who are never breastfed are more at risk for respiratory illness, ear infection, diarrhea, urinary tract infection, asthma and sudden infant death syndrome, to name a few.[2]

Sankar et al,[3] in a systematic review, demonstrated substantially lower rates of mortality among infants exclusively breastfed in the first six months of life, with an 88% reduction of mortality in comparison to infants that had never been breastfed, primarily in low and medium income countries.

Disparities still exist between socioeconomic (SEC) groups with much lower initiation rates at 57% in low SEC groups and 74% in higher SEC groups.[4] Disparities also are present in minority groups. While rates are increasing, the Healthy People 2020 goals of 81.9% to initiate breastfeeding is only met by one ethnic group, Hispanic and only for initiation of breastfeeding. Rates are lowest in the Black, Hawaiian/Pacific Islander and Native American groups.[5]

Azad, Vehling and colleagues[6] conducted a study concerning infant feeding and weight gain. They compared breastfeeding, bottle feeding formula vs breast milk and the addition of solid foods. They found that breastfeeding was inversely related to weight gain velocity, BMI and overweight during infancy. Early formula feeding during hospitalization did not affect weight gain velocity and BMI as long as breastfeeding was initiated and sustained for at least three months. Interestingly, they found this association was dose dependent, diminished with formula supplementation and was weaker when milk was pumped and fed from a bottle. They hypothesize that expressing and storing breast milk could reduce its bioactivity, feeding from a bottle may discourage self-regulation and even brief formula supplementation could potentially alter the developing gut microbiota and influence weight gain. Introducing solid foods before five months was associated with higher BMI but this did not hold true if solid foods were introduced after six months. Other studies have also shown higher BMI and rapid weight gain with the early introduction of solid foods.[7,8]

Cultural Beliefs

It is important to stress that as cultural beliefs are reviewed, they should not be applied universally. The mother or family being in their homeland or having immigrated to the United States (US) may change their cultural practices as well as how long they have been in the US. Foreign-born mothers, particularly from low-income countries generally have higher breast feeding rates and breast feed longer than do US born mothers from the same culture. Gibson-Davis & Brooks-Gunn[9] reported that Hispanic women born outside of the US had a greater likelihood of breastfeeding with the odds of breastfeeding reduced by 4% for each year that the parents reside in the US Black populations such as African or Caribbean have higher rates of breastfeeding than African-Americans.[10]

Newly immigrated women are often at a disadvantage regarding pumping and storage of breast milk. It is a foreign concept to many that breast milk can be pumped and stored for feeding at another time when the mother is not present. Given less extended family support, this may be an important influence on length of exclusive breast milk provision, particularly if the mother must return to work or school.

The principle of hot or cold is prevalent in many cultures around the world. This follows the humoral theory of illness cause and treatment such that there should be a balance of energy viewed as hot and cold or wet and dry.[11] In other cultures, this is referred to as yin and yang, am and duong for Southeast Asia or simply caliente and frio for Hispanic cultures. In Honduras, where

Sandy Sundquist Beauman, MSN, RNC-NIC, CNS, a neonatal nurse with more than 30 years of experience, is a research nurse coordinator at the University of New Mexico. She is also an independent consultant with Medela, LLC. and provides neonatal consultation and continuing education through CNS Consulting.

breast milk is considered "hot," mothers avoid hot activities such as sitting in the sun, exercise or strong emotions like anger or unhappiness. For Asian mothers where pregnancy is considered a state of excessive heat, birth signifies the loss of heat. Postpartum practices are centered around replenishing this heat. Cold foods are avoided, they often choose to stay indoors in a very warm environment eating specific warm foods. If cultural practices and adequate support is not present, mothers may choose not to breastfeed as this signifies additional loss of heat potentially putting the mother at risk of suffering from a "cold" disease and exposing the infant to unhealthy breast milk.

Among the Mende in Sierra Leone, sexual intercourse while breastfeeding is thought to cause diarrhea in the infant so many mothers choose to wean early to avoid questions about their morality.[11]

Human milk is regarded as the source of life and is vulnerable to becoming tainted by the "evil eye" or "shadow" if the mother goes out where this might be likely to happen. Therefore, if they must go out, they may be compelled to stop breastfeeding to prevent this.

Called different names in different cultures–afatanbah/Umol bah in Somalia, d'sai kchey in Cambodia, and Chollish din in Bengali–many societies practice a 30- to 40-day postpartum period of intensive family support that keeps the mother and infant indoors to receive healing rituals and nurturing.[11] Such practices have supported postpartum maternal survival in less advantaged societies. This period also permits sanctioned support by family and friends to help the mother and infant focus on bonding and breastfeeding. Migration to the US without establishment of a new supporting community disrupts this cultural network of support, and the lack of this support system has been identified as an important factor that may result in stopping breastfeeding.

This period may also be seen as a period where it is important to protect from the "evil eye".[11] Human milk is regarded as the source of life and is vulnerable to becoming tainted by the "evil eye" or "shadow" if the mother goes out where this might be likely to happen. Therefore, if they must go out, they may be compelled to stop breastfeeding to prevent this.

Native American

Most studies involving Native Americans show high initiation rates and support from important people in the mother's life for breastfeeding. However, Eckhardt et al[12] found a lack of knowledge regarding the specific benefits of breastfeeding for the infant, particularly the benefits related to obesity and type II diabetes, both of which are significant issues in this population. They also found a tendency to introduce solid foods early on which can have an impact on continued breastfeeding and specifically milk production and has been shown to increase the risk of obesity later in life as already mentioned.

Wright and colleagues[13] studied the breastfeeding culture of the Navajo Nation and found 81% of the women interviewed breastfed their infants at hospital discharge. However, 62% of them gave formula within the first week. The beliefs they had were generally supportive of breastfeeding and included that breastfeeding:

- Was provided by the Holy People as the proper way to feed an infant
- Provides the original symbol of relationships between people, and models the sharing of food
- Passes on maternal attributes
- Promotes growth and development
- Makes the child feel loved and secure
- Promotes self-discipline and a better life

The Navajo culture is matrilineal meaning that inheritance is through the maternal line. Many families would live close to the mother's family. Grandmothers were generally supportive of breastfeeding and when questioned, many women did not know the father's attitude about breastfeeding. They focused primarily on the benefit to the infant, not to the mother. Some voiced the opinion that breastfeeding caused the mother to gain weight. How to manage problems with breastfeeding was not generally addressed nor were the maternal benefits to breastfeeding. Not having adequate information may lead to early termination of breastfeeding.

Reasons were elicited regarding why women did not initiate breastfeeding and why formula was started. The top reason for stopping breastfeeding was that the baby didn't want or like the breast. Most likely, this was related to the early introduction of the bottle which led to a perceived preference to the artificial nipple. Another reason for stopping breastfeeding was insufficient milk which may speak to the lack of knowledge on how to increase milk supply as well as the early introduction of formula and therefore less frequent breastfeeding.

At the time of this study, breastfeeding support in the hospitals was lacking as well. All of these women would have delivered at an Indian Health Services Hospital. Breastfeeding support and rates have increased in this population but are still lower in this ethnic group than in whites or Hispanics.[5]

African American

In-depth ethnography reveals a value for independence among inner-city, low-income African-American mothers, interpreted as a culturally evolved response to the daily unpredictable stresses and losses in life.[10] Breastfeeding, therefore, is viewed to foster the baby's early dependence on the mother, which potentially would lead to an overly "needy" or "spoiled" personality. In addition, some related the forced role of wet-nursing historically as an influence on the cultural attitude around breastfeeding.[14,15]

Early introduction of solid foods is often practiced due to the perception of the infant not being full enough (eating too often). Cereal is often added to the bottle resulting in the infant eating less often. Cereal is not thought of as solid food though, simply an addition to the milk. Solid foods like mashed potatoes are often introduced within a month, sometimes as early as one to three weeks. Bottled baby food is usually introduced much later. In one study,[16] teen African American mothers who were interviewed knew that solids should not be introduced until six months but grandmothers had a strong influence over what the infant was fed. At least in one interview, the grandmother admitted to feeding solids when the mother was unaware.

Nommsen-Rivers et al[17] found that comfort with formula feeding explained 37% of racial differences in breastfeeding intention. Women also pointed to the ease and convenience of formula—it is consistently available, often provided for free by Women, Infants and Children (WIC) nutrition services, and can be prepared by any caregiver—as motivation to choose this method of infant feeding.[17,18,19]

Hispanic

Practices of Hispanic populations vary greatly by specific areas of the world, since Hispanic encompasses a widely heterogenic population. One source (www.pewhispanic.org) lists the 10 largest Hispanic origin groups as Mexicans, Puerto Ricans, Salvadorans, Cubans, Dominicans, Guatemalans, Colombians, Hondurans, Ecuadorians and Peruvians. As one can see, these categories cover a wide range of people and likely different cultures. Just because they share a language, customs and practices may be quite different.

Breastfeeding rates are higher in Hispanics outside the US. Rates in Mexico in 1999 were reported as greater than 90% initiating breastfeeding and 33% still breastfeeding at one year postpartum.[11] Harley, Stamm & Eskenazi[20] found that length of time in the US for Mexican women specifically resulted in a decreased length of exclusive breastfeeding. This varied from exclusive breastfeeding for two months in women who had lived in the US for less than five years to those having lived in the US for more than 11 years breastfeeding exclusively for only one week. Anderson et al[21] found that this trend in decreased breastfeeding or time of exclusive breastfeeding did not apply to the Puerto Rican Hispanic population. This group, in the Anderson study, had no difference in breast feeding initiation or duration related to length of time in the US. High rates of breastfeeding among Hispanic mothers has been offered to help explain the "Hispanic paradox," in which health outcomes are better than might be expected based on socioeconomic status, an effect attributed to the protective effects of breastfeeding.[22]

Breastfeeding rates are higher in Hispanics outside the US. Rates in Mexico in 1999 were reported as greater than 90% initiating breastfeeding and 33% still breastfeeding at 1 year postpartum.

Adding cereal early on is common as some Hispanic mothers say infants feel fuller, gain more weight, have better nutrition and are calmer and sleep longer when cereals are added to the bottle.[23] Hispanic mothers of Mexican descent may still have some beliefs effecting breastfeeding such as reducing or ceasing breastfeeding due to beliefs about anger or fright that is believed to be transferred to the milk and result in illness or diarrhea in the infant.[11]

In a study by Lindsay and associates,[24] 29 Brazilian immigrant mothers were interviewed. The Brazilian immigrant population is at high risk for obesity at 48.2% so breastfeeding is viewed as important to decrease this risk. All 29 of these mothers initiated breastfeeding. However, it was often non-exclusive breastfeeding of relatively short duration at less than 4 months. In addition, they introduced solid foods early, serving juices and adding cereal when bottles were fed, practices linked with higher rates of obesity. In addition, this practice of early supplementation serves to decrease direct suckling at the breast and therefore, decreases the mother's milk supply resulting in less milk available and early termination of breastfeeding.

Chinese

In an integrative review of studies about Chinese immigrant families and breastfeeding practices, eight studies took place in Australia with one each in Canada, Ireland and the US.[25] The Chinese population has a higher risk of developing cardiovascular disease and type II diabetes at a lower BMI. Therefore, the protective effect to the mother of breastfeeding may be more important. It is not known why this is but may be related to genetic differences in body composition and metabolic responses. Studies in Australia showed high initiation rates from 53.2% to 94.1% with rates dropping to around 34% by three months and in one study to 6% by six months. In most cases, breastfeeding is not exclusive. Formula is often added within days or may be the first feeding for the infant due to beliefs about the colostrum not being good for the infant.[11]

Positive beliefs about breastfeeding included "breastfeeding is natural," "provided the best nutrition for the infant for growth and health." The study done in Canada revealed that mother's were concerned about their infant's weight and size. Perceived poor growth was believed to be related to either low quality milk or not enough milk. This belief that a fat baby is a healthy baby was common across other studies and if they felt their infant was not getting enough milk, formula was given. That might be in the form of changing to exclusive formula feeding or a mixed feeding of both formula and breastfeeding.

Negative attitudes about breastfeeding included being an embarrassing practice in public, adverse to the mother's figure, father feeling left out, bottle feeding reducing the risk of neonatal infections, and breastfeeding babies becoming too attached to the mother. In the Ireland study, concerns included that benefits of breastfeeding only last until the infant is weaned, that mothers should not breastfeed if they have a cold and that infant formula should be fed to all newborns. Not surprisingly, those mothers who had these negative feelings were less likely to breastfeed or breastfed for a shorter amount of time. It was not uncommon for formula to be introduced in the absence of these negative feelings within the first three months of life. This might be done for reasons such as to familiarize the infant with formula or to prevent problems when breastfeeding was reduced or stopped.

Solid foods were often introduced as early as three months and included traditional Chinese foods. Perceived benefits included that it would make the infant's bones stronger, make them feel fuller/sleep better, help them learn how to swallow foods other than milk, lead to steady or accelerated growth and improve the digestive system of the baby based on the appearance of the infant's stools.

The Chinese culture practices the yin-yang theory (theory of hot and cold) and zuo yuezi (sitting in for the first month or doing the month). During the zuo yuezi period "hot" foods (protein rich) and "cold" foods (fruits and vegetables) are eaten in balance. Specific protein rich food like fish, chicken, pork, duck and rabbit were believed to address breastfeeding issues such as low milk supply. Mothers perceptions about breast milk was determined by their beliefs of physical health and restoring balance of the body.

At least five of the 11 studies found that the longer Chinese immigrant mothers were in their new country, they were more likely to breastfeed longer and adopt local feeding practices which resulted in positive infant outcomes.[25] This is in contrast to other cultural groups whose immigration leads to lower breastfeeding rates.

Family support is important in this population. Mothers need to align fathers' preference as well as opinions of extended families. Advice from health care professionals is also acknowledged and evidence shows that traditional medical practitioners in China advise exclusive breastfeeding during the time of zuo yuezi. It is also important to note that most mothers participating in all 11 of these studies reviewed were relatively affluent, highly educated and aged 22 to 59 years old at the time they were interviewed. Most did not work outside the home and had lived in their country of immigration for at least five years. Their beliefs and practices may be different from other Chinese immigrant groups.

Conclusion

Several cultural practices and beliefs of various ethnic groups have been reviewed in this article. Again, it is important not to assume that the beliefs of the culture are the beliefs of the individual. Ask about their beliefs and preferences and then provide support and education as some beliefs may not be based on scientific information. Effective interventions are those that incorporate understanding of the cultural beliefs of the population being served. Support from their own peer or ethnic groups have been found to be helpful. Another important point is that early supplementation should be avoided, including formula and solid foods. The addition of solid foods before six months decreases time of breastfeeding duration and leads to increased weight gain and higher BMI which may last a lifetime.

The study in the Navajo communities[13] reported on an intervention to impact breastfeeding rates. This study first identified actual practices and cultural beliefs about infant feeding. The intervention this group designed consisted of three components. First, hospital practices were implicated in the early introduction of formula so these practices were addressed to provide support and education for breastfeeding while mothers and infants were inpatient. A community intervention was undertaken to involve community members in defining and solving problems, to use existing structures and programs in breastfeeding promotion. A final part of the intervention occurred at the level of the individual mother and her family, focusing on the provision of culturally sensitive educational materials and assistance in addressing physical and logistic barriers to breastfeeding. Perhaps most importantly, the investigative team in this project included some Navajo students. These students were part of the community and therefore, the message was culturally appropriate.

Finally, this quote from a paper published by the United States Public Health Service in 1968 still seems applicable. "…all different cultures, whether in a tropical village or in a highly urbanized and technologically sophisticated community, contain some practices and customs which are beneficial to the health and nutrition of the group, and some which are harmful. No culture has a monopoly on wisdom or absurdity."

References

1. Horwood LJ, Darlow BA, Mogridge N. Breast milk feeding and cognitive ability at 7–8 years. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2001 Jan 1;84(1):F23-7.
2. Ip S, Chung M, Raman G, et al. Breastfeeding and maternal and child health outcomes in developed countries. AHRQ Publication No. 07-E007; 2007.
3. Sankar MJ, Sinha B, Chowdhury R, et al. Optimal breastfeeding practices and infant and child mortality. A systematic review and meta-analysis. Acta Paedia 2015;104:3-13.
4. Louis-Jacques A, Deubel TF, Taylor M, Stuebe AM. Racial and ethnic disparities in US breastfeeding and implications for maternal and child health outcomes. InSeminars in perinatology 2017 Aug 1 (Vol. 41, No. 5, pp. 299-307). WB Saunders.
5. Rates of any and exclusive breastfeeding by sociodemographics among children born in 2015. https://www.cdc.gov/breastfeeding/data/nis_data/results.html; 2019Accessed1.10.2019.
6. Azad MB, Vehling L, Chan D, Klopp A, Nickel NC, McGavock JM, Becker AB, Mandhane PJ, Turvey SE, Moraes TJ, Taylor MS. Infant feeding and weight gain: separating breast milk from breastfeeding and formula from food. Pediatrics. 2018 Oct 1;142(4):e20181092.
7. Forbes JD, Azad MB, Vehling L, Tun HM, Konya TB, Guttman DS, Field CJ, Lefebvre D, Sears MR, Becker AB, Mandhane PJ. Association of exposure to formula in the hospital and subsequent infant feeding practices with gut microbiota and risk of overweight in the first year of life. JAMA pediatrics. 2018 Jul 1;172(7):e181161-.
8. Seach KA, Dharmage SC, Lowe AJ, Dixon JB. Delayed introduction of solid feeding reduces child overweight and obesity at 10 years. International journal of obesity. 2010 Oct;34(10):1475.
9. Gibson-Davis CM, Brooks-Gunn J. Couples' immigration status and ethnicity as determinants of breastfeeding. American Journal of Public Health. 2006 Apr;96(4):641-6.
10. Reeves EA, Woods-Giscombé CL. Infant-feeding practices among African American women: Social-ecological analysis and implications for practice. Journal of Transcultural Nursing. 2015 May;26(3):219-26.
11. Pak-Gorstein S, Haq A, Graham EA. Cultural influences on infant feeding practices. Pediatrics in review. 2009 Mar 1;30(3):e11.
12. Eckhardt CL, Lutz T, Karanja N, Jobe JB, Maupomé G, Ritenbaugh C. Knowledge, attitudes, and beliefs that can influence infant feeding practices in American Indian mothers. Journal of the Academy of Nutrition and Dietetics. 2014 Oct 1;114(10):1587-93.
13. Wright AL, Naylor A, Wester R, Bauer M, Sutcliffe E. Using cultural knowledge in health promotion: breastfeeding among the Navajo. Health Education & Behavior. 1997 Oct;24(5):625-39.
14. Asiodu, I., & Flaskerud, J. (2011). Got milk? A look at breastfeeding from an African American perspective. *Issues in Mental Health Nursing*, *32*, 544–546. doi:10.3109/01612840.2010.544842
15. Mattox, K. (2012). African American mothers: Bringing the case for breastfeeding home. *Breastfeeding Medicine*, *7*(5), 343–345. doi:10.1089/bfm.2012.0070
16. Bentley M, Gavin L, Black MM, Teti L. Infant feeding practices of low-income, African-American, adolescent mothers: an ecological, multigenerational perspective. Social science & medicine. 1999 Oct 1;49(8):1085-100.
17. Nommsen-Rivers LA, Chantry CJ, Cohen RJ, Dewey KG.

Comfort with the idea of formula feeding helps explain ethnic disparity in breastfeeding intentions among expectant first-time mothers. Breastfeeding Medicine. 2010 Feb 1;5(1):25-33.
18. Kaufman L, Deenadayalan S, Karpati A. Breastfeeding ambivalence among low-income African American and Puerto Rican women in north and central Brooklyn. Maternal and child health journal. 2010 Sep 1;14(5):696-704.
19. Robinson K, VandeVusse L. Exploration of African-American women's infant feeding choices. Journal of National Black Nurses' Association: JNBNA. 2009 Dec;20(2):32-7.
20. Harley K, Stamm NL, Eskenazi B. The effect of time in the US on the duration of breastfeeding in women of Mexican descent. Maternal and Child Health Journal. 2007 Mar 1;11(2):119-25.
21. Anderson AK, Damio G, Himmelgreen DA, Peng YK, Segura-Perez S, Perez-Escamilla R. Social capital, acculturation, and breastfeeding initiation among Puerto Rican women in the United States. Journal of Human Lactation. 2004 Feb;20(1):39-45.
22. McCann MF, Baydar N, Williams RL. Breastfeeding attitudes and reported problems in a national sample of WIC participants. Journal of Human Lactation. 2007 Nov;23(4):314-24.
23. Ashida S, Lynn FB, Williams NA, Schafer EJ. Competing infant feeding information in mothers' networks: advice that supports v. undermines clinical recommendations. Public health nutrition. 2016 May;19(7):1200-10.
24. Lindsay AC, Wallington SF, Greaney ML, Hasselman MH, Tavares Machado MM, Mezzavilla RS. Brazilian immigrant mothers' beliefs and practices related to infant feeding: A qualitative study. Journal of Human Lactation. 2017 Aug;33(3):595-605.
25. Lindsay A, Le Q, Greaney M. Infant feeding beliefs, attitudes, knowledge and practices of Chinese immigrant mothers: an integrative review of the literature. International journal of environmental research and public health. 2017 Dec 23;15(1):21.

Cervical Mass in a Neonate

Shabih Manzar, MD

A female newborn delivered by normal spontaneous vaginal delivery was noted to have 3x4 cm mass of the left side of the neck. She was transferred to level IV NICU for surgical intervention. The only pertinent clinical finding at admission was stridor on moving the neck to the right side. Radiological imaging tests, including MRI, were performed (Figure1).

A surgery was performed and three days later, infant was discharge home on ad lib feeds with a follow up appointment with hem-oncology team. The pathology of the specimen showed a benign immature teratoma.

Cervical neonatal teratoma are rare congenital neoplasms. A careful and timely management approach with adequate follow up is advised.

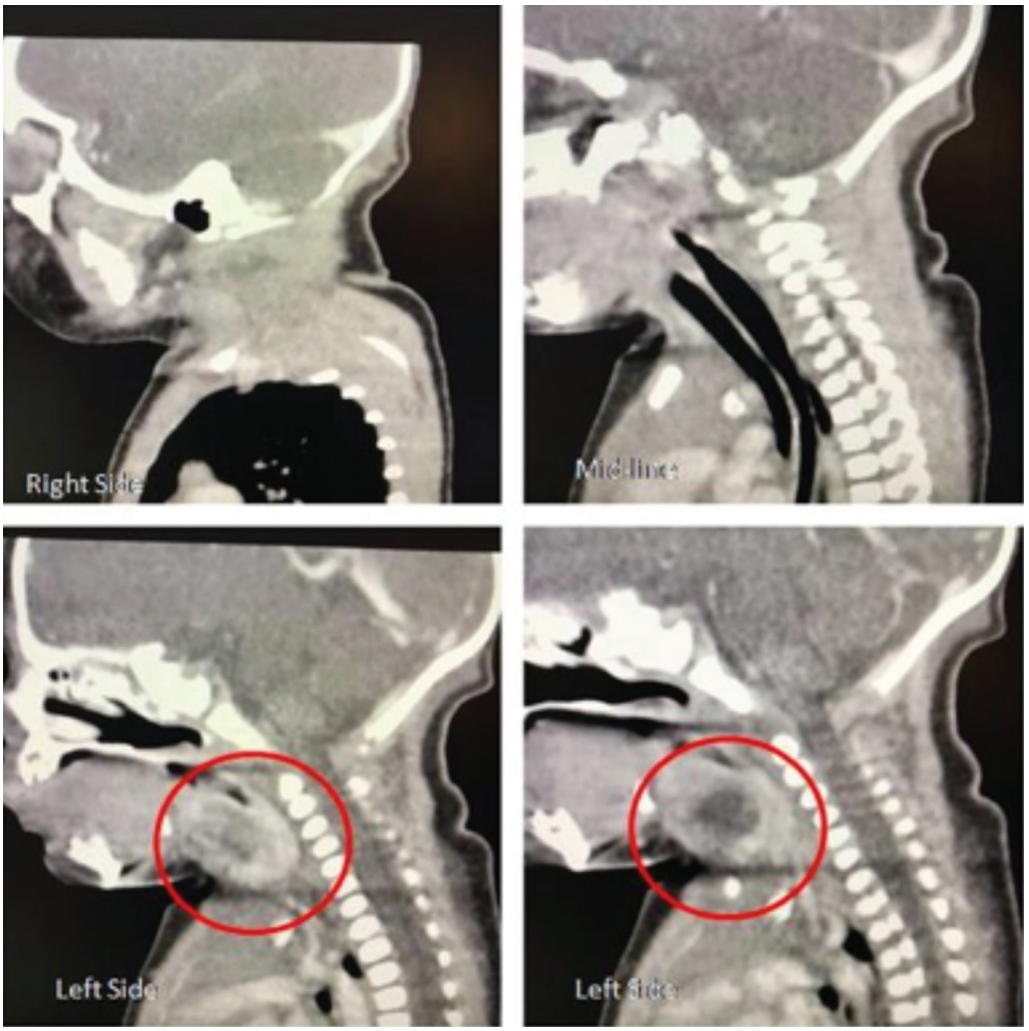


Figure 1. Sagittal MRI images showing the mass on the left side of the neck

Contributed by Shabih Manzar, MD, Children's Hospital at Erlanger, 910 Blackford St, Chattanooga, TN 37403. Email : shabihman@hotmail.com.

Examining High-flow Nasal Cannula for Respiratory Support in Preterm Infants

Chris Campbell

Nasal High Flow (NHF) therapy is increasingly being used as an alternative form of respiratory support in the Neonatal Intensive Care Unit. NHF is a form of noninvasive respiratory support that delivers heated and humidified gas via small nasal cannulae. As use of the therapy increases, more clinicians are seeking evidence to support and understand appropriate use of this therapy.

To answer the question, "In preterm infants, is the use of NHF as effective as other non-invasive methods of respiratory support in preventing chronic lung injury and death?", a Cochrane Review was published in 2016, which included data from fifteen randomized controlled trials (RCTs) comparing NHF to other noninvasive therapies.

Review Methods

Wilkinson et al searched clinical trials databases, conference proceedings and the reference lists of retrieved articles. Selection criteria was randomized or quasi-randomized trials comparing NHF to other noninvasive forms of respiratory support. Studies reported in abstract form were included in the 'Studies awaiting classification' category. Data from one unpublished study (published only in abstract form) were obtained from the authors for inclusion in the review.

Participants were striated by gestational age (GA):

1. < 37 weeks' GA receiving respiratory support after birth, without a prior period of intermittent positive pressure ventilation (IPPV).
2. < 37 weeks' GA receiving respiratory support following a period of IPPV.

NHF was defined as a flow rate greater than 1L/min, and alternative interventions included headbox oxygen, low flow nasal cannula (gas flow rates less than or equal to 1L/min), CPAP, NIPPV or NHF using an alternative technique (ie unhumidified).

Results

The Cochrane Review identifies primary treatment and post-extubation as the two main populations for NHF therapy use.

When used as primary treatment in preterm infants, infants on NHF experienced a longer duration of respiratory support, however there were no differences in other secondary outcomes.

Chris Campbell is the Senior Editor of Neonatal Intensive Care.

"When used as primary respiratory support after birth compared to CPAP (4 studies, 439 infants), there were no differences in the primary outcomes of death (typical risk ratio (RR) 0.36, 95% CI 0.01 to 8.73; 4 studies, 439 infants) or chronic lung disease (CLD) (typical RR 2.07, 95% CI 0.64 to 6.64; 4 studies, 439 infants)," the authors wrote.

When used for post-extubation (total 6 studies, 934 infants), there were no differences between NHF and CPAP in the primary outcomes of death (typical RR 0.77, 95% CI 0.43 to 1.36; 5 studies, 896 infants) or CLD (typical RR 0.96, 95% CI 0.78 to 1.18; 5 studies, 893 infants). In addition, there was no difference in the rate of treatment failure (typical RR 1.21, 95% CI 0.95 to 1.55; 5 studies, 786 infants) or reintubation (typical RR 0.91, 95% CI 0.68 to 1.20; 6 studies, 934 infants).

Infants randomized to NHF had significantly less nasal trauma (typical RR 0.64, 95% CI 0.51 to 0.79; typical risk difference (RD) −0.14, 95% CI −0.20 to −0.08; 4 studies, 645 infants). There was a small reduction in the rate of pneumothorax (typical RR 0.35, 95% CI 0.11 to 1.06; typical RD −0.02, 95% CI −0.03 to −0.00; 5 studies 896 infants) in infants treated with NHF. Subgroup analysis found no difference in the rate of the primary outcomes between NHF and CPAP in preterm infants in different gestational age subgroups, though there were only small numbers of extremely preterm and late preterm infants. One trial (28 infants) found similar rates of reintubation for humidified and non-humidified NHF, and two other trials (100 infants) found no difference between different models of equipment used to deliver humidified NHF.

For infants weaning from non-invasive respiratory support (CPAP), two studies (149 infants) found that preterm infants randomised to NHF had a reduced duration of hospitalisation compared with infants who remained on CPAP."

Conclusions

- The evidence indicates that for preterm infants aged ≥28 weeks' GA, NHF and CPAP are associated with similar efficacy and safety.
- The use of NHF resulted in significantly lower rates of nasal trauma, with no additional risk of adverse events, compared to CPAP.
- For infants <28 weeks, there is limited data and insufficient evidence to change the current practice of using CPAP for post-extubation or primary respiratory support.
- The authors suggest that further RCTs are required to

investigate:

- NHF compared to other forms of primary noninvasive support after birth and for weaning from non-invasive support.
- The safety and efficacy of NHF in extremely preterm and mildly preterm subgroups, and to compare different NHF devices.

References

Studies included in Wilkinson et al. 2016

- Abdel Hady 2011 {published and unpublished data} Abdel-Hady H, Shouman B, Aly H. Early weaning from CPAP to high flow nasal cannula in preterm infants is associated with prolonged oxygen requirement: A randomized controlled trial. Early Human Development 2011;87(3):205–8. [PUBMED: 21276671]
- Badiee 2015 {published data only} Badiee Z, Eshghi A, Mohammadizadeh M. High flow nasal cannula as a method for rapid weaning from nasal continuous positive airway pressure. International Journal of Preventive Medicine 2015;6:33. [PUBMED: 25949783]
- Campbell 2006 {published data only} Campbell DM, Shah PS, Shah V, Kelly EN. Nasal continuous positive airway pressure from high flow cannula versus infant flow for preterm infants. Journalof Perinatology 2006;26(9):546–9. [PUBMED: 16837929]
- Ciuffini 2014 {published data only} Ciuffini F, Pietrasanta C, Lavizzari A, Musumeci S, Gualdi C, Sortino S, et al. Comparison between two different modes of non-invasive ventilatory support in preterm newborn infants with respiratory distress syndrome mild to moderate: preliminary data. La Pediatria Medica e Chirurgica: Medical and Surgical Pediatrics 2014;36(4):88. [PUBMED: 25573704]
- Collins 2013 {published and unpublished data} Collins CL, Barfield C, Davis PG, Horne RS. Randomized controlled trial to compare sleep andwake inpreterm infants less than 32 weeks of gestation receiving two different modes of non-invasive respiratory support. Early Human Development 2015;91(12):701–4. [PUBMED: 26529175] Collins CL, Barfield C, Horne RS, Davis PG. A comparison of nasal trauma in preterm infants extubated to either heated humidified high-flow nasal cannulae or nasal continuous positive airway pressure. European Journal of Pediatrics 2014;173(2):181–6. [PUBMED: 23955516] Collins CL, Holberton JR, Barfield C, Davis PG. A Randomized Controlled Trial to Compare Heated Humidified High-Flow Nasal Cannulae with Nasal Continuous Positive Airway Pressure Postextubation in Premature Infants. Journal of Pediatrics 2013;162(5): 949–54. [PUBMED: 23260098]
- Ignacio L, Alfaleh K. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. Journal of Neonatology 2013;2(2):75–7. [PUBMED: 24049748]
- Iranpour 2011 {published and unpublished data} Iranpour R, Sadeghnia A, Hesaraki M. High-flow nasal cannula versus nasal continuous positive airway pressure in the management of respiratory distress syndrome. Journal of Isfahan Medical School 2011;29(143):1.
- Kugelman 2015 {published and unpublished data} Kugelman A, Riskin A, Said W, Shoris I, Mor F, Bader D. A randomized pilot study comparing heated humidified high-flow nasal cannulae with NIPPV for RDS. Pediatric Pulmonology 2015;50(6):576–83. [PUBMED: 24619945]
- Liu 2014 {published and unpublished data} Liu C, Collaborative Group for the Multicenter Study on Heated Humidified High-flow Nasal Cannula Ventilation. Efficacy and safety of heated humidified high-flow nasal cannula for prevention of extubation failure in neonates. Zhonghua Er Ke Za Zhi. Chinese Journal of Pediatrics 2014;52(4):271–6. [PUBMED: 24915914] Manley 2013 {published and unpublished data}
- Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, et al. High-flow nasal cannulae in very preterm infants after extubation. New England Journal of Medicine 2013;369(15):1425–33. [PUBMED: 24106935]
- Miller 2010 {published data only} Miller SM, Dowd SA. High-flow nasal cannula and extubation success in the premature infant: a comparison of two modalities. Journal of Perinatology 2010;30(12):805–8. [PUBMED: 20237485]
- Mostafa-Gharehbaghi 2014 {published and unpublished data} Mostafa-Gharehbaghi M, Mojabi H. Comparing the effectiveness of nasal continuous positive airway pressure (NCPAP) and high flow nasal cannula (HFNC) in prevention of post extubation assisted ventilation. Zahedan Journal of Research in Medical Sciences 2015;17(6):e984.
- Nair 2005 {unpublished data only} Nair G, Karna P. Comparison of the effects of Vapotherm and nasal CPAP in respiratory distress. Pediatric Academic Societies Meeting; 2005 May 14-17; Washington, DC; http://www.abstracts2view.com/pas/ (accessed May 2015): E–PAS2005:57:2054.
- Sadeghnia 2014 {published data only} Sadeghnia A, Badiei Z, Talakesh H. A comparison of two interventions for HHHFNC in preterm infants weighing 1,000 to 1,500 g in the recovery period of newborn RDS. Advanced Biomedical Research 2014;3:172. [PUBMED: 25250286]
- Woodhead 2006 {published data only} Woodhead DD, Lambert DK, Clark JM, Christensen RD. Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal extubation: a prospective, randomized, masked, crossover trial. Journal of Perinatology 2006;26(8):481–5. [PUBMED: 16724119]
- Yoder 2013 {published and unpublished data} Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics 2013;131(5):e1482–90. [PUBMED: 23610207]

F&P FlexiTrunk

F&P Optiflow Junior 2

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

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

CPAP and NHF for post-extubation care

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

< 28 weeks GA

CPAP first

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

Consider NHF once stable to:

- Reduce nasal trauma and head molding
- Facilitate developmental care

≥ 28 weeks GA

NHF first + Rescue CPAP

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

Consider CPAP as as "rescue" therapy if required

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

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

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

Manley et al. 2013

N Engl J Med.

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

Collins et al. 2013

J Pediatr.

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

Liu et al. 2016

Chinese J Pediatr.

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

Campbell et al. 2006

J Perinatol.

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

Mostafa-Gharehbhagi et al. 2015

Zahedan J Res Med Sci

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

Yoder et al. 2013

Pediatrics

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

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

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

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

Please contact your local representative for further information.

www.fphcare.com

Fisher & Paykel HEALTHCARE

Neonatal Transport Call: Do We Know What We Know?

Shabih Manzar, MD, FAAP

Case

At 5:26 am a regional hospital emergency department physician called the university transport center hot line. The dispatcher connected the ED doctor to the neonatal staff. The details of the transport log are given in Box 2.

On arrival, the transport team noted the infant to be in moderate distress with cool extremities. Four limbs blood pressures were 25/10 – 29/16 mm Hg in the lower limbs. The team obtained an intravenous access gave glucose bolus and started prostaglandin drip. The infant was intubated and transferred to the level IV NICU. Later an echocardiogram confirmed the diagnosis of critical coarctation of the aorta.

Discussion

Neonatal transport requires skill and training.[1,2] Transports are mostly conducted by trained neonatal transport team. However, there is no formal training on how to receive and respond to a neonatal transport call. For example, as noted in the case presented that the call receiving person did not address the issue of obtaining emergency IV access. The ED physician of regional hospital tailored the talk more towards dehydration and sepsis. To expedite the process and alleviate the referring staff's anxiety a detailed discussion was not carried out.

To make transport smooth and seamless, most level IV NICUs use a template (eg Box 1). This is a good uniform practice. However, it does not provide complete information. Once the transport is accepted, the nursing staff calls and gets the details. A face sheet is faxed for demographic information. The referring hospital will arrange for copy of charts, labs and x-rays.

The responsibility of neonatal providers encompasses a wide range of neonatal care. It has been reported that neonatal providers are not given adequate training in dealing with antenatal consultations.[3] Similarly, no structured educational module is followed in training neonatal providers in the area of transport. This is very well pointed out by Dewan et al.[4] They highlighted on the need for curriculum-based training for residents about high-value care. On the same token, the NICU curriculum should have a separate chapter and some dedicated time, may be 2-3 weeks rotation, to learn more about the details

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.neonatologysolution.com.

Telephone Transport Log

Call receiving person: Time: Date: Reason for call: Transfer or Consultation

Calling Physician: Hospital : Phone: City: State:

Preliminary diagnosis:

Patient's Name: Gender: Birth: Date/Time Gestational age: Weight:

Apgars: / / 1,5 and 10 mins Rupture of membrane: hours Meconium: yes/ no

Resuscitation at Delivery: Yes/no, if yes PPV/Fluid/Blood/Meds

Respiratory Support: Vent/ O2 IV access (Lines): UAC/UVC/PIV

Last Blood gas: Last Glucose:

History and Progress:

Recommendations:

Transport: accepted/ referred/ denied (Reason)

Time dispatched: Team to go: RT/ RN, RT/RN/NNP or RT/RN/MD

Figure 1. Box 1: Telephone Transport Log Template

Telephone Transport Log

Call receiving person: XYZ Time: 5:26 am Date: 1/21/2019 Reason for call: Transfer or Consultation

Calling Physician: ABC Hospital : Regional Phone: xxx City: CT State: XX

Preliminary diagnosis: 3 day old infant with vomiting

Patient's Name: QRS Gender: M Birth: Date/Time 1/18/19, 1:30 pm
Gestational age: Term Weight: 7 lbs

Apgars: 9 / 9 /9 1,5 and 10 mins Rupture of membrane: ? hours Meconium: yes/ no

Resuscitation at Delivery: Yes/no, if yes PPV/Fluid/Blood/Meds

Respiratory Support: Vent/ O2/Room air IV access (Lines): UAC/UVC/PIV/none

Last Blood gas: not done Last Glucose: un-recordable (low)

History and Progress:

3-day-old infant discharged today at 1:30 pm from nursery. At 11 pm noted to have vomiting and at about 3 am brought to ED. At ED infant noted to have low temperature and oxygen saturation by pulse oximetry showed 88%. Oxygen was provided via nasal cannula. A septic work up was done and IM antibiotics dose was given. A naso-gastric tube was inserted and D10W 10 ml was given.

Recommendations:

Try to obtain IV access and give IV D10W at 2 ml/kg and follow repeat one-touch glucose.

Transport: accepted/ referred/ denied (Reason)

Time dispatched: 5:35 Team to go: RT/ RN, RT/RN/NNP or RT/RN/MD

Figure 2. Box 1: Telephone Transport Log Template completed by on-call provider

of neonatal transport. A mock call should be run periodically to assess the readiness and skills of neonatal transport team.

References

1 Ohning, BL, et al. Transport of the Critically Ill Newborn. Medscape. Jan 09, 2015

2 Romito J, Insoft RM, Schwartz HP. Guidelines for Air and Ground Transport of Neonatal and Pediatric Patients, 4th Edition Fourth Edition.

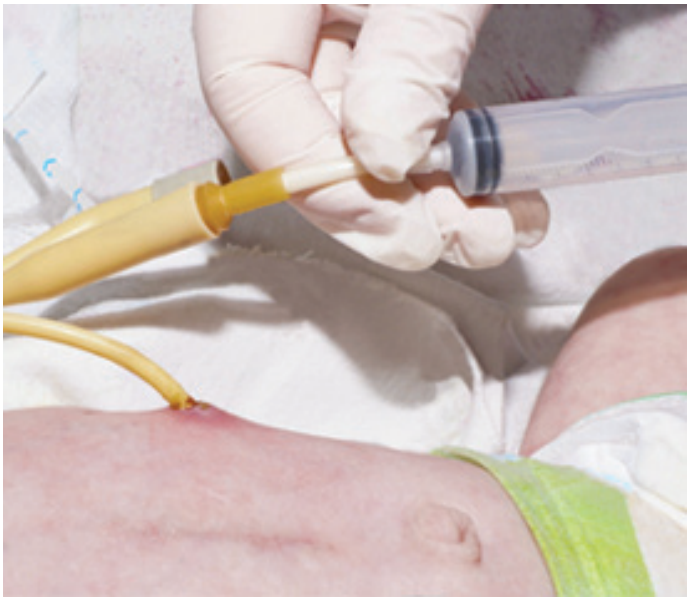
3 Stokes TA. Watson KL, Boss RD. Teaching antenatal counseling skills to neonatal providers. Semin Perinatol 2014 Feb;38(1):47-51. doi: 10.1053/j.semperi.2013.07.008.

4 Dewan M, Herrmann LE, Tchou MJ, et al. Development and evaluation of high-value Pediatrics: A high-value care pediatric resident curriculum. Hospital Pediatrics 2018; 785-792; DOI: 10.1542/hpeds.2018-0115

Tube Securement for Preemies & Babies

A Medical Tape for the Most Delicate Skin

Caregivers understand that a strong hold is needed to keep vital tubes in place. They also understand that there is a balance and while a strong hold is important, patient skin is even more important. As a producer of one of the worlds most gentle medical tapes, we place patient care ahead off everything else. When attending trade shows and industry events, we speak to doctors, nurses, care providers, and parents about their challenges when fixing a medical device or tube on their patient or child. We've received emails, phone calls, and been contacted via social media about applications and product recommendations and are always happy to assist and provide product samples.



Below are some resources that we have gathered that can assist with securing tubes, devices, and dressings on the youngest patients.

Securing & Stabilizing Children's G-tube

Mothers and caregivers of babies and toddlers with a gastrostomy tube understand that keeping tubes secure and stable is absolutely necessary in order to keep the site safe and allow time for it to heal.

There are several ways to stabilize the tube. Depending on the situation, a NICU nurse may opt for a long tube with a tension loop held using a non-reactive gentle tape.

Nasal Cannula on Infants & Children

For infants and children dealing with lung disease, birth issues, and those going through oxygen therapy the securement of a nasal tube carrying vital gasses and medications to their lungs is paramount. It is also important that it is gentle on the skin and comfortable to wear.

When preparing your home for an infant or child needing oxygen, professionals recommend:

- Have a multiple back up oxygen tanks
- Changing out the nasal prongs weekly or more often if in the presence of mucus and moisture
- Purchasing and utilizing a full length of tubing to prevent inhibited movement throughout your home
- If applicable contacting your insurance provider to see if you can secure 2 oxygen concentrators in instances where a home may be more than 1 floor
- Replacing your tubing every 3-6 month
- Make sure to have a well stocked travel bag with scissors, emergency tubing, sensors, and a gentle waterproof tape
- A spare portable oxygen tank in case of emergencies

Submitted for Neonatal Intensive Care by Hy Tape International. www.hytape.com.

The Waterproof Latex Free Tape Parents & Caregivers Trust

The Original Pink Tape®

HY-TAPE® INTERNATIONAL INC.

Available in 8 widths from
1/4" to 4" wide by 5 yards long

Nurse Approved Non-Reactive Zinc Based Formula

Hy-Tape is a unique waterproof and washable tape, especially suited for the tender skin of a neonate. It remains intact in the presence of moisture and its thin conforming profile is perfect for hard to tape areas and resists curling. The zinc oxide based adhesive soothes the skin, aids in the reduction of epidermal stripping and reduces the risk of other injuries. Hy-Tape is particularly indicated for newborns and pediatric patients because it is so gentle to delicate skin.

Order or request a sample: www.hytape.com or call 1-800-248-0101

MADE IN USA

FDA REGISTERED

Latex Free • Zinc Oxide Based • Waterproof • Secure Adhesion • Easy Removal • UPF 50+

Congenital Mydriasis in the Multisystemic Smooth Muscle Disorder: A Harbinger of Progressive Vasculopathy, Expanding the Phenotype of the ACTA2 R179C Mutation

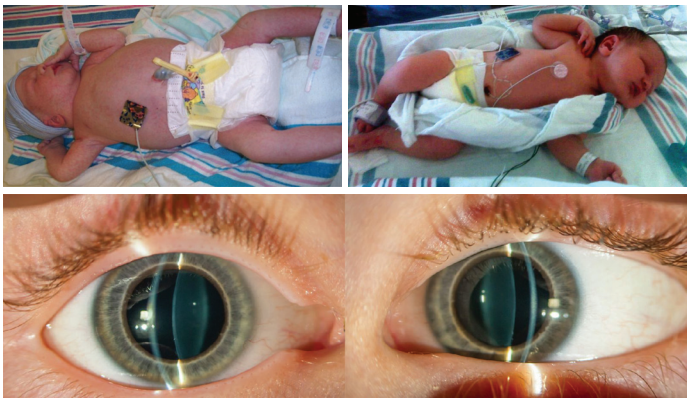
Joseph N Peeden MD,[1,2] Robert Booher MD,[2] Benjamin Pardue BS[3]

Rationale

This case study was selected to draw attention to progressive vasculopathy associated with Multisystemic Smooth Muscle Dysfunction Syndrome (MSSMD), and to expand the phenotype of the ACTA2 R179C mutation, for which the cardinal findings are present at birth.

Case Summary

A child with congenital mydriasis born by C-section to a 32-year-old at term. He was noted to have had hydronephrosis upon prenatal ultrasonography, a massively enlarged bladder, and severe right hydronephrosis. VCUG revealed no reflux. The urethra was not visualized, as he would not void spontaneously. Upon cystoscopy, a rudimentary urethral valve was resected. He required intermittent catheterization to achieve bladder emptying. A small patent ductus arteriosus was confirmed on echocardiography. Ophthalmology consultation confirmed congenital mydriasis with pupils, 7 to 7-1/2 mm and non-reactive.



Results

At six months, subclinical hypoxia was noted during MRI. A chest X-ray showed findings consistent with bronchopulmonary dysplasia. He developed pulmonary hypertension, and during cardiac catheterization, systemic pulmonary artery pressure was found. There was a large PDA without evidence of coarctation. During surgery to repair the PDA, tissue was friable and would not hold suture or bovine patch. Prolonged cross clamping of the aorta was required to achieve hemostasis. Spinal cord infarction T11-12 occurred, and the patient developed spastic paraplegia.

1-Department of Medicine, University of Tennessee Graduate School of Medicine, 2-East Tennessee Children's Hospital, Knoxville, TN, 3-VCOM-Auburn, Auburn, AL

	Stroke		
CHD Repair	Yes	No	**Total**
<2 months	4	12	16
>2 months	5	10	15
Total	9	22	31

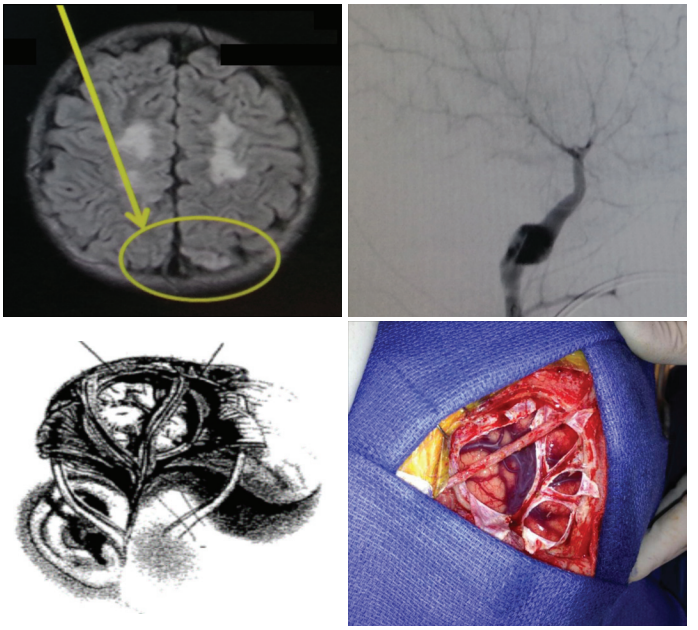
RRR= .25

	Aortic Event (>10 yo)		
CHD Repair	Yes	No	**Total**
<2 months	2	4	6
>2 months	9	2	11
Total	11	6	17

RRR= .593

	Aortic Event (>10 to <20 yo)		
CHD Repair	Yes	No	**Total**
<2months	1	4	5
>2months	4	1	5
Total	5	5	10

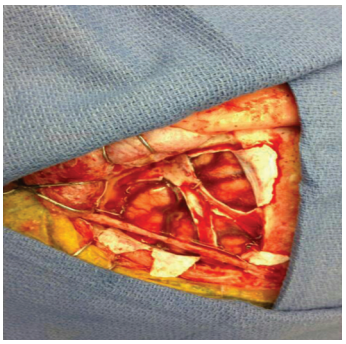
RRR= .75



Other than his paraplegia, the patient was normal neurologically. At age 5, he had an episode of left arm shaking that could not be stopped with pressure. EEG was noted as normal. No further neurological issues developed until age 8, at which time an altered mental status was noted. Multifocal strokes were present upon MRI, along with grossly abnormal neurovasculature. Multiple acute cortical infarctions, due to hypoperfusion/

	Arg179Cys	Arg179His	Arg179Leu	Arg179Ser	Total
# of patients	7	24	1	1	33
Median age at diagnosis	4	13	5.2	16	11
Mean age at diagnosis	8.1	13.5			10.7

infarction, were found. MRA revealed a moyamoya pattern with fusiform aneurysmal dilation of bilateral petrous internal carotid arteries. He successfully underwent bilateral encephalo-duro-arterio-myo-synangiosis. He was found to have a de novo ACTA2 c. 535C>T in exon 6, leading to p.R179C amino acid substitution.



Conclusion

Although the repair of PDA in children with ACTA2 mutations and MSSMD syndrome have been successful, fatalities have occurred during surgery. Our patient survived, with significant neurological injury. Vascular friability is, we believe, more likely with the R179C mutation. It is likely that the size of the PDA may contribute to vascular friability. Clearly, early diagnosis is critical to mitigate surgical complications and anticipate future vascular events. The presence at birth of mydriasis alone, especially with megacystis and PDA, strongly suggest this disorder.

Acknowledgements

Partially supported by the Graduate School of Medicine.

The End of an Error

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

Kelley Karp MSN, BS RN

Introduction

We all know that the NICU is an intense and complex clinical environment where you are dealing with the most precious of patients. This complexity also presents many opportunities for error, specifically involving infant feeding management.

At this time, there are no universally accepted national standards to regulate safety management for preparation and administration of infant feedings in hospitals. As an added complication, literature available in the feeding management space is limited when compared to other topics in the healthcare industry. Furthermore, when you review what is available much of the citations speak only to the dangers of these errors; infection risks, HIPAA violations, Joint Commission sentinel events, etc. While that information is incredibly important and well documented, I would prefer to look at the root causes of these errors.

To put this in perspective, the few published studies that have completed an FMEA for infant feeding management found that there are between 32-282 potential failure modes in feeding preparation and administration that require a human to detect and prevent.[7,8]

A recent large scale Six Sigma study put the overall risk for breast milk error to be 1 in 10,000 feeds, which is the monthly feed volume for most average-sized NICUs.[1] Articles focused on these topics regularly reference this study even though that rate is actually a predictive model based on blood transfusion administration error rates.

This was the best information we had, but also let's think about how controlled the blood administration process is. Unfortunately, this is certainly not the case with infant feeding management.

Specific to our topic, when identified, the most common types of errors are feeding an infant the wrong milk, feeding an infant expired milk, and errors in milk preparation. All with potentially significant consequences.

The topic of errors is multifactorial and this three-part article series will cover the many reasons we have errors and what can be done to mitigate them. Here in part 1, we'll cover cognitive behaviors contributing to errors, human factors, and lastly the current state of electronic management and opportunities to improve safety in these processes.

> "Distractions and interruptions include anything that draws away, disturbs, or diverts attention from the current desired task, forcing attention on a new task at least temporarily."[2]

Cognitive Demands

To work through the many pieces of this puzzle, we need to look at all the cognitive reasons errors occur. We can look at this from five angles: distractions, prospective memory, cognitive fatigue, inattentional blindness, and mental validations.

Distractions in healthcare delivery and their implications for patient safety are well established. One well-documented example of these phenomena is errors during medication preparation and administration.

In 2012 the Institute of Safe Medication Practices (ISMP) published an article speaking to distractions in healthcare related to medication preparation and administration.

Nurses, pharmacists, and technicians are distracted and interrupted as often as once every two minutes.[2,3,4] Medication error risk increases by 12.7% with each interruption.[2,5]

As a general rule, I hesitate to apply or extrapolate data for topics on which the studies were not originally conducted. However, to date, I have not found any publications addressing interruptions during infant feeding preparation and administration. Experience has shown me how frequent and similar disruptions during these two these two points of patient care can be.

When interruptions occur our **prospective memory**, or the ability to remember to do something that must be deferred, is impaired.[2,3] When an individual makes a plan to complete a task, a signal is set to remind them to actually complete that task. In the case of a distraction, the individual has pulled away from the task they are set to perform. If that signal is encountered in the

Kelley Karp is the Clinical Director at Keriton. www.Keriton.com. Tel +1-267-307-7657. kelley@keriton.com

future, that reminder is supposed to be triggered.[2,6] What if that signal does not happen? What if that reminder is not triggered?

> **Example:** A RN is in the middle of mixing a feed. He or she then has to leave the feeding prep process and area (regardless of where that is) to attend to a crisis alarm. What happens next? What is the cue to remember to go back to what they were doing (or delegate it out)? Do they see the clock and realize the feed is late? Does someone ask them if they need their patient fed? Do they see another staff member feeding a baby and remember? Do they remember where in the process they were? Do they remember at all?

In the event an individual does remember to go back to the initial task, they risk omitting or duplicating steps. In certain situations, the entire workflow may need to be repeated which can be extremely problematic depending on what they were doing. Adding insult to injury, in an attempt to complete the new task the individual has an increased likelihood of committing an error with either of the tasks because "**the stress of the distraction or interruption causes cognitive fatigue, which leads to omissions, lapses, and mistakes**."[2]

Inattentional blindness, a phenomenon in which the brain fails to see an object or detail when attention or focus is not completely centered on the object. Also known as perceptual blindness, the brain will interpret what it expects to see or conversely, looks at something and does not really see it. This is something we probably all have done. We expect to see a certain patient name or a medication and see what is not actually there.

Mental Validation

Now let us build a little more on these phenomena. On top of the interruptions and associated cognitive failures, you have to take into account all of the mental validations needed to manage the processes for infant feedings.

Pulling from an FMEA at a large urban hospital they found as many as 15-20 mental validations are required to prepare feedings for one infant. Validations such as; patient verification, order verification, complex recipe management, combing for volume and fortification, expiration updates, parsing out feedings, planning for real-time and future feeding times, thawing milk, and freezing milk.

NICU nurses generally have 2-4 infants in their care, eating 3-4 times in a 12 hr shift. A nurse/tech could realistically prepare 12 feeds in one day. This would be >180 mental validations in one shift for one clinician specifically related to feeding preparation.

These tasks can overlap multiple times throughout a typical shift, leaving every validation point open to potential error. When you consider the need for validation amidst the likely impact of distractions and interruptions the opportunity for error is high.

Conclusion

The science behind infant-specific recipe management continues to gain momentum and we learn more about tailoring these feeding plans to the individual infant.

As we have started to touch on, infant feeding management is extremely complex and involves multiple processes and players. With the added complexity of more intricate recipes and feeding regimens, we have to be ready to handle the workload safely.

Amongst all the distractions, we are relying on humans to not only detect but prevent dozens of potential failure points. Considering what we have discussed regarding cognitive failures and mental validations how can we expect to be successful?

What impacts errors and our ability to detect and prevents them continues to be a complex conversation. Many more factors come into play and need consideration in addition to what we have reviewed here.

We have only scratched the surface of these issues. Part 2 of The End of an Error will focus on what human factors influence these processes and contribute to or prevent errors.

Referenences

1 Lutton et al Got the right milk? How a blended quality improvement approach catalyzed change. 2015 Advances in Neonatal Care Vol 15 No 5 2015

2 https://www.ismp.org/resources/side-trac ks-safety-express-interruptions-lead-errors-and-unfinished-wait-what-was-i-doing

3 Relihan E, O'Brien V, O'Hara S, Silke B. The impact of a set of interventions to reduce interruptions and distractions to nurses during medication administration. Qual Saf Health Care. 2010;19:e52.

4 Silver J. Interruptions in the pharmacy: classification, root-cause, and frequency.

5 Westbrook JI, Woods A, Rob MI, Dunsmuir WT, Day RO. Association of interruptions with an increased risk and severity of medication administration errors. Arch Intern Med. 2010;170(8):683-690.

6 Grundgeiger T, Sanderson P. Interruptions in healthcare: theoretical views. Int J Med Inform. 2009;78(5):293-307.

7 Steele, Caroline and Bixby, Christine. Centralized Breastmilk Handling and Bar Code Scanning Improve Safety and Reduce Breastmilk Administration Errors. BREASTFEEDING MEDICINE. 2014. Volume 9, Number 9 . DOI: 10.1089/bfm.2014.0

8 Oza-Frank R, Kachoria R, Dail J, et al. A Quality Improvement Project to Decrease Human Milk Errors in the NICU. Pediatrics. 2017; 139(2):e20154451

News…continued from page 13
recognize the scent of amniotic fluid as a sensory cue prompting them to breastfeed, with one study indicating that newborn suckling responses were indeed extended when exposed to their own amniotic fluid. And early bathing of newborns has also been associated with hypothermia in the baby, which is also thought to affect breastfeeding rates.

Newborn Falls in Hospitals, While Rare, May Increase With Rooming-In

Hospital efforts to support breastfeeding by having babies room-in with mothers may have a rare unintended consequence: an increased risk of newborn falls. Neonatal falls are increasingly recognized as a postpartum safety risk, with as many as 1,600 newborn falls occurring in US hospitals each year, researchers note in a paper. While this represents a miniscule fraction of all births, doctors are increasingly concerned that at least some of these falls may be resulting from new mothers falling asleep while breastfeeding babies in their hospital beds. To assess the potential for breastfeeding programs to influence the risk of newborn falls, researchers looked at three cases that happened after one hospital initiated several changes designed to support breastfeeding and mother-baby bonding. "To encourage successful breastfeeding, it is important to keep mothers and babies together in one room, as much as possible," said lead study author Dr Colleen Hughes Driscoll of the University of Maryland School of Medicine in Baltimore. "This practice is somewhat different from earlier decades when babies spent a significant part of the postpartum hospitalization in the nursery, away from their mother," Driscoll said. "Though this separation was likely a barrier to successful breastfeeding, it may have provided additional opportunities for mothers to rest and recover."
The researchers examined data on newborn falls recorded in medical records from January 2011 to February 2018. They also looked at data on breastfeeding from medical records and from patient surveys done starting in 2015 as part of a new effort to support breastfeeding and rooming-in at the hospital. Three falls occurred within one year of starting a range of breastfeeding supports the hospital needed to implement in order to be designated as a "baby friendly hospital." Qualifying as Baby-Friendly, under the joint WHO and UNICEF program that created the designation, requires policies that include educating families to make informed decisions about infant feeding, encouraging mothers to hold babies skin-to-skin right after birth, allowing rooming-in and offering lactation support.

Immune Development in the Neonate: The Role of the Gut Microbiome

Tracy Shafizadeh, PhD

A direct role of the gut microbiome in the education and function of the immune system in humans has now been established, but the exact mechanisms by which our gut microbes orchestrate immune function continues to be explored. The short period of time from birth through weaning is a critical window of immune development, including establishment of adaptive immunity as well as immune tolerance. Recent studies now highlight the important interaction between the newborn gut microbiome and the development of the immune system, specifically during the first 100 days of life, which impacts both acute pathogen defense and potentially longer-term risk of auto-immune disorders later in life.[1,2,3] During this same period of time, the infant gut microbiome also undergoes pronounced development from a nearly sterile environment in utero, to the rapid acquisition of gut microbes beginning at birth. The composition of the infant gut microbiome is largely dependent on birth mode, infant diet and exposure to antibiotics, and the resulting community of microbes highly influence gut function, immune system programming and nutrient utilization by the infant.[4,5]

> Specifically, the role of *Bifidobacterium* in immune development is now thought to be particularly important.

As the infant gut microbiome takes shape during these early days of life, the presence or absence of specific bacteria have the potential to directly influence the conditions under which the newborn immune system develops. Recent reports suggest that microbial-driven intestinal inflammation during infancy can have significant long-term health consequences, possibly through disruption of immune system maturation.[2] A longitudinal study of newborn infants found that gut dysbiosis in the first months of life is associated with altered development of the immune system, characterized by increased circulating endothelial cells, activated effector T cells, and inflammatory cytokine production. Specifically, the role of *Bifidobacterium* in immune development is now thought to be particularly important,[6] where low levels of this bacterium early in life are associated with higher risk of autoimmune disorders at later time points.[7] Further studies reveal increased colonic mucin layer degradation and significantly increased fecal endotoxin levels in infants who lack *Bifidobacterium*.[8,9]

> Restoration of *Bifidobacterium* resulted in an 80% reduction in the abundance of pathogenic bacteria associated with intestinal inflammation and antibiotic resistance gene carriage.

Numerous publications have documented *Bifidobacterium longum* subsp. *infantis* (*B. infantis*) as the predominant strain to colonize the breastfed infant microbiome due to its unique ability to consume human milk oligosaccharides (HMOs).[10] These complex carbohydrates found in breastmilk are a collection of over 200 chemical structures which are completely indigestible by the human body. Instead, HMOs are broken down and utilized by gut microbes, and preferentially support the growth of *B. infantis* in the infant gut. However, more recent studies reveal that *B. infantis* is now far less abundant in the gut microbiome of infants born today in industrialized nations compared to reports from low income countries.[8,11] This is hypothesized to be due to common medical and dietary practices used in industrialized countries, such as C-section delivery, formula feeding and widespread antibiotic use, which are known to disrupt the transfer and growth of beneficial gut bacteria passed from mom to baby during vaginal delivery. Recently, probiotic supplementation with *B. infantis* EVC001 in exclusively breastfed infants has been shown to effectively restore *Bifidobacterium* to levels observed in infants naturally colonized by these bacteria.[8] Importantly, this restoration of *Bifidobacterium* resulted in an 80% reduction in the abundance of pathogenic bacteria associated with intestinal inflammation and antibiotic resistance gene carriage, as well as higher risk for the development of asthma, eczema, allergy and T1D later in life. This, together with new evidence highlighting the importance of the first 100 days of life in immune development, have spurred ongoing studies investigating the beneficial effects of feeding *B. infantis* EVC001 to breastfed infants in reducing enteric inflammation.

This dynamic period of development for both immune function and gut microbiome composition, along with the ability to restore protective bacteria to the infant through

Tracy Shafizadeh is a Nutritional Scientist and Director of Scientific Communications at Evolve BioSystems.

supplementation, presents a new opportunity for clinicians to positively influence the health trajectory of newborns under their care.

References

1. Olin, Axel, et al. "Stereotypic immune system development in newborn children." Cell 174.5 (2018): 1277-1292.
2. Arrieta, Marie-Claire, et al. "Early infancy microbial and metabolic alterations affect risk of childhood asthma." *Science translational medicine* 7.307 (2015): 307ra152-307ra152.
3. Laforest-Lapointe, Isabelle, and Marie-Claire Arrieta. "Patterns of early-life gut microbial colonization during human immune development: an ecological perspective." *Frontiers in immunology* 8 (2017): 788.
4. Bäckhed, Fredrik, et al. "Dynamics and stabilization of the human gut microbiome during the first year of life." *Cell host & microbe* 17.5 (2015): 690-703.
5. Dominguez-Bello, Maria G., et al. "Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns." *Proceedings of the National Academy of Sciences* 107.26 (2010): 11971-11975.
6. Insel, Richard, and Mikael Knip. "Prospects for primary prevention of type 1 diabetes by restoring a disappearing microbe." *Pediatric diabetes* 19.8 (2018): 1400-1406.
7. Vatanen, Tommi, et al. "Genomic variation and strain-specific functional adaptation in the human gut microbiome during early life." *Nature microbiology* (2018): 1.
8. Frese, S. A., et al. "Persistence of supplemented Bifidobacterium longum subsp. infantis EVC001 in breastfed infants. mSphere 2: e00501-17." (2017).
9. Karav, Sercan, Giorgio Casaburi, and Steven A. Frese. "Reduced colonic mucin degradation in breastfed infants colonized by Bifidobacterium longum subsp. infantis EVC001." *FEBS open bio* 8.10 (2018): 1649-1657.
10. Sela, D. A., et al. "The genome sequence of Bifidobacterium longum subsp. infantis reveals adaptations for milk utilization within the infant microbiome." *Proceedings of the National Academy of Sciences* 105.48 (2008): 18964-18969.
11. Lewis, Zachery T., et al. "Maternal fucosyltransferase 2 status affects the gut bifidobacterial communities of breastfed infants." *Microbiome* 3.1 (2015): 13.

Algorithms for Interpreting Capnography Waveforms

Gina Farquharson, MS, MBA, RRT-NPS, CPPS; Gregory K Spratt, BS, RRT, CPFT

Capnography was first proposed for use in the operating room in 1978 and has since become the standard of care for monitoring ventilation.[1] Capnography is rapidly growing in use for intubated and non-intubated applications across hospital environments including the ICU, resuscitation, procedural sedation, and postoperative monitoring of patients receiving opioid analgesia.[1,2]

When used appropriately, capnography has been cited as meaningful in providing key, often life-sustaining, information in dozens of different clinical applications. These range from common indications such as monitoring for apneas, hypoventilation, hyperventilation, and airway integrity during procedural sedation or in postoperative patients; to monitoring ETT placement, quality of chest compression, and return of spontaneous circulation during resuscitation efforts; to screening for diabetic ketoacidosis, pulmonary embolism, bronchospasm, and even sepsis in the emergency setting.[1-4] This value has led to capnography being recommended or required for various applications by over 80 clinical societies in over 100 guidelines, standards, and statements in just the past 8 years.

Despite the vast number of societal guidelines and clinical articles touting its value, I have met clinicians who state they do not see much value in capnography. What's the difference between these two groups? Does it work for some and not for others? Of course not. The difference is in their knowledge and ability to correctly apply and interpret the results in a meaningful manner. With any monitoring parameter, effective application is dependent upon interpreting the parameter values (eg, $etCO_2$, RR, waveforms, and trends) within the broader context of the patient's signs, symptoms, and other clinical data available, and then using their using their expertise to assimilate this information to inform best interventions. Capnography waveforms can be insightful for clinical intervention and require a similar systematic approach, much like ECG interpretation.

Systematic approaches to waveform interpretation for other parameters have been documented and published. The development of clinical decision tools can be used for waveform interpretation and a systematic approach could possibly reduce errors of interpretation or clinical intervention. Such a tool can serve as a bridge to fill gaps in knowledge while the clinician develops a better understanding of the basic principles of interpretation. Like all physiologic monitors, each has limitations and requires a standardized method for interpretation and translating this information into clinical practice.[5]

A systematic approach for capnography waveform analysis is presented here in Table 1 (intubated patients) and Table 2 (non-intubated patients) below. Changes in the waveform provide the earliest indication of problems when ventilation becomes abnormal. For example, a patient experiencing an apnea will have a flatline capnography waveform immediately after the apnea begins, and yet oximetry may not indicate a desaturation for several minutes.

Begin by looking at the shape of the waveform following the algorithms in the tables. Many clinicians will only look at the $etCO_2$ value itself. In doing so, a clinician would be missing some key information for making clinical interventions. The trend, shape, height, and width of the waveform all provide useful clues as to the quality of ventilation and appropriate interventions. For example, does it plateau, indicating that you're getting a true alveolar sample?

When looking at the end-tidal carbon dioxide ($etCO_2$) reading, start by noting the patient's baseline value, does it fall in the 35-45 mmHg normal range? Changes in this reading, with a clear alveolar plateau, can indicate changes in ventilation, perfusion, or metabolic status as indicated in the examples seen in the flow chart. Also consider the respiratory rate derived from the $etCO_2$ readings, and changes caused by tachypnea or bradypnea to the end-tidal reading.

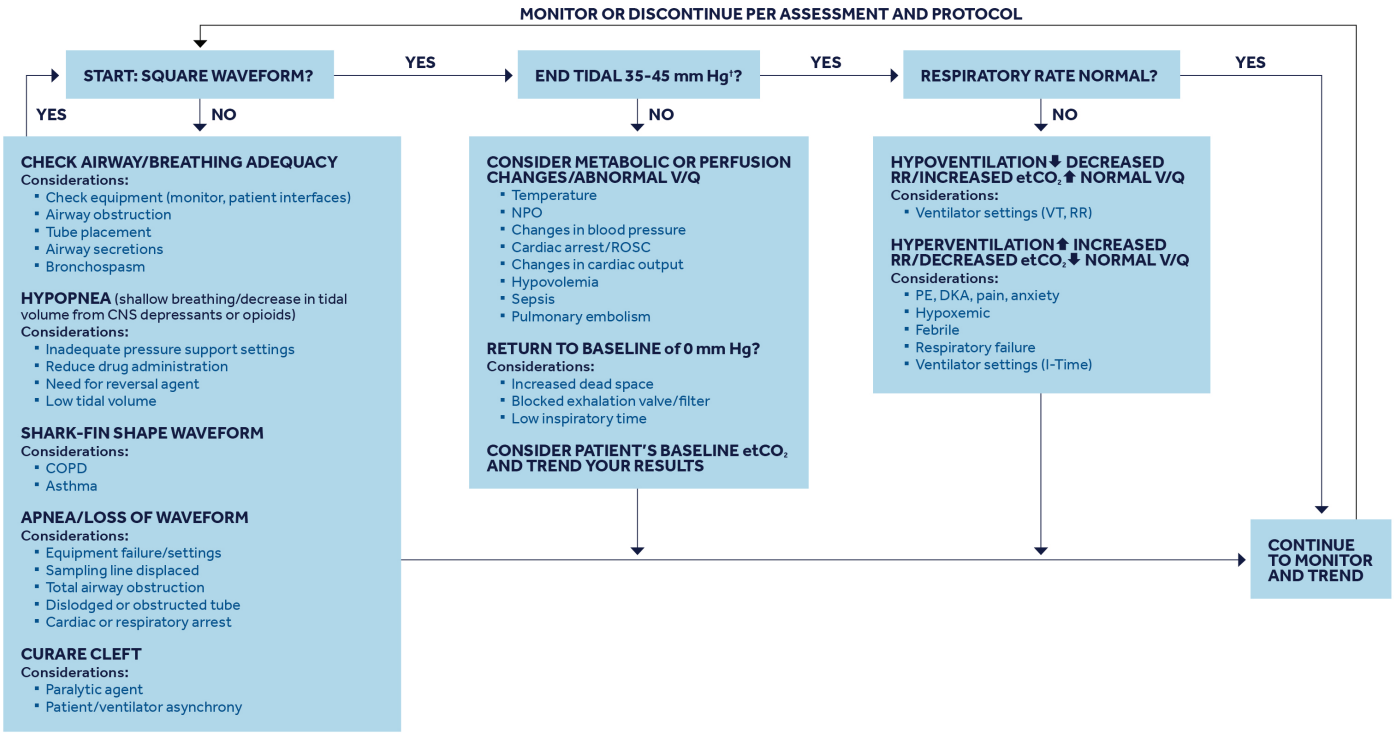
Finally, trend graphs can be helpful for looking at changes over time. A good example is a patient with obstructive sleep apnea, where $etCO_2$ values will show repetitive drops and increases subsequent to apneic/hypopneic events.

In the example, Figure 1, you will notice the capnograph reading and the $etCO_2$ of five. First, look at the shape of the waveform. It is not square in shape, so the clinician should evaluate equipment and proper placement of the sampling line (eg, cannula), check the airway for integrity (eg, reposition and jaw thrust), considering possible airway obstruction or hypopneic breathing (suspect shallow breathing when waveforms are non-plateauing). This patient had received a benzodiazepine and opioid narcotic

Gina Farquharson, MS, MBA, RRT-NPS, CPPS and Gregory K Spratt, BS, RRT, CPFT work in Global Market Development at Medtronic Patient Monitoring in Boulder, CO to improve clinical solutions for respiratory compromise. Gina works as a Senior Technical Consultant on Capnography and Greg is the Director of Market Development.

Table 1. Capnography waveforms for intubated patients[6-15]

A SYSTEMATIC APPROACH FOR INTUBATED PATIENTS



†Patient baseline may be higher or lower than normal 35–45 mm Hg.

for procedural sedation and as the patient did not exhibit symptoms of airway obstruction, the patient was encouraged to take deep breaths and sedation medication was reduced which brought the waveform back to a normal appearance and the $etCO_2$ reading back to a normal range. Note that the SpO_2 reading is normal (97%) as oxygen desaturations generally lag minutes after the onset of changes to ventilation, especially when supplemental oxygen is in use. Although the alarm is alerting the clinician to the low $etCO_2$, the first intervention is to assess airway and breathing adequacy and intervene appropriately. A number of additional example waveforms can be viewed by downloading this interactive tool at http://www.medtronic.com/covidien/en-us/clinical-education/catalog/interactive-pdf-capnography-waveforms.html.

Figure 1. Capnograph waveform and $etCO_2$ reading.

Summary

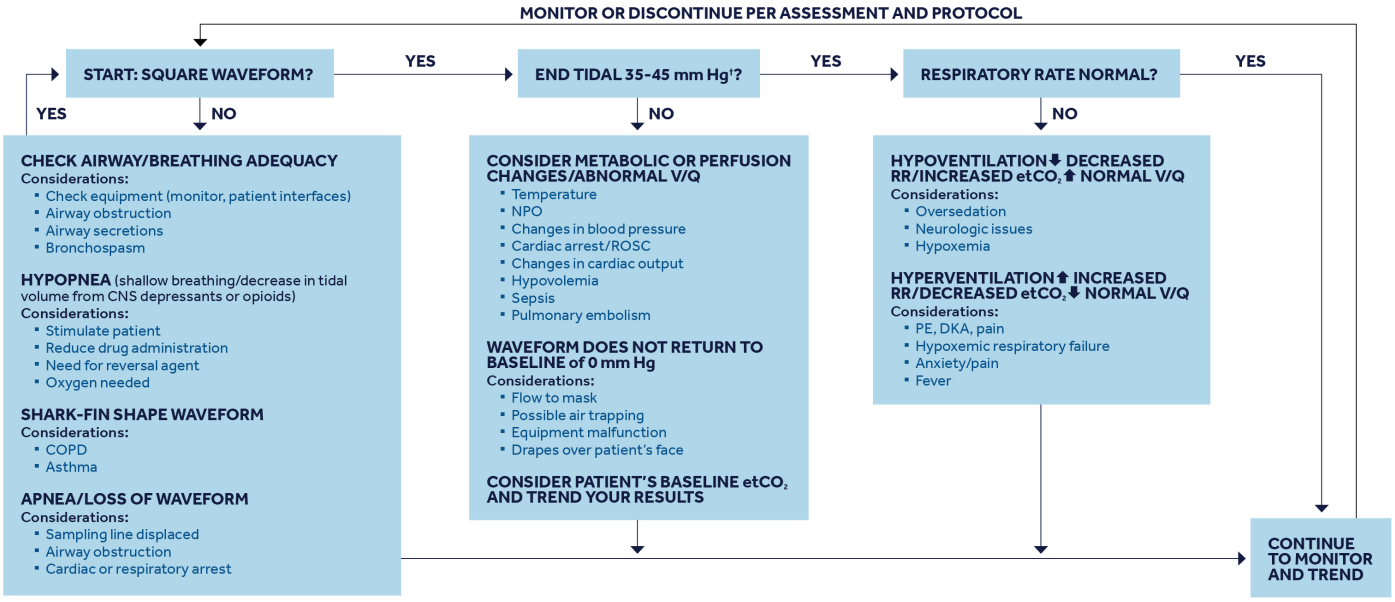
Capnography and the associated waveforms can provide the clinician with useful information to inform intervention for a variety of clinical scenarios for both intubated and non-intubated patients. Data from the capnograph should always be assessed within the context of the patient's overall condition including signs, symptoms, vital signs, and other monitoring parameters. A systematic approach to the interpretation of the waveform could lead to earlier intervention with appropriate clinical response and treatment.

References

1. Whitaker DK, Benson JP. Capnography standards for outside the operating room. Curr Opin Anesthesiol 2016, 29:485–492.
2. Kodali BS. Capnography Outside the Operating Rooms. Anesthesiology 2013; 118(1):192-201.
3. Krauss B, Silvestri S, Falk JL. Carbon dioxide monitoring (Capnography) www.uptodate.com 2014.
4. Brast JS, Bland E, Jones-Hooker C, Long M, Green K. Capnography for the radiology and imaging nurse: A primer. *Journal of Radiology Nursing*. Published September 2016.
5. Krauss B, Hess DR. Capnography for procedural sedation and analgesia in the emergency department. *Ann Emerg Med*. 2007;50(2):172-181. Epub Jan. 12, 2007.
6. Chameides L, Samson RA, Schexnayder SM, Hazinski MF, eds. Pediatric Advanced Life Support Provider Manual: Professional Edition. Dallas, TX: American Heart Association; 2011.
7. Badgwell JM, Kleinman SE, Heavner JE. Respiratory frequency and artifact affect the capnographic baseline in infants. *Anesth Analg*. 1993;77:708-711.
8. Gravenstein JS, Jaffe MB, Gravenstein N, Paulus DA, eds.

Table 2. Capnography waveforms for non-intubated patients[6-15]

A SYSTEMATIC APPROACH FOR NONINTUBATED PATIENTS



This resource is intended for educational purposes only. It is not intended to provide comprehensive or patient-specific clinical practice recommendations for capnography monitoring. The clinical choices outlined in this text may or may not be consistent with your own patient requirements, your clinical practice approaches, or guidelines for practice that are endorsed by your institution or practice group. It is the responsibility of each clinician to make his/her own determination regarding clinical practice decisions that are in the best interest of patients. Readers are advised to review the current product information, including the Indications for Use currently provided by the manufacturer. Neither the publisher, authors, nor Covidien LP, a Medtronic company, assumes any responsibility for any injury and or damage to persons or property resulting from information provided in this text.

Capnography. 2nd ed. New York, NY: Cambridge University Press; 2011.

9. Huether SE, McCance KL. Understanding Pathophysiology. 2nd ed. St. Louis, MO: Mosby; 2000.
10. Beitz A, Riphaus A, Meining A, Kronshage T, Geist C, Wagenpfeil S, et al. Capnographic monitoring reduces the incidence of arterial oxygen desaturation and hypoxemia during propofol sedation for colonoscopy: a randomized, controlled study. *Am J Gastroenterol*. 2012;107(8):1205-1212.
11. Bhananker SM, Posner KL, Cheney FW, Caplan RA, Lee LA, Domino KB. Injury and liability associated with monitored anesthesia care: a closed claims analysis. *Anesthesiology*. 2006;104(2):228-234.
12. MedicineNet.com. Definition of hyperventilation. http://www.medicinenet.com/script/main/art.asp?articlekey=3853. Accessed May 8, 2018.
13. Curry JP, Jungquist CR. A critical assessment of monitoring practices, patient deterioration, and alarm fatigue on inpatient wards: a review. *Patient Saf Surg*. 2014;8:29.
14. Anderson CT, Breen P. Carbon dioxide kinetics and capnography during critical care. *Crit Care*. 2000;4(4):207-215.
15. Ward KR, Yealy DM. End-tidal carbon dioxide monitoring in emergency medicine, part 2: clinical applications. *Acad Emerg Med*. 1998;5(6):637-646.

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

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

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

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

Introduction

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

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

Oxidative Stress As Pathogenic Factor In The Preterm Infant

The oxidant/antioxidant status balance is a process that begins before birth (8), and premature infants are particularly susceptible to oxidative stress (9, 10). Most of the complications of prematurity, such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and punctate white matter lesions (PWML), appear related to oxidative stress (11, 12), mostly occurring due

TABLE 1 | Main oxidants and anti-oxidants.

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

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

1 Department of Pharmacy, University of Genoa, Genova, Italy, 2 Laboratory of Molecular Nephrology, IRCCS Istituto Giannina Gaslini, Genova, Italy, 3 Neonatal Intensive Care Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy, 4 Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy.

to a mismatch among the free radical production and the anti-oxidative capacity of the premature neonate (10). Accordingly, Saugstad hypothesized that all of these complications may belong to one entity, "the oxygen radical disease of neonatology" (13). This topic was recently reviewed by Buonocore et al. (14).

Birth exerts the challenge of a hyperoxic insult due to the sudden exposure to a normoxic environment (100 mmHg oxygen tension, PO_2) of an organism primed to develop in a hypoxic (20–25 mmHg, PO_2) environment as the womb is. For this reason, current indications on neonatal resuscitation highlight the importance of starting respiratory support using the lowest oxygen concentration to reduce the postnatal oxidative stress (15). A randomized trial performed on neonates of 24–34 weeks gestational age who received resuscitation demonstrated that the use of room air, instead of 100% O_2 as the initial resuscitation gas resulted lower oxidative stress, decreasing respiratory morbidities (16).

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

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

TABLE 2 | Main antioxidant Treatments.

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

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

Oxidative Stress-Related Brain Injury

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

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

Cerebral WM injury is a full-spectrum of lesions named periventricular leukomalacia (PVL), that occurs in two overlapping forms: cystic PVL, in which the periventricular focal necrosis is macroscopic and evolves to multiple cysts; and non-cystic PVL, in which the focal necrosis are microscopic and evolve principally to glial scars (29). Evidence of PVL is found in 25 to 75% of VLBW infants with neuropathological examination (10). The incidence of cystic PVL declined significantly starting from late nineties of last century, now occurring in a minority of infants with abnormal neurodevelopmental outcome (30). Contemporary cohorts of preterm survivors commonly display milder forms of injury, primarily diffuse white matter injury (DWMI) and punctate white matter lesions (PWML), that even though do not involve pronounced neuronal loss may be also associated with a clear WM damage and neurodevelopmental disabilities (29, 31, 32). DWMI and PWML are currently the most common causes of brain injury in preterm infants (33, 34). Signs of DMWI occurs in about 50% of very low birth weight infants (35), while more than 10% of premature infants <32 weeks develop lesions visible at MRI performed at term corrected age. Oxidative stress is among the main causes of PWML (36–41). In fact, the optimal concentration of oxygen for resuscitation of very preterm infants is currently strictly monitored (15). Risk factors for the development of PWML and for oxidative stress production are similar, including hyperoxia, hypoxia, ischemia-reperfusion, hemorrhage, and maternal/fetal inflammation (33). Inflammatory microglial response in cerebral white matter can generate free radicals (42). A number of epidemiological studies have shown an association between infections and cerebral

palsy (43) and intrauterine T cell activation and risk of cerebral lesions (44). VLBW infants with neonatal sepsis were shown to have increased rates of cerebral palsy and WM lesions, by a large cohort study (45). Another mismatch among demand and supply in the premature babies would regard insulin-like growth factor 1 (IGF-1), a mitogenic hormone involved in growth and metabolism. Increased chemical energy demand but low IGF-1 concentrations characterize preterm birth, which appears associated with complications such as especially ROP (46, 47).

Oligodendroglial Precursor Injury As The Main Cause Of Brain Damage

It has been reported that brain injury mostly affects WM, being oligodendroglial death the most important cause of PVL and PWML (35, 48, 49). Studies on both human brain and animal models assessed that the developing oligodendrocyte (OL) is the principal cellular target (49, 50). All of the cited risk factors can cause toxicity to the oligodendroglial precursors. For example, proinflammatory cytokines produced in response to hypoxia and infection can become toxic to the oligodendroglial precursor cells (pre-OL) (43). Glutamate excitotoxicity and free radical injury have recently been implicated in pre-OL death (39). Free iron, in turn causing oxidative stress, contributes to the onset of the OL dysmaturation (18).

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

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

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

Future Directions

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

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

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

References

1. Czerska M, Mikołajewska K, Zielinski M, Gromadzinska J, Wasowicz W. Today's oxidative stress markers. *Med Pr*. (2015) 66:393–405. doi: 10.13075/mp.5893.00137
2. Rahal A, Kumar A, Singh V, Yadav B, Tiwari R, Chakraborty S, et al. Oxidative stress, prooxidants, and antioxidants: the interplay. *Biomed Res Int.* (2014) 2014:761264. doi: 10.1155/2014/761264
3. Fato R, Bergamini C, Leoni S, Strocchi P, Lenaz G. Generation of reactive oxygen species by mitochondrial complex I: implications in neurodegeneration. *Neurochem Res.* (2008) 33:2487–501. doi: 10.1007/s11064-008-9747-0
4. Sies H. Oxidative stress: a concept in redox biology and medicine. *Redox Biol.* (2015) 4:180–3. doi: 10.1016/j.redox.2015.01.002
5. Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. *Int J Biomed Sci.* (2008) 4:89–96.
6. Lugrin J, Rosenblatt-Velin N, Parapanov R, Liaudet L. The role of oxidative stress during inflammatory processes. *Biol Chem.* (2014) 395:203–30. doi: 10.1515/hsz-2013-0241
7. Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol.* (2007)

39:44–84. doi: 10.1016/j.biocel.2006.07.001
8. Marseglia L, D'Angelo G, Manti S, Arrigo T, Barberi I, Reiter RJ, et al. Oxidative stress-mediated aging during the fetal and perinatal periods. *Oxid Med Cell Longev.* (2014) 2014:358375. doi: 10.1155/2014/358375
9. Dani C, Cecchi A, Bertini G. Role of oxidative stress as physiopathologic factor in the preterm infant. *Minerva Pediatr.* (2004) 56:381–94.
10. Ozsurekci Y, Aykac K. Oxidative stress related diseases in newborns. *Oxid Med Cell Longev.* (2016) 2016:2768365. doi: 10.1155/2016/2768365
11. Buonocore G, Perrone S, Bracci R. Free radicals and brain damage in the newborn. *Biol Neonate* (2001) 79:180–6. doi: 10.1159/000047088
12. Giuffrè M, Rizzo M, Scaturro G, Pitruzzella A, Gammazza AM, Cappello F, et al. Oxidative stress markers at birth: analyses of a neonatal population. *Acta Histochem.* (2015) 117:486–91. doi: 10.1016/j.acthis.2015.01.007
13. Saugstad OD. The oxygen radical disease in neonatology. *Indian J Pediatr.* (1989) 56:585–93. doi: 10.1007/BF02722373
14. Buonocore G, Perrone S, Tataranno ML. Oxidative Stress in the Newborn. *Oxid Med Cell Longev.* (2017) 2017:1094247. doi: 10.1155/2017/1094247
15. Armanian AM, Badiee Z. Resuscitation of preterm newborns with low concentration oxygen versus high concentration oxygen. *J Res Pharm Pract.* (2012) 1:25–9. doi: 10.4103/2279-042X.99674
16. Kapadia VS, Chalak LF, Sparks JE, Allen JR, Savani RC, Wyckoff MH. Resuscitation of preterm neonates with limited versus high oxygen strategy. *Pediatrics* (2013) 132:e1488–96. doi: 10.1542/peds.2013-0978
17. Liu Y, Wei J, Chang M, Liu Z, Li D, Hu S, et al. Proteomic analysis of endothelial progenitor cells exposed to oxidative stress. *Int J Mol Med.* (2013) 32:607–14. doi: 10.3892/ijmm.2013.1419
18. Buonocore G, Perrone S, Longini M, Vezzosi P, Marzocchi B, Paffetti P, et al. Oxidative stress in preterm neonates at birth and on the seventh day of life. *Pediatr Res.* (2002) 52:46–9. doi: 10.1203/00006450-200207000-00010
19. Thibeault DW. The precarious antioxidant defenses of the preterm infant. *Am J Perinatol.* (2000) 17:167–81. doi: 10.1055/s-2000-9422
20. Abdel Ghany EAG, Alsharany W, Ali AA, Youness ER, Hussein JS. Anti- oxidant profiles and markers of oxidative stress in preterm neonates. *Paediatr Int Child Health* (2016) 36:134–40. doi: 10.1179/2046905515Y.0000000017
21. Mutlu M, Sariaydin M, Aslan Y, Kader S, Dereci S, Kart C, et al. Status of vitamin D, antioxidant enzymes, and antioxidant substances in neonates with neonatal hypoxic-ischemic encephalopathy. *J Matern Neonatal Med.* (2015) 29:2259–63. doi: 10.3109/14767058.2015.1081889
22. Gitto E, Marseglia L, Manti S, D'Angelo G, Barberi I, Salpietro C, et al. Protective role of melatonin in neonatal diseases. *Oxid Med Cell Longev.* (2013) 2013:980374. doi: 10.1155/2013/980374
23. Gitto E, Pellegrino S, Gitto P, Barberi I, Reiter RJ. Oxidative stress of the newborn in the pre- and postnatal period and the clinical utility of melatonin. *J Pineal Res.* (2009) 46:128–39. doi: 10.1111/j.1600-079X.2008.00649.x
24. Vladan B, Panfoli I. Melatonin and abeta, macular degeneration and alzheimers disease: same disease, different outcomes? *Med hypothesis, Discov Innov Ophthalmol J* (2012) 1:24–32.
25. Morgillo D, Morgillo-Mitchell J, Fontanta M, Steurer M, Schmitt-Mechelke T, Bauder F, et al. Outcome of extremely low gestational age newborns (ELGANs) following a pro-active treatment approach: a Swiss single centre experience over 10 years. *Swiss Med Wkly.* (2014) 144:w14014. doi: 10.4414/smw.2014.14014
26. Cornette LG, Tanner SF, Ramenghi LA, Miall LS, Childs AM, Arthur RJ, et al. Magnetic resonance imaging of the infant brain: anatomical characteristics and clinical significance of punctate lesions. *Arch Dis Child Fetal Neonatal Ed.* (2002) 86:F171–7. doi: 10.1136/fn.86.3.F171
27. Bassi L, Chew A, Merchant N, Ball G, Ramenghi L, Boardman J, et al. Diffusion tensor imaging in preterm infants with punctate white matter lesions. *Pediatr Res.* (2011) 69:561–6. doi: 10.1203/PDR.0b013e3182182836
28. Inder TE, Warfield SK, Wang H, Hüppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. *Pediatrics* (2005) 115:286–94. doi: 10.1542/peds.2004-0326
29. Khwaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. *Arch Dis Child Fetal Neonatal Ed.* (2008) 93:F153–61. doi: 10.1136/adc.2006.108837
30. Hamrick SEG, Miller SP, Leonard C, Glidden D V, Goldstein R, Ramaswamy V, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leukomalacia. *J Pediatr.* (2004) 145:593–9. doi: 10.1016/j.jpeds.2004. 05.042
31. Rutherford MA, Supramaniam V, Ederies A, Chew A, Bassi L, Groppo M, et al. Magnetic resonance imaging of white matter diseases of prematurity. *Neuroradiology* (2010) 52:505–21. doi: 10.1007/s00234-010-0700-y
32. Martino F, Malova M, Cesaretti C, Parazzini C, Doneda C, Ramenghi LA, et al. Prenatal MR imaging features of isolated cerebellar haemorrhagic lesions. *Eur Radiol.* (2016) 26:2685–96. doi: 10.1007/s00330-015-4053-0
33. Sannia A, Natalizia AR, Parodi A, Malova M, Fumagalli M, Rossi A, et al. Different gestational ages and changing vulnerability of the premature brain. *J Matern Neonatal Med.* (2015) 28:2268–72. doi: 10.3109/14767058.2013.796166
34. Ramenghi LA, Fumagalli M, Groppo M, Consonni D, Gatti L, Bertazzi PA, et al. Germinal matrix hemorrhage: intraventricular hemorrhage in very-low- birth-weight infants: the independent role of inherited thrombophilia. *Stroke* (2011) 42:1889–93. doi: 10.1161/STROKEAHA.110.590455
35. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol.* (2009) 8:110–24. doi: 10.1016/S1474-4422(08)70294-1
36. Kaindl AM, Favrais G, Gressens P. Molecular mechanisms involved in injury to the preterm brain. *J Child Neurol.* (2009) 24:1112–8. doi: 10.1177/0883073809337920
37. Back SA, Rivkees SA. Emerging concepts in periventricular white matter injury. *Semin Perinatol.* (2004) 28:405–14. doi: 10.1053/j.semperi.2004.10.010
38. Back SA, Rosenberg PA. Pathophysiology of glia in perinatal white matter injury. *Glia* (2014) 62:1790–815. doi: 10.1002/glia.22658
39. Elitt CM, Rosenberg PA. The challenge of understanding cerebral white matter injury in the premature infant. *Neuroscience* (2014) 276:216–38. doi: 10.1016/j.neuroscience.2014.04.038
40. Back SA. White matter injury in the preterm infant: pathology and mechanisms. *Acta Neuropathol.* (2017) 134:331–49. doi: 10.1007/s00401-017-1718-6
41. Qaseem A, Wilt TJ, McLean RM, Forciea MA, Clinical Guidelines Committee of the American College of Physicians.

Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the american college of physicians. *Ann Intern Med.* (2017) 166:514–30. doi: 10.7326/M16-2367
42. Deng YY, Lu J, Ling E-A, Kaur C. Role of microglia in the process of inflammation in the hypoxic developing brain. *Front Biosci (Schol Ed)*. (2011) 3:884–900.
43. Leviton A, Dammann O, Durum SK. The adaptive immune response in neonatal cerebral white matter damage. *Ann Neurol.* (2005) 58:821–28. doi: 10.1002/ana.20662
44. Duggan PJ, Maalouf EF, Watts TL, Sullivan MH, Counsell SJ, Allsop J, et al. Intrauterine T-cell activation and increased proinflammatory cytokine concentrations in preterm infants with cerebral lesions. *Lancet* (2001) 358:1699–700. doi: 10.1016/S0140-6736(01)06723-X
45. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* (2004) 292:2357. doi: 10.1001/jama.292.19.2357
46. Hellström A, Engström E, Hård A-L, Albertsson-Wikland K, Carlsson B, Niklasson A, et al. Postnatal serum insulin-like growth factor I deficiency is associated with retinopathy of prematurity and other complications of premature birth. *Pediatrics* (2003) 112:1016–20. doi: 10.1542/peds.112.5.1016
47. Hellstrom A, Ley D, Hallberg B, Lofqvist C, Hansen-Pupp I, Ramenghi LA, et al. IGF-1 as a drug for preterm infants: a step- wise clinical development. *Curr Pharm Des.* (2017) 23:5964–70. doi: 10.2174/1381612823666171002114545
48. Back SA, Miller SP. Brain injury in premature neonates: a primary cerebral dysmaturation disorder? *Ann Neurol.* (2014) 75:469–86. doi: 10.1002/ana.24132
49. Volpe JJ, Kinney HC, Jensen FE, Rosenberg PA. The developing oligodendrocyte: key cellular target in brain injury in the premature infant. *Int J Dev Neurosci.* (2011) 29:423–40. doi: 10.1016/j.ijdevneu.2011.02.012
50. Kinney HC, Brody BA, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants. *J Neuropathol Exp Neurol.* (1988) 47:217–34.
51. French HM, Reid M, Mamontov P, Simmons RA, Grinspan JB. Oxidative stress disrupts oligodendrocyte maturation. *J Neurosci Res.* (2009) 87:3076–87. doi: 10.1002/jnr.22139
52. Panfoli I, Cassanello M, Bruschettini M, Colella M, Cerone R, Ravera S, et.al. Why do premature newborn infants display elevated blood adenosine levels? *Med Hypotheses* (2016) 90:53–6. doi: 10.1016/j.mehy.2016.03.007
53. Stevens B, Porta S, Haak LL, Gallo V, Fields RD. Adenosine: a neuron- glial transmitter promoting myelination in the CNS in response to action potentials. *Neuron* (2002) 36:855–68. doi: 10.1016/S0896-6273(02)01067-X
54. Stevens B, Ishibashi T, Chen J-F, Fields RD. Adenosine: an activity-dependent axonal signal regulating MAP kinase and proliferation in developing Schwann cells. *Neuron Glia Biol.* (2004) 1:23–34. doi: 10.1017/s1740925x04000055
55. Saugstad OD. Oxidative stress in the newborn – A 30-year perspective. *Neonatology* (2005) 88:228–36. doi: 10.1159/000087586
56. Tataranno ML, Perrone S, Buonocore G. Plasma Biomarkers of Oxidative Stress in Neonatal Brain Injury. *Clin Perinatol.* (2015) 42:529–39. doi: 10.1016/j.clp.2015.04.011
57. Marseglia L, D'Angelo G, Manti M, Aversa S, Fiamingo C, Arrigo T, et al. Visfatin: new marker of oxidative stress in preterm newborns. *Int J Immunopathol Pharmacol.* (2016) 29:23–9. doi: 10.1177/0394632015607952
58. Colella M, Zinni M, Pansiot J, Cassanello M, Mairesse J, Ramenghi L, et al. Modulation of microglial activation by adenosine A2a receptor in animal models of perinatal brain injury. *Front Neurol.* (2018) 9:605. doi: 10.3389/fneur.2018.00605
59. Endesfelder S, Weichelt U, Strauß E, Schlör A, Sifringer M, Scheuer T, et al. Neuroprotection by Caffeine in Hyperoxia-Induced Neonatal Brain Injury. *Int J Mol Sci*. (2017) 18:187. doi: 10.3390/ijms1801018
60. Rangarajan V, Juul SE. Erythropoietin: emerging role of erythropoietin in neonatal neuroprotection. *Pediatr Neurol.* (2014) 51:481–8. doi: 10.1016/j.pediatrneurol.2014.06.008
61. Maiese K, Chong ZZ, Hou J, Shang YC. Erythropoietin and oxidative stress. *Curr Neurovasc Res*. (2008) 5:125–42.
62. Reiter RJ, Tan DX, Osuna C, Gitto E. Actions of melatonin in the reduction of oxidative stress. a review. *J Biomed Sci*. (2000) 7:444–58. doi: 10.1159/000025480
63. Gitto E, Reiter RJ, Sebatino G, Buonocore G, Romeo C, Gitto P, et al. Correlation among cytokines, bronchopulmonary dysplasia and modality of ventilation in preterm newborns: improvement with melatonin treatment. *J Pineal Res*. (2005) 39:287–93. doi: 10.1111/j.1600-079X.2005.0 0251.x
64. Miller SL, Yawno T, Alers NO, Castillo-Melendez M, Supramaniam V, VanZyl N, et al. Antenatal antioxidant treatment with melatonin to decrease newborn neurodevelopmental deficits and brain injury caused by fetal growth restriction. *J Pineal Res*. (2014) 56:283–94. doi: 10.1111/jpi.12121
65. Kaandorp JJ, Benders MJ, Schuit E, Rademaker CM, Oudijk MA, Porath MM, et al. Maternal allopurinol administration during suspected fetal hypoxia: a novel neuroprotective intervention? A multicentre randomised placebo controlled trial. *Arch Dis Child Fetal Neonatal Ed*. (2015) 100:F216–23. doi: 10.1136/archdischild-2014-306769
66. Van Bel F, Shadid M, Moison RMW, Dorrepaal CA, Fontijn J, Monteiro L, et al. Effect of allopurinol on postasphyxial free radical formation, cerebral hemodynamics, and electrical brain activity. *Pediatrics* (1998) 101:185–93.
67. Dajas F, Abin-Carriquiry JA, Arredondo F, Blasina F, Echeverry C, Martínez M, et al Quercetin in brain diseases: potential and limits. *Neurochem Int.* (2015) 89:140–8. doi: 10.1016/j.neuint.2015.07.002
68. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Caffeine therapy for apnea of prematurity. *N Engl J Med.* (2006) 354:2112–21. doi: 10.1056/NEJMoa054065
69. Ohlsson A, Aher SM. Early erythropoiesis-stimulating agents in preterm or low birth weight infants. *Cochrane Database Syst Rev.* (2017) doi: 10.1002/14651858.CD004863.pub5

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

Probiotic Research In Neonates With Congenital Gastrointestinal Surgical Conditions – Now Is The Time

Shripada C Rao[1,2]* and Sanjay K Patole[2,3]

The major congenital gastrointestinal surgical conditions (CGISC) include oesophageal atresia, gastroschisis, exomphalos, malrotation and volvulus, duodenal atresia, intestinal atresia, meconium ileus, hypoplastic colon, meconium peritonitis, intestinal stenosis, congenital short bowel syndrome, Hirschsprung disease (HD), anorectal malformations and others. In addition to surgical repair, strategies for managing such conditions include early commencement of enteral feeds, standardization of feeding advancement, strict hand hygiene and aseptic precautions for indwelling catheters (Graham, 2010; Lauriti et al, 2014; Savoie et al, 2016; Dama et al, 2017). Despite such best practices and advances in surgical techniques, morbidities including feed intolerance, healthcare-associated infections, cholestatic jaundice, growth failure and neurodevelopmental disabilities continue to impose significant health burden on this cohort (Willis et al, 2010; Bishay et al, 2012; Wang et al, 2014; Dwyer et al, 2016; Hong et al, 2018). Additional strategies are hence required to improve their outcomes.

Gut dysbiosis in infants with CGISC

Neonatal gut microbiota develops rapidly after birth and achieves an adult-like composition and stability by 2-3 years of age (Arrieta et al, 2014). The evolution of gut microbiome is affected in infants with CGISC admitted in intensive care units (ICUs). These infants receive parenteral nutrition (PN), get exposed to multiple courses of antibiotics, do not receive early enteral feeding and optimal maternal skin to skin contact. Decontamination of the skin for surgery, exposure to gastric acid suppressants, breakdown of natural barriers due to invasive procedures and indwelling tubes and catheters, colonization of the ICU room surfaces and hands of the healthcare providers also contribute to the risk of gut dysbiosis in infants with CGISC (Donnell et al, 2002; van Saene et al, 2003; Hussey et al, 2011; Fouhy et al, 2012; Ralls et al, 2016; Rogers et al, 2016; Kitsios et al, 2017).

(i) **PN and gut dysbiosis:** The role of PN in gut dysbiosis deserves attention as it is often the main/only source of nutrition in infants with CGISC. Lavallee et al. (2017) randomized neonatal piglets to receive total parenteral nutrition (TPN) or sow feeds (SF) for 14 days. Ileal segments and mucosal scrapings were used to assess the microbiota composition by 16S rRNA gene sequencing. Significant dysbiosis was noted in the TPN group, especially in those which received soy-based lipids. In another study, using a mouse model, Ralls et al. (2016) reported permeation of TPN-derived nutrients into the gut lumen, where they were preferentially utilized by Enterobacteriaceae, which then flourished.

(ii) **Antibiotics and gut dysbiosis:** Fouhy et al. (2012) compared the gut microbiota of nine newborn infants treated with parenteral ampicillin and gentamicin, with that of nine matched healthy infants. Gut microbiota of the antibiotic-treated infants showed significantly higher proportions of Proteobacteria and lower proportions of Actinobacteria and the associated genus Bifidobacterium, as well as the genus Lactobacillus compared with the untreated controls 4 weeks after the cessation of treatment. Even by week 8, Proteobacteria levels remained significantly higher in the treated infants (Fouhy et al, 2012). Increased abundance of Proteobacteria is a concern because it is considered as a potential diagnostic signature of dysbiosis and risk of disease (Shin et al, 2015).

(iii) **The ICU ecosystem and gut dysbiosis:** In a study in adult ICU patients, McDonald et al. (2016) showed evidence of extreme dysbiosis. The phylogenetic diversity at discharge was significantly lower than at admission. Faecal samples tended to have a lower relative abundance of Firmicutes and Bacteroidetes and an increased relative abundance of Proteobacteria and well-recognized pathogens such as Enterobacter and Staphylococcus (McDonald et al, 2016). In a study in paediatric ICUs, Rogers et al. (2016) reported taxonomic alterations in the gut microbiota. These included enrichments of gut pathogens such as Enterococcus and Staphylococcus at multiple body sites and depletion of commensals such as Faecalibacterium and Ruminococcus from stool samples. Alpha and beta diversity were unstable over time (Rogers et al, 2016).

Studies have shown an association between gut dysbiosis and morbidities such as hospital-acquired infections in neonates with surgical conditions (Donnell et al, 2002; van Saene et al, 2003) and Hirschsprung-associated enterocolitis (HAEC) (Li et al, 2016).

Probiotics for CGISC

Given that gut dysbiosis occurs and is associated with morbidities in infants with CGISC, optimization of gut microbiota

[1]Neonatal Intensive Care Unit, Perth Children's Hospital, Hospital Avenue, Nedlands, WA 6009, Australia. [2]Centre for Neonatal Research and Education, University of Western Australia, Perth, WA, Australia. [3]Neonatal Directorate, King Edward Memorial Hospital for Women, Perth, WA, Australia.

by probiotics is a potentially beneficial strategy to improve their outcomes.

Probiotics are defined as live microorganisms that when administered in adequate amounts confer health benefits on people with specific illnesses (Hill et al, 2014). Probiotics inhibit gut colonization with pathogenic bacteria (Sassone-Corsi and Raffatellu, 2015), enhance gut barrier function (Bron et al, 2017), facilitate colonization with healthy commensals (Garrido et al, 2012), protect from enteropathogenic infection through production of acetate (Fukuda et al, 2011), reduce antimicrobial resistance (Taft et al, 2018), enhance innate immunity (Giorgetti et al, 2015) and increase maturation of the enteric nervous system and promote gut peristalsis (Hyland and Cryan, 2016; De Vadder et al, 2018). Through these mechanisms, probiotics have the potential to decrease the risk of sepsis, improve feed tolerance and minimize parenteral nutrition-associated cholestasis in infants with CGISC.

(i) **Evidence from studies in adult patients:** A recent meta-analysis of 20 RCTs (N = 1374) concluded that probiotic/symbiotic supplementation decreases the risk of surgical site and urinary tract infections in patients undergoing abdominal surgery (Lytvyn et al, 2016). Another meta-analysis that included 28 RCTs (n = 2511) involving adult patients undergoing gastrointestinal surgery came to similar conclusions (Yang et al, 2017). The durations of hospital stay and antibiotic therapy were shorter in the probiotics/symbiotic group vs controls (Yang et al, 2017). The need for caution in interpreting the results was emphasized considering the high risk of bias in included studies (Lytvyn et al, 2016; Yang et al, 2017).

(ii) **Evidence from studies in paediatric patients:** In a RCT, 30 children (<15 years) with various surgical (majority gastrointestinal) conditions were supplemented with probiotic Bifidobacterium breve BBG-01 or placebo daily from 7 days before the surgery until discharge. Probiotic supplementation was safe. It improved the gut flora, increased the concentration of faecal acetic acid and decreased the risk of septicaemia (Okazaki et al, 2016). A recent meta-analysis that included 198 infants with HD (two RCTs, three observational studies) reported that the incidence of HAEC 22.6% in the probiotic group vs 30.5% in the controls, but the difference was not statistically significant (OR 0.72; 95% CI 0.37–1.39; P = 0.33; Nakamura et al, 2018). Majority of the infants in the included studies were outside the neonatal period.

(iii) **Evidence from studies in neonates:** A systematic review (Rao et al, 2018) that focussed on CGISC exclusively in the neonatal population found only two small RCTs (Murakami et al, 2016; Powell et al, 2016). The Powell et al. (2016) RCT included 24 neonates with gastroschisis (Probiotics: 12, Placebo: 12). The probiotic supplement was administered for 6 weeks or until hospital discharge, whichever came first. Significant dysbiosis was noted in the study infants, and it was partially attenuated by administration of Bifidobacterium longum subsp. infantis (Powell et al, 2016). In the RCT by Murakami et al. (2016), four surgical neonates (duodenal atresia, anorectal malformations) received probiotics, four received no probiotics. Bifidobacteriaceae was more abundant in neonates who had not received probiotics. It was concluded that surgical stress appeared to affect the intestinal microbiota considerably. The need for further RCTs in this area was emphasized.

Safety of probiotics

Evidence from over 35 RCTs with a total sample size of nearly 12 000 and observational studies with over 14 000 participants show that probiotics are beneficial and safe in preterm non-surgical infants (Olsen et al, 2016; Rao et al, 2016; Sawh et al, 2016; Dermyshi et al, 2017). Even a large RCT that did not show benefits of probiotic supplementation acknowledged that short-term safety of probiotics was good in preterm infants (Costeloe et al, 2016). Recent meta-analyses have shown that probiotics do not increase or decrease the risk of intraventricular haemorrhage, chronic lung disease, retinopathy of prematurity and neurodevelopmental outcomes in preterm non-surgical infants (Cavallaro et al, 2017; Villamor-Martinez et al, 2017; Upadhyay et al, 2018). These findings provide reassurance regarding medium-term safety of probiotics in preterm infants. However, there are few case reports of sepsis due to probiotic organisms (Ohishi et al, 2010; Vallabhaneni et al, 2015; Brecht et al, 2016). Hence, constant vigilance and quality assurance of the product while conducting RCTs of probiotic supplementation in infants with CGISC are warranted.

Ongoing RCTs of probiotics in infants with CGISC

To our knowledge, currently, there are two ongoing RCTs evaluating the role of probiotics in this area. One trial is being conducted in Calgary (Canada) and aims to recruit 88 infants born between 23 and 42 weeks of gestation who require gastrointestinal surgery (Mugarab-Samedi et al, 2017). The probiotic supplement is FloraBabyTM (Renew Life Canada, Oakville, ON, Canada). Each sachet (1 g) will have 4 billion colony-forming units (CFU) of probiotics, consisting of Bifidobacterium breve (HA-129), Lactobacillus rhamnosus (HA111), Bifidobacterium bifidum (HA-132), Bifidobacterium longum subsp. infantis (HA-116) and Bifidobacterium longum subsp. longum (HA-135). Placebo is maltodextrin. The primary outcome of interest is length of hospital stay. Stool microbial analysis using culture independent 16S rRNA studies will be undertaken.

The other study (ours) is being conducted in Western Australia (Rao et al, 2017). Sixty infants (≥35 weeks' gestation) with major CGISC will be recruited. The probiotic group will receive 3×10^9 CFU/day (ie 3 billion organisms) in 1.5 ml of the expressed breast milk or sterile water, given as a single daily dose via the orogastric/nasogastric feeding tube or orally. The probiotic sachet (Morinaga Industries, Tokyo, Japan) will contain a mixture of three strains (B. breve M-16V, B. longum subsp. infantis M-63 and B. longum subsp. longum BB536 (1×10^9 CFU of each strain per 1 g sachet). Placebo is maltodextrin. Supplementation will be commenced as soon as possible after admission once the baseline stool samples are collected and will be continued until discharge. Primary outcome will be gut microbiota (using 16 s ribosomal RNA Pyrosequencing studies for phylogenic profiling) on stool samples. Secondary outcomes will be stool short-chain fatty acids and relevant clinical outcomes.

Conclusions

In summary, probiotic supplementation has the potential to minimize gut dysbiosis and improve clinical outcomes of neonates with CGISC. Though small, the completed and ongoing RCTs will provide important data and confidence to embark on adequately powered large RCTs in this exciting area.

Conflict of interest

None declared.

References

- Arrieta, M.C., Stiemsma, L.T., Amenyogbe, N., Brown, E.M., and Finlay, B. (2014) The intestinal microbiome in early life: health and disease. Front Immunol 5: 427.
- Bishay, M., Pichler, J., Horn, V., Macdonald, S., Ellmer, M., Eaton, S., et al. (2012) Intestinal failure-associated liver disease in surgical infants requiring long-term parenteral nutrition. J Pediatr Surg 47: 359–362.
- Brecht, M., Garg, A., Longstaff, K., Cooper, C., and Andersen, C. (2016) Lactobacillus sepsis following a laparotomy in a preterm infant: a note of caution. Neonatology 109: 186–189.
- Bron, P.A., Kleerebezem, M., Brummer, R.J., Cani, P.D., Mercenier, A., MacDonald, T.T., et al. (2017) Can probiotics modulate human disease by impacting intestinal barrier function? Br J Nutri 117: 93–107.
- Cavallaro, G., Villamor-Martinez, E., Filippi, L., Mosca, F., and Villamor, E. (2017) Probiotic supplementation in preterm infants does not affect the risk of retinopathy of prematurity: a meta-analysis of randomized controlled trials. Sci Rep 7: 13014.
- Costeloe, K., Hardy, P., Juszczak, E., Wilks, M., and Millar, M.R. (2016) Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial. Lancet (London, England) 387: 649–660.
- Dama, M., Rao, U., Gollow, I., Bulsara, M., and Rao, S. (2017) Early commencement of enteral feeds in gastroschisis: a systematic review of literature. Eur J Pediatr Surg 27: 503–515.
- De Vadder, F., Grasset, E., Manneras Holm, L., Karsenty, G., Macpherson, A.J., Olofsson, L.E., and Backhed, F. (2018) Gut microbiota regulates maturation of the adult enteric nervous system via enteric serotonin networks. Proc Natl Acad Sci USA 115: 6458–6463.
- Dermyshi, E., Wang, Y., Yan, C., Hong, W., Qiu, G., Gong, X., and Zhang, T. (2017) The "golden age" of probiotics: a systematic review and meta-analysis of randomized and observational studies in preterm infants. Neonatology 112: 9–23.
- Donnell, S.C., Taylor, N., van Saene, H.K., Magnall, V.L., Pierro, A., and Lloyd, D.A. (2002) Infection rates in surgical neonates and infants receiving parenteral nutrition: a five-year prospective study. J Hosp Infect 52: 273–280. Dwyer, G.M., Walker, K., Baur, L., and Badawi, N. (2016)
- Developmental outcomes and physical activity behaviour in children post major surgery: an observational study. BMC Pediatr 16: 123.
- Fouhy, F., Guinane, C.M., Hussey, S., Wall, R., Ryan, C.A., Dempsey, E.M., et al. (2012) High-throughput sequencing reveals the incomplete, short-term recovery of infant gut microbiota following parenteral antibiotic treatment with ampicillin and gentamicin. Antimicrob Agents Chemother 56: 5811–5820.
- Fukuda, S., Toh, H., Hase, K., Oshima, K., Nakanishi, Y., Yoshimura, K., et al. (2011) Bifidobacteria can protect from enteropathogenic infection through production of acetate. Nature 469: 543–547.
- Garrido, D., Barile, D. and Mills, D.A. (2012) A molecular basis for bifidobacterial enrichment in the infant gastrointestinal tract. Adv Nutri (Bethesda, Md.) 3, 415s–421s.
- Giorgetti, G., Brandimarte, G., Fabiocchi, F., Ricci, S., Flamini, P., Sandri, G., et al. (2015) Interactions between innate immunity, microbiota, and probiotics. J Immunol Res 2015: 501361.
- Graham, P.L. 3rd (2010) Simple strategies to reduce healthcare associated infections in the neonatal intensive care unit: line, tube, and hand hygiene. Clin Perinatol 37: 645–653.
- Hill, C., Guarner, F., Reid, G., Gibson, G.R., Merenstein, D.J., Pot, B., et al. (2014) Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 11: 506–514.
- Hong, C.R., Zurakowski, D., Fullerton, B.S., Ariagno, K., Jaksic, T., and Mehta, N.M. (2018) Nutrition delivery and growth outcomes in infants with gastroschisis. J Parenter Enteral Nutr 42: 913–919.
- Hussey, S., Wall, R., Gruffman, E., O'Sullivan, L., Ryan, C.A., Murphy, B., et al. (2011) Parenteral antibiotics reduce bifidobacteria colonization and diversity in neonates. Int J Microbiol 2011, pii: 130574.
- Hyland, N.P., and Cryan, J.F. (2016) Microbe-host interactions: influence of the gut microbiota on the enteric nervous system. Dev Biol 417: 182–187.
- Kitsios, G.D., Morowitz, M.J., Dickson, R.P., Huffnagle, G.B., McVerry, B.J., and Morris, A. (2017) Dysbiosis in the intensive care unit: microbiome science coming to the bedside. J Crit Care 38: 84–91.
- Lauriti, G., Zani, A., Aufieri, R., Cananzi, M., Chiesa, P.L., Eaton, S., and Pierro, A. (2014) Incidence, prevention, and treatment of parenteral nutrition-associated cholestasis and intestinal failure-associated liver disease in infants and children: a systematic review. J Parenter Enteral Nutr 38: 70–85.
- Lavallee, C.M., MacPherson, J.A.R., Zhou, M., Gao, Y., Wizzard, P.R., Wales, P.W., et al. (2017) Lipid emulsion formulation of parenteral nutrition affects intestinal microbiota and host responses in neonatal piglets. J Parenter Enteral Nutr 41: 1301–1309.
- Li, Y., Poroyko, V., Yan, Z., Pan, L., Feng, Y., Zhao, P., et al. (2016) Characterization of intestinal microbiomes of hirschsprung's disease patients with or without enterocolitis using illumina-miseq high-throughput sequencing. PLoS ONE 11: e0162079.
- Lytvyn, L., Quach, K., Banfield, L., Johnston, B.C., and Mertz, D. (2016) Probiotics and synbiotics for the prevention of postoperative infections following abdominal surgery: a systematic review and meta-analysis of randomized controlled trials. J Hosp Infect 92: 130–139.
- McDonald, D., Ackermann, G., Khailova, L., Baird, C., Heyland, D., Kozar, R., et al. (2016) Extreme dysbiosis of the microbiome in critical illness. mSphere 1, pii: e00199-16.
- Mugarab-Samedi, V., Howlett, A., Hicks, M., Arrieta, M.-C., Beaudry, P., Dersch-Mills, D., and Alshaikh, B. (2017) Probiotics supplementation and length of hospital stay in neonates with gastrointestinal surgery. Int J Surg Protoc 6: 13–16.
- Murakami, H., Shimomura, Y., Matsumoto, M., Lane, G.J., Yamataka, A., and Okawada, M. (2016) Intestinal microbiota in neonates requiring urgent surgery: assessing the role of probiotics using fecal DNA sequencing. Pediatr Surg Int 32: 37–43.
- Nakamura, H., Lim, T., and Puri, P. (2018) Probiotics for the prevention of Hirschsprung-associated enterocolitis: a systematic review and meta-analysis. Pediatr Surg Int 34:

189–193.
- Ohishi, A., Takahashi, S., Ito, Y., Ohishi, Y., Tsukamoto, K., Nanba, Y., et al. (2010) Bifidobacterium septicemia associated with postoperative probiotic therapy in a neonate with omphalocele. J Pediatr 156: 679–681.
- Okazaki, T., Asahara, T., Yamataka, A., Ogasawara, Y., Lane, G.J., Nomoto, K., et al. (2016) Intestinal microbiota in pediatric surgical cases administered bifidobacterium breve: a randomized controlled trial. J Pediatr Gastroenterol Nutr 63: 46–50.
- Olsen, R., Greisen, G., Schroder, M., and Brok, J. (2016) Prophylactic probiotics for preterm infants: a systematic review and meta-analysis of observational studies. Neonatology 109: 105–112.
- Powell, W.T., Borghese, R.A., Kalanetra, K.M., Mirmiran, M., Mills, D.A., and Underwood, M.A. (2016) Probiotic administration in infants with gastroschisis: a pilot randomized placebo-controlled trial. J Pediatr Gastroenterol Nutr 62: 852–857.
- Ralls, M.W., Demehri, F.R., Feng, Y., Raskind, S., Ruan, C., Schintlmeister, A., et al. (2016) Bacterial nutrient foraging in a mouse model of enteral nutrient deprivation: insight into the gut origin of sepsis. Am J Physiol Gastrointest Liver Physiol 311: G734–G743.
- Rao, S.C., Athalye-Jape, G.K., Deshpande, G.C., Simmer, K.N., and Patole, S.K. (2016) Probiotic supplementation and late-onset sepsis in preterm infants: a meta-analysis. Pediatrics 137: e20153684.
- Rao, S., Simmer, K., Patole, S., Gollow, I., Bulsara, M., Conway, P. and Keil, A. (2017). Probiotic supplementation in neonates with major gastrointestinal surgical conditions: Protocol for a Pilot Randomized Double Blind Placebo Controlled Trial. ACTRN12617001401347. URL https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373705&isReview=true.
- Rao, S., Simmer, K., and Patole, S. (2018) Probiotic supplementation in neonates with major gastrointestinal surgical conditions: a systematic review. J Matern Fetal Neonatal Med 31: 1517–1523.
- Rogers, M.B., Firek, B., Shi, M., Yeh, A., Brower-Sinning,
- R., Aveson, V., et al. (2016) Disruption of the microbiota across multiple body sites in critically ill children. Microbiome 4: 66.
- Sassone-Corsi, M., and Raffatellu, M. (2015) No vacancy: how beneficial microbes cooperate with immunity to provide colonization resistance to pathogens . J Immunol (Baltimore, Md.: 1950) 194: 4081–4087.
- Savoie, K.B., Bachier-Rodriguez, M., Jones, T.L., Jeffreys, K., Papraniku, D., Sevilla, W.M.A., et al. (2016) Standardization of feeding advancement after neonatal gastrointestinal surgery: does it improve outcomes? Nutr Clin Pract 31: 810–818.
- Sawh, S.C., Deshpande, S., Jansen, S., Reynaert, C.J., and Jones, P.M. (2016) Prevention of necrotizing enterocolitis with probiotics: a systematic review and meta-analysis. PeerJ 4: e2429.
- Shin, N.R., Whon, T.W., and Bae, J.W. (2015) Proteobacteria: microbial signature of dysbiosis in gut microbiota. Trends Biotechnol 33: 496–503.
- Taft, D.H., Liu, J., Maldonado-Gomez, M.X., Akre, S., Huda, M.N., Ahmad, S.M., et al. (2018) Bifidobacterial dominance of the gut in early life and acquisition of antimicrobial resistance. mSphere 3, pii: e00441-18.
- Upadhyay, R.P., Taneja, S., Chowdhury, R., Strand, T.A. and Bhandari, N. (2018) Effect of prebiotic and probiotic supplementation on neurodevelopment in preterm very low birth weight infants: findings from a meta-analysis. Pediatr Res. [Epub ahead of print].
- Vallabhaneni, S., Walker, T.A., Lockhart, S.R., Ng, D., Chiller, T., Melchreit, R., et al. (2015) Notes from the field: Fatal gastrointestinal mucormycosis in a premature infant associated with a contaminated dietary supplement–Connecticut, 2014. MMWR 64: 155–156.
- van Saene, H.K., Taylor, N., Donnell, S.C., Glynn, J., Magnall, V.L., Okada, Y., et al. (2003) Gut overgrowth with abnormal flora: the missing link in parenteral nutrition-related sepsis in surgical neonates. Eur J Clin Nutr 57: 548–553.
- Villamor-Martinez, E., Pierro, M., Cavallaro, G., Mosca, F., Kramer, B. and Villamor, E. (2017) Probiotic supplementation in preterm infants does not affect the risk of bronchopulmonary dysplasia: a meta-analysis of randomized controlled trials. Nutrients 9, pii: E1197.
- Wang, J., Du, L., Cai, W., Pan, W., and Yan, W. (2014) Prolonged feeding difficulties after surgical correction of intestinal atresia: a 13-year experience. J Pediatr Surg 49: 1593–1597.
- Willis, T.C., Carter, B.A., Rogers, S.P., Hawthorne, K.M., Hicks, P.D., and Abrams, S.A. (2010) High rates of mortality and morbidity occur in infants with parenteral nutrition-associated cholestasis. JPEN 34: 32–37.
- Yang, Z., Wu, Q., Liu, Y., and Fan, D. (2017) Effect of perioperative probiotics and synbiotics on postoperative infections after gastrointestinal surgery: a systematic review with meta-analysis. JPEN 41: 1051–1062.

Infant Incubators | Combination Incubator Warmer | Infant Warmers: Labor & Delivery, NICU
NeoCot Bassinet | Phototheraphy, Lighting & Accessories

ATOM

Dedicated to one purpose for over 80 years! The highest quality products and solutions for newborn infants.




ATOM MEDICAL USA, LLC

atommedusa.com | info@atommedusa.com | 1.844.ATOM.USA
150 Lake Drive, Suite 101 | Wexford, PA 15090
Proud to offer our industry leading 3 year warranty.

Now with 48-HOUR expiration* and simplified preparation instructions

Prolact CR® Human Milk Caloric Fortifier

Easy to use. Less waste. No more complicated measuring.

Human milk caloric fortifier is ideal for neonatal infants receiving low caloric content. Data show that 65% of the time, term mother's own milk (MOM) is less than 20 Cal/fl oz.[1] Prolact CR® human milk caloric fortifier can meet the need for additional calories.

- Intended for use with MOM or donor milk (DM) to increase lipids and achieve adequate growth
- Formulated to deliver at least 2.5 Cal/mL
- Available frozen in 30 mL bottles containing 10 mL of product (4 bottles per unit carton)

For complete information on Prolact CR human milk caloric fortifier, call 1-888-PROLACT (1-888-776-5228) or visit www.Prolacta.com/human-milk-caloric-fortifier.

*In-use expiration, once the thawing process begins

1. Wojcik K, et al. Macronutrient analysis of a nationwide sample of donor breast milk. *J Am Diet Assoc.* 2009;109(1):137-140. doi:10.1016/j.jada.2008.10.008.

MKT-0568 Rev-0 9/18

Prolacta® BIOSCIENCE
Advancing the Science of Human Milk