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[1] Castillo A et al. Prevention of Retinopathy of Prematurity in Preterm Infants through Changes in Clinical Practice and SpO2 Technology. *Acta Paediatr*. 2011;100(2):188-92.) [2] Chow et al. Can changes in clinical practice decrease the incidence of sever retinopathy of prematurity in very low birth weight infants? *Pediatrics*. 2003;111(2):339-345. [3] de-Wahl Granelli A et al. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. *BMJ*. 2009;8;338. [4] Ewer AK et al. NIHR Health Technology Assessment Programme: Executive Summaries. 2012.

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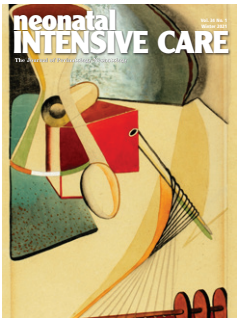


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INTENSIVE CARE

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### Russian Woman United With Baby After COVID-19 C-section and 51 Days on Life Support

A Russian woman who was admitted to hospital heavily pregnant and with what doctors said were potentially fatal levels of COVID-19 lung damage was reunited with her newborn baby after spending 51 days on a ventilator and giving birth by C-section. Oksana Shelomentseva was hospitalised in the Siberian city of Irkutsk in the 32nd week of her pregnancy, having had a high fever for three days. A scan showed catastrophic lung damage and that her unborn baby was not receiving enough oxygen. "My temperature rose to 38 degrees Celsius and I battled with it for three days, but it became clear I could not do that independently," Shelomentseva said. Doctors immediately performed a Caesarean section to deliver baby girl Liza, but still feared for the recovery of the mother who went on to spend almost two months on a ventilator to help her breathe. "It was a very serious case," said Galina Shkandriy, head of the Anaesthesiology and Intensive Care Department at the hospital where Shelomentseva was treated. "The entire ward is to thank for the patient recovering from 100% lung damage," the RIA news agency cited her as saying. "When we consulted doctors from around the city, they all said 'you probably won't be able to do anything because with those indicators, people don't survive.'" "Oksana spent 51 days in intensive care in a most serious condition. We were able to save her from the most severe lung damage and multiple organ failure," said Shkandriy. Shelomentseva was discharged on Monday and returned home to her husband and three children, including baby Liza. At 3,448,203, Russia has the world's fourth-largest tally of coronavirus cases after the United States, India and Brazil, and has reported 62,804 deaths from the virus.

### Labor Induction at 41 Weeks Tied to Lower Morbidity, Mortality Than Expectant Management

Inducing labor at 41 weeks may result in a lower risk of severe adverse perinatal and neonatal outcomes than expectant management until 42 weeks, a systematic review and meta-analysis of randomized clinical trials in PLOS Medicine suggests. Researchers examined data from three clinical trials with a total of 5,161 low-risk singleton pregnancies. They assessed a composite primary outcome of perinatal mortality, including stillbirth or neonatal mortality within 28 days of birth, and neonatal morbidity including: five-minute Apgar score below 4, hypoxic ischemic encephalopathy, intracranial hemorrhage, neonatal convulsions, respiratory distress, mechanical ventilation within 72 hours of birth, and obstetric brachial plexus injury. The analysis included individual data for 4,561 participants, including 2,281 women scheduled for labor induction at 41 weeks; four in five of these women ultimately had the scheduled induction and the rest delivered spontaneously. Among 2,280 women assigned to expectant management until 42 weeks, about 30% needed induction and the rest delivered spontaneously. In the induction group, 10 cases (0.4%) met the composite primary endpoint of perinatal death or severe neonatal morbidity; 23 cases (1.0%) occurred in the expectant management group. "The take home messages is that induction of labor will decrease the risk of adverse perinatal outcome, including mortality, without increasing the morbidity risk for the woman including cesarean delivery, perineal laceration grade III-IV and postpartum hemorrhage — especially in nulliparous women," said lead study author Dr Marten Alkmark of the University of Gothenburg in Sweden. "For parous women the risk of adverse perinatal outcome is very low with both induction of labor and expectant management," Dr Alkmark said by email. Among nulliparous women, the risk of the primary outcome was

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Cover: Composition. Artist: Andree Rexroth, born Chicago, IL 1902-died San Francisco, CA 1940

lower among those in the induction group (0.03%) than in the expectant management group (1.6%). However, the risk of the primary outcome among multiparous women was similar with induction (0.6%) and expectant management (0.3%). None of the women in the study had a history of cesarean delivery or other major uterine surgery, and all of them had low-risk singleton pregnancies with the fetus in cephalic position. Researchers also looked at perinatal secondary outcomes and found there was only one perinatal death in the induction group, a stillbirth that occurred after randomization but before induction. Seven of the eight perinatal deaths in the expectant management group were stillbirths, while one infant died because of hypoxic ischemic encephalopathy. Limitations of the analysis include the relatively small size of the study compared with other reviews of induction versus expectant management, as well as some heterogeneity in how the two trials included in the analysis defined some endpoints. "The risk of perinatal death and severe neonatal morbidity increases gradually after 41 weeks of pregnancy, probably linked to the placenta deteriorating," said Sara Kenyon, a professor of evidence based maternity care at the University of Birmingham in the U.K. who wasn't involved in the study. "However, it wasn't clear when the optimal time to induce women is and this study suggests that, particularly for nulliparous women, that this is 41 weeks," Kenyon said by email.

### Newborns Benefit From Skin-to-Skin Contact With Father After C-Section

There is an undeniable amount of research on the natural benefits of skin-to-skin contact for mum and baby. Essentially, skin-to-skin contact is simply that, babies' skin against their parents' skin immediately after birth and continuing later at home. It naturally regulates a new-born's temperature, heart rate and breathing while elevating their blood sugar which is essential for energy. It also encourages breastfeeding and colonises the baby's natural gut bacteria to that of its mother, making their intestinal bacteria more diverse, protecting them from illness and infection. Skin-to-skin is not just reserved for mum, however. It is vitally important that dad also partakes in this ancient art of snuggling with their new-born. In fact, this close contact with dad brings about many of the same remarkable benefits as it does with mum. Being warm and snug in your arms, is your new-born's favourite place to be. They often cry less, sleep better and are more content when warm against your skin. Be that mum or dads. The benefits of skin-to-skin with dad are not always advertised as strongly as they are with mum considering an important facet of this connection is establishing breastfeeding. But when a father has the opportunity to hold their baby close, skin-to-skin, we see the love hormone, oxytocin, doing exactly what it needs to — creating the natural bond between parent and child and helping you to fall in love with them. This is the same hormone that makes a woman's uterus contract in labour. Research has also shown skin-to-skin helps to develop more caring behaviour in dad and also a more sensitive approach to parenting. Furthermore, it has been shown to decrease cortisol levels in new dads which is greatly linked to anxiety. Less stress and less anxiety have a direct positive, correlation on the parent's relationship which naturally affects the family dynamic.

### Supplemental Oxygen During Childbirth May Not Be of Value to Babies

Babies who suffer oxygen deficiencies during birth are at risk of brain damage that can lead to developmental delays, cerebral palsy and even death. To prevent this, most women in labor undergo continuous monitoring of the baby's heart rate and receive supplemental oxygen if the heart rate is abnormal, with the thought that this common practice increases oxygen delivery to the baby. However, there is conflicting evidence about whether the long-recommended practice improves infant health. Now, a comprehensive analysis - led by Washington University School of Medicine in St. Louis - looking at 16 previous trials of the practice has found no benefit in providing supplemental oxygen to mothers during labor and delivery. Infants born to women who received supplemental oxygen fared no better or no worse than those born to women who had similar labor experiences but breathed room air. Each year, 1.5 million women in the US — two out of three pregnant women — receive supplemental oxygen at some point during childbirth, according to the researchers. The decades-long practice is recommended by the American College of Obstetricians and Gynecologists to treat abnormal fetal heart rates, which may indicate the baby's oxygen levels are low and pose health risks. Raghuraman added that supplemental oxygen is given mostly as a preventive measure, a practice that began during the 1960s. "Fetal monitoring can indicate a possible abnormal issue such as oxygen deprivation," she said. "But about 80% of the time, women giving birth fall into an intermediate category, in which cases are not completely benign but also not high-risk. And in cases such as these, supplementing oxygen offers no additional benefits." For the analysis, the researchers examined 16 studies published from 1982 through 2020 of randomized controlled trials in humans — including one from School of Medicine researchers — involving more than 2,052 women in childbirth. "Overall, the studies produced mixed results, with some indicating a benefit and others indicating no benefit," Raghuraman said. "That was the reason for doing a meta-analysis. By pooling the numbers of patients across the studies we could get a more definitive answer than looking at individual studies." The researchers evaluated the pH levels of the babies' blood from samples taken shortly after birth. The pH measures the body's acidity and alkalinity in blood and other fluids, with neutral equaling pH value of 7. For infants, Raghuraman said anything less than 7.1 is considered abnormal and indicates oxygen deprivation. The researchers also compared neonatal intensive care admission rates and Apgar scores - a well-established test to evaluate newborn health at one and five minutes after birth. Apgar scores check a baby's heart rate, breathing and other signs to determine if the baby needs additional medical care. "Comparing the health of the babies whose mothers received oxygen and those whose mothers didn't, we found that the differences were essentially zero," Raghuraman said.

### Hospital Survey Finds Reasons for Both Optimism and Concern About COVID-19 and Newborns

An April survey of hospitals around the world found low rates of infection with SARS-CoV-2 among newborns, but also shortages of testing equipment, personal protective equipment (PPE) and personnel. Survey responses from more than 400 hospitals queried in April, 75% of which were in the US, found a low number of newborns infected: 54 confirmed cases and 311 suspected cases of COVID-19. It also found more than 50% said they had shortages of what was needed to care for the infants, according to results published in Pediatrics. "The take-home message for us was that while the number of cases in April was low, over half of the hospitals reported shortages of equipment, testing or personnel, disrupting their ability to care for newborns," said study coauthor Erika Edwards, director of data science at the Vermont Oxford Network and a research associate professor at the University of Vermont, in Burlington. "These

results were from a survey done in April, but we continued the audit after that," Edwards said. "We did one in May, one in June, and one in September. Those audits didn't necessarily involve the same hospitals that responded in April. We haven't tracked the specific hospitals that participated." The most recent audit, Edwards said, found a much lower number of newborns with confirmed infections, 3, as well as suspected infections, 61. "But in September, 41% were still experiencing a shortage of PPE, testing equipment and personnel," she added. "So just from what we've seen from these audits, while there are still infections in newborns as far as we can tell they are not raging through nurseries." The authors note in their report that, "Preterm delivery and neonatal and postneonatal mortality increased during the 1918-1919 influenza pandemic, and more recent influenza outbreaks revealed ready transmission in NICUs. Whether SARS-Cov-2 will behave similarly is unknown."

To get a better understanding of how SARS-CoV-2 was impacting newborns and their care, Edwards and her colleagues invited hospitals via email to answer questions on Survey Monkey. Each participating hospital was asked to conduct an audit on a single day of their choice and report the results on that website. The first part of the survey identified the census of infants admitted within 28 days of birth, confirmed infant cases, and suspected infant cases on the day of the audit in mother-infant rooms; level I, II, III or IV neonatal units, and special units created for the care of infants with COVID-19. For the second part, hospitals were asked about shortages of personal protective equipment, beds, medical devices or equipment, or medications; about the availability or timeliness of testing; and about the availability of physicians, nurses, respiratory therapists or other personnel who significantly impacted the care of infants and families. A total of 434 hospitals participated and 359 completed the audit. The 275 hospitals completing the first part reported 54 confirmed cases and 311 suspected cases of COVID-19 among 11,341 eligible infants. Overall, 62% of the hospitals reported no confirmed or suspected cases, while 90% reported three or fewer cases. Of the 332 hospitals that completed the second part, 54% reported significant shortages of equipment, testing or personnel and 73% reported minor disruptions in care for infants and families, with 3% reporting an inability to care for some, most, or all infants. One limitation of the study, the researchers note, is the possibility that hospitals with high numbers of COVID-19 cases were less likely to participate or that hospitals with limited numbers of cases were more likely to participate, which would potentially result in over- or under-estimates of the impact.



### Infection Control and Remote Patient Monitoring During Current Health Climate

As concern over the COVID-19 virus continues to grow and many pulmonary function labs remain open for testing, there is an increased scrutiny on patient safety and how patient health is monitored. These topics have always been on the forefront of MGC Diagnostics' commitment to their customers and they have complete health solutions to ensure you can provide the best care to your patients.

Having clear and defined infection control policies is important for staff and patient safety. Infection control has seen a marked increase in the last year with augmented cleaning procedures to ensure the safety of staff and patients. Pulmonary function labs have been vigorous in their attempts to clean any part or surface that might be contaminated. With MGC Diagnostics, changing patient testing supplies is complete in less than a minute with no warm-up time or recalibration of the system. With options to sterilize and reuse or dispose, you're able to make the choice that is right

for you. MGC Diagnostics' preVent® flow sensor has a simple snap-in setup and is accurate and low cost. Also available are filters, mouthpieces and a patient circuit to complete your patient testing setup.

So, you're able to test patients safely, but how long before you can test the next patient? ATS recommendations state that you should have sufficient time between patients to allow for adequate room ventilation. They recommend a negative pressure room, if one is available. The time varies depending on whether the room is under negative pressure and whether there is a concomitant use of a high efficiency particulate air (HEPA) filter or ultraviolet light decontamination. According to the CDC, if you only have 10 air changes per hour in your lab, you need to wait 28 minutes for 99% efficiency for airborne-contaminant removal.

The AirPura UV614 HEPA filter offered by MGC Diagnostics is a system that combines both a Super HEPA filter and UV light to help decontaminate the air in your testing room and speed up the wait time between patients. With a maximum airflow of 560 CFM, the UV614 can provide up to 26 air changes per hour based on a 12'x12x9' room. When combining the UV614 with the facility's HVAC system, this could bring the wait time to under 15 minutes. The Super HEPA filter has a 99.99% efficiency in removing airborne particles 0.3 microns in size or larger.

In order to maximize patient safety and potential harmful contacts, Remote Patient Monitoring should be considered, when possible. The GoSpiro® spirometer offered by MGC Diagnostics provides laboratory quality diagnostic testing that can be conducted outside of the clinic and in the comfort of a patient's home. After all, when a patient is comfortable you will get the most accurate test results. The GoSpiro spirometer provides easy-to-follow, on-screen instructions to simplify testing and provide patient guidance. The GoSpiro is the only spirometer to have an Avatar enabled coach that walks patients unfamiliar with performing spirometry through the process and provides post-test comments to guide patients to optimal performance. To learn more about the MGC Diagnostics advantage, visit www.mgcdiagnostics.com.

### Breastfeeding, Rooming-in Can Be Practiced by Mothers With SARS-CoV-2

For women with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, rooming-in and breastfeeding are feasible for those who can care for their infants, with postnatal transmission occurring infrequently, according to a study published online Dec. 7 in JAMA Pediatrics. Andrea Ronchi, M.D., from the Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico in Milan, and colleagues examined the risk for postnatal transmission of SARS-CoV-2 from infected mothers to their neonates following rooming-in and breastfeeding in a prospective, multicenter study involving mother-infant dyads followed up for 20 days of life. Participants included 62 neonates born to 61 mothers with SARS-CoV-2 infection who were eligible for rooming-in based on their clinical condition and negative infant nasopharyngeal swab result at birth. The researchers found that only one infant (1.6 percent) was diagnosed as having SARS-CoV-2 infection at postnatal checks. In that case, due to severe worsening of the mother's clinical condition, rooming-in was interrupted on day 5 of life. On day 7 of life, the neonate became positive for the virus and developed transient mild dyspnea. Almost all (95 percent) neonates were breastfed. "We believe that SARS-CoV-2-infected mothers in good clinical condition and willing to take care of their babies should be encouraged to practice rooming-in and breastfeeding after being carefully instructed about the appropriate droplet and contact precautions," the authors write.

### New case suggestive of in utero SARS-CoV-2 transmission

A new report of mother-to-fetus transmission of SARS-CoV-2 through umbilical cord blood adds to a small but growing body of evidence that the virus can be transmitted in utero. Further, this case suggests such infections may not be easily detectable in neonates until days after birth. In a report published in the Journal of The Pediatric Infectious Diseases Society, Isabelle Von Kohorn, MD, PhD, of Holy Cross Health in Silver Spring, Md., and colleagues, described a case of neonatal infection with SARS-CoV-2 in a boy delivered by C-section at 34 weeks to a mother diagnosed with COVID-19 some 14 hours before. The newborn was immediately removed to a neonatal ICU and reunited with his mother a week later, once the mother had recovered. Dr Von Kohorn and colleagues reported that, while the infant's nasopharyngeal swab test for SARS-CoV-2 was negative at 24 hours after birth, repeat molecular tests (using different assays) from 49 hours on were positive and indicated an increasing viral burden, although the infant never developed symptoms of COVID-19. In addition to being found in the nasopharynx, viral RNA also was detected in cord blood and in urine. No viral RNA was found in the placenta. The circumstances of the birth, and the care taken to keep mother and her infant at a safe distance along with masking of the mother, made it "extremely unlikely" that the infant acquired his infection by the respiratory route, Dr Von Kohorn and colleagues wrote. "While we cannot rule out microscopic maternal blood contamination of cord blood in this or any other delivery, cord blood collection procedures are designed to avoid gross contamination with maternal blood. Microscopic contamination would not explain the RNA levels observed in our patient's cord blood," they wrote. Clinicians should note that a neonate born to a mother with COVID-19 may take time to test positive for SARS-CoV-2 , the investigators argued, though the current recommendation of the American Academy of Pediatrics is to test nasopharyngeal secretions of well newborns at 24 and 48 hours but not again in the absence of symptoms. "This case suggests that some cases of SARS-CoV-2 in newborns may be detectable only after 48 hours of life." The authors hypothesized that virus transmitted by cord blood "seeded the nasopharynx and required 2 days for incubation and replication sufficient for detection."

### Fetal Exposure to Biologics, Thiopurine Not Linked to Worse Pregnancy Outcomes

Women with inflammatory bowel disease (IBD) who take biologics with or without thiopurine during pregnancy are not at increased risk of adverse outcomes, according to a new prospective study. "The data from PIANO in 1,490 pregnancies of which 869 were exposed to a biologic (alone or in combination with thiopurine) showed no evidence of harm with biologic exposure - no increase in birth defects, pregnancy loss or complications, infant infections or infant development," Dr Uma Mahadevan of the University of California, San Francisco, said. IBD itself, especially active disease, confers a greater risk of preterm birth, miscarriage and other adverse outcomes, she and her colleagues note in Gastroenterology. The American Gastroenterological Association's clinical care pathway recommends that women with IBD continue medical treatment during pregnancy and breastfeeding, but guidelines from Europe and elsewhere advise stopping biologic therapy at 22 weeks to reduce fetal exposure.

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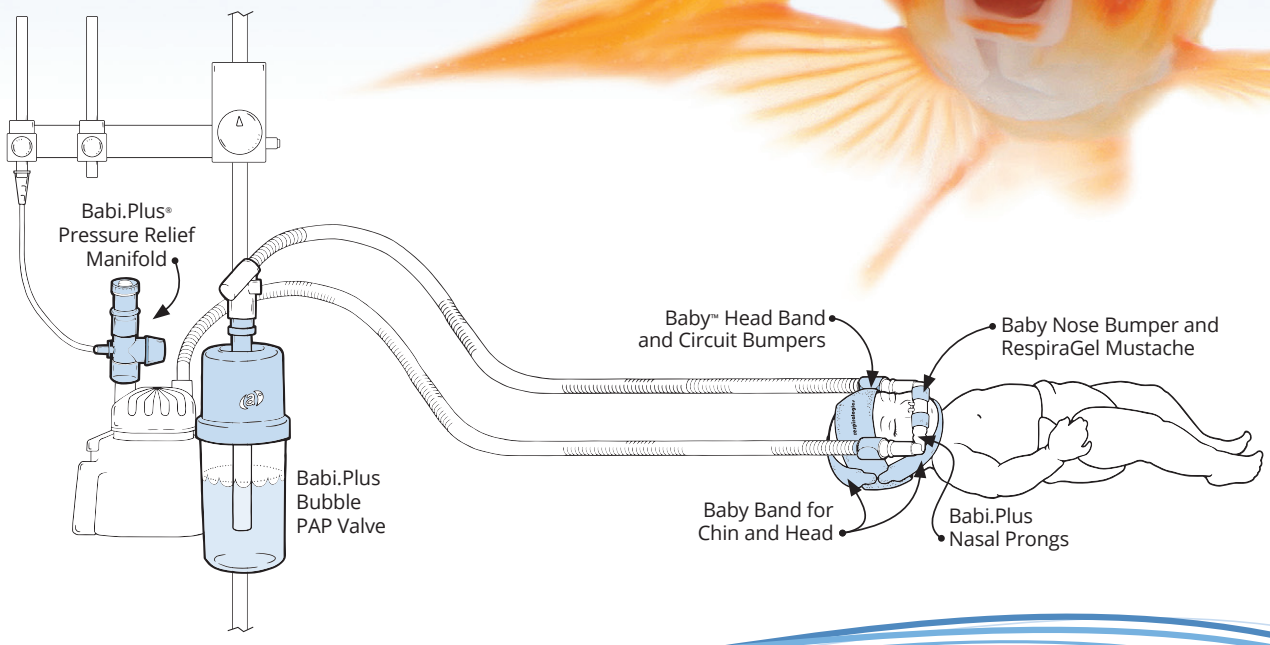


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"However, this practice has clearly been associated with an increase in flares which can then lead to increased adverse outcomes for the baby," Dr Mahadevan said. She and her colleagues looked at outcomes for 1,490 completed pregnancies and 1,431 live births for women with IBD enrolled from 30 centers between 2007 and 2019. Data on infant outcomes at one year were available for 1,010 children. There were 379 completed pregnancies in women not exposed to biologics or thiopurines, and 242 in women exposed to thiopurines, 642 in women exposed to biologics, and 227 in women exposed to both drug types. Congenital malformations occurred in 133 infants (9%), while there were 42 spontaneous abortions (3%), 91 (7%) low birth weights, and 132 (10%) preterm births. There were also 58 (4%) children who were small for gestational age, 30 (2%) with intrauterine growth restriction and five (0.30%) stillbirths. There was no association between drug exposure and congenital malformations, spontaneous abortions, preterm birth or low birth weight or infant infections, Dr Mahadevan and her colleagues found. However, women with higher disease activity were significantly more likely to miscarry (hazard ratio, 3.41), and infants delivered preterm were at increased risk of infection during their first year (odds ratio, 1.73). "Providers and patients should be reassured by this data," the researcher said. "As always, 'more studies are needed' but this study of 1,490 patients with outcomes out to 4 years is very reassuring. Continue biologics during pregnancy, make sure the mother is in remission and all IBD pregnancies should be followed as high risk, as even in remission they can have increased complications compared to others their age."

### Late-Onset Sepsis Reduced in Premature Infants Fed Prolacta's 100% Human Milk-Based Fortifiers as Part of an Exclusive Human Milk Diet

Implementing Prolacta Bioscience's products as part of an exclusive human milk diet (EHMD) reduced the incidence of and evaluations for late-onset sepsis among premature infants, according to clinical studies that compared Prolacta's 100% human milk-based fortifiers to cow milk-based fortifiers. Premature infants can face many life-threatening complications. Among the most prominent of these risks is late-onset sepsis, a dangerous systemic response to infection and a leading cause of mortality in neonatal intensive care units (NICUs). It is estimated that premature infants have up to a 26% chance of developing this serious complication. In addition to predisposing infants to other morbidities, and subsequent neurodevelopmental disabilities, sepsis significantly increases NICU costs. "We developed our human milk-based fortifiers to provide the precise nutrition that vulnerable infants need to have the best possible start in life," said Melinda Elliott, MD, FAAP, and chief medical officer of Prolacta. "We are encouraged by the reduction in late-onset sepsis incidence and evaluations observed with the use of Prolacta's products as part of an EHMD. Less sepsis means less suffering for infants as well as resource savings for already budget-strapped NICUs." Minimizing the incidence of sepsis may include limiting premature infants' exposure to interventions that have been shown to increase sepsis risk, such as central venous lines, extended parenteral feeding, and using cow milk-based fortifiers. Clinical evidence demonstrates that one way hospitals achieved this is with Prolacta's 100% human milk-based fortifiers. A 2014 study showed that for every 10% increase in the volume of milk containing cow milk-based protein fed to preemies, the risk for sepsis increased by 17.9% ($P < 0.001$). Similarly, a 2013 study showed the odds of sepsis decreased by 19% for every 10 mL/kg/day increase in the feeding dose of human milk in the critical first 28 days of life ($P = 0.008$). By implementing Prolacta's products as part of an EHMD, the University of Virginia (UVA) NICU achieved a 12.5% decrease ($P = 0.06$) in late-onset sepsis evaluations. In 2016, researchers showed multiple clinical outcome improvements that suggest a direct association to the use of Prolacta's products as part of an EHMD, including an 11.3% reduction in incidence of late-onset sepsis ($P < 0.00001$).

### Medtronic Launches the First and Only Pediatric and Neonatal Acute Dialysis Machine in the US

Medtronic announced the US commercial launch of the Carpediem Cardio-Renal Pediatric Dialysis Emergency Machine. Following the US Food and Drug Administration's (FDA) marketing authorization, granted earlier this year, the first Carpediem systems in the United States were successfully installed and are in use at Cincinnati Children's Hospital Medical Center. The first of its kind Carpediem system is indicated for use in acute kidney injury or fluid overloaded patients requiring hemodialysis or hemofiltration therapy. It is intended to provide continuous renal replacement therapy (CRRT) to patients weighing between 2.5 and 10 kilograms. Critically ill patients are at a high risk for fluid overload and acute kidney injury, conditions in which the kidneys do not function properly in their vital role of filtering waste products and excess fluid from the blood to produce urine. Fluid overload is common in critically ill neonates and children, particularly after procedures such as cardiac surgery. The mortality rate for neonates with acute kidney injury has been reported to be as high as 60 percent. "CRRT procedures performed for critically ill infants using previously available technology are not optimal largely because dialysis machines available in the US are not designed to treat these small, fragile patients, and can potentially expose them to many risks," said Stuart L Goldstein, MD, professor of pediatrics and director, Center for Acute Care Nephrology at Cincinnati Children's Hospital Medical Center, who has been instrumental in raising awareness of the critical need for safe pediatric-specific dialysis. "This new system is designed specifically for these patients which enables increased precision of neonatal CRRT treatment and, potentially, reduces these risks. We are grateful to be the first site in the US with this technology to help the children in our care." CRRT is the most common treatment for critically ill patients whose kidneys are not functioning properly. In this form of renal replacement therapy, the patient's blood is pumped through a hemofilter to gently remove waste and excess fluid while minimizing the risk for hypotension (low blood pressure) and cardiac stability. Pediatric patients requiring CRRT have historically been treated with systems designed and indicated for adults and not approved for pediatric use, which can create potential clinical complications for neonatal patients. The Carpediem system is intended to address many of the challenges associated with current machines because it is the first CRRT system designed specifically for patients weighing between 2.5 and 10 kilograms. This system was championed by Professor Claudio Ronco, Director, Department of Nephrology and International Renal Research Institute of the San Bortolo Hospital, Vicenza, Italy (IRRIV). "At Medtronic, we strive to provide a portfolio of renal care solutions that improve outcomes, access to care, and quality of life for patients affected by severe renal injury or disease globally—no matter their size or age," said Ven Manda, president, Renal Care Solutions, which is reported as part of the Medtronic Minimally Invasive Therapies Group. "For the first time, some of the tiniest and most vulnerable patients can be treated with technology designed specifically for them. We cannot make the world a healthier

place alone. That is why collaboration with clinical experts, such as Prof. Ronco and Dr Goldstein, is critical to bringing new treatment options to underserved populations."

### Newborns and Breast Milk

Newborns are unlikely to contract SARS-CoV-2 while breastfeeding and rooming-in with mothers infected with the virus that causes coronavirus disease 2019 (COVID-19), if precautions such as wearing a mask and practicing careful hand hygiene are taken, a new study suggests. The study, published in JAMA Pediatrics, included 62 infants born to 61 mothers who tested positive for SARS-CoV-2 at 6 maternity centers in northern Italy between March 19 and May 2. During follow-up over 3 weeks, only one infant tested positive for the virus. "COVID-19 positive mothers who mask, perform excellent hand hygiene can know it is safe to room-in with their newborn as well as provide breast milk if they feel well enough to care for their baby," David A. Kaufman, MD, a professor in the Department of Pediatrics at the University of Virginia School of Medicine, said. Kaufman co-authored an editorial published in association with the study on JAMA Pediatrics. Early in the pandemic, the American Academy of Pediatrics recommended that new mothers with COVID-19 be physically separated from their newborns to avoid transferring the virus. The AAP has since updated its recommendations to allow rooming in with precautions such as mask wearing and hand hygiene. Rooming-in promotes the mother-child relationship and breastfeeding. All of the mothers who participated in the study had mild symptoms or were asymptomatic at the time of delivery and felt well enough to care for their infants. In the one case where they infant tested positive for SARS-CoV-2, rooming-in was interrupted at Day 5 when the mother's condition worsened, requiring ICU admission and mechanical ventilation. The infant displayed mild symptoms that resolved after a few days, and the infant was discharged to the father's care at Day 18. Among the infants, 95% were breastfed, including 73% who were exclusively breastfed. "Breastfeeding or receiving expressed breast milk should be considered protection against infection and not as a risk for the virus to be transmitted to the newborn via the breast milk," Kaufman said. To qualify for rooming-in practices, mothers had to be well enough to care for their infants with temperatures less than 38°C (100.4°F) and no need for supplemental oxygen or respiratory support. Infants were born at 34 weeks of gestational age or later with birth weights over 2000 grams (4.4 pounds) and healthy physical examinations and vital signs. Mothers were educated about droplet and contact precautions, hand hygiene and rigorous application of recommendations to prevent transmission of the virus.

### Common Newborn Hearing Test Promising for Early Detection of Autism

A commonly used newborn hearing test shows promise in the early detection of autism spectrum disorder (ASD), new research shows.

Results from one of the largest studies of its kind show the auditory brainstem response (ABR) test, which is carried out on most newborns, represents "a huge untapped potential" to detect autism, lead author Oren Miron, research associate, Department of Biomedical Informatics, Harvard Medical School, Boston, Massachusetts, and a PhD candidate at Ben Gurion University in Beersheba, Israel, said. "The findings further reinforce our understanding that autism, in many cases, has

a sensorial and auditory aspect to it," said Miron, adding that an adverse response to sound is one of the earliest behavioral signs of autism. Autism spectrum disorder (ASD), which involves problems in social communication and interaction, affects an estimated one in 59 children. Early identification and intervention are critical for improving outcomes and decreasing the economic burden associated with ASD. The ABR test, which is used for Universal Newborn Hearing Screening (UNHS), uses surface electrodes to measure auditory nerve and brainstem responses to sound. Previous studies identified abnormal ABR amplitude in children with ASD. However, it's unclear whether healthy newborns who later develop autism also show ABR differences vs those who don't develop the disorder. Researchers used UNHS data, which allowed them to examine a larger, younger, and healthier sample compared with previous studies. The study included 321 newborns later diagnosed with ASD and 138,844 controls without a subsequent ASD diagnosis. The mean ABR testing age was 1.76 days for newborns later diagnosed with ASD and 1.86 for those in the non-ASD group. The ASD group was 77% male and the non-ASD group was 51% male. The rate of neonatal intensive care unit admission was 8% in the ASD group and 10% in the non-ASD group. The hearing test involves placing an earpiece in the baby's ear and delivering a click sound at 35 dB above normal hearing level (nHL) at a rate of 77 clicks per second in the right ear and 79 clicks per second in the left ear.

### Nebulized Surfactant Shows Promise in Large Cohort

Nebulized delivery of surfactant reduced the need for intubation and liquid surfactant administration by half among newborns with signs of respiratory distress syndrome, according to results from a large randomized, multicenter trial. Neonatologists have long sought alternatives to intubation for administering surfactant to newborns with respiratory distress syndrome (RDS). An effective noninvasive aerosolized treatment has remained elusive, with small clinical trials that have produced mixed results. In research published in Pediatrics, James J. Cummings, MD, of Albany (N.Y.) Medical Center, and colleagues, randomized 457 infants (mean 33 weeks' gestational age) with signs of RDS to either usual care or a nebulized bovine surfactant. Infants were recruited at 22 neonatal ICUs in the United States. Investigators were not blinded to treatment allocation and the decision to intubate was left up to the individual treating physician, because to do so, the authors wrote, would add "pragmatic strength" to the study, and "be ethically compliant with the infant's best interest." Infants in the study received usual care or up to three treatments 4 or more hours apart of 35 mg/mL calfactant suspension, 210 mg phospholipid/kg body weight delivered into the mouth through a nebulizer modified with a pacifier. Dr Cummings and colleagues found that intubation and liquid surfactant administration within the first 4 days after birth was 26% in the intervention group and 50% in the usual care group ($P < .001$). The results remained significant after investigators adjusted for gestational age, birth weight, age when randomized, sex, delivery mode, and antenatal steroids. Rates of intubation for surfactant administration were lower for infants in the intervention group in all gestational age brackets except the youngest (23-24 weeks); all of these infants needed intubation. Respiratory support at days 3, 7, and 28 did not differ between study groups. "Our study is the first to reveal the efficacy of an aerosolized surfactant delivery system that does not require a respiratory circuit interface," the investigators wrote. In previous trials of aerosolized surfactants, they noted, treatment was delivered with nasal continuous positive airway pressure. "By using a separate, pacifier interface, both the aerosol delivery and [nasal continuous positive airway pressure] flow can be managed independently, which should allow for safer patient care." Dr Cummings and colleagues also acknowledged several important limitations of their study, including its nonmasked, nonblinded design, and that it enrolled few infants with less than 28 weeks' gestation. It takes 1-2 hours to deliver aerosolized calfactant, and "we did not want to delay definitive treatment."

### Proposed Withdrawal of Approval of Preterm Drug: Two Opposing Views

The Oct. 5, 2020 move by the Food and Drug Administration's Center for Drug Evaluation and Research (CDER) suggesting the withdrawal of the approval of Makena incited some opposition. Amag Pharmaceuticals' 17 alpha-hydroxyprogesterone caproate (17OHP) injection received accelerated approval in 2011 to reduce the risk of recurrent preterm birth in women with previous unexplained preterm birth. Makena is the only drug approved for preventing recurrent preterm birth. The approval was based on findings from a randomized, placebo-controlled trial that demonstrated a 34% relative risk reduction in births before 37 weeks — from 55% in the placebo arm to 36% in the 17OHP-treated arm. The trial was not designed to measure neonatal outcomes, with the surrogate outcome of recurrent preterm birth being determined as "reasonably likely" to predict benefit to the neonate. Subsequently, results of the required postapproval confirmatory PROLONG trialproduced conflicting results, failing to show a benefit of 17OHP on either preterm birth or neonatal outcome, which prompted the proposed withdrawal of the drug's approval. The CDER advisory committee agreed unanimously that the PROLONG trial did not support the clinical benefit of 17OHP, but the committee was not unanimous in deciding what to do. Of the 16 members, 9 voted to withdraw the drug's approval, while seven voted to retain it and require another confirmatory trial. When CDER recommends withdrawal, the company can request a public hearing, which it has done. The FDA commissioner will recommend whether to grant this request. In the meantime, the New England Journal of Medicine has published opposing views on withdrawal of FDA approval of 170HP: one from a group of three doctors who are against it and the other from the CDER. "We sympathize with women who are at risk for recurrent preterm birth that could result in death or significant lifelong health effects in neonates, but retaining on the market a drug not shown to be effective for this use does not protect or promote their health," wrote Christina Chang, MD, MPH and associates from CDER.On the other hand, "the widespread use of 17OHP after accelerated approval has not uncovered important safety signals," countered Michael F. Greene, MD, from Massachusetts General Hospital, Boston; David Harrington, PhD, from the Harvard T. Chan School of Public Health, Boston; and Mark A. Klebanoff, MD, MPH, who was coauthor on the original preapproval study and is with Nationwide Children's Hospital, the Ohio State University College of Medicine, and Ohio State University College of Public Health, all in Columbus. "Withdrawal of the approval for 17OHP, as imperfect as it may be, will leave a very vulnerable demographic group of US women at high risk for this complication of pregnancy with absolutely no available therapeutic option." While both the preapproval study and postapproval PROLONG trial had the same enrollment criteria — namely women with a singleton pregnancy and previous singleton spontaneous preterm birth — all parties acknowledged that the studies ended up with very different

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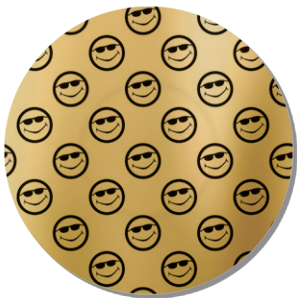

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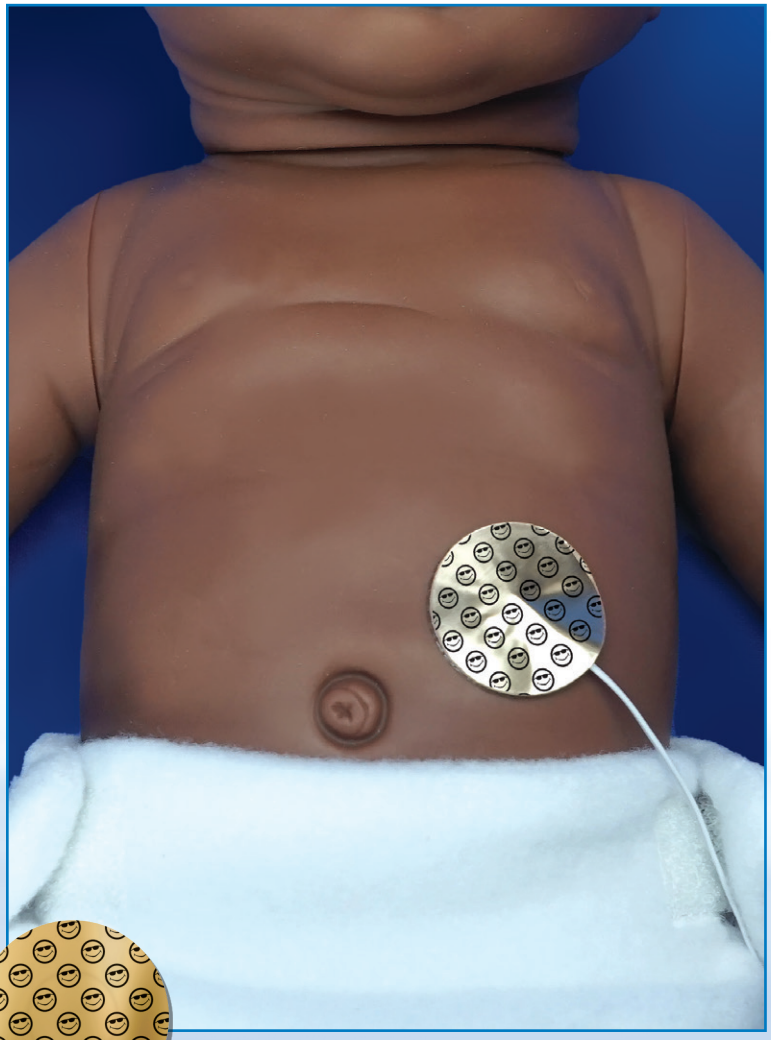

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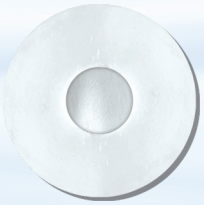

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# Preventing Misfeeds Using the SafeBaby® Feeding Management System in the NICU

**In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Mary Ann Blatz, DNP, RNC-NIC, IBCLC and Rosella Dempsey, RN, IBCLC who work in the University Hospitals Rainbow Babies and Children's Hospital's Level III NICU located in Cleveland, Ohio.**

**Neonatal Intensive Care:** The primary reason NICUs implement SafeBaby® for their feeding management needs is to eliminate misfeeds, ensuring that the right child gets the right nutrition at the right time. If a child is given breast milk from the wrong mother, what are some things that can happen?
**Rosella Dempsey:** Misappropriation of breast milk is a major issue. There is testing involved. You have to notify family. There's a lot of anxiety on [the] family's part.
**Mary Ann Blatz:** There are infectious disease risks. There is also the loss of trust from a family. You have to be transparent with the family and tell them the error occurred. They lose trust in the healthcare team. [There is also] the potential for litigation.

**NIC:** What are some things that can happen if a baby has expired milk or if a wrong product was administered to a child?
**RD:** We always worry about feeding intolerance or putting the baby at risk for infection. The baby could have a feeding intolerance. If we gave them a high calorie formula, if it was a really tiny baby and we gave them the wrong thing, we might have to stop feeds or put an IV in. There's a whole cascade of things that could happen if the baby didn't tolerate [the feeding].
**MAB:** If you're using fortifiers, when they fit whatever substrate you're feeding the baby, if you're using fortifiers that will potentially increase the risk for bacterial growth. Breast milk for a full term, healthy baby, they let that go for 5 to 8 days, depending on what source you're looking at, but our parameters are much more conservative in the NICU. SafeBaby® lets you know if milk is expired beyond one minute.

**NIC:** Before SafeBaby® was implemented, did your NICU use the 2-nurse check system? How compliant were nurses on that system? Was there an area in the system where nurses were prone to skip steps or take shortcuts?
**MAB:** We used the 2-RN check. 2 nurses would look at the medical record number and compare that with the baby's medical record number. Or if a parent brought the milk over, the parent could look at it and say, "Yes, this is my milk." and look at the name and number and know their handwriting.
**RD:** Nurses had to check and sign off that it was the correct baby, correct feeding. We were fairly compliant with it because [both nurses] had to actually sign the chart. I can't give you a percentage because I don't know. When moms would bring milk

The University Hospitals Rainbow Babies and Children's Hospital's Level III NICU is ranked among the top in the nation for neonatology according to US News & World Report, and is among the best in the nation-with some of the highest NICU survival rates.

we would just look at the label, put it in the refrigerator or the freezer.

**NIC:** What were some of the greatest risks inherent in the 2-nurse check system?
**RD:** If somebody just misread a label or did not notice the expiration. You might not notice a similar name.
**MAB:** It was just if people decided to skip steps. When the tool is not used, that's when you have an issue.

**NIC:** How were you trained on the SafeBaby® System at the initial go-live?
**RD:** [The SafeBaby® trainer from Paragon] came and did the training. It was a pretty thorough training; there was a video we watched which was helpful to introduce the subject, but the hands-on training was much more beneficial. He was here for the implementation; there was a whole team here when we went live.

**NIC:** When you began using SafeBaby® in production, did you feel that you had been adequately prepared?
**RD:** Yes, I thought the training was good. You really got a handle on the basics, but it is a steep learning curve. [Training is] not going to go over every scenario, but over time, [Paragon] has made the screens more user friendly. [They've] made [the handling of] multiples much easier [and] allowed us to [fix] things much easier in case we do make a mistake.

**NIC:** How are nurses currently trained on the SafeBaby® system? Who does the education? What training materials are used?

**MAB:** They get a brief overview from me but SafeBaby® is like driving; you have to do it to learn it. They are trained on the SafeBaby® system by their preceptor and then we periodically have competencies to demonstrate that they can do the various functions. We have training materials available for the staff.

**NIC:** How long is it between starting and that initial competency?
**MAB:** The NICU nursing orientation program is about 3 months. SafeBaby® technology is used throughout the orientation experience and competencies are documented as the orientees successfully demonstrate the various SafeBaby® functions.

**NIC:** Once you were feeling comfortable, how did you feel about SafeBaby® overall?
**RD:** I was fine with it because I was comfortable using it. Once you learn it and you use it, it's fine; it just takes a while to learn it.

**NIC:** How long did it take you to feel comfortable? How do other clinical staff feel about SafeBaby®?
**RD:** Maybe a month or two. I would have to go in and fix [nurses'] mistakes, so I got a different understanding of how [SafeBaby®] actually works. We have a few staff people who love clicking and scanning and who are really good at it.

**NIC:** Can you describe a situation when the SafeBaby® customer support line was used?
**RD:** I know we have called. [The SafeBaby® tech] has been great; very responsive. We were trying to backtrack and figure out how something happened, and he was able to help us through things.
**MAB:** [The SafeBaby® tech] is very helpful with issues. We only need to contact him every couple of months. [He] is always timely with his response. Some things can wait, and some things can't so I would call him if I needed to have a telephone conversation. He showed us how to merge mothers. Sometimes people put twins in incorrectly so [he] brought the Merge Mothers function to our attention. He identified that that would be a way to address those issues. For another issue, he sent me information about how to fix it so the labels don't skip when you print them. When we upgraded, there were issues and he was on it; he took care of everything.

**NIC:** Was there any particular aspect of the software you liked?
**RD:** The double-check. You're making sure you have the right food for the right baby. If you follow all the steps and don't skip anything, it will stop you from making an error. It has caught errors. If someone has an expired feed and they scan and try to administer it, [SafeBaby®] will stop you. [If] you scan the wrong baby, it will stop you.
**MAB:** The audit function is very helpful. If we need to investigate a situation, I can audit the bottle. Maybe somebody said they moved it to the freezer, but it was still in the fridge. Why is SafeBaby® telling me this milk is expired? I can use the audit function to explain the "journey" of each container with the audit report.

**NIC:** Have you been using SafeBaby® during an upgrade from one version of the software to an updated version? How did the transition go? Did you gain any value through the upgrade?
**RD:** I have. I thought it was pretty smooth. I don't remember any hurdles. I don't think there were any big problems on our side. You guys were responsive to some of our concerns and made some changes…There were some good changes that happened.
**MAB:** [The SafeBaby® tech] got almost all the issues ironed out. [Paragon has] incorporated several of our suggestions into the upgrade.

**NIC:** Different mothers' milk has different macronutrient content. The fat, the protein and the carbohydrate contents vary between mothers. Targeted fortification involves scanning a mother's milk using a mid-IR milk scanner to determine exactly what amount of a specific additive a patient needs. SafeBaby® 3.0 (currently

in production) will be able to track the macronutrient content in the future. Is that something that will prove useful if and when milk scanners become more readily available? What is your opinion on the future of milk scanners and targeted fortification?
**RD:** I think [having a milk scanner] would be great if we could do that to make [feedings] very specific to the baby's needs. We certainly don't have the capability to [get a milk scanner] here now but I think it would be wonderful if we could design the milk to meet exactly what the baby needs.

**NIC:** Does SafeBaby® offer any cost-cutting measures for the NICU?
**RD:** It stops you from making an error and [prevents] the costs of dealing with the repercussions. But we're not after this for cost cutting. We want to provide the safest care that we can for the babies. That's where we're coming from.

*Challenges…continued from page 12*
cohorts. Approval of the drug in the United States made it difficult to recruit US participants for the second trial "because of a lack of equipoise perceived by health care providers and patients," noted Dr Greene and associates, resulting in 75% of the PROLONG study's cohort coming from Europe. This meant that 59% of those in the first study were non-Hispanic black compared with just 6.6% in the PROLONG study, a difference that is important because of the increased risk of preterm birth in Black women. "Black women are generally underrepresented in US clinical trials, and they are clearly underrepresented in the PROLONG study," noted Dr Greene and colleagues, adding that "the total number of qualifying composite neonatal outcome events among Blacks or African Americans in the entire PROLONG study population of 1,700 participants was 9 (6 of 69 in the 17OHP group and 3 of 40 in the placebo group). This is not a robust database from which to conclude that there is no effect in Black women." But, Dr Chang and the CDER group argued, while the first study showed 17OHP "reduced the risk of recurrent preterm birth in both Black and non-Black participants, the lack of even a trend toward efficacy among either Black or non-Black women in [the PROLONG study] argues that the smaller proportion of Black women [in the PROLONG study] does not explain the lack of efficacy." In addition to race, there were other risk factors for preterm birth, such as tobacco, alcohol, and street drug use; marital status; and age that differed between the two study cohorts. Even after subcategorizing PROLONG trial participants into higher or lower risk for preterm birth based on these risk factors, Dr Chang and associates still found no evidence of benefit to 17OHP treatment in any risk group. Withdrawing approval of 17OHP for a recurrent preterm indication would still allow off-label prescribing, but would most likely end insurance coverage and eventually manufacturing of the drug, noted Dr Greene and associates. "When the majority of a population achieves little benefit from a drug, but a minority demographic group at greatest risk for a serious medical problem appears to obtain significant benefit, any decision that will ultimately make it impossible to obtain the drug should be undertaken cautiously," they warned. "This issue is particularly pressing when that minority group may be the least able to find and financially afford work-arounds to obtain the needed medication in our complex medical system that has a history of failing to serve them well."

### Report May Inform First Dietary Guidelines for Americans From Birth to 24 Months

The US Department of Agriculture and the Department of Health & Human Services released new dietary guidelines by the end of 2020. For the first time, the guidelines are mandated to include dietary recommendations from birth to 24 months and for women who are pregnant or lactating. An advisory committee submitted to the agencies a scientific report that examines relationships between diet and health at various life stages. Four chapters focus on dietary considerations for infants and toddlers, and two chapters focus on diet during pregnancy and lactation. The report may inform the development of the new guidelines. The advisory committee's recommendations include introducing infants to foods that are rich in zinc and iron at about age 6 months and having women who are lactating eat sources of omega-3 and omega-6 fatty acids, such as fish, to improve the fatty acid status of infants. Ahead of the release of the 2020-2025 Dietary Guidelines for Americans, Joan Younger Meek, MD, discussed parts of the scientific report at the annual
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# Monitoring Heart Rate Characteristics (HRC) and Late Onset Sepsis Journal Club Report

Alfonso Pantoja, MD

When heart rate patterns become abnormal, they may signal an underlying pathology. The analysis of these patterns offer a 'window' into autonomic nervous system function. Preterm infants, particularly ELBW infants, are extremely vulnerable to sepsis, which is often associated with decreased heart rate variability (HRV) and transient heart rate decelerations. The HeRO monitor was developed to analyze these abnormal heart rate characteristics (HRC) and display to clinicians a score, which may indicate the risk of an infant deteriorating from sepsis or other important clinical conditions in the upcoming days.

The main study to support this new technology comes from the study by Moorman et al.[1] In this large, multicenter randomized trial they studied the impact of monitoring heart rate characteristics (HRC) in VLBW infants. The theory behind this interventions is that the response to sepsis involves the cholinergic nervous system. By examining the HRC as a readout of that system will potential become an early biomarker of developing sepsis. This group has previously developed and validated a risk score for sepsis and demonstrated that a rising risk score preceded clinical signs of sepsis.

In this study, about 3000 VLBW infants were randomized to either routine monitoring or the addition of HRC monitoring with HeRO (Medical Predictive Science Corporation), with the risk of the development of sepsis displayed continuously for clinicians to use as they wished.

HRC monitoring was associated with an absolute risk reduction in the mortality rate from 10.2% to 8.1% (hazard ratio, 0.78; 95% CI, 0.61-0.99; *P* = .04; number needed to monitor = 48), and there was a trend toward increased days alive and ventilator-free (95.9 of 120 days compared with 93.6 in control subjects, *P* = .08). The mortality benefit was concentrated in ELBW infants (birth weight <1000 g) (hazard ratio, 0.74; 95% CI, 0.57-0.95; *P* = .02; number needed to monitor = 23. The mortality rate reduction associated with HRC monitoring was likely related to the reduced mortality rate from sepsis. HRC monitoring was associated with a 6.1% absolute risk reduction for mortality after sepsis. There were no significant differences in the other outcomes. This study suggested that HRC monitoring allowed early detection of VLBW infants who were developing sepsis and perhaps to be treated promptly and in consequence increasing their survival.

**PICO question:**
P: VLBW infants in NICUs
I: Heart rate characteristic (HRC) monitoring,
C: Patients not monitored
O: Reduction of mortality and length of stay

In a retrospective analysis of the patients in the original RCT,[2,3] infants randomized to receive HRC monitoring were more likely than controls to be discharged alive and prior to day 120 (83.6% vs 80.1%, *P* = .014). The postmenstrual age at discharge for survivors with positive blood or urine cultures was 3.2 days lower among infants randomized to receive HRC monitoring when compared with controls (*P* = .026).

Other clinical conditions in the VLBW population may produce elevated HRC scores. One of this is NEC. In the original RCT of 97 infants with NEC and HRC data,[4] 33 underwent surgical intervention within 1 week of diagnosis. The baseline HRC index from 1 to 3 days before diagnosis was higher in patients who developed surgical vs medical NEC (2.06±1.98 vs 1.22±1.10, P 1⁄4 0.009). The HRC index increased significantly 16 h before the clinical diagnosis of surgical NEC and 6 h before medical NEC. At the time of clinical diagnosis, the HRC index was higher in patients with surgical vs medical NEC (3.3±2.2 vs 1.9±1.7, P<0.001).

The findings of the multicenter study have not been uniformly reproduced in other isolated reports.[5] In that study HRC scores were often elevated in NICU patients who did not have bloodstream infection (BSI). Among patients with definitive BSI, HRC elevations ≥2 or ≥5 were infrequent in the 48 h preceding the time of sepsis evaluation.

Other conditions that may produce increased HRC scores are:

**Respiratory deterioration** without infection, possibly due to apnea, hypoxia, acidosis or lung inflammation. In a study of multiple cardiorespiratory measurements in VLBW NICU patients, an elevated HeRO score was highly predictive of the need for non-elective intubation.[6]

**Surgery** and procedures requiring anesthetic or anticholinergic medications, including treatment for retinopathy of prematurity, tend to cause decreased HRV and an acute rise in the HeRO score. In uncomplicated cases, the score rises quickly and returns to baseline within 12 to 18 hours.

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**Medications** known to affect the HeRO score include atropine, paralytics and dexamethasone. Premedication is increasingly used for intubation in NICU patients and atropine and paralytics depress HRV and raise the HeRO score. Dexamethasone administration tends to lower the HeRO score, possibly in part by reducing cytokine production and systemic inflammation.[7] Other medications commonly used in the NICU have not been observed to affect the HeRO score.

**Cardiac arrhythmias.** The most common arrhythmia in NICU patients, supraventricular tachycardia, leads to a dramatic decrease in HRV and, if persistent, a large increase in the HeRO score.

**Brain injury** may be associated with decreased HRV in NICU patients.[8] Preterm infants with severe intraventricular hemorrhage may have chronic intermittent increases in their HeRO score, not attributable to infection in the first few weeks after birth, possibly reflecting neurological dysfunction or a chronic systemic inflammatory response to the hemorrhage.

Highlighting the risk of sepsis by use of HRC monitoring could trigger an increase in antibiotic usage in infants who are monitored, with unpredictable and possibly adverse results. In the original RCT, there was no statistically significant increase in antibiotic usage in the monitored group.[1] However, if the HeRO monitoring is introduced in a NICU like ours, with a very proactive program of antibiotic stewardship, antibiotic usage will need to be closely monitored.

Like with any other diagnostic test that is applied to a certain population, the sensitivity, specificity, positive and negative predictive values will depend on the prevalence of the disease. In NICUs like ours where the incidence of LOS (5-10%) is lower than the mentioned in the original RCT, the use of the HRC monitor may prove to be beneficial in reducing mortality and length of stay only for those infants that are at highest risk for sepsis: ELBW with central lines.

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**Editor's Note:** this review was developed during evaluation of an initial purchase of HeRO monitors by St. Joseph's in Denver, CO. After six months of usage, they placed a subsequent order to double HeRO coverage.

*News…continued from page 16*
meeting of the American Academy of Pediatrics, held virtually this year. While the 2015-2020 guidelines use ChooseMyPlate to help people implement the recommendations, it is not known how the new guidelines will be presented to the public, she said. "Many of you will remember the pyramids earlier and different food groups before that." The advisory committee's report notes that diet in the first years of life contributes to long-term health and shapes taste preferences, said Dr Meek, professor of clinical sciences at Florida State University, Orlando. Human milk or infant formula are primary sources of nutrition until approximately 6 months, when families may introduce complementary foods and beverages. Between 6 months and 24 months, children transition to the typical family diet. Dr Meek highlighted some of the advisory committee's findings and recommendations. Infants who are ever breastfed have a reduced risk of overweight or obesity, type 1 diabetes, and asthma. Likewise, longer duration of breastfeeding is associated with lower risk of type 1 diabetes and asthma, and exclusive breastfeeding is associated with lower risk of type 1 diabetes. Complementary foods and beverages should not be introduced before age 4 months. Limited evidence indicates that their introduction before 4 months may be associated with increased odds of overweight or obesity. Introducing complementary foods or beverages at 4 or 5 months, compared with 6 months, is not associated with long-term advantages or disadvantages. Introducing peanut and egg after age 4 months may reduce the risk of food allergies. From age 12 months to 24 months, children should consume a variety of nutrient-rich protein sources from animals — including meat, poultry, seafood, eggs, and dairy — plus nuts, seeds, fruits, vegetables, and grains. The report prioritizes oils over solid fats, and whole grains over refined grains. It also discourages added sugars, particularly from sugar-sweetened beverages. Other sources of added sugars include sweets, baked goods, and sweetened dairy products.

### Pasteurizing breast milk inactivates SARS-CoV-2 virus

Researchers at the University of Toronto and Sinai Health have found that a common technique to pasteurize breast milk inactivates the virus that causes COVID-19, making it safe for use. It's the first time the impact of pasteurization on coronaviruses in human milk has been reported in the scientific literature and the findings provide assurance for parents and families who use human milk banks to feed their infants. Current advice is for women with COVID-19 to continue to breastfeed their own infants and it is standard care in Canada to provide pasteurized breast milk to very-low-birth-weight babies in hospital until their own mother's milk supply is adequate. "In the event that a woman who is COVID-19-positive donates human milk that contains SARS-CoV-2, whether by transmission through the mammary gland or by contamination through respiratory droplets, skin, breast pumps and milk containers, this method of pasteurization renders milk safe for consumption," the authors write in their study, published in the Canadian Medical Association Journal. The lead author on the paper was Sharon Unger, a professor of paediatrics and nutritional sciences at U of T and neonatologist at Sinai Health, who is medical director of the Rogers Hixon Ontario Human Milk Bank. Unger said the current pandemic is a time for extra efforts to protect the supply of donated human milk, in part because formula was scarce and previous pandemics — notably HIV/AIDS — created major challenges for human milk bank supply. The Holder method, a technique used to pasteurize milk in all Canadian milk banks
*Continued on page 56…*

# Persistent Reversed End Diastolic Flow in the Fetal Middle Cerebral Artery (MCA-REDF) with Favorable Outcome

Boris M Petrikovsky MD, PhD, Michael Terrani MD, Alison Dillon RDMS

## Introduction

Persistent middle cerebral artery end diastolic flow MCA-REDF is a rare finding with only a few cases reported in the literature.[1-5] In all these cases, the finding of persistent MCA-REDF have been associated with poor fetal and neonatal outcome (fetal demise, growth restriction, severe fetal anemia, and intraventricular hemorrhage, among others). All the researchers stress the importance of early recognition of persistent MCA-REDF and consideration for prompt delivery of the fetus at risk. We report a case of persistent MCA-REDF with a normal neonatal outcome.

## Case Series

We observed four cases of persistent REDF in MCA among 2,657 third trimester fetal ultrasound examinations (prevalence 0.15%). Unfavorable outcome (fetal demise -1, intraventricular hemorrhage -2) was detected in three cases. One case, however, had a normal outcome and is presented below. The patient was a 35-year-old G6P2 whose obstetrical history was complicated by a previous cesarean section. She underwent a routine ultrasound examination at 30 weeks of pregnancy, which demonstrated an appropriately grown fetus with a normal amount of amniotic fluid and normal umbilical cord Doppler values. A persistent MCA-REDF was noted (Fig 1). The fetal biophysical profile was normal. The patient was followed by twice weekly ultrasound assessment, which included fetal interval growth, umbilical Doppler (Fig. 2), and biophysical profiles with NST were normal. A Kleihauer-Betke test was negative as were parvovirus and toxoplasmosis titers. The patient received steroids to enhance fetal lung maturity in anticipation of early delivery. Pregnancy was allowed to continue until full-term, since MCA-REDF was the only abnormal finding. The patient underwent a repeat cesarean section at 39 weeks of pregnancy. A life male infant was delivered with Apgar scores of 9 and 9 at 1 and 5 min. respectively. The mother was discharged home with the baby on day 3 in satisfactory condition. The newborn had no signs of anemia or acidosis and is doing well 6 months after birth.

## Discussion

Fetal persistent middle cerebral artery reversed end diastolic flow is a rare and ominous finding.[1-3] Previous reported cases of persistent MCA-REDF have been all associated with intracranial hemorrhage, growth restrictions, anemia, and hepatic anomaly.[1-5] Brownfoot, et al[6] performed a literature review on the outcome of 6 cases of documented MCA-REDF

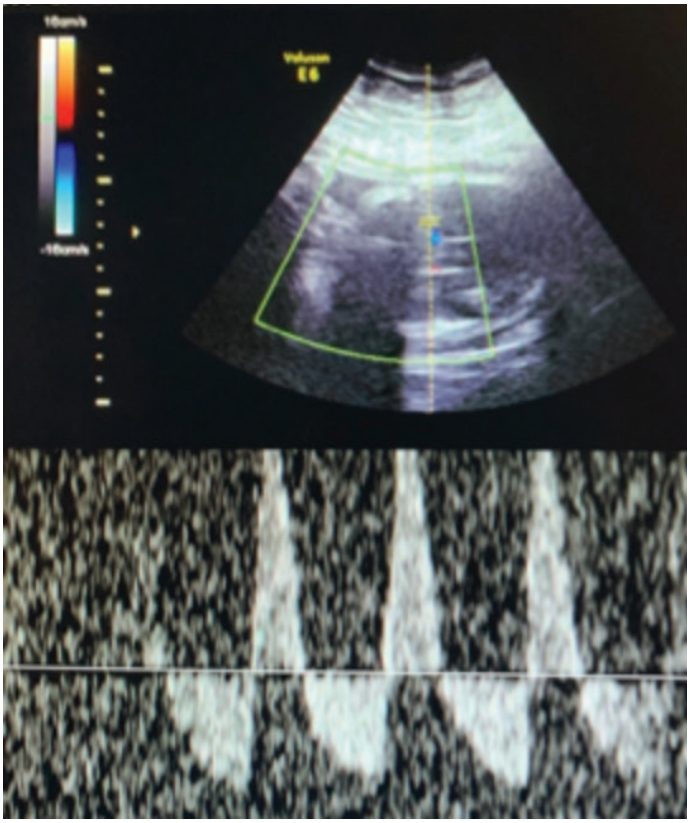

**Figure 1.** Absent end diastolic flow in the middle cerebral artery

out of which three fetuses died in utero, one died shortly after birth, one neonate was born with severe growth restriction, and one with grade III intraventricular hemorrhage. Extensive intraventricular hemorrhage led to increased intracranial pressure, increased impedance to flow, and, ultimately, reversal of flow. In addition, the extensive hemorrhage may have led to fetal anemia, which caused the elevated peak systolic velocity noted before the reversal of flow.[1] In cases of fetal hypoxia, his cerebral vasculature dilates, which causes a reduction in the MCA pulsatility index, a phenomenon known as "brain sparing effect".[7,8] "Brain sparing" is associated with abnormal venous flows with a further decrease of arterial $pO_2$ and fetal demise. High umbilical artery resistance combined with centralization of blood flow has been associated with fetal hypoxemia, hypercarbia, and lactic acidosis.[7] After loss of umbilical artery end-diastolic velocity, a consistent development of acidemia is observed with additional deterioration of venous indices in the

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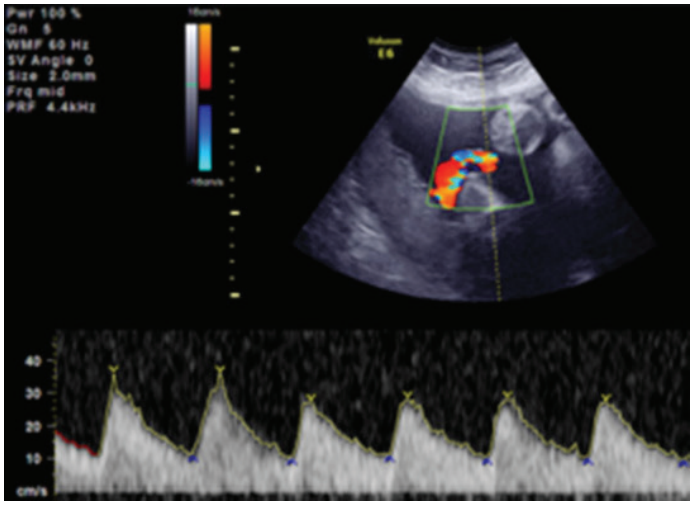


**Figure 2.** Normal umbilical blood flow

inferior vena cava or ductus venosus.[7] As the disease process progresses, the resistance in the MCA increases further.[7,8] MCA-REDF may be permanent of transient. Transient MCA-REDF is likely to occur due to excessive abdominal probe pressure and represents an artifact of no clinical consequence.[6] In our case, in spite of persistent MCA-REDF, the fetus demonstrated normal interval growth and good biophysical profile until 39 weeks of pregnancy, which allowed us to continue conservative management. It appears that we observed and reported the first case of persistent MCA-REDF with a favorable neonatal outcome. The fact that a favorable outcome is possible should not change the current approach to persistent MCA-REDF, which still remains a grave prognostic sign. Fetuses with abnormal venous flow have worse perinatal outcomes compared with those where the flow abnormality is confined to the umbilical artery.[7] In fetuses with low middle cerebral artery pulsatility serial, venous Doppler allows for the detection of further deterioration. While abnormal venous flows are significantly associated with fetal demise, gestational age at delivery appears to be the most important parameter to short-term outcome. Assessment of the fetal circulation by Doppler ultrasound is employed in various conditions including IUGR. Changes of flow velocity waveforms are observed in fetal vascular beds and Doppler surveillance is based on the relationship between circulatory changes and the fetal condition.[7] Such surveillance seeks the early detection of fetal compromise, to allow timely intervention in an attempt to prevent perinatal and long-term neonatal injury.

In conclusion, one should not undermine the seriousness of absent MCA flow for prognosis and management. However, this finding should be assessed in the context of other parameters of fetal well-being. If other tests of fetal well-being are normal (NST, umbilical Doppler, biophysical profile), a conservative management with frequent surveillance may be considered as an option.

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# To Exchange, Or Not to Exchange Is the Question

Shabih Manzar, MD


## Abstract

Exchange transfusion (ET) is used in the management of severe hyperbilirubinemia (SHB) to prevent acute bilirubin encephalopathy (ABE). Risk factors to ABE includes ongoing hemolysis and rate of the rise of bilirubin. The BIND (bilirubin induced neuronal dysfunction) score and serum bilirubin albumin (B: A) ratio has been described to assess the risk of ABE and need for ET. We present a management algorithm for SHB, based on the serum bilirubin level, BIND score and B: A ratio. A case of SHB is presented followed by literature review in support of the algorithm.


## Case

The infant was born to a 22-year-old G5P4004 at 38-5/7 weeks via precipitous vaginal delivery. Mom had limited prenatal care. All her prenatal labs were normal. Her blood group was O positive. The infant's blood group was B positive, with direct coombs positive.

Infant was admitted to normal newborn nursery (NBN). She was reported to have jaundice and difficult latching on the breast. The physical examination in the NBN showed an active infant, however, the total serum bilirubin (TSB) obtained at 20 hours of life was noted to be 24.7 mg/dl. Infant was immediately transferred to the NICU and a double volume exchange (DVE) transfusion was planned. Infant was started on intensive phototherapy and intravenous hydration.

The vital signs of the infant on admission to NICU were Temp: 97.7°F (36.5°C) Pulse: 115 Resp: 65 BP: 91/42 SpO2: 98%, Anthropometrics measurements were Head Circumference: 31.5 cm; Weight: 2700 g (5 lb. 15.2 oz.); Height: 44 cm (17.32").

Physical examination showed an active infant with strong cry. Head was normocephalic with no hematoma. Anterior fontanelle was flat. Scleral icterus was present. Neck was supple.

There was no murmur, rate and rhythm were normal with strong pulse. Chest was clear to auscultation. Abdomen was soft, no organomegaly was noted. Skin was dry with capillary refill of < 2 seconds. Infant had normal tone and neonatal reflexes.

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**Figure 1.** Showing the trend of serum Bilirubin

## NICU Course

On admission to the NICU, infant showed normal neurological examination. The BIND (bilirubin induced neuronal dysfunction) score — was zero and serum bilirubin albumin ratio was 6.4. Infant was continued on intensive phototherapy and was assessed hourly for BIND score. A preparation for DVE was made by calling the blood bank and umbilicus was soaked with saline for the line insertion. While waiting on ET, the infant responded to the intensive phototherapy and hydration. Her BIND score remained zero all along. She had good suck and was fed orally with gradual decline in TSB.

Figure 1 shows the serial serum bilirubin levels while Figure 2 depicts the course of hemoglobin, hematocrit, and reticulocyte count. Infant was transitioned from IV fluids to ad lib feeds. Phototherapy was discontinued on day 4 and infant was discharged on day 5 of life with close follow up. Infant had

| | At 3 hours | At 22 hours | At 34 hours | At 50 hours |
|---|---|---|---|---|
| WBC | 23.15 | 23.69 * | 20.45 | 15.04 |
| RBC | 2.93 ▼ | 2.64 * ▼ | 2.50 ▼ | 2.69 ▼ |
| Hemoglobin | 12.3 ▼ | 11.6 * ▼ | 10.7 ▼ | 11.6 ▼ |
| Hematocrit | 37.2 ▼ | 34.2 * ▼ | 32.0 ▼ | 34.2 ▼ |
| MCV | 127 ▲ | 130 * ▲ | 128 ▲ | 127 ▲ |
| MCH | 42.0 ▲ | 43.9 * ▲ | 42.8 ▲ | 43.1 ▲ |
| MCHC | 33.1 | 33.9 * | 33.4 | 33.9 |
| RDW | 22.6 ▲ | 24.8 * ▲ | 23.5 ▲ | 22.7 ▲ |
| Platelets | 342 | 335 * | 298 | 250 * |
| Retic Count | | | 16% | 15% |

**Figure 2.** Showing the trend of hemoglobin, hematocrit, and reticulocyte count.

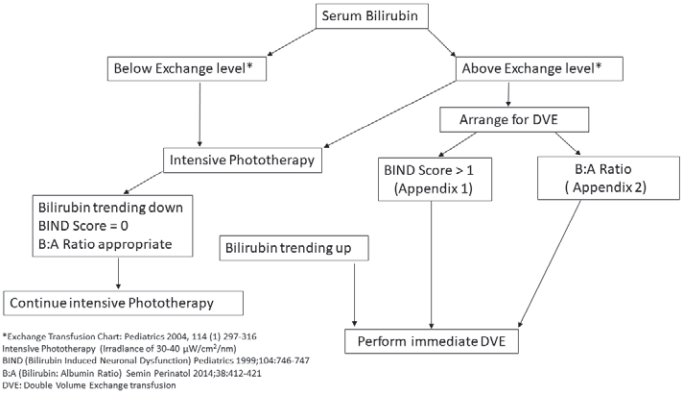


**Figure 3.** Proposed management plan for Exchange transfusion

normal neurological exam at discharge, and she passed the auditory brainstem response test.

## Discussion

Exchange transfusion (ET) is associated with electrolyte imbalance, cardiac overload, thrombocytopenia, necrotizing enterocolitis, and transmission of blood-borne diseases.[1,2] It is therefore appropriate to perform ET judiciously.

In this paper, we propose a management algorithm using BIND score (Appendix 1) and B: A ratio (Appendix 2). BIND score has been used extensively in predicting the risk of bilirubin encephalopathy in infants.[3-6] Similarly, B:A ratio is being used as a guide to ET.[7,8] The decision tree for managing severe neonatal hyperbilirubinemia and ET is depicted in Figure 3.

Olusanya et al[9] have compiled an excellent review discussing the global perspective of the management of hyperbilirubinemia and use of ET. They compared the management strategies followed in different countries and concluded that although ET is an effective treatment for preventing or limiting BIND in infants with severe hemolysis, but it is not entirely risk free. They suggested incorporating TSB level and clinical assessment in the decision making for managing severe hyperbilirubinemia (SHB). In a similar fashion, we suggest using an algorithm for the management of SHB. We suggest intensive phototherapy and IV hydration, continuous evaluation of BIND score with serial B:A ratio monitoring. A persistent zero BIND score, appropriate B:A ratio and declining TSB are reassuring. However, ET should not be delayed if bilirubin continues to rise, BIND score > 1 or B:A ratio is above the recommend ratio.

Larger randomized studies are needed to confirm the plan proposed in this study. As ET is not that frequent, such studies will take time. The proposed plan could be used an alternative to manage severe neonatal hyperbilirubinemia while we wait for larger studies.

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| Clinical Signs | BIND Score |
|---|---|
| Mental Status | |
| Normal | 0 |
| Sleepy | 1 |
| Lethargy | 2 |
| Semi-come | 3 |
| Muscle Tone | |
| Normal | 0 |
| Hypotonia | 1 |
| Hypertonia | 2 |
| Arching/Opisthotonus | 3 |
| Cry Pattern | |
| Normal | 0 |
| High Pitched | 1 |
| Shrill | 2 |
| Inconsolable | 3 |
| Total BIND Score | |

**Appendix 1.** Bilirubin Induced Neuronal Dysfunction (BIND) Score

| Risk Category | Bilirubin/Albumin Ratio (mg/dL:g/dL) |
|---|---|
| Infant > 38 week and well | 8.0 |
| Infant 35-38 week and well or > 38 week with hemolysis | 7.2 |
| Infant 35-38 week with hemolysis | 6.8 |

**Appendix 2.** Serum Bilirubin: Albumin (B: A) ratio

# Web-based Etiometry Platform Helps Clinicians Better Manage Patient Data

**In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Shane Cooke, the CEO of Etiometry.**

**Neonatal Intensive Care: What is the Etiometry Platform?**
**Shane Cooke:** Etiometry has an FDA-cleared clinical decision support platform for critical care, which is an end-to-end data management solution for collection, analysis, visualization, and archiving of clinical data. The web-based Etiometry Platform helps clinicians manage and better utilize the enormous amount of patient data to guide decision making in the very data-rich intensive care environment. Much of the patient data generated in the ICU environment is unused in actual clinical decision making—often there is just too much data, or it is difficult to access, and the information used tends to be a snapshot of a patient's condition which has already passed.

The Etiometry Platform enhances the use of available data to provide a full picture of a patient, enabling clinicians to anticipate and manage a patient's dynamic condition.

The platform consists of three integrated software components T3 Data Aggregation & Visualization, Risk Analytics Engine, and the Quality Improvement System. Together these components provide insight into the trajectory of a patient's condition and provide comprehensive data to clinicians whenever and wherever it is needed.

**NIC: Where is the Etiometry Platform most typically used?**
**SC:** Etiometry's platform is typically used in intensive care units within a hospital. Given the high acuity of patients within the ICU, and the need to make quick, informed decisions regarding a patient's care, the Etiometry Platform is well-suited for this environment. Etiometry's platform is utilized in several different ICUs, such as pediatric and adult cardiac units, pediatric ICUs, and neonatal units. The platform is also used in the Operating Room, Post-Anesthesia Care Units, step-down units, and during the COVID-19 pandemic, the platform has been installed in regional infection control units as well.

**NIC: How does the Etiometry Platform compare to other data & analytics companies or approaches?**
**SC:** Etiometry's model-based approach to analytics and algorithms is unique in the market, and differs from other analytics approaches, such as machine learning. We have built a model of human physiology that accounts for a wide range of factors that impact patient conditions such as autonomic regulation, cardiovascular mechanics, acid-base balance, pulmonary mechanics, and ventilation perfusion-mismatch.

The model is dynamic, and continuously adapts to the patient in the bed as more information is captured in our platform (e.g. vital signs, ventilator information, lab results), which enables the platform and our algorithms to determine the likelihood that a patient may be trending towards an adverse physiological state. Furthermore, our model helps to answer *why* a patient is in a particular adverse state, which helps clinicians to determine the next course of treatment.

Etiometry has two FDA-cleared risk algorithms, powered by our model of physiology, which continuously track the likelihood that a patient is experiencing inadequate delivery of oxygen (IDO2 Index) and inadequate ventilation of carbon dioxide (IVCO2 Index). Both indices are visualized on the T3 Software, helping clinicians to determine risk levels and interventions for a patient in the ICU.

**NIC: Why do I need the Etiometry Platform in the NICU?**
**SC:** In short, Etiometry can drive efficiency in care, and optimize decision-making and communication in the challenging NICU environment. Advancements in monitoring and support technologies in the NICU have helped improve the health of the smallest, most fragile patients. These advancements, however, have added to an already data and technology ladened environment making it challenging to effectively use all the data. The Etiometry Platform enables more efficient use of clinical data, providing access and visibility to a patient's complete data set when and where it is needed. The ability to see the trajectory of patient condition over the length of stay is important when caring for NICU patients.

Additionally, our risk algorithms have the potential to support clinicians' early identification of at-risk patients before an event or significant deterioration of a condition occurs. These Risk Indices have been FDA-cleared and deployed in the pediatric cardiac and general intensive care environments for several years. They are now being refined and validated for smaller patients for application in the NICU.

Additional platform features are especially well-suited to the NICU environment, such as: providing clinical surveillance and remote monitoring of all patients in the units; Tools to help organize and deploy standardized protocols and patient care guidelines; Automated reporting to streamline communication

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

and documentation; and automatic data collection for quality improvement projects and clinical research.

**NIC: How does Etiometry support its clinicians to optimize the benefits of the system?**
**SC:** Etiometry's platform has been utilized in the critical care environment for several years, and we understand the patients, the challenges, and obstacles in optimizing the use of technologies and data. Our goal is to address these challenges and support the clinicians in patient care by providing a best-in-class platform, as well as clinical training and support. We are a nimble, growing company, with a talented clinically focused field team supporting our customers at the bedside and a team of engineers and data scientists to help find new ways to address clinical challenges with our technology.

The Etiometry Platform supports existing clinical guidelines in hemodynamic management, respiratory management, communication, and quality improvement. Our Quality Improvement System (QIS) is a permanent archive of all the high-fidelity patient data collected which is easily accessible and compatible with many off the shelf analytics programs for use in clinical research and quality improvement initiatives. The QIS also supports standardized reporting on clinical performance metrics, for example compliance to established patient care protocols and guidelines.

**NIC: How is T3 being used by clinicians, nurses, and respiratory therapists?**
**SC:** T3 is being used by clinicians to assess a patient's current condition and to help inform clinical decisions either at the patient bedside or remotely. Common use cases of Etiometry include assessing patient risk with our risk indices, rounding and event review analysis, and as a valuable teaching tool.

In units where the platform has been deployed effectively it has become part of the overall patient management process, providing immediate access to critical patient data from multiple sources, visualizing and tracking unit wide patient groups, efficient visualization of specific organ system parameters for critical patients needing immediate attention, and providing historical trended data for event reviews or understanding the trajectory of the patient over a period of time.

The NICU is a unique clinical environment, which has a very heterogenous patient population. There is a need for more well-established norms for patient treatments or even normal vital signs, such as blood pressure, which Etiometry's longitudinal trends can help to elucidate.

**NIC: Why should clinicians adopt the Etiometry Platform if there is nothing wrong with their current system?**
**SC:** The Etiometry Platform excels at assembling and presenting data in a way that can support critical decision-making at the bedside. EMRs were not designed to provide this level for clinical decision support. Our platform assembles data for use at three levels: first, the individual patient data is assembled and presented in a logical and concise format at the bedside to provide immediate clinical decision support. Visualization of the trajectory of the patient's condition is enabled through immediate availability of historical patient data—this level of visibility of detailed patient data at the bedside is unmatched.

Second, our model-based approach to analytics utilizes this data in the computation of a variety of risk indices. These Risk Indices can identify specific deteriorations in physiology to aid clinicians and expedite focused individualized treatment.

Third, the collected data is permanently stored in the Quality Improvement System. This database of high-fidelity patient data is available for clinical research projects and quality improvement projects, including automated reporting

**NIC: How is the Etiometry Platform different than my EMR?**
**SC:** Context is crucial when it comes to patient data and our software provides the detailed insight for clinicians to understand what is happening to their patient. The typical EMR might provide a manually updated snapshot of a patient every hour while the Etiometry Platform automatically aggregates and visualizes patient data every five seconds.

# When It Comes To Reading Infant Probiotic Labels, What's Most Important?

Rebbeca M Duar, PhD

When it comes to choosing a probiotic for your infant patients, product quality and label transparency should be top priorities. A concise and coherent label is an essential component of a product's package, as it enables clinicians to easily differentiate and critically evaluate probiotic products through an evidence-based approach. However, according to a recent study, over 60% of probiotic supplements sold in the US are missing key components in their labels.[1] This guide is aimed to help health professionals analyze, understand and interpret probiotic product labels to make informed decisions when selecting high-quality, fit-for-purpose, probiotics for their infant patients. The principles outlined are similar to those recommended for evaluating dietary supplements and food products.

### 1. Ensure proper identification of the probiotic bacteria

Having the proper nomenclature is crucial to conduct an evidence-based selection of a probiotic product. Where this information is located can vary. In some, it is located in the ingredients list, while others have a separate list of bacterial strains. The placement is not as important as having the right information. The genus, species, subspecies (when applicable) and importantly, the strain names must be clearly listed. For example, in the probiotic strain *Bifidobacterium longum* subspecies *infantis* EVC001, *Bifidobacterium* is the genus, *longum* the species, *infantis* the subspecies and EVC001 is the strain name. When conducting research on the evidence for a particular product, use the strain name to connect the product with peer-reviewed data. Keep in mind, each strain is genetically unique and the benefits of one strain may be very different from others. Similarly, safety and efficacy associated with specific strains should not be generalized to other probiotic products.[2] For instance, a recent study found important genetic differences among *B. infantis* strains added to infant probiotic products.[3] These differences were found to be related to the wide variation in the ability of strains to utilize human milk oligosaccharides (HMOs). H5-positive strains were found to be fully functional and able to efficiently metabolize HMOs. On the other hand, H5-negative strains were found to have critical genetic mutations that negatively affect their ability to access HMOs and colonize the infant gut. These findings are relevant as the benefits observed when infants are colonized with *B. infantis* EVC001, an H5-positive strain, are strongly associated with the conversion of HMOs into beneficial metabolites that positively alter the biochemistry of the infant gut.[4] These biochemical changes are associated with the displacement of potential pathogens and a significant reduction in enteric inflammation.[5,4] Due to the reduced capacity to access HMOs and colonize the infant gut, it is unlikely that H5-negative strains can provide these benefits. This same study found that over 50% of products of did not list the strain name in their labels, making it impossible for health care professionals and consumers to assess the probiotic in an evidence-based manner.[3] Thus, it is advisable to steer away from products that do not list the strain and always confirm the scientific literature is aligned with the benefits claimed for a particular strain in a probiotic product.

#### *More isn't always better when it comes to probiotics*

More species or strains in a probiotic product does not guarantee better health benefits. There is currently no scientific evidence demonstrating synergism between two or more strains in providing additional benefits. In fact, some common probiotic species are known to have antagonistic effects on one another.[6] Moreover, combining strains that have been studied individually does not guarantee an additive effect, which could explain why a higher number of species or strains listed on a label is associated with less peer-reviewed evidence.[1] In a recent position paper, experts from the globally recognized European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) stated that "use of a single strain with proven effectiveness is likely to be more efficacious than use of a combination of strains without proven effectiveness",[7] reiterating the notion that when it comes to probiotics, using clinically studied, well-documented strains allows for a more targeted and evidence-based approach to infant gut health.

#### *Be wary of sudden name changes and reclassifications*

Label changes and reclassifications to bacterial names and strain designations can be deceptive and appear as a footnote, rather than in the main label. Sudden name changes usually indicate a strain or species was misidentified or replaced, a problem that has been notorious in products containing bifidobacteria due to the technical difficulties in differentiating the species.[8] The consequences are not minor. If misidentified, comparisons of outcomes across cohorts, units or clinical trials become meaningless. If replaced, an unintended bacterial strain may be incorporated into a standard of care and may impact patient outcomes. Official name changes in bacteria require agreement from a panel of international experts and when the changes take place the results are published in official journals. One example is the recent reclassification of the genus *Lactobacillus*, which was a process that spanned over two decades and

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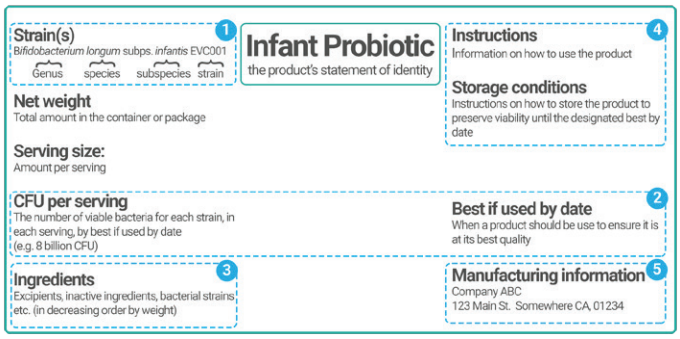


involved a global panel of industry and academic experts.[9] So beware, sudden name changes and reclassifications may not be innocuous and should be investigated closely. When in doubt, contact the manufacturer and enquire about the change.

### 2. Check the CFU and "Best if Used by Date"

CFU stands for colony forming units and is the measure of the number of viable bacterial cells by plate count. CFUs are determined by allowing the organism to grow on appropriate media under controlled conditions and then counting the number of colonies present. This method is a long-standing industry standard and is the notation recommended by the US Food and Drug Administration for probiotic labels.[10] Quantities can vary, but are typically in the millions or billions per unit. Most importantly, the CFU should be explicitly indicated for each individual strain contained in a product rather than the sum of all bacterial strains. Listing a total CFU as a total would be the equivalent of listing the total vitamin dose in a multivitamin product without a dosage breakdown for each individual vitamin. Clinicians need to know exactly what and how much of an active ingredient is going into their patients. Furthermore, the CFU should be guaranteed until the end of shelf life or best if used by date. Avoid products listing CFU at the time of manufacturing. Remember, probiotics are living bacteria; exposure to light, heat, oxygen, and moisture can reduce viability. Having a guaranteed CFU through the best if used by date ensures the probiotic contains the recommended amount of viable probiotic bacteria at the time of use.

### 3. Carefully review the list of ingredients

Ingredients should be listed in descending order by weight. In addition to the probiotic microorganism, product formulations often include inactive ingredients added for packaging and feeding purposes, and to protect the bacteria. Review this list and also check the "Other Ingredients" section to confirm that the product only uses ingredients known to be safe in infants.

### 4. Check the label for clear instruction of use and storage

Probiotic products come in many different forms, including most commonly capsules, powders, and liquids. Each form has specific requirements and instructions for use and storage. Liquid products are preferred for the hospital setting to avoid cross-contamination from aerosolized powder,[11,12] and low temperature storage protects the bacteria and extends the self-life. Make sure instructions are easy to follow and compatible with the protocols set in place in your unit.

### 5. Manufacturer's identification and contact information should be provided

The product label should contain manufacturer information and a direct line of contact. This information allows clinicians to choose a probiotic product from a company with knowledgeable scientists and implementation specialists that can help incorporate the probiotic seamlessly into standard of care protocols and provide continued training and support.

In summary, when it comes to quality and efficacy, the probiotic product should be able to coherently speak for itself. Accurately labeled products, containing high-quality microorganisms and robust supporting science make the best choice for your infant patients. Clinicians face numerous challenges when caring for vulnerable infants. Concerns about probiotic product quality should not be one.

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# Considerations for Successful Implementation of Camera Streaming Technology in the NICU

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## Introduction

Neonatal Intensive Care Units (NICUs) in the US are evolving; until recently, most units were structured with an open bay or pod concept. Though this layout allows providers to maximize the available space to support many infants in a relatively small area, it is not conducive to family integrated care. Cramped spaces and lack of privacy may deter families from spending a significant amount of time at their infant's bedside, and there is limited, if any, opportunity for overnight stays. With growing evidence to support family integrated care and the associated benefits to both parents and the infant (O'Brien et al., 2015), parents are encouraged to be active participants and tandem-decision makers in their infant's care. Emphasis on providing family integrated care within the constraints of an open concept NICU gave birth to live-streaming camera technology allowing parents to stay connected to their infant when they cannot physically be in the NICU.

Technology continues to evolve and penetrate the everyday lives of all people, including in the healthcare setting. Parents today are more tech-savvy than ever and expect continuous connection and convenience. Most parents have smart devices and depend on technology to support their daily functions. They expect this level of access to technology that must be assimilated into the healthcare setting and the NICU.

Although camera streaming technology has existed for more than ten years in the NICU environment, there is still much to learn about its impact on patients, parents, extended family, and staff. Based on publicly available information, adoption before the COVID-19 pandemic was slow, with fewer than 20% of NICUs across the country using this technology. In response to the pandemic, NICU's are challenged to preserve the parent-infant connection while prioritizing infection control. Most hospitals have further limited or completely restricted visitation. As a solution, NICUs have more readily implemented live-streaming camera technology which supports the parent-baby dyad throughout an infant's hospitalization and allows extended family support (Epstein et al., 2017; Hawkes et al., 2015; Joshi et al., 2016; Kerr et al., 2017; Rhodes et al., 2015).

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Most NICUs have restricted non-parent visitors (Muniraman et al., 2020), eliminating the ability for extended family to share in the experience and support parents throughout their NICU journey. Though families benefit from this relatively sudden and recent diffusion of live-streaming technology, the impact on staff remains unknown.

Kilcullen et al. (2020) completed a thorough literature review which concluded that although the literature confirms the benefits of camera streaming technology for both parents and infants, there remains little information on the impact on staff of using live-streaming video cameras in the NICU environment. Additional research needs to be conducted to further evaluate the impact on staff as the technology becomes more widely adopted. A current study is underway by Hilliard and Nauman evaluating neonatal nurse perceptions of live-streaming camera technology using a mixed methods approach. A survey was developed and distributed to approximately 1,500 neonatal nurses using digital platforms (including email and social media) and professional organizations. Preliminary data are mixed but show several key themes:

- A considerable number, approximately 70% of early respondents, have exposure to live-streaming camera technology in the NICU setting.
- Managing live-streaming technology impacts nursing workflows and attitude.
- Most nurses acknowledge the benefits of the technology to families, especially during the current pandemic.

Study data will be analyzed to better understand the impact of live-streaming technology on NICU nurses in an effort to optimize its use in the NICU environment.

## Top 3 things to consider when evaluating camera-streaming technology in the NICU:

**1) The Product.** Both the hardware and the software platform should be evaluated thoroughly in relation to daily workflow. From a hardware perspective, functionality and ease of use play an equally important role in how easily and efficiently staff can utilize the camera. The device will likely be turned on and off several times a day, so it must be easliy accessible when needed, but also quickly moved out of the way during emergency situations. It's important to assess where key functions (i.e., power button) are located on the device in relation to the patient, the staff work area, and other medical equipment. The ability to maneuver and manipulate the hardware and the

footprint of the hardware itself should also be evaluated. Lastly, the durability of the device, its life expectancy, and any warranty should be considered.

From a software perspective, the platform should be assessed for overall functionality and ease of use from both the staff and family perspectives. First and foremost, security and HIPAA compliance should be reviewed to ensure protection of patients, families, and the organization. It is critical to understand the workflows associated with creating and managing a family account from the staff perspective such as how family accounts are created and managed and how families are linked to the appropriate patient. Special consideration is necessary for the following scenarios: families of multiples, how family account access is handled (i.e., who controls access for multiple family members or friends to view the infant), and how non-native (English) speaking families are supported. Next, focus on evaluating integration options which allow for a simple, turn-key experience for staff. Ask about single sign-on and active directory integrations which support account management for staff. Integration into the facility's bed management system (likely part of the EHR) can be critical in reducing the time to onboard families, in moving/reassigning cameras when infants move bed spaces, and automating the infant/family discharge process from the software. Evaluate the process for updating software and the length of time devices can be expected to be out of service if hardware must be repaired or replaced.

Additionally, it is imperative to understand the entire platform and all solutions available from the vendor. For example, some platforms offer services in addition to the camera streaming technology that may be beneficial to NICU or other departments in the organization. This could offer a considerable cost savings through bundling, as well as organizational alignment of products.

**2) The Implementation Process.** The second element to consider is technical and clinical implementation support offered. It is essential to have a project management plan to ensure effective implementation, training, and adoption. Special attention should be given to how implementation will impact staff workflows from account creation and management to camera positioning and utilization. This technology becomes an integral part of the bedside equipment for patients and is frequently utilized approximately 16 hours per day. Consideration should also be given to staff support not just through basic education of how to use the device, but the resources available to support safe, uninterrupted patient care after go-live. Staff support involves having the appropriate resources and documents to consent and set clear expectations for families, guidelines to ensure the appropriate use of the technology, and annual training and competencies that will lead to consistent adoption and high satisfaction by the staff.

Change management that focuses on staff adoption is vital for the successful implementation and utilization of camera streaming technology. There is a fine balance between providing technology that addresses both family needs and safe, efficient staff workflows while ensuring safety and confidentiality. How the camera technology is introduced to staff, how they are supported throughout the implementation process, and how leaders are guided in identifying workflows and processes prior to implementation are all important aspects of the evaluation process.

Who you're working with throughout implementation and go-live is crucial. It is ideal to work with a multi-disciplinary team including project managers, technical professionals, and clinicians with a NICU background who can collaborate with hospital leadership throughout the implementation process. This can save significant time for those implementing the technology and improve satisfaction from staff.

**3) Ongoing Support: Technical and Strategic.** Due to the high frequency of use and dependency by families, ongoing technical support cannot be underestimated. Ensure the device and platform are reliable. Utilize peers that have experience with the vendor to evaluate the overall performance history of the device including understanding the amount of downtime to expect during upgrades and the anticipated turnaround time if a camera must be repaired or replaced. Families learn to rely on the technology for peace of mind during their child's stay so it is important to consider all the factors that could impede the device from working and ensure that risk is minimized to keep staff and families satisfied. Discuss who is providing technical support and when it is available for both families and staff. Additionally, evaluate the process for requesting enhancements or software updates.

Relationship management is equally important and may involve providing support for any technical issues, keeping your team abreast of upcoming updates, ensuring staff adoption and utilization of the technology, as well as monitoring for success. Some companies may also provide support for research and quality improvement projects as they strive to learn more about the impact of live-streaming camera technology in various settings.

## Conclusion

It is evident that the use of live-streaming camera technology is here to stay. The increasing momentum of the family integrated care movement coupled with a more tech savvy workforce and equally technologically inclined parents support the continued use of cameras. The increased value placed on patient and family satisfaction and the experience during hospitalization compounds pressure as organizations aim to satisfy the needs and expectations of families. Adding to this pressure, a global pandemic resulting in drastic visitation restrictions creates a paradigm shift for NICUs around the country. Live-streaming camera technology is becoming a standard of care. It is more important than ever to thoroughly evaluate camera streaming technologies prior to implementing them.

### Ten Questions to Ask

1. How easy is the hardware to maneuver and position?
2. What type of project management support is available?
3. Do you provide resources and tools to ensure a successful implementation?
4. Are clinical advisors available to speak peer-to-peer for support?
5. What type of education and training is provided?
6. How much time does it take for staff to create and manage family accounts?
7. What ongoing, post-implementation support is provided?
8. Is technical support available 24/7?
9. What is the estimated downtime if hardware must be replaced or repaired?
10. What is the process for updating software?

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# Supporting NICU Families with Initiating and Maintaining a Milk Supply in a COVID-19 Environment

Darlene N Silver MSN, RN, IBCLC

Initiation and maintenance of milk supply, already a significant challenge for families with infants in the neonatal intensive care unit (NICU) or special care nursery (SCN) has been compounded by additional stressors being faced during the pandemic. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19 has prompted changes in visitation policies, limited the ability of extended family and friends to provide support, limited outpatient resources and unfortunately, for some families has led to significant changes in income or healthcare benefits. These stressors are having or have had a palpable and negative impact on families with an infant in the NICU. Parents predisposed to anxiety and depression have expressed more difficulty managing their anxiety and verbalized feelings of frustration or hopelessness. Mothers and families with infants in the NICU are sharing multiple challenges coping with daily life related to the pandemic. Mothers are also reporting how these additional stressors are adversely affecting their ability to initiate and maintain their milk supply. Empowering families to locate resources and tools to cope with the evolving challenges related to COVID-19 is paramount during this unprecedented pandemic.

Although anxiety and stress responses are a normal part of the human experience, excessive anxiety and chronic stress are not and can have deleterious effects on the body. Both are known to increase cortisol levels that interfere with the release of oxytocin resulting in minimizing or inhibiting the milk ejection reflex (MER). Consequently, the volume of milk expressed while pumping or when direct breastfeeding is potentially compromised. When working with families who have infants in the NICU or SCN, assisting them in the utilization of stress and time management strategies is essential. Consider how the pandemic has profoundly impacted these families as day-to-day life has changed due to local, state, federal and international regulatory requirements related to health care delivery, access to care, other essential services, employment, education, business transactions, public transportation and travel.

Initiation and maintenance of an adequate milk supply when a dyad is separated requires alternative modalities to stimulate and express breast milk. Multiple variables influence lactogenesis II, including maternal co-morbidities, parity, gestational age at time of birth, along with intrapartum or postpartum complications. Access to medical care and mental health services is an additional challenge during the pandemic. Regardless of our role in the clinical setting, seeing families with infants in the NICU experiencing higher levels of stress and anxiety is a reality. Unfortunately, even when mothers have the tools to pump at their infant's bedside and at home, mothers are reporting they are not pumping as frequently as they should because they are feeling *overwhelmed*, *exhausted*, *and stressed out*. Mothers are also reporting they are seeing their milk supply decrease which exacerbates the stress and anxiety they are already feeling.

> "We appreciate it when you check-in and give us tips or suggest resources. It means a lot to us."

These factors have made bedside clinical care even more significant to families. Incorporating questions about how mothers are feeling, how they are managing stress, how they are coping with additional responsibilities and limited resources during the pandemic is essential. Supporting their efforts while using a nonjudgmental approach is helpful. Mothers have said, *"I only pumped twice yesterday and once, today. Is that bad? Is it too late? Can I get my supply back up? Should I give up?"* Talking to them about what a typical day at home is like and exploring ways to find time to fit pumping in to their daily routine is key. Unfortunately, when well-intended providers and clinicians say, "You must pump every 2-3 hours." without exploring why the mother is having difficulty pumping compounds the mother's stress. In fact, it may lead a mother who already feels guilty to feel even worse and stop pumping completely. Giving families resources and ideas on how to manage their time or recommending a social work consultation to help locate community-based resources is critical. Many families have said, how important it is to have access to lactation support while their infants are in the NICU.

Scheduling times to periodically observe mothers while they pump is also important to verify the mother is using correctly fitted breast shields and using the breast pump safely within optimal settings. Observing her posture, giving her tips on breathing and relaxation while pumping to help reduce cortisol levels which interfere with the milk ejection reflex

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can be helpful. Reminding a mother to drop her shoulders, to take cleansing breaths while pumping, to consider wearing headphones with soothing music or using aromatherapy at home may be beneficial. Encourage mothers to set up a special place at home for pumping, one where she can have a sense of peace and calm while pumping. One mother shared that checking her work email helped her the most because it kept her from *"getting fixated on how much was coming out."* She found the volume she expressed was much higher.

Additionally, when educating mothers about pumping, timing is crucial. If the mother is experiencing a high or excessive level of stress it is best to postpone the educational session related to pumping as it will interfere with their ability to retain what was taught. Periodically observing the mother use the pump after the initial education and reinforcing areas where there may be deficits is essential. Reviewing the physiology of lactogenesis to ensure mothers fully understand the rationale for more frequent pumping is also important. Mothers may not fully understand the relationship between frequent emptying and the initiation and maintenance of their milk supply. Again, these mothers are experiencing high levels of stress and their ability to learn or retain what they have learned is not optimal.

Education regarding the different types of breast pumps is essential. Not all breast pumps are equal and using an inferior breast pump can significantly impact volume outcomes. Hospital-grade, multi-user, double electric breast pumps are recommended over personal use breast pumps when mothers are not able to breastfeed and are pump dependent. Breast pumps outfitted with Initiation Technology™ have been shown to improve milk volumes in several clinical studies (Meier, 2011, Torowicz 2015, Post 2016, Meier 2016).

Another area to discuss is nutrition and caloric intake. Helping find resources related to meal planning and suggesting a consultation with a dietitian may be needed. Offering resources so family and friends interested in supporting the family can organize meal preparation co-ops can be valuable. Asking a mother to recall what she has eaten over the last 24 hours can be an indicator of her nutritional intake. Discussing water intake and any supplements she may be taking is also helpful along with encouraging frequent nutrient dense snacks. As many mothers will ask about foods and galactagogues to help increase their supply, review the importance of frequent pumping, as often the frequency of pumping is the core issue. Helping mothers fully understand this point is critical.

There are many challenges families with infants in the NICU are facing related to the pandemic from limited public transportation, to not being able to have grandparents visit as they normally would to help care for other children, prepare meals, or help with housework. Parents with older children are finding themselves homeschooling and caring for their children who would normally be at school giving them less time to visit their infants at the hospital. Keep in mind, parents are trying to manage their stress and anxiety while simultaneously helping their family members or other children cope with having a newborn in the hospital. In general, families are spending much more time indoors in close quarters with an undercurrent of anxiety and stress related to the pandemic. Providers and clinicians are not immune to the stress or anxiety and they too, may be working in conditions less than ideal while managing family life.

The daily feed of reports, research and policy changes can be exhausting for clinicians and providers. Clarifying information and debunking misinformation is another challenge. The public is coping with a barrage of news and information constantly streaming and not necessarily accurate, helpful or safe which increases the stress and anxiety in patients and families. Providers and clinicians are frequently being asked questions related to the virus, the vaccine for the virus, and the variant strains of the virus being discovered. Mothers who are COVID-19 positive may fear their milk may not be safe for their infants. Ensuring they understand the importance of their milk and how the immunologic properties benefit their infants is critical.

The pandemic has and will continue to significantly change how we interact with our loved ones, how we work and navigate within our respective communities. As providers and clinicians, we must manage our own stress and anxiety and that of our loved ones. I would ask each of you to practice mindfulness, take a deep breath, drop your shoulders and pause before you approach a patient or family to discuss the plan of care. I can only speak for myself, but I have found it to be helpful and it allows me to show my patients and families the level of care, compassion and competence they should expect and deserve, particularly those with infants in the NICU. Below are links to resources you may find helpful.

- Medela, *Initiating Maternal Milk Supply* https://www.medela.us/mbus/for-professionals/innovating-practice-initiating-maternal-milk-supply
- *The 9 Best Meditation & Breathing Apps to Reduce Anxiety* https://www.thegoodtrade.com/features/best-meditation-apps
- *The 3 Best Websites for Coordinating Meals* https://coolmomtech.com/2017/07/best-websites-for-coordinating-meals/
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# Congenital Central Hypoventilation Syndrome: Not Just A Respiratory Sleep Disorder

Gabriela Ortiz, BSRT, RCP

## What is Congenital Central Hypoventilation Syndrome?

Congenital Central Hypoventilation Syndrome (CCHS), also known as Ondine's curse, is a rare disorder of decreased respiratory function and impaired autonomic regulation. It is a lifelong and life-threatening disease, typically occurring in newborns and with a milder, later-onset presentation in children and adults (Weese-Mayer et al., 2014). According to the CCHS Network (2021), every affected person has a 50% risk of transmitting the disorder to each child they may have. Undergoing fetal testing and monitoring is considered when the parents are known to have CCHS. Genetic testing reveals autosomal dominant inheritance or a de novo mutation in genes and chromosomes (happening at the stage of a germ cell in fertilization [egg or sperm]). According to the National Organization of Rare Diseases, the occurrence of CCHS diagnosis may be underestimated, with approximately 1200 children worldwide who are clinically affected (Sencen, 2015). If a child dies of CCHS, it may be confused with sudden infant death syndrome (SIDS). Differences in the occurrence of signs and symptoms have not been reported, including with relevance of race and gender, with both male and female being equally affected.

At birth, the customary APGAR scoring (1 to 10 scale) is used. This assessment tool is a good indicator of deficiencies in appearance, pulse, grimace, activity, and respirations. If the child presents with an APGAR score of less than 7, clinicians will continue therapies to increase the score: if no success occurs, a continuance of further assessment is conducted. The baby may present with a normal to midrange score at first but may decline rapidly with presentation symptoms such as shallow breathing, apnea, duskiness, and oxygen saturation decrease to between 70 and 80%.

With congenital central hypoventilation syndrome, whether it is an early onset or a late onset, respiratory insufficiencies are most apparent while asleep. Hypoventilation during sleep, in the absence of neuromuscular, cardiac, metabolic, or pulmonary disease is the typical sign. In severe cases, hypoventilation is also present while awake, showing as a variance in oxygenation and an increase in carbon dioxide (Chin et al., 2017).

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## Who does it affect?

The disorder may be present at birth, but CCHS may not be detected early enough to diagnose, depending on the severity or lack of awareness and experience of clinicians. If the parents carry the disorder, whether symptomatic or asymptomatic, then it is a higher likelihood that the child may also inherit CCHS, thus making it easier to support the diagnosis with additional testing. However, not all CCHS patients are familial cases, and there is the possibility of later onset with signs and symptoms of respiratory decline while awake or asleep. The American Sleep Association (ASA) reports findings that this disorder may develop in rare cases through serious brain or spinal trauma suffered later in life (ASA, 2007).

Individuals with an early onset of CCHS may live to 20 to 30 years of age, and late onset diagnosed as late as age 20 may live to 55 years of age (Weese-Mayer et al., 2014). In a study by Chin et al. (2017), researchers reported about twins who carried the same gene mutation. One twin exhibited early onset complications, and the other twin did not present any complications until approximately age five. Rashdi et al. (2011) presented a case study of a six-year-old girl, born at normal gestational age and with no neonatal problems, and with healthy parents and siblings. The child underwent dental extraction under general anesthesia, failing three attempts of extubation post-surgery due to apnea and shallowing breathing. Past medical history did not indicate previous episodes of cyanosis, loss of consciousness, nausea, gastroesophageal reflux, constipation, altered perception to pain, profuse sweating, or urinary incontinence. Neurological assessments, while awake and off the ventilator, were normal. MRI did not show any abnormalities, and electrolyte studies were within normal range. Upon each extubation, she appeared to have tachycardia, profuse sweating, and drowsiness, which were suggestive of hypercarbia and hypoxia, showing quick improvement after reintubation. After continued failure of extubation, the child received a tracheostomy and nighttime mechanical ventilation. This initiated the need for further studies. Genetic testing revealed an increase in expansion mutation in the PHOX2B gene, which helps identify CCHS, showing an increase in the number of alanines (amino acids).

## Presentation of CCHS

"A mutation in the *PHOX2B* gene is required for the diagnosis of CCHS" (Chin et al., 2019). As stated by Weese-Mayer et al. (2014), *PHOX2B* is the only gene in which mutation is known to cause CCHS. CCHS Network (2021) confirms that approximately 92% of people with CCHS have a type of mutation within coding of axon 3 in the PHOX2B gene, called a polyalanine repeat expansion mutation (PARM).

The normal PHOX2B gene, which promotes the development of neurons, contains a 20-alanine coding, presenting as 20/20 (normal range) on lab readings. [Wikipedia (2020) definition for alanine (symbol Ala or A) "is an α-amino acid that is used in the biosynthesis of proteins"]. The coding of alanine is presented as the normal count over mutated count (normal/mutation), showing as 20/24, 20/25, etc., presenting a higher value in the lower (second) number, when the mutation is present. The two major types of *PHOX2B* variants observed in CCHS are polyalanine repeat expansion mutations (PARMs) and non-polyalanine repeat expansion mutations (NPARMs).

The Chin et al. (2017) study showed a correlation between increased expansion of alanines. and an increased need for continuous ventilatory support. CCHS patients with 20/27-20/33 are typically symptomatic at birth and require full-time ventilatory support. What also was noticed is that with a more complicated mutation of genes presentation of cardiac anomalies appeared, which may require a pacemaker. Gronli et al. (2008) completed a study examining 39 children with CCHS, observing cardiovascular signs consistent with the autonomic nervous system dysregulation and dysfunction (ANSD) phenotype (physical characteristics). With the relative amount of high genotype (genetic characteristics), 67% of the children received cardiac pacemaker application due to visually seeing a prolonged r-r interval on the electrocardiogram (ECG), other arrhythmias, like sinus bradycardia, and transient asystole. These symptoms occur because unstable regulation and function of the autonomic nervous system (ANS) and the brain not using the phrenic nerves causes the body to be unable to control breathing; sense oxygen and carbon dioxide levels in the blood; and lead irregularities in heart rate, blood pressure, temperature, bowel and bladder control, and more.

Chemoreceptors are responsible for sensing any chemical changes within the body; they are also responsible for stabilizing it. The central chemoreceptors are those responsible for breathing, found in the respiratory center at the base of the brain. Those with insufficiency of chemoreceptors will present a decrease in ventilatory sensitivity to hypercarbia and hypoxemia. Gourine (2005) explains that the peripheral and central respiratory chemoreceptors are ultimately responsible for maintenance of constant levels of arterial oxygenation ($P_{O2}$), arterial carbon dioxide ($P_{CO2}$). This regulation protects the brain from hypoxia and ensures that breathing is always appropriate for metabolism.

CCHS affects and disrupts the chemoreceptors signal; therefore, ventilatory regulation becomes the primary dysfunction caused by progressive hypercapnia and hypoxemia when asleep, along with significantly impaired responses to adequate gas exchange. Because of the inability to control breathing, it also is standard practice to conduct sleep studies, looking for ventilation and oxygenation disturbances which occur during different stages of sleep. The clinical presentation of patients with CCHS varies with the severity of hypoventilation.

## Infancy

Some infants who present with apnea will require assisted respiratory support in the newborn nursery. Most babies who present in this manner do not spontaneously breathe during the first few months of life but with maturity may develop a pattern of breathing during wakefulness which is sufficient over time to support respiration; however, apnea or central hypoventilation continues during sleep. Other infants may present respiratory insufficiencies at a later age. When including cyanosis and edema, these may be signs of right-sided heart failure and may be first indications of CCHS. In some cases, these symptoms in infants have been mistaken for congenital heart disease.

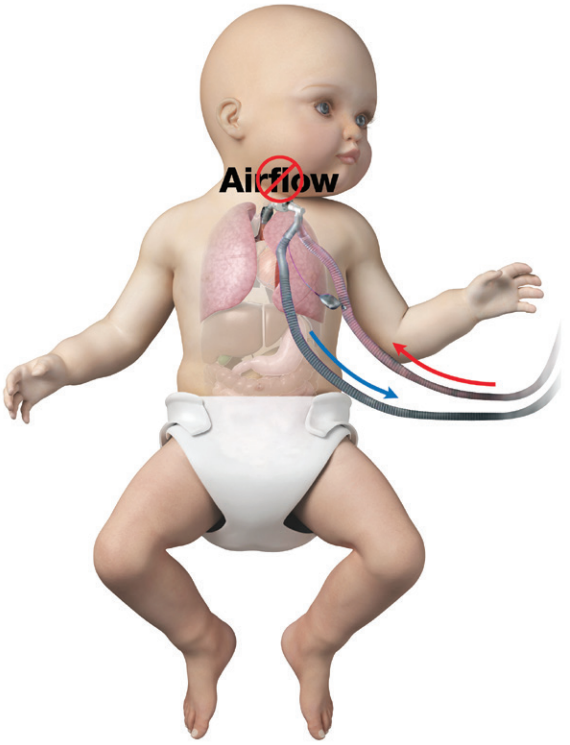


**Figure 1.** Infant with cuffed tracheostomy tube and mechanical ventilation tubing.

While the typical symptoms may be respiratory and lead to cardiac issues, about 20% of patients with CCHS may also have Hirschsprung disease, which affects the muscles in the bowels and creates inefficiency in the passing of stools through the intestines. According to the National Organization for Rare Disorders (NORD), Hirschsprung disease affects males three to four times more often than females (Frykman, 2017). Other findings in the disorder are neural crest tumors (ex. neuroblastomas), that may develop in 5-10% of CCHS patients. In viewing the central nervous system structure, using MRI reveals a reduction in gray matter volume in areas that regulate autonomic, mood, motor, and cognitive functions (Chin et al., 2017).

## Treatments

Though, there is no cure or medication for CCHS, treatments to provide adequate respiratory function are accessible. Patients may manage the condition through the support of invasive or non-invasive breathing devices.

Methods may include:

- Mechanical Ventilation with positive pressure via tracheostomy.
- Non-invasive bi-level positive airway pressure ventilation via masks or prongs that is typically utilized in milder forms of the disorder.
- Diaphragm pacing, a minimally invasive process, stimulates the phrenic nerve enabling more natural breathing.

When placement of a tracheostomy with invasive mechanical ventilation is necessary, growth and development may continue; however, eating, practicing phonation, and speech with use of Passy-Muir® Tracheostomy & Ventilator Swallowing and Speaking Valve may help individuals communicate and progress towards developmental milestones. Usually around seven years of age and with overall medical stability, invasive ventilation may be downgraded to non-invasive mask ventilation along with diaphragmatic pacing to ensure adequate respiration.

When the phrenic nerve is unable to sense the need to breathe properly, a diaphragm pacer may be placed, using a minimally invasive surgery. The pacer delivers electrical impulses to the diaphragm to help restore breathing function for those with chronic respiratory insufficiency, such as those, whose diaphragm, lungs, and phrenic nerves have limited function. These two modalities, pacer and ventilator may be considered life-long, with adjustments and titrations according to the life span of the devices, the need for ventilation, and growth and development of a child.

Although devices may offer relief to a life-long disorder, tracheostomy for invasive ventilation and mask ventilation-both may pose the likelihood of failure, leading to an emergency need for aggressive ventilatory support. This support may involve intubation with continuous life support equipment. Cardiac pacemakers for cardiac anomalies, surgeries, and chemotherapy for the treatment of tumors, also may help decrease or prevent rapid deterioration of overall health.

## Conclusion

Whether insufficiencies are apparent during wake periods or during sleep, hypoventilation and hypercapnia seem to be the first symptoms observed. The outcomes for children and adults with congenital central hypoventilation syndrome (CCHS) have noticeably changed with earlier detection and diagnosis of the disorder. Having knowledge of family history promotes genetic testing, starting in utero or when the child is born. Detection of gene mutation in PHOX2B, helps validate the diagnosis and justifies the need for other instrumental diagnostics. Instrumentals include echocardiograms, to determine the severity of cardiac anomalies; MRIs to identify any neurologic abnormalities; metabolic screenings; chest x-rays; and CT scans may aid in ruling out lung dysfunction. With no cure for CCHS, it becomes most important to create a platform for adequate ventilatory support to help prevent recurrent hypoxemic episodes that lead to deterioration of homeostasis. Invasive or non-invasive mechanical ventilation with the aid of diaphragm pacers, when a child is older, may undoubtedly pose on overall health outcomes by maintaining adequate and effective breathing. As a team, the decision for mechanical support becomes relevant; supportive and multidisciplinary care becomes imperative to improve and sustain the quality of life for individuals with CCHS.

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# Use of an Exclusive Human Milk Diet in Preterm Infants to Lower Healthcare Costs – Short-Term and Long-Term Perspectives

Victor Iskersky, MD

Healthcare costs in the US and elsewhere in the world continue to skyrocket, with costs stemming from care in the neonatal intensive care unit (NICU) playing an important role. It is necessary to prioritize interventions in this context that not only reduce morbidity and mortality but also have the potential for economic savings, both in the short-term and the long-term. An important population in this regard is preterm infants. A 2019 analysis by Cheah[1] revealed that more than 50% of NICU costs can be attributed to treatment aimed at preterm infants and estimated that lifetime costs of extremely preterm infants can be as high as $450,000.

> "…this analysis does not capture the full societal benefits of using an EHMD, as societal savings from reductions in NEC, late onset sepsis, and long-term consequences of short bowel syndrome are not included due to data limitations. We also only consider lost productivity amongst survivors, and not amongst non-survivors."

Over the past decade, use of an exclusive human milk diet (EHMD), which includes nutritional fortifiers made exclusively from vat pasteurized human milk by Prolacta Bioscience (Duarte, CA), has emerged as a potential avenue through which morbidity[2-7] and mortality[5-7] can be reduced among preterm infants, with increasing evidence demonstrating a cost benefit as well. Given the evidence, it is important to think of an EHMD not just as an optional diet for these infants but as a medical intervention that results in better outcomes.

In 2020, van Katwyk et al[8] conducted a cost analysis in a Canadian tertiary hospital setting to estimate the potential cost savings of an EHMD, based on avoidance of attributable complications among low birth weight infants. They conducted a meta-analysis to derive input parameters, followed by an analysis to determine the probability that an EHMD including vat pasteurized human milk-based products reduces costs. Providing an EHMD to preterm infants born weighing < 750 g and at the highest risk of developing major complications was estimated to save $107,567 CDN per year. In addition, extending an EHMD to infants born at higher weights may also confer cost savings, depending on the cost of the human milk-based fortifier and the baseline risk of complications in the hospital setting.

This study was the latest in a series of analyses demonstrating the likely short-term cost savings associated with implementing an EHMD among select preterm infants. In 2016, Assad et al[9] conducted a retrospective study that included 293 infants born at ≤ 28 weeks gestation and/or with a birth weight ≤ 1500 g who were treated at a US hospital NICU between March 2009 and March 2014. These infants were divided among those fed an EHMD using Prolacta's fortifiers (born March 2012 to 2014); those fed a cow milk-based fortifier and maternal milk (born March 2009 to 2012); those fed a combination of maternal milk, cow milk-based fortifier, and cow milk-based formula (born March 2009 to 2012); and infants fed formula alone (born March 2009 to 2012). Compared with the other groups of infants, those who received an EHMD had lower total hospitalization costs of up to $106,968 USD per infant ($P < 0.004$). These savings were driven, at least in part, by lower rates of feeding intolerance ($P < 0.0001$), a lower number of days to full feeds ($P < 0.001$), and a lower incidence of necrotizing enterocolitis (NEC) ($P < 0.011$).

In 2019, Hampson et al[10] conducted an economic analysis of an EHMD, compared with the usual practice of using cow milk-based products among very low birth weight (VLBW) infants in the US. For this study, costs were evaluated from the perspective of the healthcare payer, with societal costs considered in sensitivity analyses. An EHMD, including Prolacta's vat pasteurized human milk-based products, was found to substantially reduce patient mortality, improve several health outcomes, and result in a cost savings of $16,309 USD per infant by reducing adverse clinical events. The cost savings increased to $117,239 per infant when wider societal costs were included, notably societal costs of cerebral palsy, including costs of healthcare, specialized childcare, specialized education, and housing; lost productivity and reductions in lifetime earnings attributable to lower IQ resulting from NEC and sepsis; and productivity losses for both patients and caregivers due to visual impairment resulting from retinopathy of prematurity.

It is important to note that the long-term cost savings of optimizing outcomes among fragile infants with an EHMD are

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**Average cost savings of implementing an EHMD**

- **$107,567 CDN savings per year in-hospital costs**
  Preterm infants born weighing < 750 g and at the highest risk of developing major complications[8]
- **$106,968 USD savings per infant in-hospital costs**
  Preterm infants born at ≤ 28 weeks gestation and/or with a birth weight ≤ 1500 g[9]
- **$117,239 USD savings per infant in-hospital and wider societal costs**
  Combined savings from reduced patient mortality, reduced adverse clinical events, and wider societal costs including costs of care, specialized childcare, specialized education, housing, and lost productivity[10]

yet to be fully evaluated. Hampson et al[10] write of their study that "this analysis does not capture the full societal benefits of using an EHMD, as societal savings from reductions in NEC, late onset sepsis, and long-term consequences of short bowel syndrome are not included due to data limitations. We also only consider lost productivity amongst survivors, and not amongst non-survivors."

Lapcharoensap et al[11] conducted a retrospective cohort study of California births from 2008 to 2011 that included infants born weighing 401 to 1500 g and with a gestational age < 30 weeks to determine the 1-year hospitalization costs due to bronchopulmonary dysplasia (BPD), a common complication of prematurity. Among the 33.7% of nearly 8000 preterm infants who developed BPD, median hospitalization cost in the first year was $377,871 USD per infant, compared with $175,836 among the preterm infants without BPD. Infants with BPD also had a longer length of stay and a higher likelihood of rehospitalization. Notably, an EHMD has been shown to reduce the risk of developing BPD and similar lung conditions.[3,4,6] In their 2018 update of pulmonary and other outcomes of premature infants, Cheong et al[12] concluded that "long-term outcomes for children born extremely preterm will improve if the rate of BPD can be substantially reduced."

Similarly, both NEC and sepsis have been shown to put infants at increased risk for motor impairment at 2 years,[13-15] and use of an EHMD, including Prolacta's vat pasteurized human milk-based products, has been shown to reduce the risk of NEC[5,7] and sepsis[3,6] among select preterm infants. How reductions in such impairment might impact long-term productivity and the general ability to contribute to society over a lifetime are unknown but may well be substantial.

In 2019, Visuthranukul et al[16] published a study of 51 premature infants (birth weight ≤ 1250 g) fed an EHMD, including Prolacta's vat pasteurized human milk-based products, who were examined at the age of 12 to 15 months. They found that the 18 infants born small for gestational age experienced more catch-up growth than those born appropriate for gestational age. Importantly, this catch-up growth was not associated with increased adiposity or greater insulin resistance.

In 2020, Bergner et al[17] conducted a prospective pilot study of 51 preterm infants with an average gestational age of 27.8 weeks and average birth weight of 893 g who were fed an EHMD, including vat pasteurized human milk-based products. At 2 years, these infants' body composition, including lean mass and bone density, was similar to term-matched controls. These findings are important in light of the fact that more than 90% of VLBW infants have growth restriction at the time of NICU discharge,[18,19] and there is concern that later catch-up growth results in increased adiposity, which can elevate the risk of developing metabolic syndrome.[20] In addition, none of the children had severe cognitive developmental delay.

As an increasing number of preterm infants receive an EHMD including Prolacta's vat pasteurized human milk-based products, it is likely that the potential benefits of this medical intervention will be further elucidated, in terms of short- and long-term costs and clinical outcomes. What is clear from the evidence available today is that select preterm infants fed an EHMD have better outcomes, and this may well lead to both reduced costs in the NICU as well as reduced healthcare and societal costs over the long term.

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# Risk Factors For Readmission For Phototherapy Due To Jaundice In Healthy Newborns: A Retrospective, Observational Study

Amit Blumovich, Laurence Mangel, Sivan Yochpaz, Dror Mandel and Ronella Marom

## Abstract

**Background:** The guidelines of the American Academy of Pediatrics (AAP) for monitoring neonatal jaundice recommend universal postnatal screening for hyperbilirubinemia within 48 h from discharge. We observed that neonate with low-risk jaundice were more likely to be readmitted to hospital for phototherapy compared to neonate with high-risk jaundice. The aim of this study was to identify additional factors that increase the risk for jaundice-related readmission.

**Methods:** This observational case-control study was performed on 100 consecutive neonates with jaundice who were readmitted to hospital for phototherapy treatment and were compared to 100 neonates with jaundice during hospitalization who were not readmitted after discharge. The data retrieved from the medical records of all participants included maternal characteristics, delivery type and noteworthy events, gestational age at delivery, birth weight and weight loss, neonate physical findings, Apgar scores, laboratory findings, length of hospital stay, and administration of phototherapy during hospitalization. The length of time since discharge and readmission for jaundice was also recorded.

**Results:** The risk of readmission decreased by 48% [odds ratio (OR) =0.52; 95% confidence interval (CI) 0.341–0.801] with every day added to the original hospitalization stay, and by 71% (OR = 0.29; 95% CI 0.091–0.891) if phototherapy had been administered during postnatal hospitalization. In contrast, the risk increased by 28% (OR = 1.28; 95% CI 1.164–1.398) with every elevation by 1% in hematocrit, and by 2.78 time (95% CI 1.213–6.345; $p$ = 0.0156) when the delta in infant weight was > 5% (the difference between birth weight and weight at discharge during the postnatal hospitalization).

**Conclusions:** The risk factors for readmission, such as substantial weight loss (> 5% difference between birth and discharge) and elevated hematocrit should be taken into account in the decision to discharge neonate with low-risk jaundice. The AAP guidelines for decreasing readmission rates of neonatal jaundice by postnatal screening for hyperbilirubinemia alone may be more appropriate for neonate with high-risk jaundice.

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**Keywords:** Neonatal jaundice, Readmission, Phototherapy, Hospitalization stay

## Background

Postnatal hospital stay in many developed countries has been decreasing over the past few decades.[1,2] In Israel, the national health insurance covers a hospital stay of 48 h after an uneventful vaginal birth and a stay of 3 days after an uncomplicated caesarean delivery as the accepted length of stay (LOS) for mothers and infants. A similar trend was observed in a Canadian study that evaluated close to 2 million live births and found that approximately 47% of mother-infant dyads were hospitalized for 1 day following a vaginal birth and that approximately 49% were hospitalized for 3 days following a caesarean delivery.[3] While there are many benefits to early discharge, including cost reduction, higher availability of hospital beds for other mothers,[1] and reduced risk for nosocomial infections to mothers and infants, there are also specific risks associated with premature discharge, even of healthy infants, with hyperbilirubinemia being chief among them.[4] Physiological jaundice typically appears in over 80% of newborn babies. It develops between the second and fourth day of life and peaks between the fourth and fifth day,[5] thus, under current practices, it is most likely to peak after the neonate has left the hospital.

A recent study conducted in the UK analyzed over 4 million live births and reported a readmission rate for neonatal jaundice of 5.2%.[2] A Canadian study observed that 4.2% of infants following a vaginal birth and 2.2% following a caesarean delivery were readmitted for neonatal jaundice.[3] The findings of analyses that compared length of postnatal stay and readmission for neonatal jaundice have been inconclusive, however, the correlation appeared to be stronger for term infants than for late preterm infants.[2-4] Guidelines issued in 2004 by the American Academy of Pediatrics (AAP)[6] and updated in 2009[7] on the follow-up and management of infants post-discharge recommended a visit at a healthcare provider within 48 h from discharge. The Israeli guidelines on hyperbilirubinemia management also include a recommendation for all infants to be seen by a healthcare professional within 2-3 days post-discharge, irrespective of total serum bilirubin levels at discharge and the presence or absence of risk factors for developing severe hyperbilirubinemia.[8] Accordingly, several reports suggested that implementation of universal postnatal screening for hyperbilirubinemia within 48 h from discharge might decrease hospital readmission rates due to neonatal jaundice.[9,10] However, it was our impression that there were additional factors that increased the risk for jaundice-

related readmission. The aim of the present study was to identify those risk factors.

## Methods

### Setting and study population

This work is a retrospective observational case-control study. We reviewed the medical records of all term and late preterm neonates admitted to the Lis-Maternity hospital at the Tel Aviv Medical center between January 2015 and March 2016. Our institute hosts 12,000 births per year. We used the diagnosis key word "readmission" to recruit the study cases defined as neonates with jaundice in their first hospitalization and readmitted for phototherapy. Only 100 consecutive cases of neonates readmitted to the newborn nursery for phototherapy treatment were retrieved (study group). To these study cases, 100 neonates who had neonatal jaundice during hospitalization but were not readmitted to the hospital for phototherapy (control group) were matched. The subjects in the control group were matched on the basis of gestational age (GA) and birth date (±7 days) to the subjects of the study group. We included neonates presenting solely with neonatal jaundice and no additional morbidities.

### Data collection and handling

The collected data included maternal and infant demographics, clinical and laboratory information, and details on the course of jaundice. The study was approved by our local Institutional Review Board which waived informed consent.

### Statistical methods

Risk factors for readmission were compared by means of univariate analyses between newborns that were readmitted and those who were not. A 2-sample Student's t-test or Wilcoxon 2-sample test was applied for continuous variables (depending upon the normality of the distribution), and the $\chi^2$ test for categorical variables. A multivariate logistic regression was applied to identify the significant independent predictors of readmission by considering predictor variables whose associated $p$ value in the univariate analysis was < 0.05 or if the variable was thought to be clinically relevant. A backward stepwise selection procedure was used to establish the final multivariate model. A 20% significance level of the $\chi^2$ score was selected for entering an effect into the model, and a 10% significance level of the Wald $\chi^2$ for an effect to stay in the model. The statistical analysis was performed using the SAS software version 9.4 for Windows.

## Results

The study included data on 200 infants, of whom 100 were in the readmission group (study group) and 100 were in the no-readmission group (control group). The average maternal age in both groups was approximately 33 years, the median maternal parity was 2.0 in both groups (Q1, Q3; 1.0, 3.0) (Table 1), and the median GA was 38 weeks (Q1, Q3; 37.0, 39.0) (Table 2).

### Delivery and maternal factors (univariate analyses)

Table 1 lists the selected factors related to maternal demographics and clinical characteristics that were assessed. There were significant differences between the study and control groups in prevalence of caesarean delivery (3 and 18%, respectively; $p < 0.01$) and in the prevalence of a positive Coombs test (1 and 23%, respectively; $p < 0.01$) (Table 1).

### Infant and jaundice-related factors (univariate analyses)

The results of the evaluations of selected clinical characteristics of the infants as well as those specific to jaundice and its management are presented in Table 2. There were significant differences between the groups in formula feeding (4 and 12% in the study and control groups, respectively; $p = 0.037$) and postnatal hospital length of stay (LOS) (medians 2 days and 4 days, respectively; $p < 0.001$). In addition, the control group was significantly different from the study group in terms of infant weight loss (i.e., the difference between birth weight and weight at postnatal discharge) above 5% (57% in the study group and 42% in the control group; $p = 0.034$). Laboratory findings (total bilirubin, hemoglobin, hematocrit, and reticulocytes), number of visits at the outpatient jaundice clinic (a median of 1 in the study group and 3 in the control group; $p < 0.001$), and phototherapy during the first hospitalization (10% versus 63%, respectively; $p < 0.001$) were also significantly different between the groups.

### Multivariate analyses

The multivariate analyses revealed that the risk of readmission decreased by 48% with every day added to the postnatal hospital LOS (OR = 0.52; 95% CI 0.341–0.801; $p = 0.0029$), and by 71% if

**Table 1.** Delivery and Maternal Characteristics in the Study and Control Groups

| Variables | No-Readmission Control Group | | Readmission Study Group | | *p* Value |
|---|---|---|---|---|---|
| | (*N* = 100) | | (*N* = 100) | | |
| Maternal age, mean (SD) | 33.1 | (4.9) | 33.4 | (4.3) | 0.66 |
| Parity, median (Q1, Q3) | 2.0 | (1.0, 3.0) | 2.0 | (1.0, 3.0) | 0.53 |
| Gravidity, median (Q1, Q3) | 1.5 | (1.0, 2.0) | 2.0 | (1.0, 3.0) | 0.24 |
| Gestational diabetes mellitus | 17 | (17%) | 11 | (11%) | 0.22 |
| Meconium-stained amniotic fluid | 12 | (12%) | 10 | (10%) | 0.65 |
| Group B streptococcus | 5 | (5%) | 8 | (8%) | 0.39 |
| Hypothyroidism | 5 | (5%) | 7 | (7%) | 0.55 |
| Other[a], | 11 | (11%) | 6 | (6%) | 0.21 |
| Multiple gestations | 2 | (2%) | 1 | (1%) | 0.56 |
| Mode of delivery | | | | | 0.003 |
| Vaginal | 70 | (70%) | 83 | (83%) | NS |
| Vacuum | 12 | (12%) | 14 | (14%) | NS |
| Caesarean | 18 | (18%) | 3 | (3%) | < 0.001 |
| Rupture of membranes | 19 | (19%) | 15 | (15%) | 0.45 |
| Positive Coombs | 23 | (23%) | 1 | (1%) | < 0.001 |

[a]Other – RH factor, in-vitro fertilization, use of selective serotonin re-uptake inhibitors or pre-eclampsia, *NS* non-significant, Data are expressed as n (%),

**Table 2.** Infant- and Jaundice- Related Characteristics in the Study and Control Groups

| Variable | No Readmission Control Group (N = 100) | | Readmission Study Group (N = 100) | | p Value |
|---|---|---|---|---|---|
| Female, n | 49 | (49%) | 41 | (41%) | 0.26 |
| Birth weight, gr, mean (SD) | 3201.0 | (434.7) | 3163.3 | (416.7) | 0.53 |
| Gestational age (weeks), median (Q1, Q3) | 38.0 | (37.0, 39.0) | 38.0 | (37.0, 39.0) | 1.00 |
| Late preterm neonate (< 37), n | 8 | (8%) | 8 | (8%) | 1.00 |
| Size for gestational age, n (%) | | | | | 0.41 |
| Appropriate | 81 | (81%) | 86 | (86%) | |
| Large | 15 | (15%) | 9 | (9%) | |
| Small | 4 | (4%) | 5 | (5%) | |
| G6PD deficiency, n (%) | 14 | (14%) | 14 | (14%) | 1.00 |
| Apgar 1 (range 5–7), n | 7 | (7%) | 2 | (2%) | 0.09 |
| Apgar 5 (range 5–7), n | 1 | (1%) | 0 | (0%) | 0.32 |
| Feeding, n | | | | | 0.11 |
| Breastfeeding | 49 | (49%) | 51 | (51%) | 0.78 |
| Mixed | 39 | (39%) | 45 | (45%) | NS |
| Formula | 12 | (12%) | 4 | (4%) | 0.037 |
| Postnatal LOS, median (Q1, Q3) | 4.0 | (3.0, 5.0) | 2.0 | (2.0, 3.0) | < 0.001 |
| Weight loss > 5% n (%) | 42 | (42%) | 57 | (57%) | 0.034 |
| Laboratory findings during first hospitalization | | | | | |
| Highest value of total bilirubin, umol/L, mean (SD) | 13.4 | (2.3) | 11.9 | (2.9) | < 0.001 |
| Hemoglobin, g/dl, median (Q1, Q3) | 17.6 | (16.0, 19.2) | 19.6 | (18.8, 21.4) | < 0.001 |
| Hematocrit (%), median (Q1, Q3) | 53.0 | (48.0, 58.0) | 59.0 | (56.0, 63.0) | < 0.001 |
| Reticulocyte > 5%, n | 40 | (40%) | 9 | (9%) | < 0.001 |
| Highest value of total bilirubin during second hospitalization | . | | 17.9 | (1.8) | . |
| Visits to jaundice clinic, median (Q1, Q3) | 1.0 | (0.0, 2.0) | 3.0 | (2.0, 4.0) | < 0.001 |
| Phototherapy during first hospitalization, n | 63 | (63%) | 10 | (10%) | < 0.001 |

*NS* non-significant, *LOS* length of stay

phototherapy was provided during that hospital stay (OR = 0.29; 95% CI 0.091– 0.891; $p = 0.0308$). In contrast, the risk increased by 28% (OR = 1.28; 95% CI 1.164–1.398; $p < 0.0001$) with every 1% elevation in hematocrit, and by 2.78 time (95% CI 1.213–6.345; $p = 0.0156$) with an infant weight loss greater than 5% (Table 3).

## Discussion

In this study, we analyzed various potential risk factors for hospital readmission of newborns for phototherapy due to jaundice following discharge. The results of the analyses revealed that the length of postnatal hospital stay and the administration of phototherapy were significantly associated with a lower risk for readmission. Our medical center adheres to the Israeli guidelines for the management of neonatal jaundice;[8,11] which are based on the AAP guidelines.[6] Implementing guidelines for monitoring hyperbilirubinemia and universal screening for bilirubin have proven effective in reducing the overall rate of readmission for treating jaundice in the high-risk group,[4] such as, preterm infants, neonates with early jaundice during the first 24 h of life, neonates with ABO incompatibility and positive coombs test or other hemolytic disease (eg, G6PD deficiency).[9] Hence, the neonates in the No-Readmission group had longer hospitalization stay due to ABO incompatibility or preterm jaundice that needed phototherapy treatment and which finally was associated with a significantly reduced risk of readmission.

Our data suggest that the neonates in the Readmission group have been assessed as having none of the major risk factors for developing hyperbilirubinemia and as being in the low-risk zone according to the AAP guidelines and therefore discharged early.[7] In fact, these newborns were not at such a low-risk and experienced a post-discharge elevation of bilirubin leading to readmission for phototherapy treatment.

Several studies reported a correlation between the status of a newborn as a "late preterm" and increased risk for readmission.[2,7,12] There was no comparable correlation in our study population, most probably due to the extended hospitalization stay of late preterm newborns as in the high risk group. The same discrepancy between the findings of others and our current ones was noted with respect to levels of bilirubin at discharge.[13] It is possible that an intensive post-discharge management contends with that risk and offsets the

**Table 3.** Multivariate Analysis

| Parameter | Category | Odds ratio | 95% Wald Lower CI | 95% Wald Upper CI | *p*-value |
|---|---|---|---|---|---|
| Hospital LOS after birth (days) | | 0.52 | 0.341 | 0.801 | 0.0029 |
| Hematocrit | | 1.28 | 1.164 | 1.398 | < 0.0001 |
| Weight loss > 5% | Yes vs. No | 2.78 | 1.213 | 6.345 | 0.0156 |
| Phototherapy during first hospitalization | Yes vs. No | 0.29 | 0.091 | 0.891 | 0.0308 |

*LOS* length of stay

need for readmission. Interestingly, we found an increased risk of readmission associated with a shorter LOS. This is in line with the study of Ruth et al. work who found that a birth stay of ≤2 calendar days increased the risk of readmission and the magnitude of that risk remained unaffected by infant GA.[14] Similarly, Jones et al. found that the vast majority of infants (94%) admitted for physiological jaundice had a hospital duration of ≤3 days.[15]

Furthermore, we showed that an elevated hematocrit at discharge was also associated with a higher risk of readmission, possibly reflecting polycythemia among the readmitted infants. Even when the hematocrit is within a physiologic range such as in Cernadas et al. study.[16] Indeed, Mimouni et al. reported that polycythemia was associated with hyperbilirubinemia via the breakdown of the increased mass of red blood cells.[17] The elevated hematocrit observed in the current study group may partly be a consequence of a delay in umbilical cord clamping. Such an association between late cord clamping and jaundice[14] through elevated hematocrit was demonstrated by McDonald et al.[18]

In line with the known association between weight loss and hyperbilirubinemia,[6] substantial weight loss (the difference between birth weight and discharge weight) was a significant risk factor for readmission in our population. This finding is consistent with the study by Campbell Wagemann et al. which showed that the main risk factor for readmission due to severe hyperbilirubinemia was excessive weight loss in newborn between 4 and 7 days after birth.[19] However, contrary to our expectations, there was no significant difference in post-delivery weight loss between breastfed babies and formula-fed babies. Yet, a weight loss above 5% remained as an independent risk for readmission (logistic regression—Table 3).

Newborns with jaundice should have bilirubin levels closely monitored before and after discharge from the hospital to prevent potentially serious complications of hyperbilirubinemia. The clinical practice guideline published by the American Academy of Pediatrics (AAP) in 2004 recommended that all neonates born at ≥35 weeks of gestation be assessed before discharge for the risk of severe hyperbilirubinemia by using clinical risk factors and/or bilirubin measurements. Weight loss nor hematocrit level are among the criteria included in the assessment before discharge for the risk of severe hyperbilirubinemia in the AAP guidelines. We suggest that both of these criteria should be considered in deciding whether to release home in order to prevent readmission.

This study has some limitations that bear mention. This is a retrospective study on a small cohort. In addition, since we only evaluated infants diagnosed with jaundice prior to their postnatal hospital discharge and not the entire infant population before discharge during the study period, our results cannot be generalized. Further research is warranted to support these preliminary findings.

## Conclusion

In the present study, we identified the haematocrit level, an infant weight loss > 5%, and a shorter LOS as being additional risk factors for increased risk of readmission of low-risk neonates presenting with physiological jaundice. We suggest that while the AAP guidelines are appropriate for the management of high-risk neonates presenting with jaundice, they are less suitable to low-risk neonates presenting with physiological jaundice. We conclude that the criteria for hospital discharge of the latter neonates need to be more stringent.

## Abbreviations

LOS: Length of stay; AAP: American Academy of Pediatrics


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## Authors' contributions

Drs. MR and BA conceptualized and designed the study, analyzed the results, drafted the initial manuscript, and reviewed and revised the manuscript. Drs. ML and MD participated in conceptualizing and designing the study and in analysis of the results, and reviewed and revised the manuscript with important intellectual contribution. Drs. YS designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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# Donor Human Milk Programs In German, Austrian And Swiss Neonatal Units – Findings From An International Survey

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## Abstract

**Background:** Donor human milk (DHM) has been recommended for premature infants if mothers' own milk is not available. The aim of this study was to increase the knowledge about the utilization rate and handling of DHM among neonatal units in Germany, Austria und Switzerland.

**Methods:** Online survey of utilization rates and handling practices of DHM of all neonatal units within Germany, Austria and Switzerland providing care for premature infants less than 32 weeks of gestation.

**Results:** DHM utilization rate of 35% is low (50/142) within those 54% of units that responded to our survey (142/ 261). Only 26/50 units have DHM routinely integrated into their nutritional management protocols. Lacking access and difficult procurement were cited as the main obstacles for not using DHM. However, eight out of ten respondents currently not using DHM would like to introduce DHM in their unit if available. There were differences in most aspects of DHM handling including donor recruitment and screening, testing and treatment of milk microbiota and commencement of DHM utilization. Breastmilk feeding rates were increased in units utilizing DHM compared to those not utilizing DHM.

**Conclusions:** DHM is underutilized in most neonatal units caring for premature infants within participating countries. Lacking access to DHM represents the main barrier for utilizing DHM for premature infants.

## Background

Donor human milk (DHM) is recommended for feeding premature infants when mothers' own milk is unavailable or not fit for consumption.[1,2] Donor human milk banks (DHMB) are the means by which DHM may be made available for premature infants. Subsequently, the number of DHMB is increasing in many parts of the world. Several national human milk bank associations described their DHMB networks and detailed their respective mode of operations.[3,4]

However, the knowledge about the actual DHM utilization rates in neonatal intensive care units providing care for very premature infants is limited.[5-7] The aim of this study is to provide an overview about the actual utilization rate of DHM, the procurement and handling of DHM, the implementation of feeding strategies using DHM or to identify the barriers to its use within German, Swiss and Austrian neonatal units. DHM programs and DHMB within these countries are established, operated and funded exclusively by individual neonatal departments setting their own policies concerning procurement and handling of human donor milk.

These data are needed to inform health care professionals, authorities and stakeholders about the extent and practice of current DHM programs within the participating countries, to support them to establish or evaluate local or national guidelines concerning DHM utilization and DHM handling and to improve the availability of DHM for preterm infants.[8-10]

## Methods

We sent a stratified online questionnaire to neonatologists within every neonatal unit that was providing care to preterm infants of less than 32 weeks of gestational age in Germany, Austria and the German speaking part of Switzerland.

The questionnaire was developed by the authors who are experienced in managing DHMB within their own neonatal departments and contained a maximum of 21 questions, depending on the strata. The questionnaire was pre-tested amongst neonatologists experienced with managing DHM programs. Participants were identified by personal knowledge or by internet research and consisted of individual neonatologists either in charge of the respective neonatal unit (i.e. the head of the neonatal department) or in charge of the DHM program of a respective neonatal unit. They were provided with information about the purpose of this study, the process of data collection and the intended publication of anonymized data. By replying to our survey, the contacted individuals consented to participate in this study. Withdrawal of their consent or supplied data and thus of participation, was possible at any time.

We asked participants to provide unit specific policies concerning the use of DHM, handling routines, the source of

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**Table 1** Use of Donor human milk in participating neonatal units within Germany, Austria and Switzerland[a]

| | Germany | | Austria | | Switzerland[a] | |
|---|---|---|---|---|---|---|
| Level of neonatal care[b] | Level III | Level II | Level III | Level II | Level III | Level II |
| Contacted centers (n) | 165 | 58 | 7 | 17 | 7 | 7 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Response rate | 91 (58) | 27 (47) | 6 (86) | 6 (35) | 6 (86) | 6 (86) |
| No use of DHM | 65 (72) | 18 (67) | 1 (17) | 3 (50) | 0 (0) | 5 (83) |
| Use of DHM | 26 (28) | 9 (33) | 5 (83) | 3 (50) | 6 (100) | 1 (25) |
| Routinely[c] | 13 (50) | 1 (11) | 4 (80) | 2 (67) | 6 (100) | 0 (0) |
| Regularly | 2 (8) | 1 (11) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Occasionally | 4 (15) | 4 (44) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Rarely | 7 (27) | 3 (33) | 1 (20) | 1 (23) | 0 (0) | 1 (100) |

[a]German speaking part of Switzerland
[b]Level III = level of maximum care
[c]as part of a standardized feeding regimen
*DHM* donor human milk

DHM and the overall breastfeeding rates at discharge for each unit. Screening of donors and donated milk, exclusion and reimbursement of donors were also surveyed. We inquired about the participant's personal reasons to support the use of DHM in their unit. Rates of any or exclusive breast milk feeding (BMF) at discharge were sought. Barriers to prevent the use of DHM were enquired from those participants not utilizing DHM in their unit.

Data were collected from June 2016 to December 2018. The ethics committee of the Albert-Ludwigs-University, Freiburg, Germany, approved this study (No. 484/16).

We performed a descriptive analysis reporting quantitative data as mean and standard deviation or median and interquartile range where applicable. Categorical variables are presented in absolute numbers and percentages. The denominator represents the number of replies of any given questions to account for skipped questions. We applied a Wilcoxon rank sum test to compare unit size and breastfeeding rate between units and considered a $p$-value < 0.05 to be significant (GraphPad Prism V8, GraphPad, San Diego, CA).

## Results

We contacted neonatologists from 261 different units and 142 of those replied (54%). One hundred and three of the participating units provided the highest level of neonatal care (level III) and 39 units provided level II neonatal care (Table 1).

The median (IQR) number of very low birth weight infants (VLBW) per unit with a birth weight < 1500 g was 52 (36–72) in the year prior to the survey participation.

### Utilization of donor human milk

Any DHM was utilized in 50/142 neonatal units (35%). Within the year of participation, the median (range) number of neonates receiving any DHM per unit was 20 (2–59). Those units were caring for a median (IQR) of 61 (50–87) VLBW in the year prior to the survey participation, which compared to a median of 50 (33–67) VLBW in those 92 units that were not utilizing any DHM ($p$ = 0.001).

DHM feeding was commenced either immediately after birth ($n$ = 29), when mothers' own milk was not available after a few days of life ($n$ = 3), or commencement of feeding with DHM was decided on an individual basis ($n$ = 13).

DHM was acquired from different sources. Most neonatal units with DHM programs operated an institutional DHMB ($n$ = 27). In the remainder DHM was provided as a direct milk donation from another mother on the neonatal ward ($n$ = 10) whereby the DHM was handled on the neonatal ward lacking the infrastructure and service of a dedicated DHMB. In some cases neonatal units without an own DHMB and that were not performing direct milk donations within their unit ($n$ = 11) purchased DHM from other neonatal units, all of which operated a DHMB ($n$ = 7). None of the neonatal units purchased commercially available DHM products within their year of survey participation.

No neonatal unit (and their respective DHMB) distributed DHM to private non-hospitalized individuals.

The main reasons to prefer DHM over preterm formula was improved neonatal short term outcome parameters (Fig. 1). Explicit parental request was cited by two participants as additional reason to feed DHM.

Non-availability of DHM and the complex process of procuring DHM were the main reasons for not utilizing DHM but general concerns about the use of DHM were also voiced (Fig. 2). However, eight out of ten respondents that did not have access to DHM would like to introduce DHM in their unit once it would become available, citing reasons similar to those participants already utilizing DHM.

### Donor recruitment and donor screening

In 24 units donors are recruited amongst lactating mothers from other infants within the neonatal unit itself or the respective children's hospital (e.g. mothers of infants suffering from congenital heart disease), recruited amongst lactating mothers from the community not being connected to the respective hospital (external milk donation, $n$ = 21) or recruited from both donor pools ($n$ = 15).

A combination of a health history questionnaire regarding lifestyle, health indicators, medical and travel history, and serological testing to screen for donor eligibility was applied by all neonatal units that were procuring DHM (Table 2).

Additionally, according to individual participants' comments, donors were questioned for any treatment with blood products or immunizations with live vaccines, international travel to

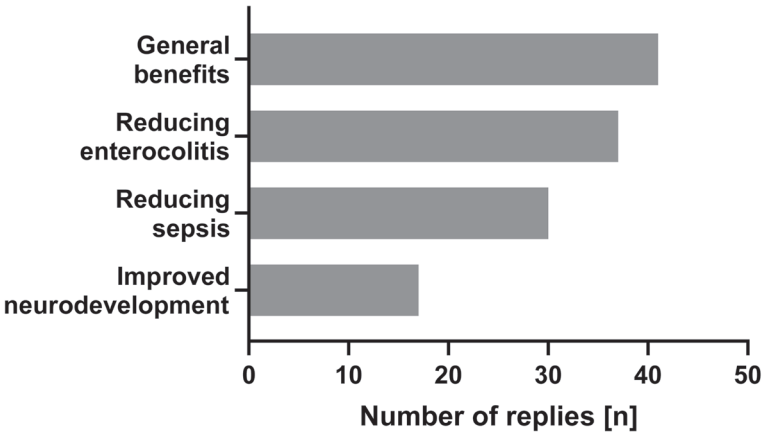



**Fig. 1** Reasons for using donor human milk amongst participants (multiple replies possible)

certain geographic areas, new skin tattoos, permanent make up or piercings up to 6 months prior to DHM donation but these items were not systematically surveyed by our questionnaire. Donors to some neonatal units were tested for nicotine ($n$ = 3), recreational drugs ($n$ = 5), medication levels ($n$ = 5) or alcohol levels ($n$ = 2).

Actual donor expenses related to the donation, such as travel costs, were reimbursed by 12 units. In no instances were donors paid for sharing their milk.

### Screening and handling of donor human milk

Donor milk was screened for bacterial count by 31/40 units. Screening was performed daily for every single bottle or pooled samples of DHM ($n$ = 12), once a week ($n$ = 10) or as random samples ($n$ = 9). However, according to our survey DHM was not tested for bacterial contamination in nine cases. Post-pasteurization cultures of DHM and cytomegalovirus studies from DHM were rarely performed ($n$ = 4). DHM was never tested for milk adulteration, e.g. adding water or non-human milk to DHM or for toxicological substances, e.g. alcohol or recreational drugs.

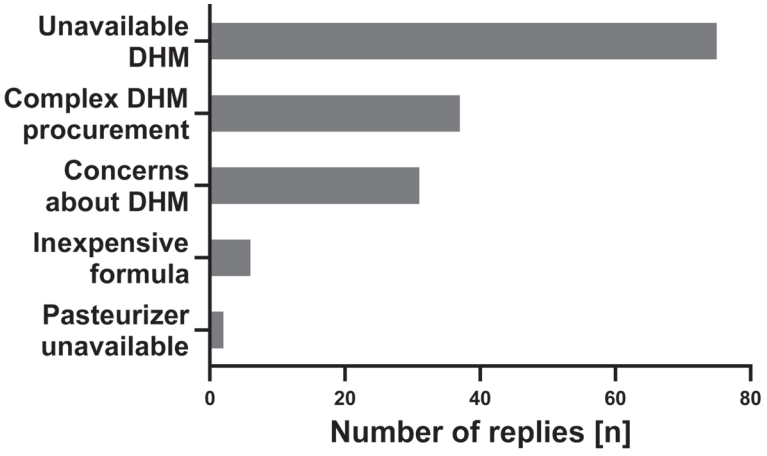
Depending on the bacterial content, DHM was left untreated (i.e. unpasteurized after being refrigerated and frozen) in 7/41 units, Holder pasteurized (i.e. DHM heated at 62.5 °C for 30 min) in 25/41 units, subjected to short-time pasteurization (i.e. 62 °C for 5 s, $n$ = 2) or subjected to freeze-thawing ($n$ = 11) before being distributed to preterm infants. Only one unit used DHM that has never been frozen and remained unpasteurized after cultural testing for bacterial count and bacterial identification.

### Lactation consultation and breast milk feeding

Lactations consultants were available in all but one unit. Rates of any BMF and for exclusive BMF at discharge from neonatal care were estimated by the participants for their respective unit. Rates of any BMF for preterm infants < 1500 g birthweight at discharge were increased in those units utilizing DHM ($n$ = 45) compared to those units ($n$ = 91) that are not utilizing DHM (median any BMF rate 71–80% versus 61–70%, $p$ = 0.0008). Estimated rates for exclusive BMF at discharge were also increased in those units supplying DHM compared to those not utilizing DHM (median exclusive BMF rate 51–60% versus 41–50%, $p$ = 0.019).

## Discussion

Sixty-five percent of those neonatal units that were participating in our survey did not utilize DHM in their nutritional management of very premature infants. Only half of the units that were feeding DHM used it as part of routine nutritional management, and in a third of units, DHM appeared to be used on a case by case basis only. Neither the overall utilization rate nor the implementation in those units feeding DHM reflects the actual recommendations concerning the use of DHM for premature infants.[1,2] This is in line with previous reports from other health care systems and underlines the need to improve




DHM, donor human milk

**Fig. 2** Reasons for not utilizing donor human milk amongst participants (multiple replies possible)

**Table 2** Items for screening for donor eligibility

| | Screening items |
|---|---|
| **Health history and lifestyle questionnaire (*n* = 37)** | n (%) |
| Chronic illness or long term medication | 37 (100) |
| Nicotine abuse | 37 (100) |
| Alcohol consumption | 37 (100) |
| History of drug abuse | 35 (95) |
| Promiscuity | 29 (78) |
| Frequent consumption of caffeine | 27 (70) |
| Special diets (vegan, vegetarian) | 24 (65) |
| **Serological Screening (*n* = 40)** | |
| HIV 1 and 2 | 40 (100) |
| Hepatitis B | 40 (100) |
| Syphillis | 33 (83) |
| Hepaptitis C | 32 (80) |
| CMV | 30 (75) |
| HTLV 1 and 2 | 10 (25) |

*CMV* cytomegalovirus; *HIV* human immunodeficiency virus; *HTLV* human T-lymphotrophic virus

the utilization rate of DHM and its implementation in clinical care.

Interestingly, some of the respondents that performed direct milk donations within their own unit did not consider themselves as maintaining a DHM program. However, the need for obtaining informed consent from donors and parents of recipients, screening of donors and donated milk, preparation, distribution and tracking of DHM applies irrespective of the source of DHM. Therefore, any distribution of DHM within a health care facility may be considered as "milk banking" and should be subjected to adequate rigorous quality management according to the respective recommendations or regulations.[12-14]

DHM screening for adulteration or substance abuse was not applied by our participants, this emphasizes the importance of donor screening and selection, especially when external milk donations are accepted. There was no reimbursement for milk donations to the non-profit DHM programs provided by neonatal departments in our cohort, this may reduce the financial incentive for milk adulteration that has been reported from commercially oriented milk sharing models.[15]

Pasteurization of DHM is recommended to prevent the transmission of potentially harmful microbiota to the premature recipients.[12,16,17] The adverse impact of Holder-pasteurization on the quality of banked DHM is well known but alternatives to Holder pasteurization are limited.[18,19] Freeze-thawing and short time pasteurization as performed in some units may not effectively inactivate cytomegalovirus or sufficiently reduce bacterial counts.[20,21] Some units are dispensing unpasteurized DHM based on maternal cytomegalovirus (CMV) serostatus and on DHM bacterial counts for which many different threshold levels have been described and therefore remain somewhat arbitrary.[22,23]

Lactation and breastfeeding support are the prerequisites for any DHM program. All efforts must have been undertaken to provide mothers own milk first before considering an infant as a suitable DHM recipient. All but one unit offered such lactation support. However, we did not enquire about the level of expertise of these lactation consultants. Furthermore, lactation support should be available at all times but the number of lactations consultants needed to staff an effective lactation program remains to be determined.[1,24]

Estimated exclusive and any breastmilk feeding (BMF) rates at discharge did not indicate lower BMF rates in participating units utilizing DHM compared to those not utilizing DHM. We acknowledge the limited methodology, i.e. estimation, for assessing BMF rates. Our results however, are in line with previously published results that did not show decreased BMF rates in neonatal units offering DHM service.[25,26] Nevertheless, the introduction of DHM may be detrimental to BMF efforts if mothers own milk is not adequately prioritized.[27]

Lacking access to DHM was the main obstacle to utilize DHM and most participants would introduce DHM in their unit if accessible. Objections against the use of DHM were also raised by some respondents. These objections were not specified by our survey but should be addressed to understand the care providers' concern and to identify further barriers for the use of DHM.

Some respondents purchased DHM from other neonatal departments. This may increase short-term availability and utilization of DHM but questions of interdepartmental DHM sharing (liability, regulatory framework and sustainability) remain. Costs of processing DHM are reported to exceed comparable costs for feeding mother's own milk and preterm formula considerably.[28] Although cost effectiveness of DHM has been repeatedly demonstrated in other health care settings reimbursement for the procurement of DHM has not been established within the participating countries which may further limit the neonatal departments' access to DHM.[29]

### Limitations

DHM utilization rate and handling procedures for DHM might have changed within the data acquisition period of this survey. However, this does not change our main finding of underutilization of DHM and our data may still provide a guiding framework for establishing DHM programs if national guidelines are not available. At the time of our survey the recently published guidelines of the European Milk Bank association were not available.[12] Therefore it would be worthwhile to review the variability of DHM handling practice and utilization over time. We aimed to distribute a concise and time efficient questionnaire. Therefore, we were not able to survey all different variations of DHM handling routines or to assess the percentage of eligible infants receiving DHM within a given unit. This may need a more in-depth analysis focusing on neonatal units DHM policies by other methods. We surveyed the German speaking part of Switzerland only, therefore the degree to which these results can be generalized to the whole country is limited and due to a limited participation rate we might have underestimated the true extent of DHM utilization. Nevertheless, 27 of 33 neonatal units with officially listed DHMB within the three countries (as of December 2018) participated in this survey. Therefore, we included most of those units regularly handling and utilizing DHM.

## Conclusions

Most participants would like to utilize DHM but lack access to DHM resulting in an underutilization of DHM within most

German, Austrian and Swiss neonatal units compared to the existing recommendations. These findings highlight the need to increase accessibility to DHM for premature infants.[8]

## Abbreviations

BMF: Breast Milk Feeding;; CMV: Cytomegalovirus; DHM: Donor Human Milk; DHMB: Donor Human Milk Bank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## Authors' contributions

DK, CG and HF conceptualized the study and designed the questionnaire. SJ and DK collected data and performed the data analysis. CG, RG, NH and HF contributed to data collection and analysis. All authors were involved in drafting, reviewing and contributing to the manuscript and approved the final version for submission.


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## Ethics approval and consent to participate

The ethics committee of the Albert-Ludwigs-University, Freiburg, Germany, approved this study (No. 484/16). By providing answers to this survey the respondents consented to participate.

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# Influence Of Time Under Mechanical Ventilation On Bronchopulmonary Dysplasia Severity In Extremely Preterm Infants

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## Abstract

**Background:** The relation between mechanical ventilation (MV) and bronchopulmonary dysplasia (BPD) — a common disease in extremely premature newborn (PTNB) — is well stabilished, but is unknown, however, how much time under MV influences the severity of the disease.

**Aim:** To define the duration under MV with greater chance to develop moderate to severe BPD in extremely PTNB and to compare clinical outcomes before and during hospitalization among patients with mild and moderate to severe BPD.

**Methods:** Fifty-three PTNB were separated into mild and moderate to severe BPD groups and their data were analyzed. Time under MV with a greater chance of developing moderate to severe BPD was estimated by the ROC curve. Perinatal and hospitalization outcomes were compared between groups. A logistic regression was performed to verify the influence of variables associated to moderate to severe BPD development, such as pulmonary hypertension (PH), gender, gestational age (GA) and weight at birth, as well the time under MV found with ROC curve. The result of ROC curve was validated using an independent sample ($n$ = 16) by Chi-square test.

**Results:** Time under MV related to a greater chance of developing moderate to severe BPD was 36 days. Moderate to severe BPD group had more males (14 vs 5, $p$ = 0,047), longer time under MV (43 vs 19 days, $p$ < 0,001), more individuals with PH (12 vs 3, $p$ = 0,016), worse retinopathy of prematurity (grade 3, 2 vs 11, $p$ = 0,003), longer hospital length of stay (109 vs 81,5 days, $p$ < 0,001), greater PMA (41 vs 38 weeks, $p$ < 0,001) and weight (2620 vs 2031 g, $p$ < 0,001) at discharge and the mild BPD group had more CPAP use prior to MV (12 vs 7, $p$ = 0,043). Among all variables included in logistic regression, only PH and MV < 36 days were significant in the model, explaining 72% of variation in moderate to severe BPD development. In the validation sample, prevalence of preterm infants who needed MV for more than 36 days in the moderate to severe BPD group was 100% ($n$ = 6) and 0% in mild BPD group ($p$ = 0,0001).

**Conclusion:** Time under MV related to moderate to severe BPD development is 36 days, and worst outcomes are related to disease severity. PH and time underMV for more than 36days are related to development of moderate to severe BPD.

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## Background

Bronchopulmonary dysplasia (BPD) is a multifactorial disease that occurs due to interactions among exposures during pregnancy, injuries from oxygen use and postnatal invasive mechanical ventilation (MV), as well as other injuries such as infections and inadequate nutrition after birth.[1] Diagnosis and classification remain uncertain, as there is still no consensus on the ideal postmenstrual age (PMA) for assessment of oxygen-dependent premature newborns. The 2000 National Heart, Lung and Blood Institute workshop recommends that for preterm infants with gestational age less than 32 weeks, BPD is defined as oxygen exposure for ≥28 days. It can also be categorized as mild (in room air at 36 weeks of PMA or at discharge — whichever comes first), moderate (supplemental oxygen at 36 weeks of PMA or at discharge — whichever comes first), or severe (supplemental oxygen ≥30% and/or positive pressure at 36 weeks of PMA).[2] BPD is a morbidity associated with extreme prematurity, and it has now been debated that milder forms of BPD do not seem to have severe consequences, such as serious respiratory morbidity and neurosensory impairment.[1,3]

Extremely preterm infants, those born at < 28 weeks of PMA,[4] are frequently submitted to MV,[5] which despite being a necessary and widely used treatment, has well established adverse effects. The risk of death is 8 times higher in extremely low birth weight preterm infants undergoing MV for more than 6 weeks compared to those exposed only to 7 days or less of invasive ventilation. This risk increases to 13 times when isolated only to cardiorespiratory causes.[6] Morbidities such as pneumothorax, ventilator-associated pneumonia, retinopathy of prematurity (ROP) requiring surgical intervention and even neurodevelopmental impairments are also associated with MV in preterm infants.[7-9] In addition, duration of MV is a strong predictor for BPD development: each additional week increases 2.7 times the odds for BPD.[10] Although the relationship between invasive mechanical ventilation and the development of the disease is well established, the duration of MV that interferes with severity classification of BPD remains unknown.

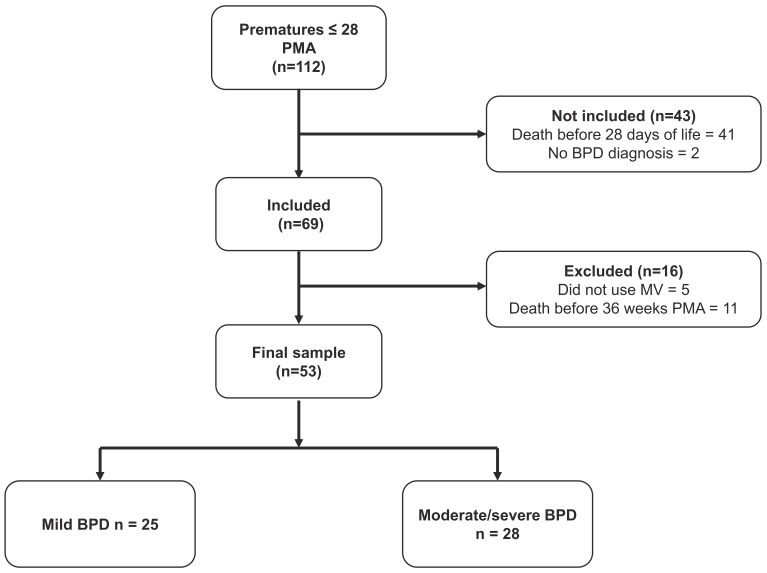


**Fig. 1** Flowchart of the study

Therefore, the aim of this study was to determine how many days of mechanical ventilation has a greater chance of developing moderate and severe bronchopulmonary dysplasia. Moreover, we aimed to compare clinical variables during hospitalization and prenatal data between patients with mild and moderate to severe dysplasia.

## Methods

### Design and sample

This was a retrospective cohort study (with clinical data prospectively entered in a national database) which was conducted at the University Hospital of the Londrina State University – Brazil. All preterm infants born at ≤28 weeks PMA between January 2015 and December 2017, admitted to the neonatal unit who survived for more than 28 days and were diagnosed with BPD were eligible. Infants who did not use invasive mechanical ventilation during hospitalization and those who died before 36 weeks of PMA were excluded. This was considered as a pilot study since we assessed data from only one hospital which participates in the Brazilian Neonatal Research Network. The study was approved by the Research Ethics Commitee Involving Human Beings – Londrina State University – Brazil (commitee's reference number: 3.362.155).

### Procedures

Patients included in the study were allocated into two groups: (I) mild BPD, those with diagnosis of BPD breathing in room air at 36 weeks of PMA; and (II) moderate to severe BPD, preterm infants diagnosed with BPD who required oxygen or some type of ventilatory support at 36 weeks of PMA. The definition of BPD and its severity were described by Jobe and Bancalari.[2]

#### *Perinatal variables were didactically divided into four groups*

a) *Maternal and gestational characteristics*: use of tobacco during pregnancy, use of antenatal corticosteroids and clinical diagnosis of chorioamnionitis;
b) *Perinatal variables*: postmenstrual age — weeks and days of gestation determined by ultrasound in the first trimester or date of last menstruation — birth weight, gender, Apgar score at 5th minute of life and type of stabilization required in the delivery room — intubation or noninvasive ventilation through continuous positive airway pressure — CPAP;
c) *Outcomes during hospitalization*: time under invasive mechanical ventilation, CPAP use before intubation, surfactant admnistration, vasoactive drugs (VADs) until the third day of life, degree of retinopathy of prematurity[11] and need for surgical correction — diagnosed by an ophthalmologist by retinal examination, patent ductus arteriosus (PDA) — diagnosed by a pediatric cardiologist by echocardiography — and type of treatment — drug or surgical, also indicated by cardiologist, pulmonary hypertension (PH) — also diagnosed by a pediatric cardiologist on echocardiography — clinical diagnosis of necrotizing enterocolitis (NEC),[12] pneumonia, pneumothorax and sepsis;[13]
d) *Variables at discharge*: length of stay, weight and PMA at discharge.

#### *Data on invasive mechanical ventilation*

The two main ventilation modes used in the study were time-cycled pressured-limited continuous flow ventilation and target volume ventilation. High-frequency oscillatory ventilation

**Table 1** Characteristics of patients included in the study

| Characteristics | Mild BPD group (***n*** = 25) | Moderate/severe BPD group (***n*** = 28) | ***p*** |
|---|---|---|---|
| GA, weeks | 26,34 ± 1,02 | 25,92 ± 1,37 | 0,305 |
| Weight at birth, g | 830,5 ± 150,26 | 760,07 ± 166,04 | 0,119 |
| Gender, M (%) | 5 (20) | 14 (50) | 0,047* |
| Apgar 5′ | 8 [6–9] | 8 [7–8] | 0,81 |

*GA* gestational age, *g* grams, *M* male, *Apgar 5′* Apgar score at fifth minute of life; * $p < 0,05$.

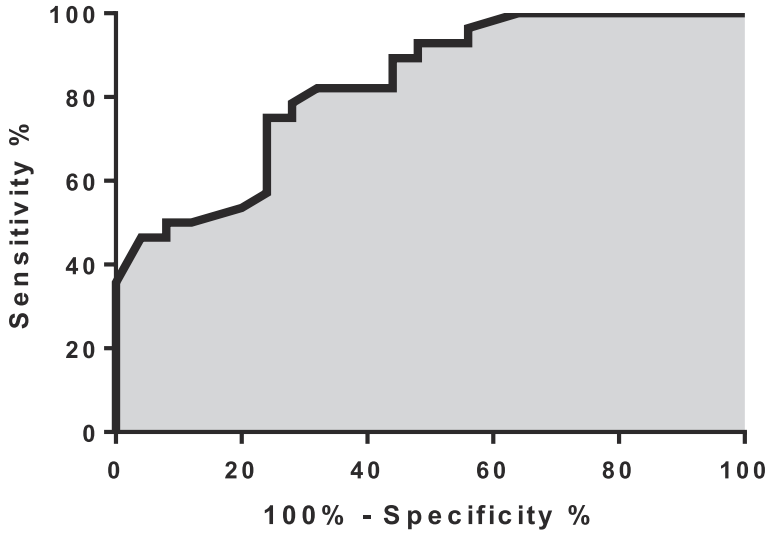


**Fig. 2** Cut-off point of time under mechanical ventilation. ROC curve showing sensibility and specificity of time under MV with greater chance to develop moderate/severe BPD. Area under the curve 0,83

was rarely used. Extubation criteria included arterial blood gases within normal limits and ventilator parameters that were considered low, in addition to the stability of the newborn.

### Statistical analysis

Statistical analysis was performed using SPSS Statistics 22 (IBM Corp, Armonk, NY) and Graph Pad Prism 6.0 software (GraphPad Software Inc.; San Diego, California, USA). Data distribution analysis was performed by Shapiro-Wilk test and data were described as percentages and mean ± standard deviation or median and interquartile range, according to the normality test. To estimate time under mechanical ventilation to predispose the highest chance of developing moderate to severe BPD, a ROC curve with time under mechanical ventilation was generated in days for both groups, and the best combination of sensitivity and specificity was used (index of Youden[14]). The area under the ROC curve (AUC) is a measure of cutoff point accuracy. AUC ROC values ≥0.90 are considered excellent, 0.80–0.89 good, 0.70–0.79 reasonable and < 0.70 are considered poor.[15] Comparison of variables between groups was performed by Student's t-test or Mann-Whitney's test for continuous data, and proportion measurements were analyzed using the Chi-square test. For comparing ROP degrees between groups, post hoc analysis involved pairwise comparisons using multiple z-tests of two-proportion with a Bonferroni correction, and statistical significance was accepted at $p < 0.006$. A logistic regression analysis was performed to verify the influence of variables previously known by their relationship with BPD development (such as PMA at birth, birth weight, gender and diagnosis of PH), as well as time under MV found by the ROC curve in the development of moderate to severe BPD. Variables that showed standard deviation greater than 2.5 in residual analysis were excluded. In order to validate the cut-off point found by ROC curve, Chi-square test was performed on a different sample ($n$ = 16) from the previously analyzed, applying the same eligibility, inclusion and exclusion criteria of the primary analysis with patients born in 2018 and 2019, using the time under MV above and below the cutoff point in each group. The statistical significance adopted was $p < 0.05$.

## Results

Of the 112 preterm infants born at ≤28 weeks PMA admitted to the unit, 41 died before completing 28 days of life and 2 were not diagnosed with BPD. Among those included in the study, 16 were excluded: 5 did not need MV during hospitalization and 11 died before 36 weeks PMA, making BPD classification not possible (Fig. 1). Data such as PMA at birth, weight, gender, Apgar score, MV time and length of stay of patients included in the study are described in Table 1.

The cutoff point for time under MV identified as the best predictor for moderate to severe BPD development identified on the ROC curve was 36 days (75% sensitivity [95% CI 55 to 89] and 76% specificity [95% CI 55 to 91]). Area under the curve was 0.83 (Fig. 2).

The comparison between the groups of preterm infants with mild BPD and those with moderate to severe BPD can be found in Table 2. There was no difference between groups regarding maternal and gestational characteristics. Both groups were similar in weight, PMA at birth, Apgar score and respiratory support needed in the delivery room, but the moderate to severe BPD group had a higher proportion of males.

Regarding the variables during hospitalization, preterm infants in moderate to severe BPD group had a longer time under MV, lower rates of CPAP use before intubation, higher rates of pulmonary hypertension, and greater severity of ROP. At discharge, individuals in the moderate to severe BPD group had been hospitalized longer and had a higher weight and were older than those in the mild BPD group.

Logistic regression which verified the influence of different clinical variables in the development of moderate to severe BPD was statistically significant ($p < 0.0005$). The model explained 72% of the variance in moderate to severe BPD and correctly classified 86% of the cases. After checking for residuals, three subjects were excluded from the analysis. Only two out of the five predictor variables were statistically relevant: PH and time under MV greater than 36 days (Table 3). Preterm infants who remained under MV for more than 36 days were 49 times more likely to develop moderate to severe BPD than those who needed MV for less than 36 days. The diagnosis of PH was associated with 37 times increase in chances of developing moderate and severe BPD.

**Table 2** Comparison between groups

| | Mild BPD | Moderate/severe BPD | *p* |
|---|---|---|---|
| **Maternal and gestational characteristics** | | | |
| Tobacco use, yes (%) | 2 (8) | 4 (14,3) | 0,672 |
| Chorioamnionitis, yes (%) | 3 (12) | 5 (18,5) | 0,705 |
| Antenatal corticosteroids, yes (%) | 23 (92) | 20 (74,1) | 0,143 |
| **Perinatal variables** | | | |
| Intubation in the delivery room, yes (%) | 12 (48) | 20 (71,4) | 0,072 |
| CPAP in the delivery room, yes (%) | 13 (52) | 8 (28,6) | 0,99 |
| **Outcomes during hospitalization** | | | |
| Time under MV (days) | 19 [7,25–38] | 43 [33,25-52,75] | < 0,001* |
| CPAP before intubation, yes (%) | 12 (56) | 7 (25) | 0,043* |
| RDS, yes (%) | 13 (76) | 24 (85,7) | 0,488 |
| Surfactant use, yes (%) | 18 (72) | 24 (85,7) | 0,313 |
| Pulmonary hypertension, yes (%) | 3 (12) | 12 (42,9) | 0,016* |
| Pneumonia, yes (%) | 23 (92) | 28 (100) | 0,218 |
| ROP classification, n (%) | | | |
| 0 | 13 (52) | 4 (14,3) | 0,009 |
| 1 | 6 (16) | 11 (39,3) | 0,23 |
| 2 | 4 (16,2) | 2 (7,1) | 0,31 |
| 3 | 2 (8) | 11 (39,3) | 0,003[a] |
| Corrective surgery for ROP, yes (%) | 1 (5,6) | 4 (15,4) | 0,634 |
| PDA, sim (%) | 22 (88) | 24 (85,7) | 1 |
| Drug treatment for PDA, yes (%) | 9 (40,9) | 11 (45,8) | 0,774 |
| Surgery for PCA, yes (%) | 2 (6,5) | 1 (4,2) | 0,6 |
| NEC, yes (%) | 3 (12) | 3 (10,7) | 1 |
| Surgery for NEC, yes (%) | 1 (33,3) | 2 (66,7) | 1 |
| Sepsis, yes (%) | 22 (88) | 26 (92,9) | 0,658 |
| VAD, yes (%) | 5 (20) | 2 (7,1) | 0,234 |
| **Variables at discharge** | | | |
| Lenght of stay (days) | 81,5 [69,5-90,5] | 109 [99–118,25] | < 0,001* |
| GA at discharge (weeks) | 38 [36,25-38,75] | 41 [39–42,75] | < 0,001* |
| Weight at discharge (g) | 2031 [1868–2328] | 2620 [2045–3030] | < 0,001* |
| $O_2$ discharge/transference, yes (%) | 0 (0) | 4 (14,3) | 0,115 |

*GA* gestational age, *g* grams, *Apgar 5'* Apgar score at fifth minute of life, *M* male, *MV* mechanical ventilation, *CPAP* continuous positive airway pressure, *RDS* respiratory distress syndrome, *ROP* retinopathy of prematurity, *PDA* patente ductus arteriosus, *NEC* necrotizing enterocolits, *VAD* vasoactive drugs, $O_2$ oxygen; * $p < 0,05$; [a]$p < 0,006$

In the validation sample, of the 16 preterm included in the analysis, 10 had mild BPD and 6 moderate to severe BPD. The prevalence of preterm infants who were under MV for more than 36 days in the moderate to severe BPD group was 100% ($n = 6$), and 0% in the mild BPD group ($p = 0.0001$).

## Discussion

The present study showed that there is greater chance of developing moderate to severe BPD in extremely premature newborns after 36 days under mechanical ventilation.[16] It is important though to make it clear that BPD is a multifactorial disease, and its development is also associated to factors such as intrauterine infections, growth restriction and nicotine exposure.[16] Due to the pathophysiology of the disease, BPD remains the most frequent morbidity in extremely premature infant,[17] and the diagnosis of moderate to severe BPD is associated with worse prognosis. A previous study comparing infants with different disease severity classifications showed that the group with moderate to severe BPD had a higher proportion of subjects with grade 3 and 4 intraventricular hemorrhage, periventricular leukomalacia, NEC, late sepsis, home oxygen use and death after discharge, in addition to the increased incidence of neurological impairment, worse mental and psychomotor development, blindness and hearing impairment.[18] In the present study, infants with moderate to severe BPD had worse ROP, higher prevalence of PH, and longer length of hospital stay, corroborating the findings in the literature that preterm infants have worse outcomes.

Studies have shown a high incidence of moderate to severe BPD in extremely premature infants (PMA up to 27-29w). Stoll et al. reported an incidence of 41% in their population.[19] Another study with extremely low birth weight infants (401–1000 g) found that 52% of the population had diagnosis of moderate to severe BPD.[18] In the present study, more than half of the preterm infants included (53%) had moderate to severe BPD (Fig. 1).

Recent studies have enhanced the harms of exposure for extremely preterm infants to MV for long periods of time. Yossef et al. observed that a group of extremely premature infants that were submitted to more than 56 days of MV had a higher incidence of moderate to severe BPD.[20] Choi et al. found an

**Table 3** Logistic Regression predicting likelihood of developing moderate/severe BPD based on MV > 36 days, GA, PH, weight and gender

| | | | | 95% C.I. for EXP | |
|---|---|---|---|---|---|
| Variable | B | *p* | RR | Lower | Upper |
| Constant | – 7528 | 0,506 | 0,001 | | |
| MV > 36 days | 3894 | 0,001 | 49,101 | 4916 | 490,415 |
| GA (days) | 0,048 | 0,469 | 1050 | 0,921 | 1196 |
| PH | 3632 | 0,011 | 37,770 | 2270 | 628,541 |
| Weight at birth | –0,005 | 0,125 | 0,995 | 0,988 | 1001 |
| Gender | 2014 | 0,143 | 7497 | 0,506 | 110,976 |

*MV* Mechanical ventilation, *GA* gestational age, *PH* Pulmonary hypertension, *B* nonstandard coefficients regression, *RR* relative risk, *C.I* confidence interval.
*Note*: Gender is for males compared to females

almost three-fold increase in the risk of mortality of extremely low birth weight preterm infants who required MV for 15 to 28 days. Furthermore, that study also associated cumulative duration of MV with ROP requiring surgical correction, neurological impairment, BPD, PH, and length of stay.[6] The major cause of the development of ROP is the exposure of preterm infants to supplemental oxygen therapy at high concentrations, therefore its relationship with prolonged MV is already expected.[11] Although the number of days under MV found in our study is different from the aforementioned studies, our findings are mostly similar to the literature. It reinforces the importance to avoid invasive MV, as well as to limit the duration that the extremely preterm infants are exposed to this treatment.

The mild BPD group had more individuals who used CPAP before MV, and it is an expected result. In centers where CPAP is used during stabilization in the delivery room, the incidence of severe BPD is 3.3%,[21] and intubation for surfactant administration alone (without MV) has shown a significant reduction in the use of MV in extremely low birth weight preterm infants.[22] In addition, compared with intubation right after birth, CPAP reduces the incidence of BPD and death at 36 weeks of PMA.[23]

Laughon et al. in their large study ($n$ = 3629 preterm infants) to develop an instrument for predicting BPD risk and death through clinical information, six variables were relevant to the model: PMA at birth, birth weight, ethnicity, gender, respiratory support and inspiratory oxygen fraction on specific days of hospitalization.[10] Factors such as PMA and weight were also related to longer time under MV[20]. In our search for predictors for development of moderate to severe BPD, in addition to time on MV greater than 36 days, the presence of PH appeared as significant in the regression model. It is associated with prolonged exposure to MV[6], and the association between PH and BPD is related to both its pathogenesis (similarly associated to complications of prematurity) and secondary PH development in BPD.[24] There was no difference between groups regarding PDA, NEC, use of VAD, chorioamnionitis and maternal use of tobacco, unlike other studies about both prolonged time under MV and higher severity of BPD,[6,20] which might have occurred due to the relatively small sample size. Additionally, a reasonable number of BPD patients did not survive until they completed 36 weeks PMA, which may also have contributed to this difference in outcomes.

Controversies regarding the definition and classification of BPD in literature may have limited our results. One premature newborn died before completing 36 weeks PMA and 41 died before 28 days of age. According to the most recent workshop on BPD, those infants could be classified as BPD type IIIa (early death from lung disease and respiratory failure),[25] and this could have influenced our findings. Our study involved preterm infants from a single institution and included a small sample compared to similar ones. Additionally, long-term outcomes such as neurodevelopment were not analyzed. However, almost all variables that may influence the development and severity of BPD were analyzed, except genetic factors. Despite the weaknesses, most of the findings of the present study, which is a pilot study, are in line with the findings from the literature.

Despite the limitations, it is noteworthy that this study is the first to investigate a cutoff point of time under MV to identify the chance of developing more severe forms of BPD. In addition, the result found was validated in an independent sample. Our study was able to define 36 days as a time of MV exposure that is associated with the development of moderate to severe BPD and, as a consequence, may have worse outcomes, such as greater severity of ROP and length of hospital stay. Therefore, it is suggested that MV should be avoided whenever possible, using strategies such as prophylactic CPAP and less invasive surfactant admnistration.[26,27] Moreover, MV should be interrupted as soon as possible, preferably before 36 days to reduce the risk of developing moderate to severe BPD, as well as to avoid impairments associated with the severity of the disease. Furthermore, a multicenter study should be performed to verify whether similar results are observed with a larger sample of patients. Indeed, this characterizes the next step for a future study in which we will include other hospitals from the Brazilian neonatal research network.

## Conclusion

In conclusion, we can state that the duration of MV exposure associated with the development of moderate to severe BPD was 36 days, and worse outcomes such as worse ROP and longer hospital staying are associated with disease severity.

## Abbreviation

BPD: Bronchopulmonary dysplasia; MV: Mechanical Ventilation; GA: Gestational age; ROP: Retinopathy of prematurity; CPAP: Continuous positive airway pressure; VAD: Vasoactive drugs; PDA: Patent ductus arteriosus; PH: Pulmonary Hypertension; NEC: Necrotizing enterocolitis; AUC: Area under the curve


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## Authors' contributions

VE: literature search, data collection, study design, data analysis, manuscript preparation, review of manuscript. DS: data collection, review of manuscript. JK: data collection, study design, review of manuscript. LF: data collection, review of manuscript. JMF: study design, review of manuscript. CAMC: study design, data analysis, review of manuscript. VSP: literature search, study design, data analysis, manuscript preparation, review of manuscript. All authors have read and approved the manuscript.


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## Ethics approval and consent to participate

Research Ethics Commitee Involving Human Beings – Londrina State University – Brazil.

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(62.5°C for 30 minutes), is effective at neutralizing viruses such as HIV, hepatitis and others that are known to be transmitted through human milk. In this study, researchers spiked human breast milk with a viral load of SARS-CoV-2 in U of T's combined containment level three unit and tested samples that either sat at room temperature for 30 minutes or were warmed to 62.5°C for 30 minutes. The virus in the pasteurized milk was inactivated after heating.

### Effectiveness of Antibiotics for Cesarean Section Births

Antibiotics for cesarean section births are just as effective when they're given after the umbilical cord is clamped as before clamping -- the current practice -- and could benefit newborns' developing microbiomes, according to Rutgers co-authored research. The study, by far the largest of its kind and published in the journal Antimicrobial Resistance & Infection Control, challenges current recommendations for antibiotic use. Administering antibiotics after clamping does not increase the risk of infection at the site of C-section incisions, the study concludes. "Most national and international guidelines, including those of the World Health Organization, recommend that women receive antibiotics before the skin incision for cesarean section," said co-author Maria Gloria Dominguez-Bello, Henry Rutgers Professor of Microbiome and Health, professor of microbiology and anthropology, and director of the New Jersey Institute for Food, Nutrition, and Health in the School of Environmental and Biological Sciences at Rutgers University-New Brunswick. "That exposes the baby to antibiotics during birth, affecting the microbiome assembly in the newborn. Early disturbance of bacterial colonization and the developing healthy microbiome may have consequences for immune development, leading to immune malfunctions later in life." A healthy microbiome helps guard against infection and antibiotics disrupt the microbiome, wiping out both bad and good bacteria, according to the US Centers for Disease Control and Prevention. Even stressors perceived as small, such as a hospital birth, can affect the neonatal microbiome, as shown by Dominguez-Bello's group in a 2018 study, and perturbations of the microbiome in early life possibly affect development of immunity and metabolism. Administering antibiotics to prevent infections of the surgical site is common practice and justified to minimize risks. But for cesarean section, the impact of antibiotics on the newborn and its developing microbiome should be considered, as well as the risk of infection, Dominguez-Bello said. Giving mothers antibiotics after clamping avoids additional stressors that impair transmission and colonization of maternal microbes after birth, so the current recommendation for antibiotics before clamping should be revised. The study, led by Rami Sommerstein at Bern University Hospital in Switzerland, covered 55,901 women at 75 hospitals in Switzerland from 2009 to 2018. They include 26,405 patients who received antibiotics before skin incisions for C-sections and 29,496 patients after their umbilical cords were clamped. Of the 846 documented infections after C-sections, 379 (1.6 percent) occurred in women who received antibiotics before incisions and 449 (1.7 percent) occurred in those who received antibiotics after their umbilical cords were clamped, with no statistical differences. "That means receiving antibiotics after umbilical cords are clamped to protect against maternal infections is as effective as receiving them before incisions," Dominguez-Bello said. "The guidance on the best timing for antibiotic use should be reevaluated to help promote the development of a healthy microbiome, which is essential for normal immune system development in babies. Bypassing the birth canal is already a stressor that should not be aggravated by the effect of antibiotics in the newborn."

### Pregnancy After Breast Cancer Is Rockier But Doesn't Increase Recurrence Risk

Breast cancer survivors are less likely to get pregnant and have higher risks of some delivery and fetal complications, according to a meta-analysis reported at the 2020 San Antonio Breast Cancer Symposium. However, the data also showed that pregnancy does not increase the risk of cancer recurrence. "With the availability of more effective anticancer treatments, survivorship and addressing the treatments' potential long-term toxicities has gained substantial attention," said study investigator Matteo Lambertini, MD, PhD, of University of Genova (Italy) — IRCCS Policlinico San Martino Hospital. "Returning to a normal life after cancer diagnosis and treatment should be considered, in the 21st century, as a crucial ambition in cancer care," Dr Lambertini added. "In patients diagnosed during their reproductive years, this includes the possibility to complete their family planning. Due to the constant rise in age at first pregnancy over the past years, many women are diagnosed with breast cancer before completing their reproductive plans." In that context, certain cancer treatments have the potential to reduce fertility. In addition, many women need prolonged hormone therapy, and conception is contraindicated while they are receiving it. Dr Lambertini and colleagues performed a meta-analysis using data from 39 studies that included a total of 114,573 breast cancer patients and 8,093,401 women from the general population. Results showed that breast cancer survivors were much less likely than women in the general population to become pregnant (relative risk, 0.40; $P < .001$). However, "the majority of the studies included in our meta-analysis did not capture the information on how many women tried to get pregnant," Dr Lambertini cautioned. In the few studies that did, more than half of women trying to conceive did become pregnant, and most of them were able to do so naturally, without need for assisted reproductive technologies. On the flip side, analyses also showed that pregnancies occurred in some women who did not want to conceive, underscoring the importance of comprehensive oncofertility counseling that addresses not only fertility preservation, but also contraception, Dr Lambertini said. Among women who became pregnant, breast cancer survivors did not have higher odds of spontaneous abortion or complications such as preeclampsia, and their infants were not significantly more likely to have congenital abnormalities. However, the breast cancer survivor group did have higher odds of cesarean birth (odds ratio, 1.14; $P = .007$), low birth weight (OR, 1.50; $P < .001$), preterm birth (OR, 1.45; $P = .006$), and infants small for gestational age (OR, 1.16; $P = .039$). In stratified analysis, the higher risk of having an infant with low birth weight was significant only for women who had received chemotherapy, and the higher risk of having an infant small for gestational age was significant only for women who had received chemotherapy or who had a late pregnancy (more than 2 years to 5 years after cancer diagnosis). Among breast cancer survivors, those who became pregnant actually had lower risks of disease-free survival events (hazard ratio, 0.73; $P = .016$) and death (HR, 0.56; $P < .001$). Findings were similar in the subset of studies that adjusted for the so-called healthy mother effect.

### Inventing Therapies that Save Lives

Swedish-Canadian researcher Christer Sinderby is the man behind Getinge's patented Neurally Adjusted Ventilatory Assist (NAVA). Using the patient's own respiratory drive to control

ventilator assistance, NAVA has elevated mechanical ventilation to an entirely new level and helped the tiniest premature baby in the world survive. "We are talking about the ECG of breathing," Christer says. "Using NAVA in mechanical ventilation is like adding ECG to a stethoscope when monitoring a heart. Both are based on electrical signals and more precise." The blowing of air has powered most of Christer Sinderby's life. In his youth, the talent for mastering the mighty sea breezes enabled him to compete with the best windsurfers in the world. As a scientist, the ability to control a few milliliters of air blown into a premature baby's tiny lungs has earned him and his wife Jennifer Beck respect in the entire medical world. Recently, NAVA played a major role in helping a premature baby in Japan, weighing only 258 grams at birth, survive. "It goes without saying that it is hard to sync a ventilator with rapid breaths of only 2-3 milliliters of air. We have managed to use the baby's own respiratory drive to achieve this synchronization," Christer explains. "The beauty of NAVA is that it can help all types of patients breathe; no matter if it is a tiny premature baby weighing a few hundred grams or an overweight 90-year old." NAVA has been used exclusively by Getinge since it was invented in the mid-1990s. Since 2003, Christer Sinderby is a scientist at the Keenan Research Centre for Biomedical Science, University of Toronto, Canada. "In principle, NAVA connects the patient's brain to the ventilator," Christer says. "The device uses the same electrical signal that activates the diaphragm to control the rhythm, depth and duration of our breathing. This means that the ventilator continuously is fully synchronized with the patient´s own breathing efforts." The electrical discharge of the diaphragm is captured by a special Edi catheter; placed in the esophagus and also functions as a gastric feeding tube. "Since it is the patient's own physiological signal that control the tidal volume and respiratory pattern, NAVA promotes lung-protective spontaneous breathing and reduces the risk of blowing to much or too little air into the lungs. NAVA simply delivers what the patient wants." Christer adds: "With traditional mechanical ventilation it is often easier to 'shut down' an uncomfortable patient with sedation than to finetune the ventilator to deliver the right tidal volume and frequency. This is what we want to avoid." Independent of air leakages, NAVA also facilitates non-invasive ventilation with nasal masks or prongs. A much more comfortable alternative than intubating the patient. Back in 1999, the innovation of NAVA was so remarkable that it was published in the prestigious Nature Medicine. "I think we are still the only researchers focusing on ventilator technology published there," Christer says. Christer Sinderby and Jennifer Beck are still dedicated to improve the abilities of Getinge's mechanical ventilators. "We focus on ventilation solutions that will be a reality in 5-10 years. Getinge's patience with the long-term scope that is a necessity in medical research has paved the way for a partnership with mutual respect for the corporate and scientific perspectives," Christer concludes.

### Company Earns Another Ventilation Industry Award

Dräger, an international leader in the fields of medical and safety technology, announced that Frost & Sullivan has recognized the company as a global technology innovation leader in the ventilation industry. Frost & Sullivan selected Dräger for its 2020 Global Technology Innovation Leadership Award due to the company's pioneering work to enhance patient safety and expedite recovery through innovative ventilator clinical protocols, continuous improvements in ventilation technology, and best-in-class services/support, training and continuing education. Furthermore, Dräger has significantly increased its ventilator production in 2020 to address the spike in demand driven by COVID-19. The COVID-19 pandemic has highlighted the essential need for ventilation in the treatment of critically ill patients, as well as the adverse events caused by the misuse of mechanical ventilators. During the pandemic, Frost & Sullivan analysts have been observing how the deployment of different types of ventilator models impact patient care. "We are honored to have been chosen by Frost & Sullivan for this prestigious award," said President and CEO for Dräger in North America, Lothar Thielen. "We would not be where we are today without our employees' dedication to continuous improvement in technology and services, and the support of our customers in helping us address their changing needs. Whether it is the ongoing challenges of value-based care, or the immediate needs presented by the current pandemic, we are proud to stand as a trusted partner to healthcare providers and their patients." Frost & Sullivan acknowledged Dräger in the following areas: **Ventilator technology:** "Compared to other competitors' products, Dräger's Evita ventilator models offer superior technology benefits for both patient safety and user flexibility." This includes invasive and non-invasive ventilation modes, advanced technologies that support lung protection and early weaning, and secured connectivity with other devices; **service and support:** "Dräger offers comprehensive and best-in-class services for healthcare providers with respect to ventilation along with digital solutions for connected care and data insights, which many competitors are striving to match." This includes device maintenance, IT consulting and system integration, user training, and network-based services and analysis of device data; **COVID-19:** "Dräger has upheld its guiding principle 'Technology for Life' during the COVID-19 pandemic, helping countries around the world to maintain the functionality of critical infrastructure as well as ensuring that the demand for ventilators is met across the globe by significantly increasing its production." Through its Intensive Care Online Network (ICON) emergency program, Dräger had made its ventilators available to hospitals in "hot spot" areas, along with online continuing education and a 24/7 real-time support. This is the third time in three consecutive evaluation cycles that Frost & Sullivan has recognized Dräger for best practices in ventilation therapy. In 2017, Dräger won the Frost & Sullivan North American Medical Ventilation Product Leadership Award, and in 2014 the Frost & Sullivan Best Practices Award in the Growth Excellence Leadership category for Mechanical Ventilation Equipment.

### Born too early with a 50/50 chance of survival—now she helps save other premature babies

When Sabina Checketts holds her hand a certain way, the tiny scar on the back of it looks like a rocket ship. Checketts got the scar during the first few days of her life, during a tenuous struggle for survival, after she was born at 28 weeks—12 weeks prematurely. Her rocket ship scar, and a few other small ones, are marks left by lines inserted into her tiny, frail body to keep her alive. "I don't point these out to parents," Checketts says, "but to me they're badges of honor, because I survived." The parents she's referring to are the parents of her patients. Thirty-three years after her early birth, Checketts now works as a neonatal doctor in London. Checketts decided to become a doctor at early age, when her mother routinely pointed out a man walking down the street on his way to the hospital and said, "That's the doctor who saved your life". That experience motivates her to be a source of positivity for the families of the babies she treats. "When I talk to parents about the fact that I was premature, there always is a sense of surprise, I think a

little bit even shock, you know. Oh, oh, and you're a doctor," Checketts says. "I think it's a nice way to say to them that prematurity shouldn't be a limit on what a child can do." "I mean, the advances we've made in even just the last 10, 15, 20 years mean the outcomes are much better than they used to be. And seeing me, who developed before that, as a newborn doctor, I give them a sense of hope and possibility, I think." Today, she uses vastly improved technologies and techniques to create better outcomes for other premature babies—and more hope for their parents. As vulnerable premature babies fight to stay alive one of the most critical issues is something most people never think twice about—breathing. A pivotal advance in neonatal medicine—and one that has a major impact in adult critical care—has been the development of better ventilators. "One of the main challenges for premature babies is with ventilation," says Checketts. "Their lungs are quite stiff when they're first born because they're so immature. They're very fragile." The ventilator that helped Checketts survive was a far cry from what she sees today when she treats premature babies. "We've gone from a mode of ventilation where you were breathing for the baby to one now where we can breathe with the baby as well," she says. One ventilation technique that breathes with the patient is called Neurally Adjusted Ventilatory Assist, or NAVA, developed by Getinge, a global leader in intensive care technology for both infants and adults. Before NAVA, ventilation technology had advanced to the point that a sensor in the breathing tube alerted when a baby was trying to breathe in, and the machine supplied a breath. But there was lag time, resulting in the machine sometimes not supplying air when the lungs called for it, or forcing air into frail lungs that were not ready for it—a problem amplified by premature babies' tendency to take short, rapid and uneven breaths. Sherry Courtney, a director of clinical research in neonatology, who has worked with premature babies since the 1980's explains, "The diaphragm is a muscle. When it contracts, we're going to breathe. When it relaxes, we're going to exhale. So, NAVA senses the breathing using a catheter that goes down into the stomach and rests close to the diaphragm." Courtney says she's observed many babies who switch to a NAVA-enabled ventilator almost immediately become more comfortable and less irritable. Their oxygen needs decrease, as do pressure and volume requirements. Babies can be more restful and concentrate energy on the single most important thing they can do during their premature stage—grow. "We have been switching in our unit more and more to NAVA because the babies seem to love it," Courtney says. NAVA is also approved for adults, and the features that make the technique successful for neonates translate well to adult patients. Adults on ventilators generally start with a functioning diaphragm, but it becomes weaker quickly. Getinge's Medical Director Miray Kärnekull says that advanced ventilator technologies like NAVA are used regularly in adult patients in Europe to keep patients' diaphragm muscles active. "It's really a groundbreaking technology", says Kärnekull. "NAVA gives the clinician a way to personalize not only the ventilation, but also the weaning process for adult patients". And in a very recent multicenter randomized controlled trial, results showed that patients with acute respiratory failure on NAVA spent significantly less time on the ventilator and experienced less extubation failure compared to conventional lung-protective mechanical ventilation.

**Augusto Sola, MD, Receives Pioneer Award**

Masimo announced that Augusto Sola, MD, Vice President of Medical Affairs for Neonatology at Masimo, has been awarded the 2020 Pioneer Award, Section of Neonatal Perinatal Medicine, by the American Academy of Pediatrics (AAP). The honor recognizes the groundbreaking achievements and contributions Dr Sola has made, using his Masimo SET-based protocol, to improve the health and well-being of newborn infants. Sola's impressive career in neonatology has improved the lives of countless newborns in the U.S., Latin America, and across the world. Dr Sola's innovative research on oxygen administration and monitoring oxygen saturation in preterm infants has played a key role in reducing the rate of neonatal blindness (retinopathy of prematurity) and our understanding of the impact of various neonatal practices on the developing brain. Dr Sola has published 130 original articles in peer-reviewed journals, 390 review articles, and 5 neonatology textbooks, as well as delivered more than 3,500 lectures to research and clinical groups around the world. Dr Sola also founded the Ibero-American Society of Neonatology (SIBEN), dedicated to continuous quality improvement in neonatal care throughout the Americas. Sola received his MD at Buenos Aires University School of Medicine and completed his Pediatric Residency and Chief Pediatric Residency at the University of Massachusetts, followed by a Neonatal Fellowship at the University of California, San Francisco. In neonatal practice since 1974, Dr Sola has been Professor of Pediatrics at Buenos Aires University Medical School, the University of California, San Francisco, the University of California, Los Angeles, and Emory University. In addition to his position at Masimo, Dr Sola continues to work directly with critically ill newborns. Sola's seminal work was done in 1998 at Cedars-Sinai Medical Center in Los Angeles. The results, published in 2003 by Drs Sola, Wright, and Chow, showed that using a new protocol with Masimo SET, clinicians reduced ROP to nearly zero over five years. Dr Sola and colleagues later showed at Emory that the protocol's success depended on SET technology, as the same protocol with a competing pulse oximeter did not reduce ROP. Dr Sola's work on the reduction of ROP through oxygen saturation targeting has now become the standard of care. Dr Sergio Golombek, MD, MPH, Professor of Pediatrics at New York Medical College, Neonatologist, Ex-President of SIBEN, and AAP member, commented, "In 1952, a Chicago newspaper wrote: 'The best friend a baby ever had,' referring to pediatrician Isaac A. Abt, MD, FAAP (1867-1955), founder of the AAP and its first president in 1930. He was known as a leading clinician, academic, advocate, promoter, writer, and leader. I think this has been overcome by Dr Sola, who is, in my opinion, the best friend of a baby and his or her parents and of the many neonatal professionals and trainees whom he trained!" Joe Kiani, Founder and CEO of Masimo, said, "We are incredibly proud of Dr Sola, a brilliant and caring doctor whom I have had the privilege of knowing for many years. Dr Sola's pioneering work on the oxygen saturation of neonates has made a significant impact on the prevention of blindness in infants, and his contributions to our understanding of neonatal physiology are vast. It is only fitting that the American Academy of Pediatrics has chosen to honor him. We are grateful to benefit from his expertise at Masimo, which has been especially dedicated, ever since its founding, to improving outcomes for the youngest and most fragile patients. Congratulations, Dr Sola, on this well-deserved recognition."

Dräger

# Improving Critical Care in the NICU


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## By sharing your goals, we can help you address your toughest challenges

This is what drives us: To improve critical care by offering solutions that provide clinical and financial value in the NICU. That's why Frost & Sullivan selected Dräger for its prestigious 2020 Global Ventilator Technology Innovation Leadership Award – citing our pioneering work to enhance patient safety and expedite recovery through innovative clinical strategies and continuous improvements in ventilation technology, as well as best-in-class services/support, training and continuing education.

**Visit www.draeger.com/intensivecare to learn more.**

Dräger. Technology for Life®


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Healthy development of low birth weight (LBW) premature infants' gut,[1] brain,[2] and lungs[3] are all impaired without the necessary nutrition. With Prolacta's products as a part of an Exclusive Human Milk Diet, you can safely fortify within the first week of life to provide the necessary nutrition.[3]

Half of the nation's level III and IV neonatal intensive care units have seen firsthand just how much our meticulously crafted human milk-based products matter. 63,000 premature infants throughout the world and counting.[4]

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Prolacta® BIOSCIENCE
Advancing the Science of Human Milk®

**1.** Brune KD, Donn SM. Enteral feeding of the preterm infant. *NeoReviews*. 2018;19(11):e645-e653. doi:10.1542/neo.19-11-e645 **2.** Schneider J, Fischer Fumeaux CJ, Duerden EG, et al. Nutrient intake in the first two weeks of life and brain growth in preterm neonates. *Pediatrics*. 2018;141(3):e20172169. doi:10.1542/peds.2017-2169 **3.** Huston R, Lee M, Rider E, et al. Early fortification of enteral feedings for infants <1250 grams birth weight receiving a human milk diet including human milk based fortifier. *J Neonatal Perinatal Med*. 2020;13(2):215-221. doi:10.3233/NPM-190300 **4.** Estimated number of premature infants fed Prolacta's products from January 2007 to August 2020; data on file.


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