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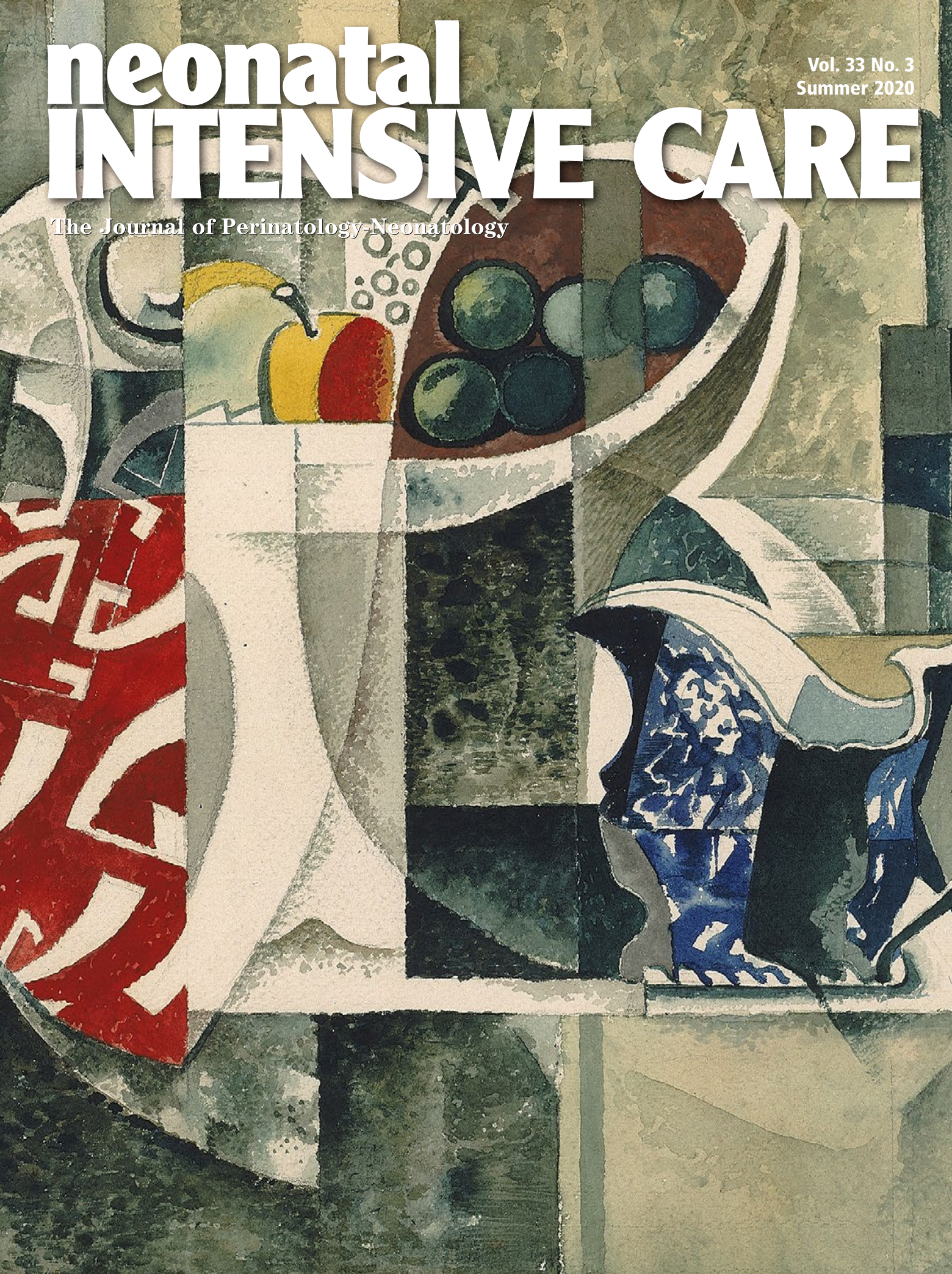

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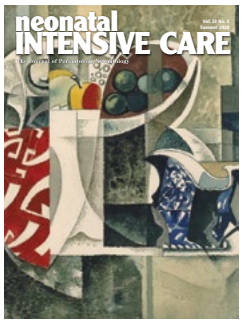

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Women, Babies at Risk as COVID-19 Disrupts Health Services

Millions of women and children in poor countries are at risk because the COVID-19 pandemic is disrupting health services they rely on, from neonatal and maternity care to immunisations and contraception, a World Bank global health expert has warned. Monique Vledder, head of secretariat at the bank's Global Financing Facility (GFF), told Reuters in an interview the agency was gravely worried about the numbers of children missing vaccinations, women giving birth without medical help and interrupted supplies of life-saving medicines like antibiotics. "We're very concerned about what's happening—particularly in sub-Saharan Africa," Vledder said as she unveiled the results of a GFF survey, one of the first seeking to assess the impact of COVID-19 on women's and children's health. "Many of the countries we work in are fragile and so, by definition, already have very challenging situations when it comes to health service delivery. This is making things worse." From late March, the GFF has conducted monthly surveys with local staff in 36 countries to monitor the impact of COVID-19 on essential health services for women, children and adolescents. Sharing the survey findings, GFF said that of countries reporting, 87% said the pandemic, fears about infection or lockdown measures designed to curb the spread of the coronavirus, had led to disruptions to health workforces. More than three-quarters of countries also reported disruptions in supplies of key medicines for mothers and babies, such as antibiotics to treat infections and oxytocin, a drug for preventing excessive bleeding after childbirth. The number of GFF countries reporting service disruptions nearly doubled from 10 in April to 19 in June, and the number reporting fewer people seeking essential health services jumped to 22 in June from five in April. GFF found that in Liberia, for example, fears about COVID-19 were preventing parents from taking their children to health clinics. In Ghana, some pregnant and lactating mothers were opting to postpone antenatal services and routine immunisations for fear of contracting the pandemic disease.

New Data on Hypertension

Using the new clinical definitions of hypertension, pregnant women with even modest elevations in blood pressure (BP) are at increased risk for preeclampsia, according to results from a large retrospective cohort study. In a 2017 guideline, the American College of Cardiology and American Heart Association changed clinical definitions of hypertension in adults. People previously deemed to have prehypertension were classed as having elevated blood pressure (systolic BP 120-129 mm Hg and diastolic BP >80 mm Hg) or stage 1 hypertension (systolic 130-139 mm Hg or diastolic 80-89 mm Hg). And while hypertension as earlier defined (at or above systolic 140 mm Hg or at or above diastolic 90 mm Hg; now called stage 2 hypertension) has been long associated with adverse maternal and fetal effects, it was unclear whether lesser elevations in blood pressure also are linked to the same. For their research published in Obstetrics & Gynecology, Elizabeth F. Sutton, PhD, of the University of Pittsburgh and colleagues looked at records from 18,162 women who had given birth to a single baby and had two or more prenatal appointments before week 20 of pregnancy. The women in the study were seen at the same institution over a 3-year period ending in 2018. Three-quarters of the cohort had normal blood pressure, while 14% had elevated blood pressure and 5% had stage 1 hypertension before 20 weeks. Another 6% of the cohort had stage 2 hypertension. The authors found preeclampsia risk increased with increasing blood pressure elevation. Among women with normal blood pressure before 20 weeks' gestation, 5% had preeclampsia,

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Phone: 310-443-4109
Fax: 310-443-4110
E-mail: s.gold4@verizon.net
Web: www.nicmag.ca

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Cover: Artist Earl Horter, born Philadelphia, PA 1881-died Philadelphia, PA 1940. Smithsonian American Art Museum, Gift of Mrs. Earle Horter, 1939.

while 7% of those with elevated blood pressure did, as did with 12% of women with stage 1 hypertension and 30% of women with stage 2 hypertension. The increase in risk of preeclampsia was because of preterm preeclampsia in the women with elevated blood pressure. Both term and preterm preeclampsia were factors in women with stage 1 and stage 2 hypertension, but preterm preeclampsia was associated with a higher risk. Although black race was associated with a higher risk of preeclampsia, the pattern of increasing risk with higher blood pressure category was similar in both black and white women. Researchers also looked at gestational diabetes, severe maternal morbidity, neonatal morbidity, and placental abruption as secondary outcomes. They found the risk of gestational diabetes increased in a stepwise fashion as blood pressure increased, compared with normotensive women. Higher risk of severe maternal and neonatal morbidities was seen only in women with stage 2 hypertension. Placental abruption was rare in this cohort and the odds were not increased in any group. The findings "highlight the importance of early pregnancy BP elevations, which may reflect prepregnancy BP status," and suggest that the new guidelines "can identify women early in pregnancy who may benefit from increased surveillance," Dr Sutton and colleagues wrote.

The Evidence for HeRO Continues to Build

Two more publications about HeRO are now available. Please check the company's publications page on its website regularly for the details and links to all the papers. If you have ideas for new research topics or if you are interested in deploying HeRO in your unit, then reach out. Following their earlier work on the use of HeRO with respect to intubation and extubation, Chakraborty et. al, have published Predicting Extubation Outcomes Using Heart Rate Characteristics Index in Preterm Infants: A Cohort Study. They present predictive models that assess readiness for extubation using physiological data and HeRO. These models are freely available, hosted by MPSC.

Cesarean Delivery Tied to Worse Outcomes in Women with COVID-19

Cesarean delivery was associated with severe maternal outcomes and clinical deterioration compared to vaginal delivery among women infected with COVID-19 in Spain. "We were really surprised by the high rate of cesarean section in (COVID-19 patients) in China," Dr David Baud of Lausanne University Hospital in Switzerland, said. "We were not so surprised to discover (in our own study) that vaginal delivery is safer in (such) patients." Baud and colleagues studied data on women in Spain with SARS-CoV-2 and singleton pregnancies between March 12 and April 6, 2020, and who delivered within the next 14 days. As reported in JAMA, among the 82 participants, four presented with severe COVID-19 symptoms, including one with concomitant preeclampsia. All four underwent cesarean delivery and required ICU admission. Seventy-eight women presented with no or mild COVID-19, including 11 who required oxygen supplementation. Forty-one (53%) delivered vaginally and 37 (47%) by cesarean delivery for obstetrical indications and eight for COVID-19 symptoms without other obstetrical indications. Compared to those delivering vaginally, women who underwent cesarean deliveries were more likely to be multiparous, obese, require oxygen at admission, and have abnormal chest x-ray findings. No severe adverse outcomes occurred in women who had a vaginal delivery. However, five (13.5%) who underwent a cesarean required ICU admission. Two (4.9%) with a vaginal delivery experienced clinical deterioration after birth vs eight (21.6%) with cesarean delivery. After adjustment for potential confounders, cesarean birth was significantly associated with clinical deterioration (adjusted odds ratio, 13.4). Eight newborns (19.5%) delivered vaginally and 11 (29.7%) born by cesarean delivery were admitted to the neonatal ICU. After adjustment, cesarean birth was significantly associated with an increased risk of NICU admission (aOR, 6.9). Three newborns delivered vaginally tested within 6 hours after birth had a positive SARS-CoV-2 RT-PCR result. However, repeat testing at 48 hours was negative. None developed COVID-19 symptoms within 10 days.

Device Helps Neonatal Oral Intubations

The SecureET Neonatal Endotracheal Tube Securement Device from Westmed (westmedinc.com) is the latest design available for neonatal oral intubations. The SecureET Endotracheal Tube holder features hydrocolloid material for skin contact and helps prevent accidental extubation by providing a secure method of stabilization. SecureET enables fast and easy application to secure endotracheal tubes sizes 2.5, 3.0, 3.5, and 4.0 mm. Each device is color coded for the size tube. SecureET facilitates placement options for the tube location in the oral cavity and may be moved to prevent palate grooving. SecureET allows for tube depth adjustment without disturbing the skin contacting hydrocolloid base. In addition, SecureET is the only neonatal ET Tube securement device with an optional head bonnet for superior security.

Doctors Can Help Parents Cope in the NICU

Parenting a newborn can be a tough journey, and bonding with a new baby in a neonatal intensive-care unit (NICU) is even more difficult given the medical uncertainties, fear and complex

emotions, according to a group of pediatricians. But healthcare providers can help parents cope, the group writes in Pediatrics, by communicating three messages: You are a parent, you are not a bad parent, you are a good parent. "When your child is sick, it is not rare for parents to wonder what they could have done to prevent the illness," said Dr Annie Janvier of Sainte-Justine University Medical Centre in Montreal, Canada, one of the authors of the report. In a NICU, the feelings are even more intense, she added. Mothers may feel their baby is sick because of their body, and fathers may feel helpless about what to do.

"Finding your parental roles in the NICU and feeling like a parent can take some time," she told Reuters Health by email. "Sometimes you can also feel ambivalence attaching because you are scared your baby will die." Janvier and colleagues at several hospitals in the US and Canada write about the stress that parents face in the NICU, as well as several strategies that doctors can take to help parents. They write from their experience as healthcare providers and also as parents or grandparents who have had children in the NICU. "Clinicians can harm parents inadvertently, for example, when they assume that 'mothers love to take their kid in their arms,' as some mothers may be frightened at first when their baby is unstable," Janvier said. Doctors and NICU providers can help parents by supporting "good parent" beliefs, which can guide parenting and decision-making and reduce anxiety, depression, prolonged grief and posttraumatic stress disorder, they write. The first message to communicate is "You are a parent," the authors write, because parents of infants in the NICU need to feel like "real" parents. They may feel conflicted about whether to invest emotionally in a baby who could die, looks fragile or could have future health problems.

When doctors use medical language such as "nonviable" or "congenital anomalies incompatible with life," these feelings are exacerbated, the authors write. Separation after birth, and breathing tubes and wires can interfere with bonding.

Possible Vertical Transmission of Novel Coronavirus

Clinicians in Italy report two cases of possible vertical transmission of SARS-CoV-2, the virus responsible for COVID-19, from the mother to the baby in utero. "To our knowledge, ours is the first report of cases of positive polymerase chain reaction (PCR) for SARS-CoV-2 in mother, neonate and placental tissues," Dr Luisa Patane and colleagues of ASST Papa Giovanni XXIII in Bergamo write in the American Journal of Obstetrics and Gynecology–Maternal Fetal Medicine. Vertical transmission of SARS-CoV-2 remains controversial and studies on placental correlations are limited. Patane and colleagues report that between March 5 and April 21, two of 22 babies born to women with COVID-19 were PCR positive for SARS-CoV-2 in nasopharyngeal (NP) swab samples. The first baby, a boy, was born vaginally after spontaneous labor at around 37 weeks' gestation to a mother who was experiencing fever and cough and had a positive SARS-CoV-2 NP swab. The mother wore a surgical mask during labor and delivery, skin to skin contact was not allowed, but rooming-in and breastfeeding with mask were allowed. The baby had positive NP swabs immediately at birth, after 24 hours, and after seven days. He remained asymptomatic, except for mild initial feeding difficulties, and was discharged from the hospital at 10 days of life. The second baby, a girl, was delivered by cesarean section at 35 weeks' gestation to a mother who had also had fever and cough and positive COVID-19 NP swab. The baby was immediately separated from the mother at birth and admitted to the neonatal intensive-care unit. The baby

had a negative NP swab at birth and a positive NP swab at day seven, with no contact between mother and neonate during that period. No neonatal complications were observed, only some feeding difficulties were reported in the first days of life; she was discharged at 20 days life 20. In both cases, SARS-CoV-2 RNA was found in placental tissue. The presence of SARS-CoV-2 RNA in the syncytiothrophoblast—the epithelial covering of the embryonic placental villi, which invades the wall of the uterus to establish nutrient circulation between the embryo and the mother—signifies presence of the virus on the fetal side, the clinicians point out. "This is the first study describing SARS-CoV-2 RNA on the fetal side of the placenta in two cases of mothers infected with COVID-19 and with neonates also positive for the virus at birth," they note.

Breastmilk of Mother with COVID-19 Tests Positive for SARS-CoV-2

Breastmilk samples from a nursing mother infected with SARS-CoV-2 has tested positive for the virus, researchers report. "The breastmilk of SARS-CoV-2-infected women may contain the virus. However, we described a single case and currently do not know how frequent this is, whether the virus in milk is infectious and whether it may indeed be transmitted to the newborn by breastfeeding," Dr Jan Muench of the Institute of Molecular Virology at Ulm University Medical Center in Germany said by email. Small studies have not found evidence of SARS-CoV-2 shedding into breastmilk, Muench and colleagues write. They tested milk from two nursing mothers with SARS-CoV-2 using RT-qPCR. Mother 1 developed symptoms of COVID-19 after delivery and tested positive for SARS-CoV-2. The newborn tested positive for SARS-CoV-2 and had respiratory symptoms. Both mother and infant recovered. Four breastmilk samples were taken from Mother 1 and all were negative for the virus. Mother 2 and Newborn 2 were put in the same room as Mother 1 and Newborn 1. They were discharged on day 4. Mother 2 developed mild COVID-19 symptoms, and both she and her baby tested positive for SARS-CoV-2. The baby was readmitted to the hospital due to icterus and breathing problems. On days 10 to 13 after initial hospital admission, breastmilk samples from Mother 2 tested positive for the virus. Two subsequent samples were negative. The authors note that Mother 2 had been wearing a surgical mask after she developed COVID-19 symptoms and followed safety precautions while feeding and handling the baby. "We plan to recruit more infected mothers to 1) determine how often SARS-CoV-2 is present in milk and at which quantities; 2) to figure out whether the virus in milk is indeed infectious; 3) to check whether the virus in milk could be inactivated by pasteurization and/or storage 4) to check for anti-SARS-antibodies in milk and their neutralization efficiency; and 5) finally proof whether the virus may be transmitted via breast milk to the newborn," Muench said.

Placental Injury Reported in Women with COVID-19

Maternal vascular malperfusion and intervillous thrombi were more common in the placentas of women infected with SARS-CoV-2, compared with historic controls, report researchers who conducted the first-of-its-kind case series in the English literature. Nevertheless, the neonates in the report appear to be healthy so far and all tested negative for the virus. Although the series examining placentas from 16 women is small, it carries a larger implication—that increased antenatal surveillance for pregnant women infected with SARS-CoV-2 may be indicated,

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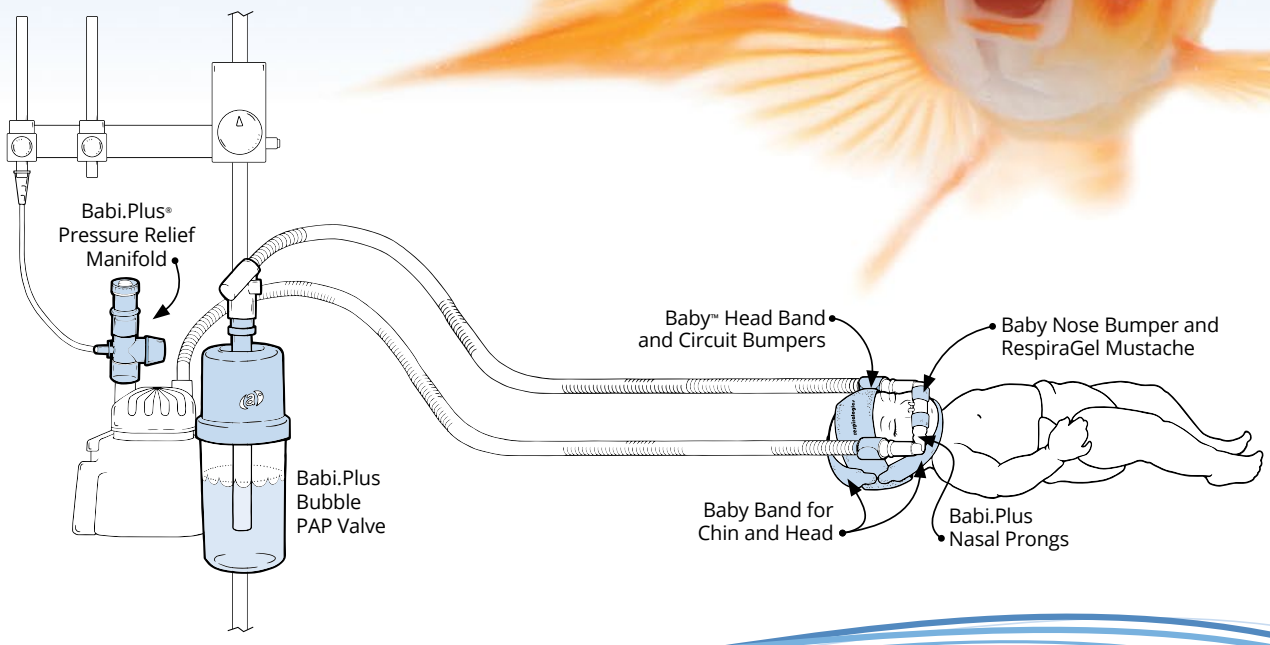

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the researchers noted. Furthermore, the results could align with other reports of coagulation and vascular abnormalities among people with COVID-19. "I would say that our findings fit into that larger picture of vascular injury. This is developing, and there are some significant ways that these feeder vessels to the placenta are different, but if this is the emerging paradigm, our findings can fit into it," Jeffrey A. Goldstein, MD, PhD, assistant professor of pathology at Northwestern University, Chicago, said in an interview. The research was published in the American Journal of Clinical Pathology. Prior case series reported in Wuhan, China, do not currently suggest that pregnant women are more likely to experience severe COVID-19, in contrast to observations during severe acute respiratory syndrome and Middle East respiratory syndrome outbreaks. "However," the researchers noted, "adverse perinatal outcomes have been reported, including increased risks of miscarriage, preeclampsia, preterm birth, and stillbirth." To learn more, Dr Goldstein, lead author Elisheva D Shanes, MD, and colleagues examined the histology of placentas from women with COVID-19 giving birth between March 18 and May 5, 2020. They compared these placentas with over 17,000 historic controls and 215 women who had their placentas evaluated as part of a melanoma history study.

Study Highlights Growth of Babies

Prolacta Bioscience, the world's leading hospital provider of 100% human milk-based nutritional products, announced the results of a long-term pilot study showing that premature infants fed an exclusive human milk diet (EHMD) including Prolacta's fortifiers reached the same healthy growth and developmental milestones by age 2 that are seen in full-term infants. The study was published in the May 2020 issue of Breastfeeding Medicine. Authored by Erynn M Bergner, MD, and colleagues, the new study is the first to concurrently evaluate long-term neurodevelopmental, growth, and body composition outcomes of preterm infants in the neonatal intensive care unit (NICU). Researchers found: Preterm infants receiving Prolacta's 100% human milk-based fortifiers returned to birth z-scores for weight, length, and head circumference by age 2; similar percentage of body fat and lean mass in preterm infants at age 2, compared to matched term controls, with adequate bone mineralization; not a single case of severe cognitive developmental delay using a Bayley Scales of Infant and Toddler Development III (BSID-III) cutoff score of <70 at 18 to 22 months corrected age (CA). "As we continue to optimize nutritional practices in the NICU and investigate an entirely human milk-based approach for the diets of preterm infants, it is important to follow the potential impact of these changes on health and development long-term," Dr Bergner wrote. Bergner et al evaluated the post-discharge growth, body composition, and neurodevelopmental outcomes of a cohort of infants ≤1,250 g birth weight who received Prolacta's fortifiers as part of an EHMD in the NICU. The infants were studied prospectively at two outpatient visits: 12 to 15 and 18 to 22 months (CA). Dual-energy X-ray absorptiometry and BSID-III were performed at 18 to 22 months (CA). "The Bergner study demonstrates what we've long suspected—that the numerous health benefits we see in the NICU with Prolacta products as part of an Exclusive Human Milk Diet translate into longer-term neurodevelopmental and metabolic health outcomes," said Melinda Elliott, chief medical officer for Prolacta Bioscience.

Continued on page 54…

Safe Handling of Human Milk Within the Hospital Setting

Caroline Steele, MS, RD, CSP, IBCLC, FAND

Introduction

The benefits of human milk (HM) are well-established, particularly for the preterm or ill infant.[1-4] However, in the hospital setting, it is more complicated to safely get HM from mother to baby than simply breastfeeding.[3-5] Critical illness or limited oral feeding skills may necessitate the administration of milk via feeding tube.[4,5] Furthermore, preterm and hospitalized infants often require fortification to meet nutritional needs.[2,4-6] Therefore, a mother often must express milk, then label and transport it to the facility where it is stored, processed, and eventually fed.[1-6] Consequently, it is critical that appropriate steps are taken for patient safety throughout the process with emphasis on three primary areas: avoiding microbial contamination, preventing misadministration (wrong HM administered), and ensuring preparation accuracy.[1,4]

Best practices regarding safe and accurate handling of HM in hospitals have been widely published.[1-6] Common themes include appropriate preparation location, use of trained staff (ideally dedicated technicians), proper identification of HM at each step to prevent misadministration, and strategies to prevent fortification errors[1-7] The goal of this article is to summarize the current published best practices for the handling of HM in hospitals.[1-8]

Human Milk Storage

Storage times and temperatures impact nutritional and bioactive components of HM as well as microbial growth.[4,9-14] Adequate refrigerator and freezer space for HM storage, with appropriate airflow, is important for proper temperature maintenance.[4] Use of dedicated HM refrigerator/freezer units which are located in areas with limited access to prevent tampering and waste is considered a best practice.[1,4] Guidelines for HM storage in the hospital are often more conservative than for the healthy term infant at home.[1,4,9] HM refrigerators must be able to maintain temperatures between 2-4°C (35-39°F) while freezers must allow for temperatures at or below –20°C (–4°F) for long-term storage.[1,4,15] At these temperatures, research supports the following storage recommendations for the hospital setting:[1,10,15-17]

- Refrigerate fresh HM for a maximum of 48 hours*
- Refrigerate thawed, unpasteurized expressed HM for a maximum of 24 hours
- Refrigerate thawed, pasteurized donor human milk (DHM) for a maximum of 48 hours
- Refrigerate fortified HM or DHM (whether fresh or thawed) for a maximum of 24 hours
- Store frozen HM for 6-12 months at ≤–20°C (≤–4°F) or beyond 12 months at –70 to –80°C (–94 to –112°F)

*Of note, one study in which HM in the NICU setting was refrigerated and only accessed once daily found no significant changes in osmolality, bacterial colony counts, or secretory immunoglobulin A, lactoferrin, total fat concentrations when stored up to 96 hours.[1,18] Therefore, it is possible that a 96-hour storage time may be appropriate for HM that is expressed under clean conditions if the fresh HM is unit dosed at the time of expression and the container not opened prior to feeding.[1] However, because most HM used in the hospital setting has been expressed at bedside or at home (where conditions are unknown), a facility may be unable to validate if the milk was expressed under optimal conditions including appropriate cleaning and sanitation of all pump parts.[1] Consequently, a 48-hour refrigeration time frame is considered appropriate for most acute care facilities. An organization desiring to implement a slightly longer storage time for fresh refrigerated HM could consider a 72-96 hour time frame if the following criteria are met:[1]

- Centralized handling of HM in a dedicated space (ideally with dedicated staff)
- Strict HM handling sanitation processes
- Unit dosing of feedings as soon as possible after collection to reduce frequency of assessing the HM storage container
- Ability to evaluate expression and transport conditions for individual mothers to ensure clean conditions

Feeding Preparation

HM and pasteurized DHM feedings should be prepared in a dedicated location that is separate from patient care areas to reduce the risk of contamination.[1,2,19,20] No handling or preparation of HM or DHM feedings should occur in any patient care area, including the patient's bedside.[1,2,6,8,20]

The preparation area should include a handwashing sink and, unless only disposable items are used, a three-compartment

Caroline Steele is the Director of Clinical Nutrition and Lactation at Children's Hospital of Orange County. Caroline is a registered dietitian (board certified in pediatrics) and international board certified lactation consultant with over 27 years of experience. She has many professional publications including serving as the co-editor/author of the Academy of Nutrition and Dietetics' publication Infant and Pediatric Feedings: Guidelines for Preparation of Human Milk and Formula in Heath Care Facilities. This manuscript was written at the request of Medela, LLC.

Figure 1. Overview of Hospital Human Milk Preparation Steps

sink or commercial dishwasher to ensure the proper cleaning and sanitizing of all non-disposable items.[1,4,21,22] Use of aseptic technique (practices that minimize the presence of pathogenic microorganisms) are critical for patient safety.[1,4] All work surfaces should be properly sanitized prior to handling any HM and between each patient's feeding preparation.[1,23] It is critical to employ processes that reduce the risk of transferring pathogens between patients.[1] Recent events have brought the novel coronavirus (responsible for causing coronavirus disease 2019 or COVID-19) into the spotlight. However, there are other viruses that could potentially be transferred with poor handling techniques including other respiratory viruses (such as influenza, adenovirus, and parainfluenza).[1] Because most facilities do not routinely test for all potential viruses and because dirty hands could result in the transfer of microbes from an individual to the outside of the bottle, it is reasonable to assume the outside of any container could be contaminated. It is not necessary and is potentially unsafe to use chemical disinfectants to wipe down the outside of HM storage containers.[23] Because microbes that may be present on the outside of a bottle could potentially be transferred to a sanitized work surface, it is prudent to avoid setting items that come in contact with the HM (such as a spoon, whisk, or milk straw) directly on the work surface.

Use of dedicated staff for HM feeding preparation is considered a best practice and has been shown to reduce risk of errors.[1-3,6] Staff should be well trained in aseptic technique, including proper hand hygiene, and demonstrate proper steps for handling HM and fortifiers.[4,24,25] Nails should be natural, short, unpolished, and neatly groomed due to the association between artificial and long natural nails and *Pseudomonas aeruginosa* outbreaks in the hospital setting.[4,26-28] Use of disposable gowns and other personal protective items including a bonnet/hairnet and gloves are recommended for further protection against cross contamination of both microbes and allergens.[1,4]

Laminar flow hoods may provide an additional barrier against contaminants but are not required for the handling of HM within the hospital setting.[1] Furthermore, their use does not result in a sterile finished product and should not be considered a substitute for aseptic technique and good handling practices.[1,4,29]

All items used for preparation and storage of HM should be made of stainless steel or food grade plastic that is bisphenol A (BPA) and Di(2-ethylhexyl) phthalate (DEHP) free.[22] While glass items are acceptable from a sanitation standpoint, they are not routinely used due to risk of exposure to glass particles should the glass crack or break.[22] Single-use, disposable items for HM collection and feeding preparation are common due to their convenience and sanitation.[4] Single use items may be sterile or clean, non-sterile as there is no evidence that use of non-sterile items increases microbial growth in expressed

HM or prepared HM feedings.[1,4,16] Reusable items must be cleaned and appropriately sanitized between uses to prevent cross contamination; sanitation methods include use of the commercial dishwasher (reaching appropriate temperatures), a three-compartment sink, or an autoclave.[1,4]

Preparation accuracy is imperative.[1,4] Care must be taken to ensure the correct fortifier or modular product is used and that recipe calculations are correct.[1] Inappropriate fortification can result in feeding intolerance and gastrointestinal complications.[1] Containers with precise graduations (to the one milliliter mark) should be used to measure HM and liquid ingredients.[1,4] A gram scale, accurate to a tenth of a gram, should be used to measure powdered fortifiers and additives.[1,4]

At present, the optimal length of time between preparation and feeding of fortified human milk is unknown.[15] However, despite any changes that may occur in fortified HM over time, the recommendation for a maximum storage time of 24 hours following fortification continues to be supported by current available research.[1,4,15,30] Furthermore, the risk of potential changes to HM composition that may occur when feedings are prepared in advance, appear to be outweighed by the benefits of centralized handling of HM (where typically 12 or 24 hours' worth of feedings are prepared at a time).[1-8,15,18,30] The time it takes to prepare and deliver feedings must also be included in the maximum storage time.[30] Rarely with centralized handling is the first feeding of a batch fed immediately after it is prepared; generally, feedings for the entire unit are prepared then delivered (creating a lag time).[30] Therefore, the total time from when the first patient's feedings are prepared to when the administration of the last feeding of a batch has concluded must fall within the 24-hour maximum storage time for fortified feedings.[30]

A method of confirming proper identity of HM is critical prior to combining bottles, feeding, or discharging HM home to ensure the correct milk is going to the correct infant.[1,4] This may be achieved by a two-person verification of two patient identifiers or the use of bar code scanning.[1,4] Scanning is often used in place of a manual two-person verification for efficiency and to reduce risk of human error.[1,3-6] In addition to preventing HM misadministration, research has shown that scanning systems (depending on specific product features) may reduce other errors and improve efficiencies by:[3-6]

- preventing fortifier/additive misadministration
- monitoring expiration dates/times of prepared feedings as well as stored HM and fortifiers/additives
- tracking lot numbers of DHM and fortifiers
- automatically calculating fortified feeding recipes
- reducing staff time needed for two-person verification, lot tracking, and recipe calculation

A general overview hospital HM preparation steps may be found in Figure 1.[1,4,15]

Summary

The use of HM with preterm and ill infants has many advantages.[1,4-6] Because of the compromised immune status of these fragile patients, the handling of HM in the hospital setting must be approached with great care and meticulous attention to detail.[1,4-6] Ensuring that feedings are prepared in a proper location, away from direct patient care areas, using aseptic technique is critical to prevent contamination.[1,4,6] Use of dedicated technicians and technology offer additional measures to reduce risk of preparation errors and misadministration.[1,4,6] All hospitals should critically evaluate their HM handling processes to ensure best practices are in place.[1,4]

References

1 Steele C, Collins E, eds. *Infant and Pediatric Feedings: Guidelines for Preparation of Human Milk and Formula in Health Care Facilities.* 3rd edition. Chicago, IL: Academy of Nutrition and Dietetics; 2019.

2 Moro GE, Arslanoglu S, Bertino E, Corvaglia L,Montirosso R, Picaud JC, et al. Human milk in feeding premature infants: from tradition to bioengineering. Proceedings of a consensus development conference—EXPO 2015. *J Ped Gastroenterol Nutr.* 2015;61:S1–19. doi: 10.1097/MPG.0000000000000897.

3 Oza-Frank R, Kachoria R, Dail J, Green J, Walls K, McClead RE Jr. A quality improvement project to decrease human milk errors in the NICU. *Pediatrics.* 2017;139:e2–7. doi: 10.1542/peds.2015-4451.

4 Steele C. Best practices for handling and administration of expressed human milk and donor human milk for hospitalized preterm infants. *Frontiers in Nutrition.* 2018;5(76):1-5. doi: 10.3389/fnut.2018.00076.

5 Steele C, Czerwin A, Bixby C. Breast milk bar code scanning results in time savings and staff efficiency. *J Acad Nutr Diet.* 2015;115:23–26. doi: 10.1016/j.jand.2014.06.360

6 Steele C, Bixby C. Centralized breastmilk handling and bar code scanning improve safety and reduce breastmilk administration errors. *Breastfeed Med.* 2014;9:426–429. doi: 10.1089/bfm.2014.0077.

7 Barbas KH. Mother's milk technicians: a new standard of care. *J Hum Lact.* 2013;29:323–27. doi: 10.1177/0890334413492910.

8 Perkey K. Delivering results: Opening an infant nutrition center. *Future Dimens Clin Nutr Pract.* 2016; 8–12.

9 Eglash A, Simon L, The Academy of Breastfeeding Medicine. ABM clinical protocol #8: human milk storage information for home use for full-term infants, revised 2017. *Breastfeed Med.* 2017;12:390–395. doi: 10.1089/bfm.2017.29047.aje.

10 Yuen JW, Loke AY, Gohel MDI. Nutritional and immunological characteristics of fresh and refrigerated stored human milk in Hong Kong: a pilot study. *Clinica Chimica Acta.* 2012;413:1549–1554. doi: 10.1016/j.cca.2012.03.018.

11 Takci S, Gulmez D, Yigit S, Dogan O, Dik K, Hascelik G. Effects of freezing on the bactericidal activity of human milk. *J Pediatr Gastroenterol Nutr.* 2012;55:146–149. doi: 10.1097/MPG.0b013e31824f7889.

12 Chang JC, Chen CH, Fang LJ, Tsai CR, Chang YC, Wang TM. Influence of prolonged storage process, pasteurization, and heat treatment on biologically-active human milk proteins. *Pediatr Neonatol.* 2013;54:360–366. doi: 10.1016/j.pedneo.2013.03.018.

13 Raoff NA, Adamkin DH, Radmacher PG, Telang S. Comparison of lactoferrin activity in fresh and stored milk. *J Perinatol.* 2016;36:207–209. doi: 10.1038/jp.2015.186.

14 Grazziotin MC, Grazziotin AL, Vidal NM, FreireMH, DaSilva RP. Analysis of the storage methods for raw human milk from mothers with infants admitted to a neonatal intensive care unit, according to Brazilian regulations. *J Hum Lact.* 2016;32:446–454. doi: 10.1177/0890334416647710.

15 Boullata JI, Carrera AL, Harvey L, Escuro AA, Hudson L, Mays A, et al. ASPEN safe practices for enteral nutrition therapy. *J Parenter Enteral Nutr.* 2017;41:15–103. doi: 10.1177/0148607116673053.

16 Jones F. *Best Practice for Expressing, Storing and Handling*

Human Milk in Hospitals, Homes and Child Care Settings. 4th ed. Fort Worth, TX: Human Milk Banking Association of North America, Inc; 2019.
17 Hamosh M, Ellis LA, Pollock DR, Henderson TR, Hamosh P. Breastfeeding and the working mother: effect of time and temperature of short-term storage on proteolysis, lipolysis, and bacterial growth in milk. *Pediatrics*. 1996;97:493–498.
18 Slutzah M, Codipilly CN, Potak D, Clark RM, Schanler RJ. Refrigerator storage of expressed human milk in the neonatal intensive care unit. *J Pediatrics*. 2010;156(1):26-28.
19 National Association of Neonatal Nurses. The use of human milk and breastfeeding in the neonatal intensive care unit. Position statement #3065. April 2015. http://nann.org/uploads/About/PositionPDFS/1.4.3_Use%20%20of%20Human%20Milk%20and%20Breastfeeding%20in%20the%20NICU.pdf. Accessed March 2, 2020.
20 The Facilities Guidelines Institute. *Guidelines for Design and Construction of Hospital and Health Care Facilities*. Washington, DC: American Institute of Architects; 2014:91-92. Standard A2.17.2.3.2(3) and Standard 2.1-7.2.3.3(5).
21 NSF International Standard/American National Standard for Food Equipment. *Commercial Warewashing Equipment.* Ann Arbor, MI: NSF International; August 2012.
22 NSF International Standard/American National Standard for Food Equipment. *Food Equipment Materials.* Ann Arbor, MI: NSF International; March 2015.
23 Human Milk Banking Association of North America. *Milk Handling for COVID-19 Positive or Suspected Mothers in the Hospital Setting.* April 14, 2020. https://www.hmbana.org/file_download/inline/a593dd72-be78-471e-ae5e-6490309108fd. Accessed April 28, 2020.
24 Centers for Disease Control and Prevention. Hand hygiene in healthcare settings. March 24, 2017. www.cdc.gov/handhygiene/providers/index.html. Accessed March 2, 2020.
25 Association of Perioperative Registered Nurses. Hand hygiene. www.aorn.org/guidelines/clinical-resources/clinical-faqs/hand-antisepsis-hygiene. Accessed March 2, 2020.
26 Moolenaar RL, Crutcher JM, San Joaquin VH, et al. A prolonged outbreak of Pseudomonas aeruginosa in a neonatal intensive care unit: did staff fingernails play a role in disease transmission? *Infect Control Hosp Epidemiol*. 2000;21(2):80-85.
27 Centers for Disease Control and Prevention. Guideline for hand hygiene in health-care settings. *MMWR Morb Mortal Wkly Rep*. 2002;51(RR-16):1-56.
28 Hedderwick SA, McNeil SA, Lyons MJ, Kauffman CA. Pathogenic organisms associated with artificial fingernails worn by health care workers. *Infect Control Hosp Epidemiol.* 2000;21:505–509. doi: 10.1086/501794.
29 The United States Pharmacopeial Convention. USP 795 pharmaceutical compounding—nonsterile preparations. In: *USP Compounding Compendium* 2016. Rockville, MD: The United States Pharmacopeial Convention; 2016:31-39.
30 Steele C, Ehwerhemuepha L, Colllins E. 24-hour versus 12-hour storage recommendations for previously frozen (thawed) fortified human milk. J Acad Nutr Diet. 2020; in press.

Wharton Jelly Proteins and Scar Healing: Can Wharton Jelly Proteins Convert Adult Pattern of Healing into the Fetal One?

BM Petrikovsky, MD, PhD

Introduction

Encouraged by the beneficial results of Wharton jelly peptides and umbilical cord blood for tissue healing, we used silicone gel impregnated with Meso-Wharton P199 to improve scar appearance after abdominal and palpebral surgery.

Material and Methods

Forty-two patients with recent surgical scars were enrolled in the study. Twenty-one patients had obstetrical and gynecological surgical procedures, 16 – repair of facial lacerations and 5 – facial plastic surgical procedures requiring stitching.

Elongated gel patches impregnated with Meso-Wharton P199 were placed over the scar with the instructions to use it for 6-12 hours a day for 3-6 months. All gel applications were performed in the office with the patients' consent. All the treatment components of gel patches are approved for local use thus eliminating the need for IRB approval. All incisions were sutured using subcutaneous technique by plastic or experienced gynecological surgeons.

We used the Vancouver Scar Scale to assess gel performance (Table 1).

Table 1. The Vancouver Scar Scale

	Scar Characteristic	Score
Vascularity	Normal	0
	Pink	1
	Red	2
	Purple	3
Pigmentation	Normal	0
	Hypopigmentation	1
	Hyperpigmentation	2
Pliability	Normal	0
	Supple	1
	Yielding	2
	Firm	3
	Ropes	4
	Contracture	5

Scores from different parameters are added together to give an overall score for the scar appearance, with higher scores representing worse scars. Scars were scored before and after Meso-Wharton P199 applications.

Statistical Analysis

Summary statistics are presented as frequencies for categorical variables and as means and SD or median and interquartile range for continuous variables. Differences in categorical variables were analyzed with the x^2 or Fisher's exact test and differences in continuous variables with the independent t test or Mann-Whitney test.

Results

A total of 42 surgical scars were assessed prior to the gel applications; 40 scars were assessed after the applications. Two patients were lost to follow-up.

Scar scoring results before and after Meso-Wharton P199 applications are reflected on Table 2.

Table 2. Average scar score before and after treatment

Type of surgery	Before	After
Cesarean Section	7 ± 4	3 ± 2
Gynecologic Procedures	8 ± 3	3 ± 1.5
Plastic surgery	3.5 ± 1.5	2 ± 1.5

*P<0.01

Discussion

In 2019, we reported our preliminary experience with using gel impregnated with Meso-Wharton P199 to improve the appearance of surgical scars.[3] Scar formation and tissue healing are complex procedures requiring and depending on many factors, including good surgical technique, proper choice of suture materials, adequate blood supply and oxygenation of the scar area, as well as the use of anti-scar remedies. The current report deals with unique healing properties of Wharton jelly protein P199. A decade ago, we shared our experience with umbilical tissue biopsy as a mean to obtain proteins and stem cells directly from the umbilical cord.[4]

Because the umbilical cord contains more multipotent stem cells at younger gestational ages, the idea of umbilical cord biopsy appears attractive if proven to be safe. Our data demonstrates that the punch biopsy of a pulsating umbilical cord after the birth of a child can be successfully performed in most cases with minimal or no damage to the umbilical cord itself.[4] We conclude

BM Petrikovsky, MD, PhD is a professor and former Chair of Obstetrics & Gynecology at Nassau University Medical Center. Author wants to express his gratitude to Professor VV Ashapkin for his valuable comments.

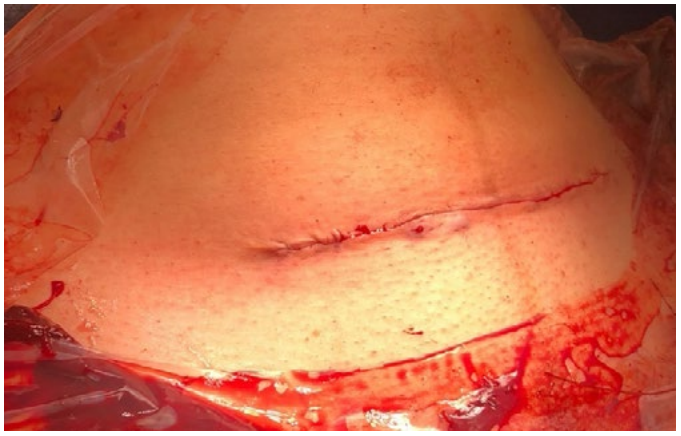

Figure 1. Fresh skin scar after cesarean section

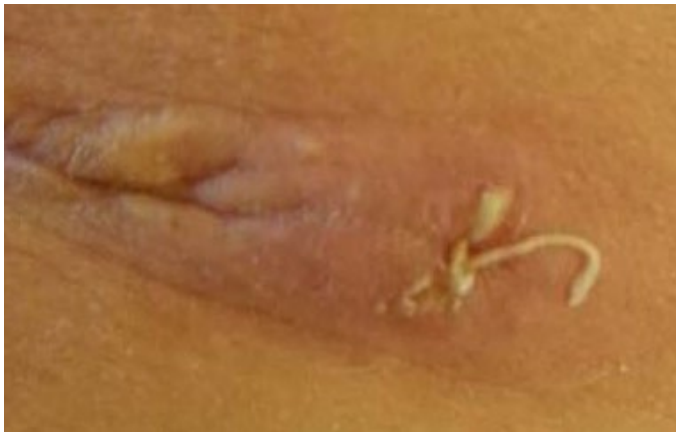

Figure 2. Inflammatory type of scar healing around the foreign body (surgical knot) before treatment)

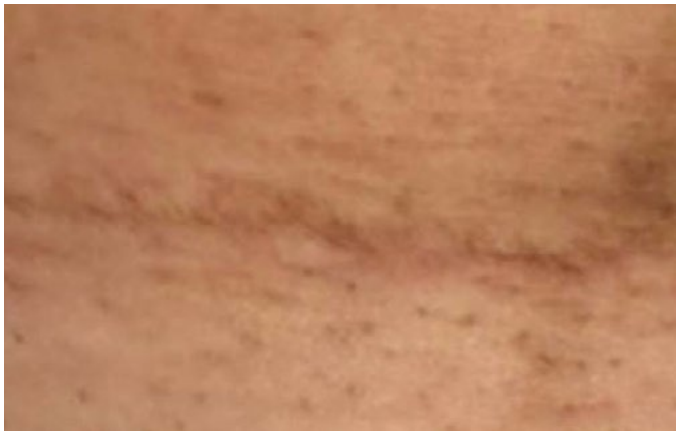

Figure 3. Scar appearance after treatment

that with appropriate instrumentation, experience after further studies, umbilical biopsy may become a useful procedure for the recruitment of stem cells.[5,6]

In our previous pilot study, we used patients' self-assessment of their satisfaction with scar healing after the application of gel impregnated with Meso-Wharton P199. Self-assessment is a subjective method to assess the effectiveness of scar treatment. In order to avoid subjectivity in the current report, we used the Vancouver Scar Scale. Scar scales have been devised to quantify scar appearance in response to treatment. There are currently at least 5 such scales. The Vancouver Scar Scale (VSS), Manchester Scar Scale (MSS), Patient and Observer Scar Assessment Scale (POSAS), Visual Analog Scale (VAS), and Stony Brook Scar Evaluation Scale (SBSES). These observer-dependent scales consider factors such as scar height or thickness, pliability, surface area, texture, pigmentation, and vascularity.[7-9] It appears that under similar circumstances (surgical suture technique, similar choice of suture materials, etc.,) gel pads impregnated with Meso-Wharton P199 improve scar appearance as judged by the results of VSS. Leung, et al.[10] addressed the issue of minimizing the scar formation by using fetal wound healing pattern as a gold standard. Fetal wound healing is characterized by a distinct growth factor profile, an attenuated inflammatory response with an anti-inflammatory cytokine profile. Recent studies have further suggested a role for fetal cells to heal wounds through their promoting effect on adhesion, proliferation, and migration of existing cells.[10-12]

Wound healing is a complex process involving cell migration, proliferation, apoptosis, and the remodeling of the extra cellular matrix. The regenerative phenotype of the fetus has shown a difference in a number of processes involved in wound healing, which may be manipulated significantly to reduce scarring. The use of Wharton jelly peptides appears to be the first ever successful attempt to convert adult type of scar healing into the fetal one. Wharton's jelly P199 is known to induce the production of host skin stem cells. These cells may play the main role in converting adult type of healing to the fetal one, thus, achieving better scar appearance and healing.

Bibliography

1 Zharov EV, Petrikovsky BM, Jakubovsky ES. Modern methods of clinical use of peptides in cosmetic medicine. AIG INFO 2011; 4: 3-5.
2 Reddi A, Ende N. The use of human umbilical cord blood for wound healing, burns, and brain injury in combat zones. Military Medicine, 176; 4: 361-2011.
3 Petrikovsky BM. Use of umbilical cord proteins to improve surgical scar appearances. Neonat Intens Care 2020; Vol. 33 No. 1.
4 Petrikovsky BM, Fuks A, Sichinava L, Zharov EV. Can umbilical cord tissue biopsy be an alternative source of stem cells? Neonat Int Care 2015; 6: 12-4.
5 Petrikovsky BM, Karsdon J. Stem cells – from jelly to gold. Editorial. Neonat Int Care 2011; 24: 1-25.
6 Petrikovsky BM. Wharton's jelly protein as a stimulant of skin stem cells. Proceedings of Tenth Anti-Aging Medicine World Congress, Monaco 2012; 29: 151-4.
7 Durani P, McGrouther DA, Ferguson MWJ. Current scales for assessing human scarring: a review. J Plastic Reconstr Aesth Surg. 2009; 62: 713-20.
8 Vercelli S, Ferriero G, Santorio F, et al. How to assess postsurgical scars: a review of outcome measures. Disabil Rehabil. 2009; 31(25): 2055-63.
9 Singer AJ, Arora B, Dagum A, et al. Development and validation of a novel scar evaluation scale. Plast Reconst Surg 2007; 120(7): 1892-7.
10 Leung A, Crombleholme TM, Keswani SG. Fetal wound healing: implications for minimal scar formation. Curr Opin Pediatr 2012; 24(31): 371-378.
11 Martin P, D'Souza D, Martin J, et al. Wound healing in the PU.1 null mouse-tissue repair is not dependent on inflammatory cells. Curr Biol 2003;13(13):1122-1128.
12 Petrikovsky BM, Karsdon J. Fetal wound healing and stem cells. Editorial Neonat Int Care 2011; 24: 5-7.

A Novel Test for the Detection of Occult Placental Insufficiency

BM Petrikovsky, MD, PhD*, M Terrani, MD,** LG Sichinava, MD, DSc***

Introduction

Exercise in pregnancy has been shown to improve or maintain physical fitness, help with weight management, reduce the risk of gestational diabetes, among others. Currently, the contraction stress test (CST) is the only existing test to assess fetal reserves. However, CST has limited use because it requires IV placement and may cause unwanted preterm labor. We propose a new test to assess reserves by measuring fetal heart rate (FHR) responses to maternal exercise.

Material & Methods

Eight hundred and nineteen patients between 36 and 42 weeks of pregnancy were included in the study. Fetal assessments were performed for the following indications: decreased fetal movements, advanced maternal age, restricted fetal growth, diabetes, post-term pregnancy, and a history of fetal distress during previous pregnancies. For maternal exercises, we used a motorized treadmill in a moderate exercise regimen (15-minute fast walk at a speed of 3 mph with an incline of 15 degrees to 25 degrees). Adverse fetal outcomes were considered if one or more of the following were present: Category III FHR tracing; 5-minute Apgar score of less than 7; admission to the neonatal intensive care nursery, unrelated to prematurity; fetal growth restriction; fetal and early neonatal demise. Statistical analysis was performed using PASW Statistics (version 18.0; IBM Corporation, New York, NY).

Results

Fetal response to maternal exercise (FRME) results have been classified into 3 separate categories: negative, positive, and inconclusive. Similar to CST, the test was read as positive if late FHR decelerations were seen during or after maternal exercise.

If no late decelerations were detected, the test was read as negative. If FHR tracing was difficult to interpret due to technical difficulties, the test was read as inconclusive. The number of individual tests was higher than the number of patients because many fetuses were tested more than once. In total, 3,022 tests were negative, 92 were positive, and 512 were inconclusive. Inconclusive results were due to artifacts and an inability to maintain a satisfactory, continuous, FHR tracing during or immediately after maternal exercise. The relationship between the value of the test (positive or negative) and the adverse perinatal outcome is reflected on table 1.

Table 1. A Relationship Between Positive and Negative Fetal Responses to Maternal Exercise (FRME) and Adverse Perinatal Outcome.

FRME Results	Incidence of Adverse Outcome
Negative	1.1
Positive	16.2

$P < 0.05$

Patients with inconclusive results were referred for conventional testing.

Discussion

We propose an FRME test as an alternative to CST.[1] It can be performed in the office without intravenous administration of oxytocin. We conducted a prospective longitudinal study using the FRME test. We included fetal and early neonatal demise as the key outcomes along with the category III FHR tracings, low 5-minute Apgar scores, and NICU admission. Like the CST, positive FRME tests were associated with a seven-fold increase in adverse perinatal outcomes.

Freeman[2] summarized his experience with OCT. Patients selected for antepartum FHR monitoring have included those patients at risk for uteroplacental insufficiency. The following is a list of categories which are currently being used as indications for the use of antepartum fetal monitoring at Los Angeles County University of Southern California Medical Center, Women's Hospital: (1) hypertensive disorders in pregnancy, (2) diabetes mellitus, (3) history of previous stillbirth, (4) clinical intrauterine growth retardation, (5) cyanotic maternal heart disease, (6) prolonged pregnancy. The conclusion Freeman made were as follows:

A negative OCT, done on a weekly basis, is very reassuring. A positive OCT is often indicative of a loss of uteroplacental respiratory reserve. If the results fall into the unsatisfactory category, the test is not interpretable and must be repeated within 24 hours.

We recently reported our experience with FRME in pregnant patients with diabetes.[3] Fetal testing in pregnant women with diabetes remains a challenge because of a limited number of tests capable of diagnosing occult placental insufficiency, which may negatively affect the fetus. Diabetes, being also a vascular

* BM Petrikovsky, MD, PhD, Professor and former Chairman Nassau University Medical Center, New York. ** M Terrani, MD, Medical Director, Garden OBGYN, New York. *** LG Sichinava, MD, DSc, Pirogov Russian National Research Medical University Moscow, Russia

disease, often damages placental circulation. We studied the possibility to use maternal exercise to test placental reserves in diabetic mothers: 160 patients had gestational diabetes, 80 had pregestational diabetes. The most common complication in fetuses with positive prenatal test results was abnormal FHR in labor (36%) followed by low Apgar score (21%) and the need for NICU admission (19%). Most of the adverse outcomes had correlation with positive results of the exercise test. In conclusion, it appears that maternal exercise causes changes in FHR, which may be used to assess placental and fetal reserves.

Conclusion

It appears that positive FRME has a high correlation with adverse perinatal outcome.

References

1 Petrikovsky BM, Sichinava L, Swancoat S. Can fetal heart rate responses to maternal exercise be used for antepartum surveillance? J Diagn Med Sonogr 2018; 34(5): 342-45.
2 Freeman RK. The use of the oxytocin challenge test for antepartum clinical evaluation of uteroplacental respiratory function. Am J Obstet Gynecol 1972; 114: 1-6.
3 Petrikovsky BM, Zharov EV, Plotkin D, Petrikovsky E. Maternal exercise uncovers placental insufficiency in diabetic mothers. Int Diab Card Dis 2019; 3(1): 91-93.

Scrotal Thermal Injury From Cooling Blanket in a Neonate

Shabih Manzar

Summary

We report a case of thermal injury to the scrotum in a neonate secondary to the use of a cooling blanket. The differential diagnosis is presented, followed by literature review.

Case

A male infant was delivered via assisted vaginal delivery at 40-1/7 weeks of gestation. Mother was 20 years old gravida 1, para 0. All her prenatal labs were negative including RPR, HIV, hepatitis B, chlamydia and gonorrhea. Significant history revealed GBS positive status and fever with highest temperature of 100°F (37.7°C), suggestive of chorioamnionitis.

The delivery was complicated by shoulder dystocia. Figure 1 showed 90 seconds of significant fetal bradycardia prior to delivery. At delivery, the infant had no cry, poor tone and poor respiratory effort. He was taken to the preheated warmer, dried, stimulated and bulb suctioned. He was initially provided continuous positive airway pressure (CPAP) via T-piece resuscitator. Within 20 seconds, he was intubated. After initial stabilization, he was transported to neonatal intensive care unit (NICU). Apgar score were 0, 5 and 5 at 1, 5 and 10 minutes respectively. Infant's physical examination was congruent with moderate neonatal encephalopathy. No dysmorphic features were noted. Weight was 3760 grams, length 55 cm, and head circumference 32 cm. Vital signs showed a temperature of 97°F (36.1°C) and heart rate of 120 beats per minute, blood pressure 69/38, respiratory rate 52. Cord blood gases is depicted in Table 1.

Hospital Course

In the NICU, while stable on ventilator, the infant developed seizure. He was started on anticonvulsant and hypothermia therapy was instituted as per unit protocol. A complete work up including CBC, serum electrolytes and blood cultures was obtained. Infant was treated with ampicillin and piperacillin-tazobactam. All his labs were reported as normal. Antibiotics were stopped after 72 hours. Brain MRI with DWI-ADC was obtained on day 5 of life that showed signs of hypoxic injury in the insular area. Electroencephalogram (EEG) was reported as normal, so phenobarbitone was stopped.

At day 6 of life, the infant was noted to have firm scrotal swelling on the right side. Ultrasound with doppler was obtained, that showed marked soft tissue and subcutaneous thickening inferior to right testicle with diffuse increased echogenicity and scattered hypoechoic areas (Figures 2 and 3). After running through the differential diagnosis, a diagnosis of thermal injury was made. At the time of this report, the infant is transitioned to full feeds. The neurological exam is normal and testicular swelling remained stable.

Discussion

Scrotal swelling in neonates could be due to testicular etiologies (testicular torsion, testicular neoplasms, supernumerary testicle) and non-testicular etiologies (scrotal hematoma, hydrocele, inguinal hernias).[1] Sonography is an established way to diagnose testicular pathologies.[2-4] The detailed report of ultrasound of the testicles showed the right testicle to measure 1.2 x 0.8 x 0.7 cm with the left testicle measuring 1.0 x 0.7 x 1.0 cm. The left testicle is located within the inguinal canal. The right testicle is located within the scrotum. The testicles are homogeneous in echo texture and symmetrical. No hydroceles are present. Normal spontaneous color flow is present using

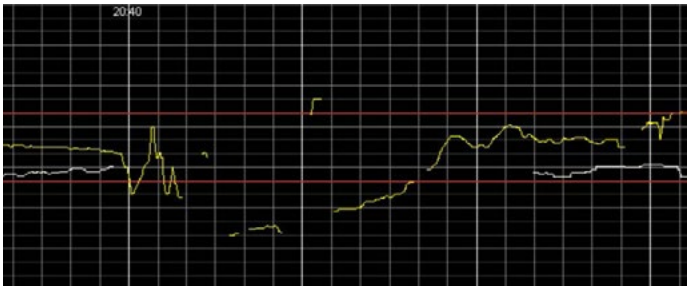

Figure 1. Cardiotocogram strip showing the fetal heart rate 10 minutes prior to delivery (note the 90 seconds of bradycardia)

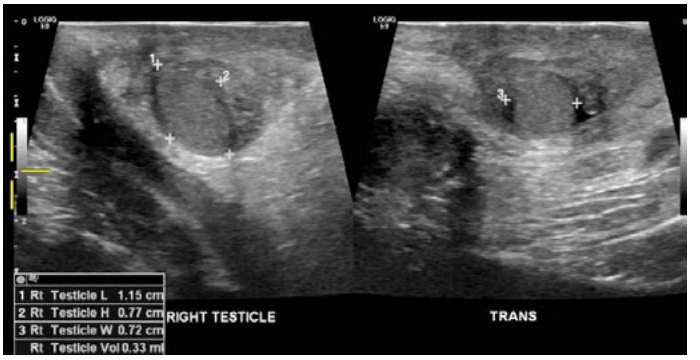

Figure 2. Scrotal ultrasound of right testicle showing the position and measurements

Shabih Manzar is a Neonatologist & Assistant Professor, Department of Pediatrics, College of Medicine, Louisiana State University Health Sciences of Shreveport.

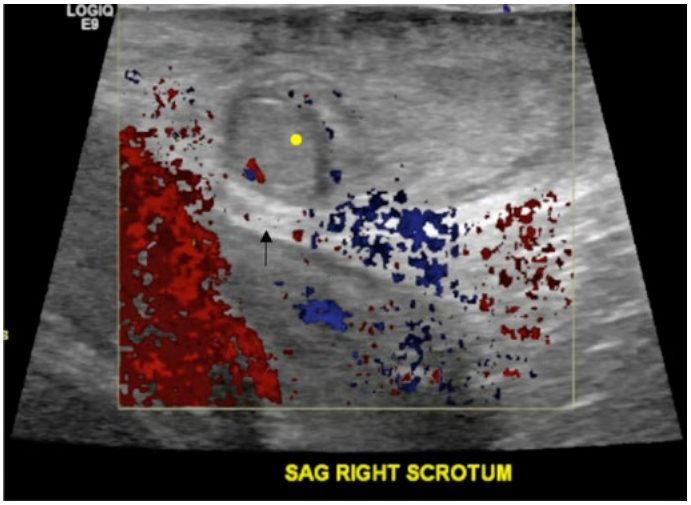

Figure 3. Scrotal ultrasound of right testicle with color doppler (yellow dot is right testicle and black arrow showed marked soft tissue and subcutaneous thickening)

color Doppler ultrasound with low resistance arterial waveforms and spontaneous venous waveforms noted bilaterally. Inferior to the right testicle within the actual scrotal sac soft tissues, there is marked soft tissue and subcutaneous thickening with diffuse increased echogenicity of this tissue and a few scattered hypoechoic areas. No vascularity was seen within this soft tissue when color Doppler was applied.

The differential diagnosis of scrotal swelling including testicular torsion, testicular neoplasms, supernumerary testicle, scrotal hematoma, hydrocele and inguinal hernia were all ruled out by the sonographic report. Testicular abscess was less likely as there was no increased vascularity noted with the color Doppler. A soft tissue thermal injury from the whole-body cooling was the suggested diagnosis by the radiologist. An extensive literature search did not show such association reported earlier.

Table 1. Cord blood gas

Source	pH	pCO_2	pO_2	HCO_3
Umbilical venous sample	7.25	39	26	16
Umbilical arterial sample	7.23	42	241	15

The cause and effect relationship is difficult to prove in this case. A direct injury from cold is less likely for two reasons; one it was unilateral, and second infant had diaper on. The subcutaneous fat necrosis (SCFN) has been reported in neonates after use of therapeutic hypothermia.[5] In the pathogenesis of SCFN an important role is played by the peripheral perfusion disturbances. We postulated a similar phenomenon of scrotal hypoperfusion resulting in the injury. However, it is difficult to explain why only one side was affected. A possible role of posture during cooling needs further evaluation.

The purpose of this report is to address on the need for vigilant periodic examination of scrotum while a neonate is placed on the cooling blanket during therapeutic whole-body cooling. All attempts should be made to protect the scrotum and testicles from the potential thermal damage.

Correspondence
Shabih Manzar, MD
1501 Kings Highway
Shreveport LA 71130
Email: smanza@lsuhsc.edu
Telephone: 318-626-1620
Fax: 318-698-4305

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Conflict of Interest
None

References

1 Basta AM, Courtier J, Phelps A, Copp HL, MacKenzie JD. Scrotal swelling in the neonate. *J Ultrasound Med.* 2015;34(3):495–505. doi:10.7863/ultra.34.3.495
2 Munden MM, Trautwein LM. Scrotal pathology in pediatrics with sonographic imaging. *Curr Probl Diagn Radiol.* 2000;29:185–205.
3 Sung EK, Setty BN, Castro-Aragon I. Sonography of the pediatric scrotum: emphasis on the Ts—torsion, trauma, and tumors. *AJR Am J Roentgenol.* 2012;198:996–1003.
4 McAlister WH, Sisler CL. Scrotal sonography in infants and children. *Curr Probl Diagn Radiol.* 1990;19:201–242.
5 Szpecht D, Bagnosz-Magnuszewska A, Szymankiewicz M, Gadzinowski J. Subcutaneous fat necrosis in neonates after therapeutic hypothermia - report of two cases. *Postepy Dermatol Alergol.* 2016;33(2):152–154. doi:10.5114/ada.2016.59164

Clinical Significance of Wharton Jelly for Fetal Well-Being

BM Petrikovsky, MD, PhD

The umbilical cord is a pipe-like structure, which connects the placenta to the fetus, providing a source of nourishment and serving as a channel to eliminate waste. At term, it is 40-60 cm long, with a girth of 1-2 cm. The umbilical cord has an outer covering of a single layer of amniotic epithelium that encloses a mucoid connective tissue through which three vessels (a vein and two arteries) carry oxygen (O_2) to the fetus and carbon dioxide (CO_2) from it.[1] Wharton's jelly (WJ), first described by Thomas Wharton in 1656, prevents the kinking of the umbilical cord vessels during fetal and maternal movement. Thomas Wharton thought that the WJ serves as a surrogate lymph transport system for the fetus.[6] However, it doesn't contain nerves or lymph and blood vessels.[2] There are three distinct regions within the human umbilical cord: the subamniotic zone and media and adventitia layers of the blood vessels.

Embryology

After implantation of the blastocyte at the end of the first week of pregnancy, the embryo connects to the endometrium through the trophoblast. This connection develops into the connecting stalk, which is formed from the extraembryonic mesoblast, secondary yolk sac, and the wall of the trophoblast. Soon, during early gut development, mesenchyme of the connecting stalk is invaded by the allantoic duct, which serves as a site of vasculogenesis and gives rise to the umbilical vessels.[4,5]

Composition of the WJ

A connective tissue matrix contains a fiber component and a ground substance. Collagen I is the predominant protein in WJ. WJ also contains small chondroitin/dermatan sulphate proteoglycans with decorin; 95% of WJ consists of extracellular matrix, glycoprotein hylauronin sulfated glycosaminoglycan and diffusible plasma proteins.[6-8]

Cellular content of the WJ

Numerous mesenchymal progenitor cell populations were found in every region of WJ.[9] The perivascular zone of the umbilical cord is populated mostly by mesenchymal stem cells.[10,11]

WJ growth and development

Ghezzi, et al.[12] studied the rate of WJ growth as pregnancy progresses. The WJ area was calculated by subtracting the vascular zone from the total umbilical cord area. A strong correlation was found between the growth of WJ and the umbilical cords itself.

Uteroplacental insufficiency and WJ

Uteroplacental vascular insufficiency, occurs when the placenta fails to deliver an adequate amount of O_2 and nutrients to the fetus. The placenta reaches its maximum size and function by 37 weeks of pregnancy and begins to slowly decrease afterwards. The longer a fetus goes without an adequate amount of nutrients and O_2, the more the risk for hypoxia at birth. The best reflection of this process is the thin appearance of the umbilical cord with decreased amounts of WJ (Figures 1 and 2).

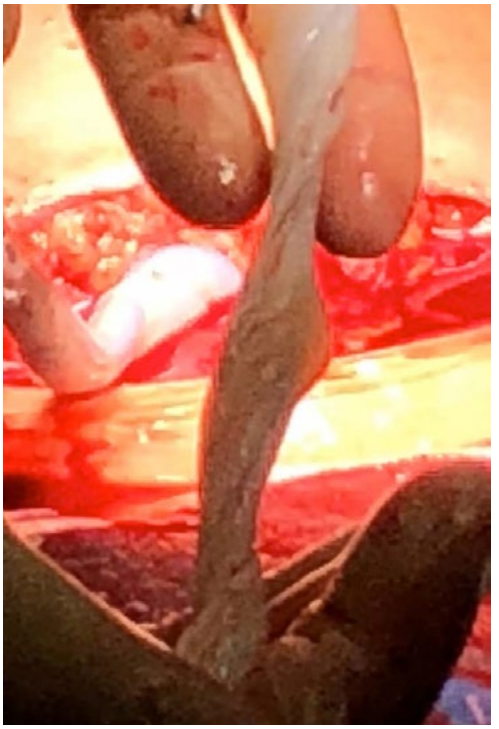

Figure 1. Thin umbilical cord with depleted WJ

It affects neonatal skin as well: A post-term infant's skin appears wrinkled. A Full-term infant's umbilical cord, on the other hand, appears thick, healthy-looking and with an appropriate amount of WJ (Figures 3 and 4).

The international research team (Nassau University Medical Center, Long Island, NY and Koltsov Institute of Experimental Biology, Moscow, Russian Federation) was able to identify

BM Petrikovsky, MD, PhD, is a professor and former Chair of Obstetrics & Gynecology at Nassau University Medical Center.

Figure 2. A postmature infant with wrinkled skin

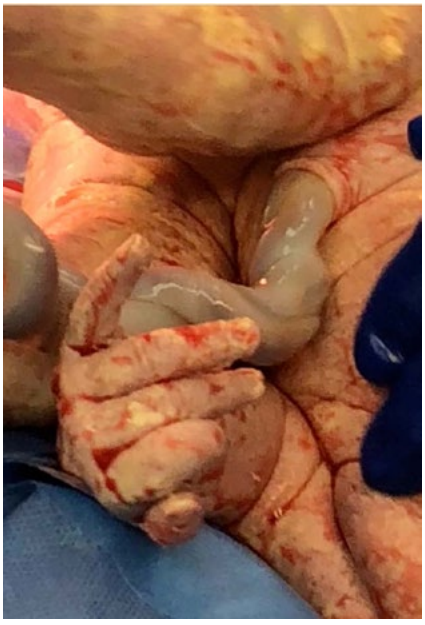

Figure 3. A normal looking umbilical cord in a term infant

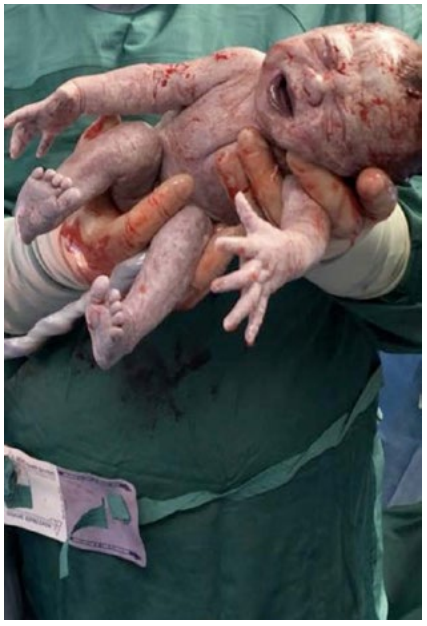

Figure 4. Healthy looking skin in a full-term infant

WJ proteins responsible for the appearance and the quality on neonatal skin. They were able to demonstrate that adding Meso-Wharton P199 to adult skin prior to plastic surgeries increases the number and biological activity of skin stem-cells. Sonographic studies confirmed an increase in the skin's thickness in adults after mesotherapeutic injections of Meso-Wharton P199.

In conclusion, components of WJ are essential for activating the skin stem cells that are responsible for its function and appearance. Analogues of WJ peptides, especially Meso-Wharton P199, have been successfully used in both medical, eg, improving scar healing, and cosmetic fields.[13,14]

References

1 Davies JE, Walker JT, Keating A. Wharton's jelly: the rich, but enigmatic, source of mesenchymal stroma cells. Stem Cell Transl Med 2017; 6: 1620-30.
2 Wharton TW. Adenographia. Translated by S. Freer. Oxford, UK: Oxford University Press, 1996, 1656: 243.
3 Nanaev AK, Kohnen G, Milovanov AP, et al. Stromal differentiation and architecture of the human umbilical cord. Placenta 1997; 18: 85-64.
4 Petrikovsky BM, Nochimson DJ, Campbell WA, Vintzileos AM. Fetal jejunoileal atresia with persistent omphalomesenteric duct. Am J Obstet Gynecol 1988; 158: 173-5.
5 Standring S, Gray H. Gray's Anatomy: The anatomical basis of clinical practice. 40th ed. (Susan Standring, ed.). Churchill Living Stone: Elsevier, 2008.
6 Ding DC, Chang YH, Shyu WC, et al. Human umbilical cord mesenchymal stem cells: a new era for stem cell therapy. Cell Transplant 2015; 24: 339-47.
7 Nagamura-Inoue T, He H. Umbilical cord-derived mesenchymal stem cells: their advantages and potential clinical utility. World J Stem Cells 2014; 6: 195-202.
8 El Omar R, Beroud J, Stoltz JF, et al. Umbilical cord mesenchymal stem cells: the new gold standard for mesenchymal stem cell-based therapies? Tissue Eng Part B Rev 2014; 20: 523-544.
9 Subramanian A, Fong CY, Biswas A, et al. Comparative characterization of cells from the various compartments of the human umbilical cord shows that the Wharton's jelly compartment provides the best source of clinically utilizable mesenchymal stem cells. PLoS One 2015; 10: e0127992.
10 Schugar RC, Chirieleison SM, Wescoe KE, et al. High harvest yield, high expansion, and phenotype stability of CD146 mesenchymal stromal cells from whole primitive human umbilical cord tissue. J Biomed Biotechnol 2009; 789526.
11 Karahuseyinoglu S, Cinar O, Kilic E, et al. Biology of stem cells in human umbilical cord stroma: In situ and in vitro surveys. Stem Cells 2007; 25: 319-331.
12 Ghazzi F, Raio L, Di Naro E. Wharton's jelly quantification during gestation and its correlation with fetal biometry. Proceed 10th World Congress on Ultrasound in Obstet Gynecol.
13 Petrikovsky BM. Use of umbilical cord proteins to improve surgical scar appearance. Neonat Int Care 2020; 33: 1-4.
14 Petrikovsky BM. Neonat Int Care. In Press.

COVID-19 (Novel Coronavirus) and Pregnancy: What Do We Know So Far?

Boris Petrikovsky MD PhD and Michael Terrani MD

Disclaimer: at the time of this writing, the author didn't care for any patient with COVID-19. This editorial is based on a literature search and author's familiarity with other viruses (flu, measles, HIV, etc.)

The current Covid-19 infection reminds me of the HIV infection decades ago, albeit on a much larger scale. The first immunosuppressed pregnant patient in Brooklyn with an unknown disease (HIV testing was not available yet), put the obstetrical team into fear of getting and dying from the disease.

With time, we gained an understanding of the nature of the HIV virus, its mode of transmission, course of illness, and finally, the means to contain and control it.

The novel coronavirus (COVID-19) is a global health emergency. Since the first case of pneumonia in Wuhan, China, in December 2019, the infection has spread rapidly to the rest of China and beyond. As of March 1, 2020, a total of 85,406 confirmed cases of the infection have been reported, together with 39,597 recovered and discharged patients and 2,933 deaths. Theoretically, pregnant women with naturally decreased immune system and lung capacity are more prone to coronavirus complications.

In 2009, pregnant women accounted for 1% of patients with influenza H1N1 virus, but they accounted for 5% of all H1N1-related deaths.

Acute respiratory syndrome coronavirus (SARS) and Middle East respiratory are known for severe complications during pregnancy, including the need for intubation, admission to an intensive care unit, and death.[2,3]

However, at the time of this writing, the prognosis for pregnant patients affected by COVID-19 is more optimistic based on limited data.

Chen, et al.[5] reported the results of a retrospective chart review of 9 pregnant patients with confirmed COVID-19 infection. All 9 patients had a cesarean section at term. Seven patients presented with a fever, cough (in four), and myalgia (in three). Five of nine patients had lymphopenia, pneumonia, none died. Nine livebirths were recorded. All nine livebirths had a 1-min Apgar score of 8-9 and a 5-min Apgar score of 9-10. Amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples from a six patient were tested for SARS-CoV-2, and all samples tested negative for the virus.

The authors concluded that pregnant women with COVID-19 pneumonia showed a similar pattern of clinical characteristics to non-pregnant adult patients.[1] The most important goal of the study was to investigate the possibility of intrauterine transmission of COVID-19 infection. The results show that SARS-CoV-2 was negative, suggesting that no intrauterine fetal infections occurred. These findings are in accordance with what was observed in SARS. Previous studies have already shown no evidence of perinatal SARS infection among infant born to mothers who developed SARS infection during pregnancy.[6,7]

Neonatal aspects of COVID-19

Infection can occur in neonates via close contact. Two such cases of neonatal COVID-19 infection have been confirmed at 36 hours and 17 days after birth, and both appear to have been infected postnatally.[8]

Therefore, early cord clamping and temporary separation of the newborn for at least two weeks is recommended to minimize the risk of viral transmission by avoiding contact with the infected mother. The neonate should be cared for in an isolation ward and monitored for any signs of infection. During this period, direct breast feeding is not recommended. A possible option is for the mother to pump her breast milk, which can be fed to the baby by a caregiver.

References

1 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
2 Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010; 303: 1517-1525.
3 Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol 2004; 191: 292-297.
4 Alfaraj SH, Al-Tawfiq JA, Mamish ZA. Middle East respiratory syndrome coronavirus (MERS-CoV) infection during pregnancy: report of two cases & review of the literature. J Microbiol Immunol Infect 2019; 52: 501-503.

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Boris Petrikovsky MD PhD Professor of obstetrics and gynecology and Michael Terrani MD Medical Director Garden Obgyn.

Preventing Skin Injury in At-Risk Populations

Introduction

Skin tears and other skin injuries present a significant clinical issue, particularly among vulnerable at-risk populations, such as older adults, neonates, or critically and chronically ill patients. These types of injuries can cause a variety of adverse medical outcomes. They can lead to patient discomfort and infection, and they can even prolong healing. Skin injury also may impact mobility, thereby compromising quality of life. This condition is even more difficult in the neonatal population because of their inability to communicate verbally.

Management of these injuries is crucial, but prevention is the best possible strategy. When the proper preventive efforts are made, and wounds are treated with appropriate dressings and gentle adhesives, patients are more likely to experience better outcomes.[1] This is particularly true for the most sensitive and vulnerable patients, neonates.

Skin Tear Etiology

Skin tears are wounds caused by shear, friction, or blunt force trauma that results in separation of the skin layers. These tears can be either partial thickness, when the epidermis and the dermis become separated, or full-thickness, when both the epidermis and the dermis become separated from underlying structures.[2] Skin tears are a unique and complex type of wound and are often the result of multiple factors. Skin tear prevalence is estimated to be between 3.3% and 22% in acute care settings and between 5.5% and 19% in home health settings.[3]

Specific skin characteristics may also contribute to skin tears, such as the presence of ecchymosis, senile purpura, hematoma, edema, photo aging, or a previously healed skin tear. Other contributors to skin tears can include xerosis, polypharmacy, inadequate nutrition, behavioral issues, improper handling of the skin, and the use of incompatible adhesives.[2] Neonatal skin, and particularly that of premature infants, is characterized by its thin stratum corneum, thus making it much more susceptible to damage and tearing.

Skin Tear Classification

Given the severity of adverse clinical outcomes that can arise from skin tears, the International Skin Tear Advisory Panel (ISTAP) sought to raise awareness of the need to prevent skin tears and adequately manage them when they do occur.

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

This panel developed a classification system that includes three types of tears:[4]

- **Type 1:** Presence of a linear rupture or cutaneous flap tear that can be repositioned to cover the wound. This type occurs without the loss of cutaneous tissue or skin.
- **Type 2:** The presence of a partial cutaneous slap loss, which can no longer be positioned to cover the wound bed.
- **Type 3:** Indicates a total cutaneous flap loss, which exposes the entire wound bed.

" ...the International Skin Tear Advisory Panel (ISTAP) sought to raise awareness of the need to prevent skin tears and adequately manage them when they do occur."

Skin Tear Risk Factors

Skin tears are often complex and multifactorial. However, certain risk factors can be identified and sometimes mitigated. Understanding these risk factors is an essential element in knowing how to prevent and manage skin tears.

Age

Patients in all age groups may experience skin tears, but older adults and neonates are especially prone to them. As skin ages, it becomes drier and more fragile and can be damaged more easily. Older adults often have other comorbidities that can increase the likelihood of developing skin tears. On the other end of the spectrum, neonates have immature and thin skin, with less collagen and fewer elastin fibers than in older children and adults. Other risk factors for skin tears in neonates include limited stratum corneum, nutritional deficiencies, and skin alkalinity.[5]

Mobility

Patients with limited mobility, reduced sensation, and vision impairment have an increased risk of falls and trauma that can lead to skin tears. Immobility can also increase the risk of mechanical injury or shear while patients are being moved.[1] This issue is also true for infants who are born at less than 32 weeks, who are at extremely high risk for pressure injuries and skin tearing.[6]

Skin Health and Nutrition

Overall skin health can strongly indicate the likelihood of tearing. Skin that has been infected or exposed to irritants is at a greater risk of tearing, as is the skin of patients who have inadequate nutrition and hydration. Dietary changes that ensure proper nutrition and hydration can reduce the risk for tears; the application of a pH-neutral, unscented moisturizer can also reduce the risk of skin tears for patients with fragile skin.[7]

Medical Adhesives

Medical adhesive–related skin trauma is a common cause of tearing. When adhesive containing items, such as tapes, dressings, stoma barriers, electrodes, and medication patches, are not placed and removed correctly, the superficial layers of the skin may be removed with the adhesive. Repeated application can compromise the skin barrier function and delay healing. Proper placement and removal techniques can minimize this type of skin trauma.[8]

> "Proper placement and removal techniques can minimize this type of skin trauma."

Skin Tear Prevention

The best way to treat skin tears is by using best practices to reduce the likelihood that patients will develop a tear. Preventing all skin tears may not be possible, but many can be avoided by identifying risk factors in patients, using proper skin protection measures and selecting optimal dressings, and ensuring that medical devices and adhesives are placed and removed properly, particularly when the skin is exceptionally fragile, such as with neonates.

Identify Risk Factors

Identifying risk factors and at-risk patients is a crucial first step in reducing the likelihood of having a patient with a skin tear. These at-risk populations include neonates and older adults because of the unique fragility of their skin composition. The general health of the periwound area should be assessed for any signs of damage or weakness. Once all risk factors have been identified, a treatment plan can be developed that will work to minimize the chances of developing a skin tear.[1]

Skin Protection and Dressing Selection

Treatment of at-risk patients should include proper strategies for minimizing risk; this includes the following:[1]

Reduce Risk of Trauma: Environmental risks present at home should be identified. These include any risks for falling or experiencing trauma.

- **Focus on Skin Health:** Skin should be cleaned and moisturized regularly. Any wounds should be debrided, if necessary, and treated with optimal dressings that maintain moisture and bacterial balance.
- **Treat Any Underlying Causes:** Factors that contribute to the increased likelihood of skin tears, such as nutrition, polypharmacy, or cognitive impairments, should be treated to the fullest extent possible, to minimize the risk.
- **Select the Right Dressing or Adhesive:** Different adhesives and dressing qualities have different impacts on wounds and the periwound area. Sensitive procedures, such as the placement of an endotracheal tube or gastrostomy tube or any procedure with a neonate, should be handled very carefully. Minimizing skin tears requires a dressing that needs only minimal force to apply but can still maintain a secure and waterproof seal. When allergies are suspected, a low-allergy or hypoallergenic tape should be selected.
- **Apply and Remove Dressings Safely:** The application and removal of dressings are among the most common causes of skin tearing. These processes should be completed delicately and slowly, especially with neonates and premature infants.

How Hy-Tape Can Help

As a leading provider of medical adhesives, Hy-Tape offers many gentle products that minimize the risk of skin tearing while still providing a strong, protective, and waterproof barrier. Hy-Tape products are ideal for those with fragile skin, including older adults and neonates, as well as for delicate procedures, such as securing endotracheal tubes, epidural catheters, gastrostomy tubes, and nasogastric tubes. Hy-Tape products are nurse approved, and in a recent study, were frequently rated as "Excellent" by health care practitioners.[9]

Hy-Tape is Gentle

Hy-Tape's zinc-oxide formula is soothing to delicate skin and prevents irritation and damage to periwound skin caused by frequent dressing changes. The adhesion is also hypoallergenic and easily removable. This ensures that the adhesives hold tight, but release gently, reducing the risk of irritation of sensitive skin. Hy-Tape does not leave behind any sticky residue, which can serve as a reservoir for bacteria and increase the likelihood of infection.

Hy-Tape is Strong

Despite the gentleness of Hy-Tape products, they are still strong enough to remain extremely secure for up to seven days, which can reduce the amount of dressing changes that are necessary. During this period, these dressings remain waterproof, ensuring that a proper moisture balance is maintained. Hy-Tape is also thin, flexible, and elastic, so it conforms to body contours and accommodates underlying tissue expansion or shrinkage.

Hy-Tape is Flexible

Hy-Tape products, including patches, rolls, and strips, come in many varieties that are designed for specific applications, but they can be cut, when necessary, to ensure a proper fit for any

wound or patient, including neonates and all other vulnerable patients.

Conclusion

Skin tears pose a significant clinical risk to patients, particularly at-risk patient populations including the chronically ill, older adults, and neonates, and these injuries have a high prevalence. These injuries can be costly, both financially and in terms of quality of life for the patient. Prevention of many skin tears can be accomplished through identifying risk factors, focusing on skin health, selecting optimal dressings and adhesives, and ensuring their proper application and removal. Hy-Tape products can help providers meet all of these goals to achieve better patient outcomes.

To learn more about how Hy-Tape can help prevent skin tears, contact one of our representatives or visit us online today at www.hytape.com.

References

1. LeBlanc K, Baronoski S, Christensen D, Langemo D, et al. The art of dressing selection: a consensus statement on skin tears and best practices. Adv Skin Wound Care. 2016;20(1):32-46.
2. Leblanc K, Baronoski S. Skin tears: finally recognized. Adv Skin Wound Care. 2017;30(2):62-63.
3. Strazzieri-Pulido KC, Peres GR, Campanili TC, Santos VL. Skin tear prevalence and associated factors: a systematic review. Rev Esc Enferm USP. 2015;49(4):674-680.
4. Silva CVB, Campanili TCGF, LeBlanc K, Santos VLCG. Cultural adaptation and content validity of ISTAP skin tear classification for Portuguese in Brazil. ESTIMA Braz J Enterostomal Ther. 2018;16:e2618.
5. Baronoski S, LeBlanc K, Gloeckner M. Preventing, assessing, and managing skin tears: a clinical review. Am J Nurs. 2016;116(1):24-30.
6. King A, Steller JJ, Blevins A, Noelle-Shah K. Dressings and products in pediatric wound care. Adv Wound Care (New Rochelle). 2014;3(4):324-334.
7. Carville K, Leslie G, Osseiran-Moisson R, Newall N, Lewin G. The effectiveness of a twice-daily skinmoisturising regimen for reducing the incidence of skin tears. Int Wound J. 2014;11:446-453.
8. Zulknowski K. Understanding moisture-associated skin damage, medical adhesive-related skin injuries, and skin tears. Adv Skin Wound Care. 2017;30(8):372-381.
9. LeBlanc K, Woo K., Christensen D, et al. Best practice recommendations for the prevention and management of skin tears. Wound Care Canada. North York, ON, Canada: Wounds Canada (Canadian Association of Wound Care); 2018. https://www.woundscanada.ca/docman/public/health-careprofessional/552-bpr-prevention-and-management-of-skin-tears/file. Accessed April 15, 2019.

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5 Chen H, Guo J, Wang C, et al.
6 Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020; https://doi.org/10.10.16/S0140-6736(20)30360-3.
7 Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol 2004; 191: 292-97.
8 Qia J. What are the risks of COVID-19 infection in pregnant women? Lancet 2020; 6707(20): 30365-2.
9 Center for Disease Control and Prevention (CDC). Interim Considerations for infection prevention and control of coronavirus disease 2019 (COVID-19) in inpatient obstetric healthcare setting. https://www.cdc.gov/coronavirus/2019-nCoV/hcp/infection-control.html. Accessed Feb 28, 2020.

Continuity of Care in the NICU: The Parents' Perspective

Shabih Manzar[a] and Melissa Volz[b]

Introduction

Continuity of care (CoC) is an important aspect of healthcare management. CoC has different perspectives in outpatient versus inpatient models. In outpatient model, due to fewer numbers of staff, CoC is relatively easy to follow. Neonatal Intensive Care Unit (NICU) is an inpatient setting where providing CoC is a clinical challenge. NICU environment is stressful to the patients (newborn infants), doctors, nurses, practitioners and parents. NICU is operated round the clock; 24/7/365 (24 hours, 7 days a week and 365 days of the year). Understandably, it is difficult to provide CoC in the NICU.

The staffing of NICU with skilled providers is challenging. Due to the shortage of experts and financial constraints, some NICUs are not covered by a physician 24/7. Neonatal nurse practitioners (NNPs) and residents are good alternatives to provide 24-hour continuous service. But due to their shift duties and training obligations, continuity is broken which may lead to patient dissatisfaction. Patient satisfaction is an important parameter for quality healthcare, and it has been associated with CoC.[1] The sense of continuity of care compliments patient satisfaction. As parents are the surrogates for their babies in the NICU, their satisfaction and perspective about the continuity is very important. To assess parents' perspective on CoC, we designed this study using Squire 2 guidelines.[2]

Methods

The neonatal intensive care unit (NICU) at LSU Health, Shreveport, is a level 3 B unit. NICU coverage is provided by the physician, neonatal nurse practitioners (NNPs) and staff nurses. Social worker works in close association with parents. Nurses worked in 12-hours shifts while NNPs in 24-hours shift. For sick infants, we have the policy of 1:1 nursing. Physician are in-house from 7 am to 5 pm, then on-call from home in nights. To find out which team member (s) of the NICU team is (are) perceived as the best in providing CoC, we asked the parents to complete a brief survey on discharge. CoC was defined as continuous provider-parent relationship. The survey was simple, the parents had to answer only one question (which one of the following NICU team member has provided a continuity of care to your baby?). The options were: MD, RN, NNP, SW. It took 2-3 minutes to answer the question. The nurse discharging the infant collected the survey. The data were recorded, stored in NICU staff room and later analyzed. The study was conducted from May 1, 2019 to July 31, 2019.

Results

The response rate was 40%. In a period of 3 months, a total of 59 neonates were discharge from the NICU. Twenty-four parents (mostly mothers) voluntarily submitted their responses. Sixty-seven percent selected nurses as the best in providing CoC, physician and NNPs were selected by 4% each, while 25% of parents selected all members as CoC providers (Figure 1).

Discussion

Continuity of care (CoC) is perceived as a continuous care relationship between physician and patient.[3] The NICU has three potential problems with CoC; a) it's an inpatient setup, b) the patients are infants and c) physicians are not available 24 hours. Our study showed that two-thirds of the parents perceived that nurses provided the CoC, while one-fourth thought that all members provided CoC. These findings reiterate on the point that nurses play a pivotal role in the NICU. Also, it replicated the notion that 'managing infants in the NICU is a team effort'.

Physicians and NNPs did not get a promising response as solo CoC provider. The reason could be the model of our practice. Depending upon the NICU level of care and staffing, there are five models of practice (Table). As many parents can't visit the NICU during regular hours they don't get the opportunity to meet the attending neonatologist in Model B, C, D and E. We practice in a model C NICU, the physician is not in-house, NNPs do their 24 hours shifts and residents do their 12 hours shifts.

Parent's needs in the NICU have been described by Cleveland[6] in six categories: (a) accurate information and inclusion in the infant's care, (b) vigilant watching-over and protecting the infant,

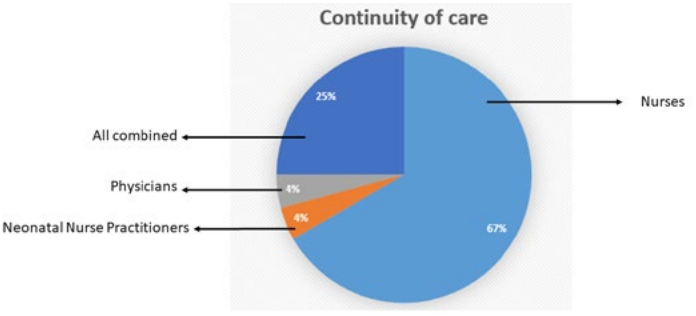

Figure 1. Summary of parents' responses

[a]Neonatologist & Assistant Professor, Department of Pediatrics, College of Medicine at Louisiana State University Health Sciences of Shreveport. [b]Staff Nurse, Neonatal Intensive Care Unit (NICU) at LSU Health, Shreveport.

Table 1. The Grid-Models of Level III NICUs

	Model A Tertiary centers Level IV*	Model B Tertiary centers Level 3 B	Model C Secondary centers Level 3 A	Model D Secondary centers Level 3 A	Model E Community Hospital Level II Plus
Physician	24 hours In-house	On-call from home	On-call from home	On-call from home	On-call from home
NNPs	24 hours	24 hours	24 hours	No	24 hours
Residents	24 hours	24 hours	24 hours	24 hours	No
Fellows	24 hours	24 hours	No	No	No

*Level of NICU: https://pediatrics.aappublications.org/content/130/3/587

(c) contact with the infant, (d) being positively perceived by the nursery staff, (e) individualized care, and (f) a therapeutic relationship with the nursing staff. Our finding of staff nurses as the lead provider for continuity care was in line with these six categories. The role of nurses in the NICU has been established in earlier reports.[7,8]

What could we do to improve CoC? Sudhakar-Krishnan and Rudolf[9] have addressed this question in their report, but all their suggestions were pertaining to out-patient set up (forward planning, shift rotas, individual clinic lists and annual leave). In NICU model B, C and E, the roles of the NNP should be pre-defined. NNPs could be a good source of CoC, they have a nursing background, and are in the NICU for an extended period. But this suggestion comes with the caveat of excellent rapport and handoff procedure between NNPs. Continuity will only happen when there is an ownership of the patient. In model D, resident could take the lead but because of other responsibilities, they are a moving target.

Physicians are expected to take a lead in CoC. In model A NICU, it could be done as physicians are available 24-hours in-house. In model B, C, D and E a well-coordinated multidisciplinary physician-led round during the day could provide a solution. Parents could be counseled on phone periodically. During the day visitation, parents should be updated by the physicians.

To our knowledge this is the first study to look at the parents' perspective on CoC in the NICU. In outpatient settings, CoC could be quantified by the mathematical formula, called COCI-Index of continuity of care,[4-5] which would be difficult in inpatient settings. We, therefore, opted for a questionnaire-based study. The strength of the study was the finding of nurses as prime member for CoC. The weakness of the study was that our survey was not validated and with 40% response. We did not record the length of stay due to the anonymity of the survey. Longer stay would have more chance of perceived as CoC as compared to shorter stay. Also, we did not assess CoC objectively. We assessed who most frequently and consistently communicated information to the parents. But as mentioned earlier, it is difficult to assess CoC objectively in inpatient settings.

In conclusion, staff nurses majorly contribute in providing continuity of care in the NICU. Further studies are needed to see if NICU educators and managers could enhance this role.

Abbreviations

NICU-Neonatal Intensive Care Unit
CoC-Continuity of care

Acknowledgements

I would like to thank all the members of the NICU staff at LSU Health for their cooperation in this project.

Appendix: Questionnaire

Continuity of care (continuous caring relationship with an identified health care professional)

Which one of the following NICU team member, you think has provided a continuity of care to your baby?

- ☐ Staff nurses
- ☐ Physicians
- ☐ Nurse Practitioners
- ☐ Social worker

References

1 Hjortdahl P, Laerum E. Continuity of care in general practice: effect on patient satisfaction. *BMJ*.1992; 304: 1287-90
2 Goodman D, Ogrinc G, Davies L, et al. Explanation and elaboration of the SQUIRE (Standards for Quality Improvement Reporting Excellence) Guidelines, V.2.0: examples of SQUIRE elements in the healthcare improvement literature. *BMJ Qual Saf*. 2016;25(12):e7.
3 Guillford M, Naithani S, Morgan M. What is 'continuity of care'? *J Health Serv Res Policy*. 2006; 11:248-50
4 Bice TW, Boxerman SB. A quantitative measure of continuity of care. *Med Care*.1977;15:347-9
5 Eriksson EA, Mattsson LG. Quantitative measurement of continuity of care. Measures in use and an alternative approach. *Med Care* 1983; 21:858-75
6 Cleveland LM. Parenting in the neonatal intensive care unit. *J Obstet Gynecol Neonatal Nurs*. 2008; 37:666-91. doi: 10.1111/j.1552-6909.2008.00288. x.
7 Turner M, Chur-Hansen A, Winefield H. The neonatal nurses' view of their role in emotional support of parents and its complexities. *J Clin Nurs*. 2014;23: 3156-65. doi: 10.1111/jocn.12558. Epub 2014 Feb 27.
8 Franklin C. The neonatal nurse's role in parental attachment in the NICU. *Crit Care Nurs Q*. 2006; 29:81-5
9 Sudhakar-Krishnan V, Rudolf MC. How important is continuity of care? *Arch Dis Child*. 2007; 92:381–83. doi:10.1136/adc.2006.099853

Jarisch-Herxheimer Reaction in a Premature Infant with Congenital Syphilis

Shabih Manzar, MD and Jennifer Henley, MD

Summary
We describe a case of severe Jarisch-Herxheimer reaction (JHR) in a preterm infant. This is the first report of JHR in a premature infant highlighting on the need for extra vigilance during treatment phase of premature neonates with congenital syphilis.

Case
A female infant was delivered by spontaneous vaginal delivery at 25-6/7 weeks of gestation. Mother was a19-year-old lady, gravida 1, para 0-0-0-0. She presented to labor and delivery unit with history of spontaneous premature rupture of membrane. She noticed leaking of watery discharge 5 days back. The fluid was clear with no foul-smelling odor. She had poor prenatal care with newly diagnosed syphilis and received a single dose of penicillin a week prior to admission. Her RPR was reactive with titer of 1:32. She was negative for HIV and Hepatitis B. She was rubella immune, gonorrhea negative but chlamydia positive. She had rash on her palms and soles.

At delivery, the infant had a heart rate of less than 100 beats per minute. Positive pressure ventilation was started with mask/Neopuff with minimal response noted. Infant was then intubated with 2.5 endotracheal tube, secured at 6 cm and given the initial surfactant dose at ~5 min of life. Infant responded well to intubation and surfactant with improved color and heart rate. She was transferred to NICU for further management.

Physical Examination showed no deformities. Anterior fontanelle was soft and flat. Cardiovascular exam showed normal rate, regular rhythm and no murmur. Pulses were strong. Chest had good vibration on the ventilator with good air entry. Abdomen was soft with no distension. All limbs were normal and there were no skin rashes except for a small area in the left hand—at base of fingers on palm-showed some peeling. Infant's weight was 0.84 kg (1 lb 13.6 oz), length was 34 cm (1' 1.39") and head circumference was 22.5 cm (8.86"). Admission vital signs were: temperature of 100.8°F (38.2°C), heart rate of 172 beat per minute, blood pressure (BP) of 46/24 mm Hg and oxygen saturation of 94% on ventilator and 35% oxygen.

Shabih Manzar is an Attending Neonatologist, Department of Pediatrics, College of Medicine, Louisiana State University of Health Sciences, 1501 Kings Highway, Shreveport, LA 71130. Jennifer Henley is a Resident, Department of Pathology, College of Medicine, Louisiana State University of Health Sciences, 1501 Kings Highway, Shreveport, LA 71130.

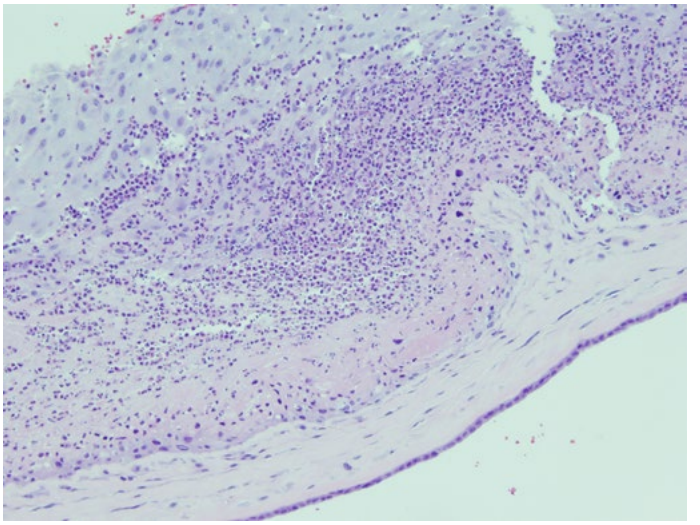

Figure 1. Severe chorioamnionitis

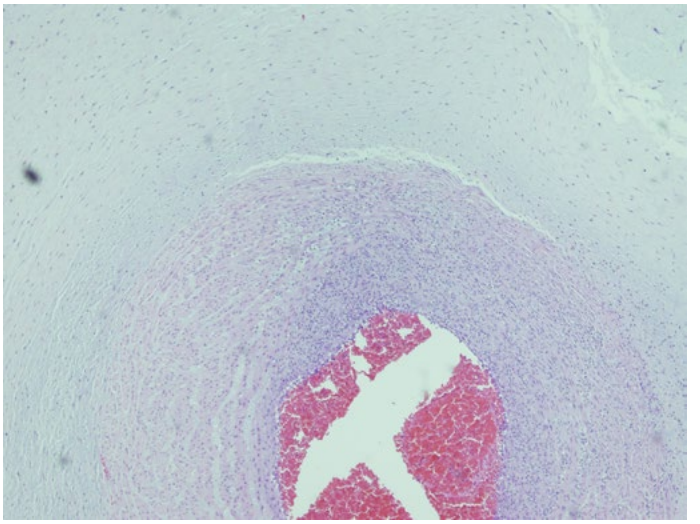

Figure 2. Severe funisitis

Infant remained stable on ventilator. After obtaining the blood culture, ampicillin and gentamycin were started. Ampicillin was changed to penicillin as per pediatric ID advice. At 16 hours of life infant's BP dropped suddenly. All resuscitative efforts were unable to revive the infant. The cause of sudden deterioration and death remained obscure. Parents were counseled and they agreed to autopsy. The pathology showed severe chorioamnionitis and funisitis (Figure 1 and 2).

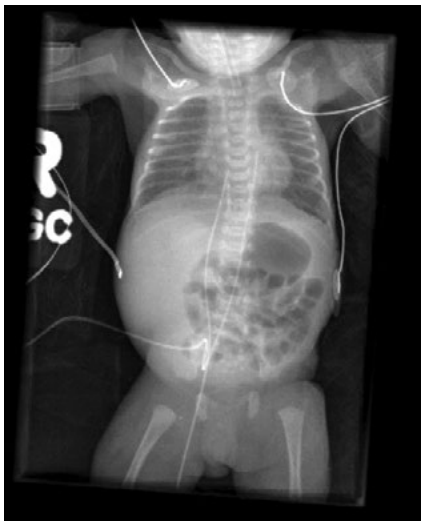

Figure 3. X-ray of the newborn infant
Chest X-ray showing endotracheal tube and umbilical lines in place. No radiological evidence of acute respiratory or cardiac pathology.

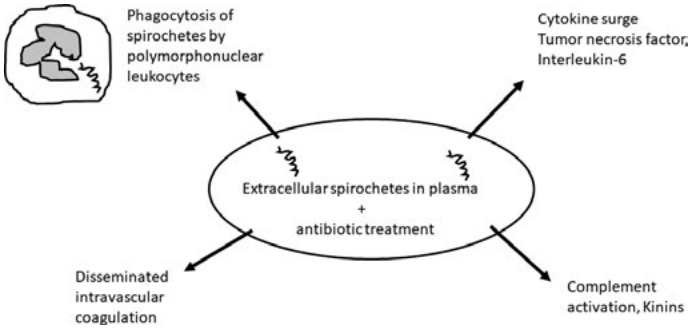

Figure 4. Proposed pathogenesis of Jarisch-Herxheimer reaction.
Adapted from Butler T The Jarisch-Herxheimer Reaction After Antibiotic Treatment of Spirochetal Infections: A Review of Recent Cases and Our Understanding of Pathogenesis. Am J Trop Med Hyg. 2017; 96:46–52.

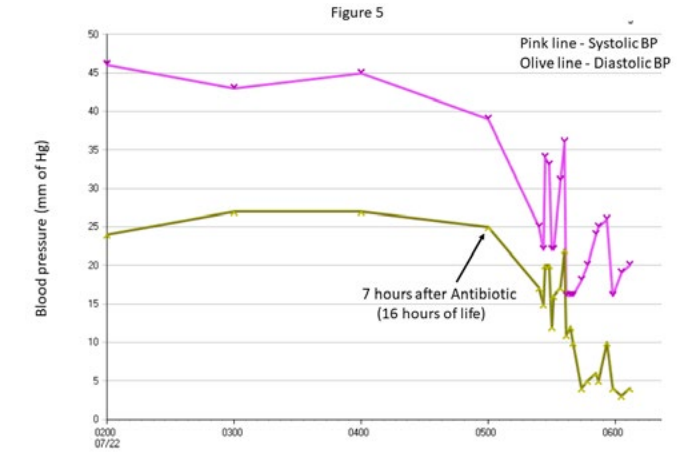

Figure 5. Graph showing blood pressure trend over time.
Note acute drop in BP at 16 hours of life, 7 hours after antibiotic administration.

Discussion

The incidence of syphilis is increasing in US with high mortality,[1,2] as seen in the case described. The sudden deterioration with drop in blood pressures was unexplainable by cardio-respiratory pathology. The chest X-ray did not show any acute pathology (cardiomegaly, pneumothorax, pulmonary infiltrates) (Figure 3). The blood culture was negative precluding common gram positive and gram-negative bacteria as the cause of death. The index of suspicion was high for congenital syphilis (CS) based on the maternal history and her RPR status. The other clue was the report of placental histology, that showed severe acute chorioamnionitis and funisitis. Mother acquired syphilis during pregnancy and due to poor prenatal care, she was inadequately treated. Her RPR on admission was reactive with titers of 1:32. The infant RPR was positive with RPR titers of 1:1. Although the physical examination of infant was normal, except for some peeling at base of the palm, the case did not fit into the classical description of CS. However, basing on CDC broadened definition: "to include all live born and still born infants, irrespective of clinical findings, who had reactive serologic tests for syphilis and delivered to women with untreated or inadequately treated syphilis", the infant could be labeled as a case of CS.[3]

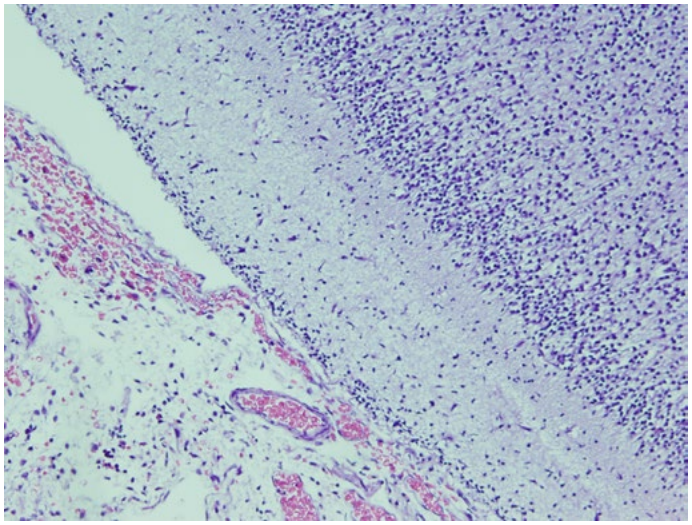

Figure 6. Microscopic slide showing leptomeningeal hemorrhages.

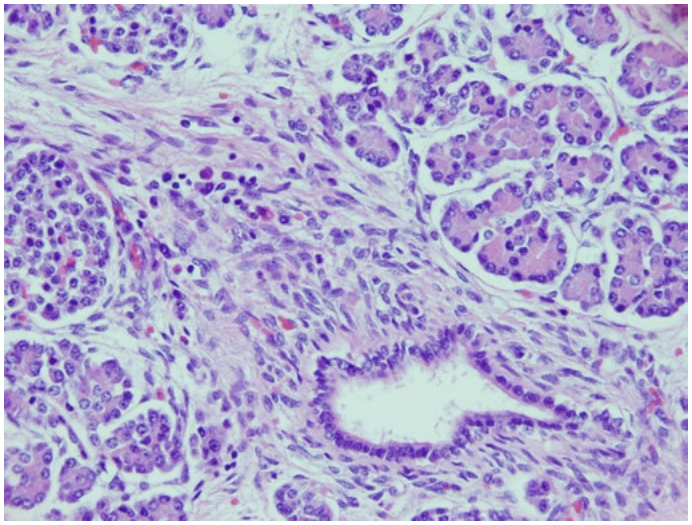

Figure 7. Microscopic slide showing inflammation of the pancreas.

We speculated Jarisch-Herxheimer reaction (JHR) as the cause for sudden deterioration. JHR is described as a reaction in patient with syphilis that is exacerbated with use of antibiotics. The reaction is manifested by fever, increase in rash and systemic effects including, tachycardia and hypotension. It can occur during pregnancy.[4,5] A neonatal case has also been described.[6] However, no lethality has been reported with JHR in premature infants.
Continued on page 33…

Oxidative Stress: Its Role in Fetal/Neonatal and Cosmetic Sciences

BM Petrikovsky, MD, PhD*, VV Ashapkin, DSc **, A Uryash, MD, PhD***

> "The Assembly at Karolinska Institute has today decided to award the 2019 Nobel Prize in Physiology or Medicine jointly to William G Kaelin Jr, Sir Peter J Ratcliffe, and Gregg L Semenza for their discoveries of how cells sense and adapt to oxygen availability."
>
> – Nobel Prize Committee Statement

The importance of oxygen (O_2) for sustaining life has been understood for centuries, but how cells adapt to changes in levels of O_2 has been largely unknown. William G Kaelin Jr, Sir Peter J. Ratcliffe, and Gregg L Semenza, 2019 Nobel Prize winners, discovered how cells sense and adapt to changing O_2 availability.[1-3] They discovered the molecular mechanisms that regulate genes in response to varying levels of O_2. A universal response to reduced O_2 involves the activation of three systems.[4] The first one is erythropoietin (*EPO*) gene expression stimulated by hypoxia-inducible factor 1 (HIF-1), which leads to increased red blood cell production. The second one is vascular endothelial growth factor A (VEGFA), which stimulates angiogenesis. The third one is ATP production in the absence of O_2 via glucose transporters and glycolytic enzymes. Intracellular O_2 concentrations are maintained within a narrow range due to the risk of oxidative damage from O_2 excess (hyperoxia), and metabolic demise from O_2 insufficiency (hypoxia). Whereas acute responses to O_2 deficiency often entail changes in the activity of preexisting proteins, chronic responses invariably involve changes in gene expression.[5] In mammals, the erythroid, cardiac, vascular, and respiratory systems require an adequate supply of O_2. HIF-1 is needed for the establishment and utilization of each of these systems. HIF-1 is a heterodimer composed of HIF-1α and HIF-1β subunits. HIF-1α subunit is regulated by cellular O_2 levels.[6]

Semenza et al studied the erythropoietin (*EPO*) gene.[1] A specific DNA segment located next to the *EPO* gene was shown to mediate the cell's response to hypoxia. These authors also researched O_2-dependent regulation of the *EPO* gene and found that the O_2 sensing mechanism was present in all tissues, not just in the kidneys where the *EPO* gene is normally expressed. Semenza et al[1] identified the cellular components mediating this response: cultured liver cells contain a protein complex that binds to the identified DNA segment called the hypoxia-inducible factor (HIF). They were able to identify the genes encoding HIF. HIF consists of two different DNA-binding proteins: HIF-1α and ARNT (HIF-1β).[7,8]

Under well-oxygenated conditions, HIF-1α is bound by the VHL binding protein, which targets HIF-1α for proteasomal degradation.[9] VHL binding protein is dependent upon hydroxylation of a specific proline residue in HIF-1α by the prolyl hydroxylase PHD2 that uses O_2 as a substrate; thus, PHD2 activity is inhibited under hypoxic conditions.[10]

Induction of gene expression is a direct effect of HIF-1 binding to gene promoters, whereas HIF1-dependent repression is an indirect effect due to HIF-1-dependent expression of transcriptional repressors.[11] The regulation of metabolism is a principal function of HIF-1. Under hypoxic conditions, HIF-1 mediates a transition from oxidative to a glycolytic pathway of metabolism. HIF-1 also mediates a subunit switch in cytochrome C oxidase, which improves the efficiency of electron transfer under hypoxic conditions.[12]

Implications for Adult, Fetal, and Neonatal Medicine

Hypoxia plays an important role in the pathophysiology of ischemic cardiovascular disease, cancer, stroke, and chronic lung disease, among others. There is a growing body of data indicating that HIF-1 contributes to the pathogenesis of cancer and hypoxic pulmonary hypertension while protecting against the ischemia and infarction.[5] The delineation of the evolutionarily-conserved PHD-VHL-HIF-1 pathway has provided multiple targets to discover of pharmacologic agents that can be used in treating these life-threatening diseases.

Lopez et al.[13] have shown that age-dependent dyshomeostasis of resting intracellular Ca^{2+} ($[Ca^{2+}]i$) and Na^+ ($[Na^+]i$), elevates reactive oxygen species (ROS) production, increases neuronal damage and cognitive deficit as well as peripheral sensory deficit and reduces skeletal muscle contractility. Valco, Cingolani et al[14,15] reported that aged neurons show elevated and age-dependent ROS production and an increase in neuronal damage. These changes resulted in a spatial learning deficit. Zhang et al[16]

*BM Petrikovsky, MD, PhD Professor of Obstetrics and Gynecology, Editorial Board Member, ACOG Life Fellow
**VV Ashapkin, DSc, Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University
***A Uryash, MD, PhD Research Associate Professor of Neonatology, Mount Sinai Medical Center, Miami, FL

demonstrated that cells show an age-dependent dysregulation in $[Ca^{2+}]i$ and $[Na^{+}]i$, mediated by plasmalemmal cation influx and by intracellular Ca^{2+} release through the RyR and IP3R.

Uryash et al[17] assessed the efficacy of noninvasive therapies in disease models with high levels of oxidative stress, eg, diabetes and Duchene muscular dystrophy. Improvement in tissue oxygenation and cellular membrane transport increased protein expression and upregulated eNOS. Noninvasive pulsatile stimulation via Whole Body Periodic Acceleration (WBPA) or Vibrational Acoustic Stimulation (VAS) led to an increase of total cellular antioxidant capacity along with an increase in the antioxidant response element transcription factor Nrf2 translocation to the nucleus and decreased ROS. Additionally, important role of Nrf2 in aging associated oxidative stress was confirmed by Gounder et al[18] Furthermore, Uryash et al[19] indicated that these advantageous changes were associated with significantly increased expression of endogenous antioxidants (Glutathione peroxidase 1 (GPX1), Catalase (CAT), Superoxide dismutase 1 (SOD1).

Our research team studied the relationship between abnormal fetal heart rate (FHR) patterns and hypoxia in 215 fetuses.[20,21] Abnormal FHR patterns (late decelerations, bradycardia, and deep spontaneous decelerations) were observed in fetuses with low O_2 tension.[21]

Fetal scalp blood sampling can provide additional information on fetal wellbeing and reserves.[22] A pH value >7.25 is regarded as normal. Values between 7.25 and 7.20 are borderline sub-normal. Values of a pH of less than 7.20 are warning signs of fetal hypoxia requiring interventions such as intrauterine resuscitation or operative delivery. Lactate concentration in the fetal scalp blood has also been investigated and tested and was found to be a reliable indicator of hypoxia.[23,24]

In growth-retarded fetuses, transplacental transfer of O_2 is often impaired.[25] This places the fetus into a situation where O_2 supply becomes limited. Enhanced erythropoiesis may improve O_2 carrying and buffering capacity through increases in red cell mass and hemoglobin concentration.[26]

Implications for Anti-Age and Cosmetic Medicine

Aged human skin is fragile partially because of fragmentation and the loss of type I collagen.[27] Dermal fibroblasts express increased levels of the collagen-degrading matrix enzymes.

The increasing prevalence of matrix destruction in aging skin is accelerated by exposure to UV irradiation and other environmental factors. UV irradiation has been shown to activate receptors of cytokines and growth factors (IL-1, TNFα, and EGF) on the surface of keratinocytes and fibroblasts through the enzymatic exchange of ROS.[28] These activated receptors enhance the activity of signal cascades leading to AP-1 dependent induction of genes encoding matrix-degrading enzymes MMP-1 (collagenase), MMP-3 (stromelysin 1), and MMP-9 (gelatinase). Elevated levels of MMPs in the UV irradiated skin lead to collagen cleavage, fibers unravelment, and production of insoluble aggregates of partially degraded collagen fragments in the dermis. Their accumulation disrupts the structure of the extracellular matrix fibrillar network and becomes the major contributor to the aging skin appearance. The age-associated cellular damage may be caused by mitochondria-generated ROS, thus explaining the existence of molecular mechanisms common to chronological and UV-induced skin aging. A most unexpected finding was that the mitochondria produce more ROS under low-oxygen conditions.[29] Therefore, a narrow safety window of the O_2 concentration appears to exist in each tissue, while both hypoxia and hyperoxia lead to excessive ROS production and accelerated aging. In human clinical studies, combined day oral supplementation and topical application of the natural carotenoid antioxidant astaxanthin improved skin condition in all layers.[30] In human dermal keratinocyte culture, carotenoid antioxidants lutein, zeaxanthin, and astaxanthin upregulated the hyaluronan synthase (*HAS*) gene expression and hyaluronic acid (HA) synthesis.[31] Despite the data showing fucoxanthin and other carotenoids to be efficient antioxidants with evident beneficial effects in human skin, their use in cosmetics is very scarce. Hopefully, as the skin permeation enhancement methods mature, the transdermal carotenoids and other antioxidant compounds will find their place in the fields of cosmetology and dermatology. One of the first products created along these lines is an injection treatment Meso-Xanthin F199® from ABG Lab containing fucoxanthin as the primary active ingredient (https://abglab.com). As we recently came to know, this same company is ready to start the production of another injection treatment that will ensure adequate oxygen delivery to the skin.

References

1 Semenza GL, Nejfelt MK, Chi SM, Antonarakis SE. Hypoxia-inducible nuclear factors bind to an enhancer element located 3' to the human erythropoietin gene. Proc Natl Acad Sci 1991; 88: 5680-5684.
2 Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci 1995; 92: 5510-5514.
3 Maxwell PH, Wiesener MS, Chang GW, et al. The tumor suppressor protein VHL targets hypoxia-inducible factors for oxygen dependent proteolysis. Nature 1999; 399: 271-275.
4 Semenza GL. Perspectives on oxygen sensing. Cell 1999; 98: 281-4.
5 Semenza GL. HIF-1, O2, and the 3 PHDs: How animal cells signal hypoxia to the nucleus. Cell 2001; 107: 1-3.
6 Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci 1995; 92: 5510-5514.
7 Mircea I, Kondo K, Yang H, et al. HIFα targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. Science 2001; 292: 464-468.
8 Jakkola P, Mole DR, Tian YM, et al. Targeting of HIF-α to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science 2001; 292: 468-472.
9 Kaelin WG Jr, Ratcliffe PJ. Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. Mol. Cell 2008; 30: 393–402.
10 Epstein AC, Gleadle JM, McNeill LA, et al. C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. Cell 2001; 107: 43–54.
11 Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell 2012; 148: 399-408.
12 Fukuda R, Zhang H, Kim JW, et al. HIF-1 regulates cytochrome oxidase subunits to optimize efficiency of respiration in hypoxic cells. Cell 2007; 129: 111–22.
13 Lopez JR, Kolster J, Uryash A, et al. Dysregulation of intracellular Ca2+ in dystrophic cortical and hippocampal

neurons. Mol Neurobiol. 2018 Jan;55(1):603-618.
14 Valko M, Leibfritz D, Moncol J, et al. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39(1):44–84..
15 Cingolani HE, Perez NG, Cingolani OH, Ennis IL. The Anrep effect: 100 years later. Am J Physiol 2013; 304(2): H175–82.
16 Zhang M, Shah AM. ROS signalling between endothelial cells and cardiac cells. Cardiovascular Research. 2014;102(2):249–57
17 Uryash A, Bassuk J, Kurlansky P, et al. Antioxidant properties of Whole Body Periodic Acceleration (pGz). PLoS One. 2015 Jul 2;10(7)
18 Gounder SS, Kannan S, Devadoss D, et al. Impaired transcriptional activity of Nrf2 in age-related myocardial oxidative stress is reversible by moderate exercise training. PLoS ONE. 2012;7(9).
19 Uryash A, Wu H, Bassuk J, et al. Low-amplitude pulses to the circulation through periodic acceleration induces endothelial-dependent vasodilatation. J Appl Physiol. 2009;106(6):1840–7.
20 Saveleva GM, Klimenko PA, Petrikovsky BM. Fetal cardiac activity and base state in normal and pathologic labor. J Obstet Gynecol (Rus) 1977; 10: 22-25.
21 Petrikovsky BM. Fetal heart monitoring in chronic hypoxia. J Fet Matern Care 1977; 1: 28-32.
22 Jørgenses JS, Weber T. Fetal scalp blood sampling in labor – a review. Acta Obstet Gynecol Scand 2014; 93: 548-555.
23 Petrikovsky BM. Fetal cardiac function in hypoxia. PhD Thesis, Moscow, 1977.
24 Nordstrom I. Fetal and Neonatal scalp blood measurements during labor – lactate or pH? Clin Biochem 2011; 44: 456-457.
25 Baschat AA, Hecher K. Fetal growth restriction due to placental disease. Semin Perinatol 2004; 28(1): 67-80.
26 Baschat AA, Harman CR. Antenatal assessment of the growth restricted fetus. Curr Opin Obstet Gynecol 2000; 13(2): 161-8.
27 Fisher GJ, Quan T, Purohit T, et al. Collagen fragmentation promotes oxidative stress and elevates matrix metalloproteinase-1 in fibroblasts in aged human skin. Am J Pathol 2000; 174 (4): 102-114.
28 Fisher GJ, Kang S, Varani J, et al. Mechanisms of photoaging and chronological skin aging. Arch Dermatol 2002; 138: 1462–70.
29 Gao L, Ortega-Sáenz P, López-Barneo J. Acute oxygen sensing – Role of metabolic specifications in peripheral chemoreceptor cells. Respir Physiol Neurobiol 2019; 265: 100-111.
30 Tominaga K, Hongo N, Karato M, Yamashita E (2012) Cosmetic benefits of astaxanthin on humans subjects. Acta Biochim Pol 59:43-47
31 Sayo T, Sugiyama Y, Inoue S. Lutein, a nonprovitamin A, activates the retinoic acid receptor to induce HAS3-dependent hyaluronan synthesis in keratinocytes. Biosci Biotechnol Biochem 2013; 77: 1282–86.

Jarisch-Herxheimer Reaction…continued from page 30
The pathogenesis of JHR involve activation of immunological pathways (Figure 4).[7-9] We noted a sudden drop in BP seven hour after the use of antibiotics (Figure 5). Due to the sudden death of the infant we were unable to obtain laboratory evidence of CS. The autopsy showed hepatosplenomegaly, leptomeningeal hemorrhages and inflammation of the pancreas (Figure 6 and 7), that was consistent with CS. We were unable to demonstrate any spirochetes in the placental tissue.

The case is the first report of JHR in a premature infant highlighting on the need for extra vigilance during treatment phase of premature neonates with CS.

References

1 Bowen V, Su J, Torrone E, Kidd S, Weinstock H. Increase in incidence of congenital syphilis—United States,2012–2014. *MMWR Morb Mortal Wkly Rep*. 2015; 64:1241–1245.
2 Su JR, Brooks LC, Davis DW, Torrone EA, Weinstock HS, Kamb ML. Congenital syphilis: trends in mortality and morbidity in the UnitedStates,1999 through 2013. *Am J Obstet Gynecol*. 2016; 214:381e1-9.
3 Centers for Disease C. Congenital syphilis—New York City, 1986-1988. *MMWR Morb Mortal Wkly Rep*. 1989; 38:825–829.
4 Myles TD, Elam G, Park-Hwang E, Nguyen T. The Jarisch-Herxheimer reaction and fetal monitoring changes in pregnant women treated for syphilis. *Obstet Gynecol*. 1998; 92:859–864.
5 Klein VR, Cox SM, Mitchell MD, Wendel GD. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. *Obstet Gynecol*. 1990; 75:375–380.
6 Hori H, Sato Y, Shitara T. Congenital syphilis presenting as Jarisch-Herxheimer reaction at birth. *Pediatr Int*. 2015; 57:299-301. Doi:10.1111/ped.12417.
7 Pound MW, May DB.
Proposed mechanisms and preventative options of Jarisch-Herxheimer reactions. *J Clin Pharm Ther*. 2005; 30:291-5
8 Akins DR, Purcell BK, Mitra MM, Norgard MV, Radolf JD. Lipid modification of the 17-kilodalton membrane immunogen of *Treponema pallidum* determines macrophage activation as well as amphiphilicity. *Infect Immun*. 1993; 61:1202–1210.
9 Butler T. The Jarisch-Herxheimer Reaction After Antibiotic Treatment of Spirochetal Infections: A Review of Recent Cases and Our Understanding of Pathogenesis. *Am J Trop Med Hyg*. 2017; 96:46–52. doi:10.4269/ajtmh.16-0434

Think Your NICU is Family-Centered? Think Again

Deb Discenza

It always amazes me as both a parent of a premature infant and a parent leader in the community, how NICUs worldwide tout their unit's benefits of the best equipment, the best space, the best clinical training but do little in the patient family care realm. They show off certifications on their websites like a Boy Scout making Eagle Scout. Yet, my being a parent leader in the preemie community gives me access to the parents who speak otherwise about the NICU's inability to include them in the care of their child. Interactions between the medical professionals and the families can easily become frostbitten. Why can't we do better knowing that this *is part of NICU care*? I talked with Sue Hall, MD, neonatologist, author of *For the Love of Babies* and a former board member of the National Perinatal Association (NPA). In 2017, NPA formed an alliance with like-minded organizations Patient+Family Care and NICU Parent Network to create online training that would make real and lasting change to better impact patient families and their outcomes. The program, whose efficacy has been demonstrated by research, has been out for several years now and is called "Caring for Babies: Providing Psychosocial Support for NICU Parents" at www.MyNICUNetwork.com.

Deb Discenza (DD): Dr Hall, thank you for speaking with me. In your career, you actually did not start out as a neonatologist but a social worker, correct? That plus your neonatologist background provided you a greater understanding of the struggles of these families. What did you see in units that gave you great pause about a NICU's ability to provide superior care in all ways and not just clinically?

Sue Hall, MD (SH): I saw parents who were neither "invited" nor welcomed into their baby's care by either the physician or nursing staff, and babies who sometimes went nearly the length of their hospital stay without the presence of parents at their bedside and without being held, talked to, or cuddled by their families. I saw NICU staff of all stripes who considered that their opinions and decisions about a baby's care outweighed the opinions and desires of parents, and who made little attempt to recognize and honor many parents' wishes to be more involved with their babies. I saw parents who were fearful of the NICU in a way that left them feeling like they were merely bystanders and observers. And more importantly, I listened to NICU parents after their hospital experiences to learn about the deep traumas many had experienced as a result of all these conditions. I came to the conclusion that parents were overlooked as very important allies in the care and treatment of their babies, and that their intimate involvement in and understanding of their baby's care would benefit not only the physical health and well-being of the baby, but the mental and emotional well-being of both the baby and the parents.

DD: Thank you for recognizing parents in the middle of this experience. I was one of those terrified parents and I look back at that time with agony. But I didn't look terrified. I was the "Smiling Mom" trying not to rock the boat and making sure they didn't take my baby away from me. Had I had you as a doctor for my child, I would have been more open for sure. But not every Neonatologist or NNP or NICU Nurse has the kind of training you have had. So this type of education is not something provided in medical school, right? Why is this the case?

SH: Only very recently has the American Academy of Pediatrics developed standards for education of pediatric trainees in the areas of behavioral and mental health of patients *and their families*. It is now widely recognized that hospitalization of an infant or child can be perceived as a traumatic experience by both the patient and his/her family, and that the whole family benefits from psychosocial support throughout the hospital stay to minimize the trauma and its potential long-lasting adverse effects. For the past several years there have been a lot of programs developed to teach both physicians and nurses how to have "crucial conversations" with families, usually relating to bereavement, but I perceived a need to teach healthcare staff how to support parents in everyday interactions, not just at moments of crisis. That's what our courses are all about.

DD: And this is why the "Caring for Babies" Program came about, yes? What has been the response?

SH: Yes. The response has been uniformly positive, and many who have taken the courses in the program have commented on how they were able to truly get an idea of what parents' experiences are like and what their needs are. This is because NICU graduate parents have been intimately involved in the design and creation of the courses from the very first moment that this project was conceived. The courses have a great many quotes, stories, audios, and videos from parents sharing their

Deb Discenza runs PreemieWorld.com, an educational products company full of free items for educating families. PreemieWorld's flagship product, The Preemie Parent's Survival Guide just published its second edition and is on sale at PreemieWorld.com. In addition, Mrs. Discenza is the founder of the 15+ year old global Inspire Preemie Community, free for parents at https://preemie.inspire.com.

feedback about both what was positive and negative about their time in the NICU. Parents helped us create our "trauma-informed scripts" that take examples of what NICU staff should NOT say to parents, why and how it makes them feel, and what is a better, trauma-informed approach that will be supportive to parents.

DD: Tell me about the program and what it does.
SH: The program consists of 7 1-hour courses providing continuing education credit; each course mirrors one of the subject areas in the original "Interdisciplinary Recommendations for Psychosocial Support of NICU Parents," which were published in December, 2015 in the *Journal of Perinatology*. (Hall, SL, and MT Hynan, eds. 2015. "Interdisciplinary Recommendations for the Psychosocial Support of NICU Parents." *Journal of Perinatology* 35: Supplement.)

Basically, the lead course describes why NICU parents need emotional support, and that is followed by courses in communication skills, involving parents in the care of their baby through family-centered developmental care, supporting parents through palliative and bereavement care, preparing families for discharge and post-NICU follow-up, as well as making peer support available to families. A final course is on the all-important topic of how we as NICU staff members can support ourselves and each other, so that we have more to give to NICU families.

In our study of 114 NICU staff—primarily nurses—in two different NICUs, we found significant levels of improvement in knowledge and attitudes towards providing psychosocial support after taking the courses, and these improvements were sustained at 6-month follow-up. (Hall, SL, ME Famuyide, SN Saxton, TA Moore, S Mosher, K Sorrells, CA Milford, and J Craig. 2019. "Improving Staff Knowledge and Attitudes towards Providing Psychosocial Support to NICU Parents through an Online Education Course." *Advances in Neonatal Care* 19 (6): 490–99.) The next stage of research would be to see if provider behavior changes, leading to improved parent satisfaction and mental health outcomes, as well as ultimately improved developmental outcomes of the babies.

DD: In the realm of NICU competition, how do you see this type of program impacting standards of care in units nationwide? In infant and patient family outcomes short-term and long-term?
SH: Women, and mothers in particular, are typically the decision-makers for families as far as where they choose to get their healthcare. So if families have a positive experience in the NICU—and by the way, their evaluation is actually less dependent on how their baby does and more dependent on how they feel they are treated—the family may choose that hospital for their care for the rest of their lives. Another way to look at our program is that it's one way that hospitals can demonstrate their commitment to providing excellence in, not just lip service to, family-centered care. Empowerment of patients/parents and development of collaborative relationships between them and providers is the direction in which healthcare is moving, and hospitals would do well to be ahead of this trend, instead of last to embrace it.

The goal of our educational program is to enhance parental resilience, well-being, and involvement in their baby's care. Their increased time spent with, and emotional connection to, baby, increased skin-to-skin care, increased breastfeeding, and increased knowledge and understanding of their baby's needs and behavioral signs will lead to improved bonding with them. All of these factors have been shown to be instrumental in guiding baby's brain development through crucial periods that sometimes take place in the chaotic atmosphere of the NICU; this is especially important in the case of fragile, preterm babies. We hope that implementation of our very clinically relevant, "hands on" recommendations for care of families will result in improved outcomes for everyone in the family in both the short-term and the long-term.

DD: Anything else?
SH: I want to add that we now also offer a condensed and very highly referenced version of "Caring for Babies" which is directed towards physicians and neonatal nurse practitioners. This "Advanced Provider" program was created specifically to meet all the requirements set forth by the Accreditation Council for Graduate Medical Education (ACGME) having to do with providing behavioral and mental health support to patients and their families. It is a 2-hour program that is also available for continuing education credit.

And finally, we recommend that the whole NICU staff takes our educational programs at the same time, to transform the NICU culture from being patient-centered to truly family-centered. So far, we have had the NICU staff at 14 hospitals take the program together. That way, change is more impactful than if a single nurse or physician took the program and changed their practice.

DD: I couldn't agree more, Dr Hall. Thank you for speaking with me about this important course work.
It's me, the former "Smiling Mom" telling you NICU professionals to get moving on the training. I support tens of thousands of parents annually worldwide and I see the same fears in those conversations that I had myself as a new parent. This is not just an item for the training budget. It's part of the marketing budget and the public relations budget and more. And yet the bonuses come back tenfold because you are able to help entire families through what is likely the most traumatic moment of their lives to date. You not only help that baby, but the family, the hospital and society as a whole. Talk about a "bang for your buck."

Mitigating Infection Risk in the NICU

Aspect Imaging, Ltd.

The need to avoid healthcare-associated infections (HCAIs) and their associated complications are well understood, especially when caring for the most fragile patients in the Neonatal Intensive Care Units (NICU). Aggressive policies and procedures relying on clinical team members to thoroughly clean and disinfect equipment, and the adoption of visitation policies designed to limit the neonate's exposure to non-parental visitors and staff, are routinely employed in NICUs today.

Despite the vigilance applied to infection prevention, NICUs are forced to accept unnecessary risks and transport fragile infants out of the controlled environment of the NICU to the radiology department when an MRI is needed. In many cases, this is the only time a baby is moved from the NICU prior to discharge from the hospital.

An evaluation of outcomes during intra-hospital neonatal transport showed that 27% of patients transported for radiology services suffered complications.[1] In addition to the risk of clinical instability while transporting sick neonates through the hospital to the MRI suite, the transport exposes them to public and clinical areas that primarily serve other patient populations and increase their risk for exposure to infectious microorganisms and cross-contamination. In 2009, the Joint Commission alerted hospitals to the importance of infection control in MRI facilities.[2] More recently, a paper in the Journal of Medical Imaging highlighted how deficiencies in infection prevention precautions exist in many radiology departments worldwide.[3]

"Any exposure to infection, even a simple sneeze or cough from a person in a hallway or elevator, can mean life or death for a baby who has been in the NICU since birth, is not immunized and may have respiratory issues," says Patricia G Bondurant, DNP, RN, Co-founder and Chief Transformation and Quality Officer, TransForm Healthcare Consulting LLC.

Dr. Bondurant is a nationally recognized expert in healthcare management, neonatal and pediatric nursing, and quality improvement. Her work has resulted in improved care and outcomes for neonates and children, and she was a key stakeholder and nursing lead in the development and implementation of the American Academy of Pediatrics NICU Levels of Care Verification Program.

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Modern hospital design is based on providing the best possible care for patients. Faster access to services, improved patient experience, greater workflow efficiency, all of these goals are considered when designing clinical areas in the hospital. NICUs now include many services within their department: pharmacy, respiratory, laboratory, even surgical suites, to provide care to critically ill neonates in the unit, and without transport. While initially driven by the need to increase timely access to services, the benefit of keeping babies in the NICU is no longer strictly a convenience or a way to increase workflow efficiency. It is more critical than ever to keep babies, and those services they require, within the protected environment of the NICU and avoid the added risk of intra-hospital transport for any reason.

"The most important point is to not move the baby," adds Dr. Bondurant. "Level 4 and most Level 3 NICUs have dedicated

ultrasound and X-ray machines to prevent infection transmission because we know that when a machine travels around a hospital it could be a vector for infections. So why should we change our practice when it comes to MRI, and not have it as contained as the rest of the NICU? It draws a natural conclusion that we should have a dedicated MRI in the NICU."

Today, that risk to move a baby from the NICU to an MRI in the radiology department is magnified with the heightened concern of COVID-19, a novel coronavirus causing widespread infection, especially with MRI equipment in most hospitals being located a great distance from the NICU, requiring long transport of babies through the hospital.[4] According to Dr. Bondurant, she's hearing from colleagues who report they are more reluctant to order MRI scans and, in some cases, postponing the exam until after discharge during the COVID-19 healthcare crisis currently facing the US and other parts of the world.

Yet, delaying an MRI for a NICU patient can impact not only their diagnosis, but also their development. It's important, Dr. Bondurant says, that parents have access to habilitative services for their child as soon as possible, especially when long-term services are needed to maximize a baby's development. The extent of an injury may not be known unless the infant has an MRI, which is more specific than an ultrasound or X-ray and is a standard of care for diagnosing brain and spinal injuries.[5]

As concern for minimizing infection risks to the most fragile patients increases, the option of providing care to neonates without leaving the NICU has transitioned from a nice-to-have approach, to a must-have approach to mitigate the risk of infection for patients at the highest risk of complications. That's where Aspect Imaging's Embrace®, the only FDA 510(k) and CE approved dedicated neonatal MRI system, can make a world of difference for the health and development of critically ill infants.

Uniquely designed to be placed within the NICU, the Embrace® offers the critically valuable, timely diagnostic information only available from MRI, without the acknowledged risk of taking the baby out of the NICU.

"The Embrace® Neonatal MRI allows us to do things we couldn't do before because of the risks of moving a baby down to the MRI suite," says Dr. Bondurant. "It gives us timely information that will allow us to provide habilitative, early intervention services when needed. Without the Embrace® we are forced to compromise our practice and transport the baby from the safe, sterile environment of the NICU to get their MRI. We shouldn't be breaking the practices that we so heartedly put into place to protect these babies in every way possible when there is another option."

References

1 Osman Bastug, Tamer Gunes, Levent Korkmaz, Ferhan Elmali, Fatma Kucuk, Mehmet Adnan Ozturk & Selim Kurtoglu (2016) An evaluation of intra-hospital transport outcomes from tertiary neonatal intensive care unit, The Journal of Maternal-Fetal & Neonatal Medicine, 29:12, 1993-1998 DOI: 10.3109/14767058.2015.1072158

2 http://www.jointcommission.org/SentinelEvents/SentinelEventAlert/sea_38.htm

3 Ilyas F, Burbridge B, Babyn P. Health Care-Associated Infections and the Radiology Department. J Med Imaging Radiat Sci. 2019;50(4):596–606.e1. doi:10.1016/j.jmir.2019.07.011.

4 Wu TW1, McLean C, Friedlich P, Grimm J, Bluml S, Seri I. Maintenance of whole-body therapeutic hypothermia during patient transport and magnetic resonance imaging. Pediatr Radiol. 2014 May;44(5):613-7. doi: 10.1007/s00247-013-2863-2. Epub 2014 Jan 18.

5 K Rademaker, C Uiterwaal, F Beek, I C van Haastert, A Lieftink, F Groenendaal, D Grobbee, and L S de Vries Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm Arch Dis Child Fetal Neonatal Ed. 2005 Nov; 90(6): F489–F493. doi: 10.1136/adc.2005.073908

Giving Back to NICU Leadership in an Innovative Way to Avoid Burnout

Deb Discenza, PreemieWorld.com

Katie and I are true survivors, having both endured chaotic childbirths, the NICU and watching our preemies struggle from birth on forward. Despite the trauma, we took those tough moments and decided to do something to help others going through this experience behind us. So I was honored to interview Katie and learn more about her experience and how it informed her higher educational work, a Master of Arts in Organizational Leadership with a Concentration in Servant-Leadership (2015) and her current studies as a PhD in Leadership Studies student. She is the Founder of Courageous Steps (http://www.courageoussteps.org/).

Deb Discenza (DD): You often speak about how having your son prematurely during a crazy set of circumstances created the impetus all that came after it. You speak of your son's premature birth, your realization of how healthcare settings vary in terms of true care, your PhD work and your consultancy, Courageous Steps. Tell me a bit about what happened and how that informed you and inspired you.
Katie Reginato Cascamo (KRC): I had a clinically healthy pregnancy. At Age 31, I owned a very successful insurance agency in the Top 100 of my state and Top 2 in my District for high performance and quality. As a respected leader in my community, my work and my life held meaning and purpose. Three years earlier I left the San Francisco Bay Area to marry an Academic Dean and Captain (now Major) in the Oregon Air National Guard. The complications in my pregnancy were perceived as external chaos and unexpected changes though nothing that would flag me as high risk. At 7-weeks pregnant I developed an enchondroma fracture and fractured my hand opening the back door at home. The Emergency Department Resident on July 3rd stated, "We do not know what caused Katherine's fracture. She could have cancer and she could die before she has the baby though we cannot do a full body X-ray until the baby is born." At 8-weeks pregnant a transvaginal ultrasound led us to discover the fracture and related trauma caused the death of my son's identical twin (vanishing twin). At 17-weeks pregnant my corporate contract changed leading me to restructure and eventually close my Agency with my continued career interest in corporate opportunities. At 26-weeks pregnant I developed Swine Flu from an asymptomatic carrier at my baby shower. With the Emergency Department that I had visited earlier reporting deaths, an Urgent Care Physicians Assistant and my Obstetrician urged me to only go to the Emergency Department in extreme emergency. At 28-weeks pregnant I received Jury Summons and told, "You do not have Swine Flu while pregnant because you would be dead. You are ordered to report for Jury Duty." At 29-weeks, 6 days I went in for hand reconstructive surgery from my fractured hand that hadn't healed. After the surgeon botched the surgery and left me with a crooked scar, I woke up from surgery with 155/115 blood pressure and was diagnosed with pre-eclampsia. With every effort made to discharge me by the surgery center, one brand new nurse suggested I walk myself over to the Birthing Center to be evaluated. I was put in a bed for evaluation and given a Betamethazone shot as my obstetrician and the birthing center team tried to figure out how they would evacuate me in the middle of a blizzard at –1 degrees outside. Poor weather grounded the helicopter and the 5500' mountain pass roads were closed. It was strategically determined that I would be sent by ambulance to a fixed wing plane, airlifted over the blizzard storm and a 5500' mountain and sent by ambulance again to the regional hospital equipped to care for me.


Katie Reginato Cascamo

The transport forever changed how I see medicine. I perceived feelings that I had been rescued from a toxic healthcare situation where my patient voice felt discounted. As the caricature of an executive, bossy woman professional, I spent my life in control of the world as I knew it. In this moment I had to make a profound interpersonal decision to give over my power to a team of healthcare providers entrusted to care for me. The transport team practiced Trauma Informed Care in a way that went beyond the methodology of the care. There was an added intangibility, an interiority within the transport team that erupted in moments of joy as my 5'10" height got stuck as they attempted multiple times to fit me into the fixed wing plane. There existed a peacefulness in their demeanor that brought me confidence and

Deb Discenza is the mom to a 30-week preemie now almost 17, the CEO/Publisher of PreemieWorld, LLC and the co-author of The Preemie Parent's Survival Guide to the NICU — with its new edition out now. Please find the book and dozens of free downloads for parents and professionals at https://preemieworld.com.

trustworthiness. As we arrived at the regional hospital a clinical team was in place to receive me of equal interior wholeness. With profound intangibility in the moment, they transported me into a birthing hospital room, their peacefulness spoke volumes. Their handiwork of attaching patches with electromagnetic cables and working alongside me etched a moment that fuels my continued work today. I imagined being in the center of the ballet 'The Nutcracker' with a team of perfectly choreographed professionals doing their work with perfection. As I watched this unfold around me, a seed of curiosity planted in my heart to learn this mystical, intangible teamwork that exceeded anything I had ever seen.

I spent four days on bedrest where I was prepared for an early term birth. A neonatologist visited us bringing clarity and confidence to a very early term birth. On Day 4 when we lost my son's heartbeat, I was rushed into an Emergency C-Section that, like my transport, was calm and comforting. This peacefulness extended to the beauty of the birth of my first child. My son was born at 30 weeks, 3 days at 2lbs, 8oz (1131 grams).

Our 56-days in the NICU continued this profound awakening and set my life on a path to wholeness. The well-established system set by our neonatologists of doing cares every three hours to equip me as part of the care team helped rebuild my confidence. The collective capacity of our neonatal team's ability for empathetic listening and foresight into what I needed to care for my child continues to this day. Ten years later when I am struggling with a paper for my PhD or consulting a client, I take a deep breath in and remember the calm assurance that comes from knowing one's trade and the ever-importance of human connection.

Two years after our NICU graduation, a disquieting instinct developed in me that almost required me to do something with my professional background in management and leadership and our lived healthcare experience. A team of mentors and influencers (including two of my neonatologists that let me interview them) invited me to reflect on my own strengths and the ways I can contribute to healthcare change. To effectively do the work that I sensed the need to do required further education. I discovered the paradigm of Servant-Leadership during this period and associated it to the profound experience in my transport to the NICU. I also recognized its absence in the healthcare offered at the rural hospital that lacked the interpersonal emotional intelligence necessary for quality patient care. The manifestation of this self-discovery process led me to pursue my Master of Arts in Organizational Leadership with a Concentration in Servant-Leadership (MAOL). My graduate work focuses on both the structural components (the systems) of healthy preemie organizations and the qualities of effective leadership known as Servant-Leadership. Through this MAOL program I took a course on resilience and grit with a professor who once served as a social worker at a NICU in Los Angeles. His insight into my world strengthened my core commitment to serving a world that had yet to be born, a world where credible parent voices just started to emerge as leaders. This course led me to meet Executive Director Kelli Kelley of Hand to Hold who introduced me to the NICU Parent Network, a collective of parent leaders like myself who contribute to the care and concern of NICU families. I met Deb Discenza of PreemieWorld who sent me a magazine during my time in the NICU and Nick and Jen of Graham's Foundation who sent a care package. Collectively every member of the NICU Parent Network weaves in the power of our sacred stories and a level of credible professionalism and expertise that is unlike anything on earth. Over an eight-year period I have been invited to speak nationally and globally and collaborate with neonatal leaders who are invested in the interdisciplinary work of improving healthcare for patients and families. This resiliency professor invited me to consider the PhD in Leadership Studies program at Gonzaga University in 2014. It took me five years of my own interpersonal and professional development to accept the opportunity. In 2019 I started my PhD in Leadership Studies where I am researching the ways servant-leadership improves organizational culture.

DD: What a journey! In healthcare settings, leadership sets the tone for the entire unit, the entire hospital's understanding of care. How does your work create that positive environment?

KRC: Many consultants approach an organization with an assumption there is a problem to be solved. I approach organizations and their leaders with appreciative inquiry, a strengths-based approach to transforming healthcare. We have enough data to support that our old way of management and leadership is failing to keep up with society's needs. We know that healthcare is suffering from a 50% or greater burnout rate and immense psychosocial suffering by healthcare providers is leading to burnout, anxiety, depression, even suicide. I see the work I do like that of a midwife helping the leader develop their own new understanding and ideas around Servant-Leadership. My role as facilitator and coach is to help leaders see new ways of approaching complex problems. I support executive and healthcare leaders in the process of discovering emerging way of leadership called Servant-Leadership.

Servant-Leadership invites each of us to discover a new way of being in the world. The old way of being in the world focuses on hierarchy and positionality. This hierarchy that is so embedded in our society no longer sustains the immediacy we need to respond to complex challenges in the moment. This new moral principle is emerging where the only authority is one that is freely given to the leader through the evidence that they are worthy to be trusted (Ferch, Spears, & Greenleaf, 2020). According to Robert K Greenleaf who first coined Servant-Leadership in 1970: "the difference manifests itself in the care taken by the servant-first to make sure other people's highest priority needs are being served. The best test, and difficult to administer, is: Do those served grow as persons? Do they, while being served, become healthier, wiser, freer, more autonomous, more likely themselves to become servants? And, what is the effect of the least privileged in society? Will they benefit or at least not be further deprived?" (Ferch, Spears, & Greenleaf, 2020).

DD: Do you see change as top down?

KRC: Global for-profit and not-for-profit industries are finding individual and organizational benefit from principles of servant-leadership. The old top down model is being replaced by consensus making and persuasion instead of a focus on authority and traditional forms of power. With servant-leadership there is an inversion in the hierarchical pyramid from a top down approach to greater emphasis on teamwork, collaboration and collective decision-making. And through the distribution of power through shared decision making, the trustworthiness in executive leadership is strengthened. This strengthening empowers executive leaders to lead. In applied terms this means that executive leadership does not make executive decisions without front-line clinicians as part of the decision-making

process. Servant-Leadership values healthcare leaders who do at least one eight-hour healthcare shift per week in addition to the role of the healthcare executive as an example. This lived experience on the front lines transforms the trustworthy relationships built among staff and the decisions made for the improvement of the organizational culture.

According to Larry Spears, CEO of the Spears Center and global author of over 35 books on Servant-Leadership, "In countless for profit and nonprofit organizations today we are seeing traditional autocratic and hierarchical modes of leadership yielding to a different way of working — one based on teamwork and community, one that seeks to involve others in decision-making, one strongly based in ethical and caring behavior, and one that is attempting to enhance the personal growth of workers while improving the caring and quality of our many institutions" (Ferch, Spears, & Greenleaf, 2020). Some people who read this imagine a toppling of the hierarchical structure and giving power to lesser qualified or positionally situated staff. Through the healthcare lens, this means the CEO and C-Suite are committed to the empathetic listening of front-line staff who are engaging with patients and providing the tools and resources necessary to care for patients.

Why does this shift in leadership understanding matter? Phrases such as "healthcare is broken," "healthcare is unsustainable," "healthcare is expensive" discredits the exceptional work and commitment of healthcare providers who are on the front lines every day saving lives. I do not believe healthcare is broken. Healthcare is ready for a breakthrough. And I believe that Servant-Leadership is that breakthrough that we need.

Collectively we need to shift how healthcare has been done for the last 30 years as a financial gain model and focus all of our attention on equipping and caring for our healthcare providers. Healthcare providers are of primary importance in the healthcare system. As healthcare providers discover renewal and wholehearted compassion for themselves, their colleagues and their patients, the natural outcome is stronger patient outcomes and patient experience. And this leads to stronger economic outcomes.

This means reinvesting in healthcare provider wellness, training and leadership development so they can provide world class healthcare to patients. This means investing in all staff, clinical and non-clinical in the shared mission of providing world class healthcare. In our NICU experience, the most unexpected of non-clinical healthcare providers emerged to offer well-rounded patient care. The non-clinical environmental services custodian who cleaned my birthing room suite and the NICU over the two months we were in the hospital practiced Trauma Informed Care and partially rounded with our nursing staff as she checked in with patients on their emotional health. To genuinely practice servant-leadership requires a transformative interior shift within ourselves. It requires healing, a commitment to growing others and forgiveness-asking. We are stewards of a healthcare system for our children and grandchildren and Servant-Leadership suggests renewal in our organizations and society.

Servant-Leadership compliments and strengthens healthcare paradigms of care such as Patient and Family Centered Care, Baby Friendly or Trauma Informed Care. It improves the way in which healthcare is delivered by developing the leadership characteristics of every person within an organization and the organizational whole. As a patient and then parent in the NICU, as our healthcare staff empathetically listened and provided competency training in the care of my son, they were equipping me to become a servant-leader in my family. And this strengthening led to my graduate and doctoral work with a desire to give back to society.

DD: Could you give me a sense of what a positive change is in healthcare leadership?
KRC: Positive change in healthcare through the lens of the servant-leadership model is a values-based, ethical form of leadership. Servant-Leadership is a person-centered model. Many of the patient centered or person-centered models align with Servant-Leadership. The strength of servant-leadership adds a holistic element of empathetic listening, healing and compassion for oneself and others. By restructuring the purpose of healthcare from a profit-driven model to a provider-driven model, positive outcomes follow. The paradigm of servant-leadership offers the healthcare provider an opportunity to reconnect to their individualized purpose for going through extensive education and training of medical school. It can lead to renewing the heart of the provider and therefore decreasing burnout. Renewal and joy struggles to exist alongside burnout and cynicism.

By investing in the patient facing healthcare provider through interpersonal skills development, growth of leadership skills and improved wellness, a provider's patient-centered focus improves patient outcomes. Patients are more apt to listen to healthcare providers who genuinely care for their needs, practices empathetic listening and empowers the patient to take responsibility for their own health. As genuine patient experience reveals a positive experience, it strengthens the healthcare system as a whole. And the healthcare provider is renewed in their work of caring for patients.

DD: How would a medical director of a unit see this type of program as cost-effective when so many hospitals are extremely spend-adverse these days?
KRC: From a cost-effectiveness perspective, what is the cost of one physician turnover? Or, the costs associated with burnout and cynicism for the patients in your care? If introducing this practice of Servant-Leadership will nurture the health and well-being of just one physician or nurse, would a $250 discovery call be worth your time and effort?

I purposely chose to build my organization to be adaptable to the needs of the leaders whom I serve. An enormous amount of consultancy time is spent pre-designing programs to be applied across all industries and sectors. The plan I build is specific to the individual or organization. I ask questions such as, "What do you need most in your organization?". And then we get to the real work of solving for the need. As a leadership educator and coach, my real work is equipping healthcare leaders to lead. I expect those whom I serve to be experts in their practice of medicine. We work together to establish outcomes that strengthen clinical practice through leadership.

My work is in developing leaders to have the courage and compassion to embark on the systemic challenge healthcare is experiencing. As a spend-adverse professional myself, my goal is to streamline costs through some cost-effective and free resources. I invite you to visit my website at www.courageoussteps.org to explore the work that I do.

It is the spend-averse fears that impact organizational culture. It adds unnecessary stress and anxiety to a complex environment and can lead to burnout and cynicism among front-line staff. While the financial model may require a level of conservatism, the work I do is to help healthcare leaders reframe their communications to one that empowers and builds front-line workers to be effective in their use of resources.

DD: Can you see this spreading out to beyond hospitals and into separate healthcare practices for specialists and more?
KRC: The work of servant-leadership organically spreads out beyond the hospital to separate healthcare practices and the society as a whole. The power of Servant-Leadership inspires every person to engage differently in the world and to see the world as whole. As a society there is an incongruence to how we live in the world, where our personal lives are expected to be separate from our professional lives in a way that discounts both. Imagine an entire healthcare system built from this fracturing of the organization to a renewed commitment of collaboration? And whether health insurance pays for or approves patient care has no impact on the interior leadership and courageous strength of the leader. The leader is trained to navigate such complexities with grace and power that dismisses fear with joy in the work of caring for people.

Servant-leadership has a specialness to it that motivates change in the people who are touched. Many people associate Servant-Leadership with a particular religious worldview. The only relationship to religion or spirituality is in the clinician who feels inspired in their own life to be empowering and transformative.

Imagine for a moment a renewed organization that is committed to the care of society. As burnout, cynicism and anxiety is replaced with empathetic listening, healing and a commitment to the growth of people, the organizational culture transforms to one of courageous caring (Ferch, Spears, & Greenleaf, 2020).

DD: Is there anything else you would like for our readers to know?
KRC: Servant-Leadership compliments such care paradigms such as Patient & Family Centered Care, Family Integrated Care, Baby First and many others that are practiced within healthcare systems. Servant-Leadership aims to develop every person within an organization so they feel equipped to do their best work.

References

- Spears, L., & Greenleaf, R. K. (2020). International journal of Servant-Leadership (S. Ferch PhD, Ed.). Retrieved June 28, 2020, from https://www.gonzaga.edu/school-of-leadership-studies/departments/ph-d-leadership-studies/international-journal-of-servant-leadership

Early Intervention for Infants Following Tracheostomy

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Laura Brooks, MEd, CCC-SLP, BCS-S, who is a speech language pathologist at Children's Hospital of Atlanta (CHOA).

Developmental milestones occur from infancy through early childhood. Swallowing, mobility, and other skills begin in utero and continue developing; however, changes in anatomy or physiology may have an impact on this progression. It is well-documented in research that the largest growth of speech and language development begins at birth and continues through about age three, and during this same timeframe, infants and toddlers are making vast changes in gross and fine motor development.[1] With advancements in medical interventions and increased survival rates for infants who are premature or with congenital anomalies, tracheostomies are occurring more frequently in infants. A tracheostomy in a developing infant or toddler can impact speech and language development, fine and gross motor development, and oral-motor sensory awareness.

Considering the impact that a tracheostomy may have, early intervention with these patients may be a key component for development. Typically, the human body functions with a pressurized system; however, a tracheostomy tube changes that physiology due to the loss of pressure through the opening. The pressurized system is a key element in the gross motor development of trunk control and postural stability.[2-3] It also impacts the ability to cough, swallow effectively, and to develop speech.[4-6] One way to restore the pressures that impact these functions is to consider the use of a one-way speaking valve. Using a bias-closed position, one-way Valve assists with closing the system and redirecting airflow through the upper airway as done when there is not a tracheostomy tube. The Valve works by closing at the end of inspiration, which redirects 100% of the airflow up through the vocal cords and out through the mouth and nose. This redirection of airflow with the Passy Muir® Valve (PMV®) has been shown in the research to assist with improving secretion management, sensory awareness, swallowing, and natural physiologic PEEP (positive end-expiratory pressure), among other benefits.[7]

Because of the age and fragility of infants, questions arise about using a Valve with this patient population; however, there is a paucity of research with infants. Brooks, Figueroa, Edwards, Reeder, McBrayer, and Landry (2019) conducted a study to investigate if there are predictors for success with use of a Passy Muir Valve in the medically complex pediatric patient.[8] This study found that the predictive factors included age, weight, ventilator rate, transtracheal pressure measurements (TTP), and voicing. The two which were most indicative of success were the TTP and voicing. The following is an interview with Laura Brooks, MEd, CCC-SLP, BCS-S (LB) who is a speech language pathologist at Children's Hospital of Atlanta (CHOA) and first author on the study. At CHOA, Laura participates with the Global Initiative Trach team and others to conduct research related to tracheostomies, speaking valves, and evidence-based care. With Laura's expertise in working with infants with tracheostomies, this interview addresses some of her considerations as to why and when early intervention should be sought.

Kristin A King (KK): What information would you share on how a tracheostomy may affect an infant's or young child's recovery, development, communication, and feeding and swallowing?

Laura Brooks (LB): A concern that parents have expressed to me is that their baby, their child with a tracheostomy, will not be able to eat or speak. They ask questions about whether they

Walter Reeder, BS, RRT (RT Educator) and Laura (Speech-Language Pathologist) often work together when evaluating these young patients.

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

can place their baby in prone position [on their stomach], which is important for gross motor development. They share concerns that they will not be able to hear their baby cry to know when they are in distress. So, it is particularly important to have a team of rehabilitation specialists (Speech-Language Pathologist (SLP), Physical Therapist (PT), and Occupational Therapist (OT)) and respiratory therapists who can work with each infant to achieve these skills to the best of their ability. The SLP can reinforce to families how using the Passy Muir Valve can restore exhalation through the child's nose and mouth, which enables vocalization, crying, cooing, babbling, and produce other sounds which are involved in speech development. Additionally, having a closed system with a PMV on the tracheostomy tube allows the baby to sense secretions that may be pooling in the pharynx, and as a result cough. Encouraging infants to cough their secretions may decrease the need for suctioning as much. Pharyngeal sensation is restored with the PMV and the infant receives sensory input when swallowing. Hyolaryngeal excursion is improved with PMV use and the patient is less likely to have pharyngeal residue (ie pyriform sinuses). Use of the PMV restores subglottic pressure which is used for many gross motor infant tasks, such as crawling, sitting, and standing. Restoration of valsalva (ie attempted exhalation against a closed airway, such as when bearing down) will assist with the ability for the infant to have a bowel movement and may reduce the need for medications to assist with bowel movements.

KK: How would you define early intervention and what approach do you consider for infants and young children with tracheostomies (meaning when you begin and what order you address aspects of assessment and care)?
LB: The earlier the better. For premature babies in the NICU, in our facility, we wait until they are off the hospital ventilator and on their home ventilator. As soon as they are on their home ventilator and their settings are good (PEEP 10 or less, PIP 40 or less, FiO_2 50% or less) the baby is ready for a PMV trial from my perspective. At that point, the ENT (Otolaryngologist), Pulmonologist, and the Hospitalist (NICU, PICU, or TICU attending) provide an order for a trial. The RT educator and I (SLP) perform transtracheal pressure manometry (TTP) with every PMV attempt until a patent airway is noted with the patient. This close monitoring for airway patency increases the team's comfort with initiating PMV trials for patients. If an infant's end expiratory pressure (EEP) is too high as measured by TTP, the RT and I implement different strategies to determine the cause of the higher pressure. We attempt position changes and distractions. We also will conduct testing when the baby is waking up or falling asleep to assess true transtracheal pressure, which is only accurate with resting breaths. So, we try every day or every other day until we get a "true" end expiratory pressure. If, at that point, the pressure is too high, we will ask ENT and Pulmonology if we may either downsize the tracheostomy tube (the lowest we can downsize is to 3.5 mm) or change to a cuffless tracheostomy tube, if appropriate. We work very closely with our ENTs and Pulmonologists to achieve use of the PMV as tolerated, and our team is very supportive of changing to a smaller trach tube and/or cuffless trach tube, if medically appropriate.

KK: Can you describe your perspective, with a few highlights, related to first using the valve, barriers you overcame, and the difference in use today as compared to when you started?
LB: Initially, I only used the PMV for patients who were off the ventilator and near ready for capping prior to development of our trach/vent program at CHOA, but after developing a program, a realization occurred about how many babies and children we had been missing. We are a teaching hospital and open to new ideas and programs that can benefit our patients.

We started a Global Trach Initiative team who meet monthly, early in the morning, and discuss patients within our system with tracheostomies and any issues surrounding them. The team includes ENTs, Neonatologists, Hospitalists (PICU attendings), RTs, and SLPs. I was able to put together a *Best Practice Recommendation* document with the support of the invested MDs and RTs. Because we work so closely together, and have earned the trust of the physicians, there are not many barriers to overcome at our hospital.

When we discuss our process and safety measures, we generally do not encounter resistance. It is very helpful to our program that we have two RT educators who do the majority of the PMV trials with me, providing consistency. They have an excellent understanding of the process and safety interventions. Barriers, at times, may occur on certain units, if the available staff are not yet educated on how to use the PMV in-line. We also still have some residents, fellows, and attending physicians in all areas of medicine who do not understand that the PMV was invented by a ventilator-dependent man and was to be placed in his ventilator circuit.

KK: What are some primary considerations about a patient's age and medical status when considering use of a speaking valve?
LB: That is a really important question. There is no age limit to when a patient can be considered a PMV candidate. It is all about the baby's medical status. For example, a baby, who is an adjusted age of four weeks with a PEEP of 8, PIP 35, and FiO2 30% on their home ventilator, is ready for a PMV as long as the physicians do not have a reason that it cannot be placed (eg presence of laryngeal stents).

Infant use of the PMV in-line with mechanical ventilation brings a smile.

KK: While some infants and children may have a tracheostomy tube without a cuff, many will have a cuff. Cuff deflation often arises as a concern. Do you recommend cuff deflation trials prior to use of a Passy Muir Valve?
LB: Since we do many of our PMV trials on patients who received their tracheostomy during the same hospitalization, the first cuff deflation trial is often during our PMV trial. Rarely do we have to stop and re-inflate the cuff because the patient did not tolerate cuff deflation. Our RTs slowly deflate the cuff, sometimes over 30-60 seconds, while also providing thorough suctioning (by both the tracheostomy tube and by mouth) before and after cuff deflation. Meanwhile, the SLP and caregivers support the baby as their airway changes. After approximately a minute or so, the RT and SLP will place the valve in the ventilator circuit. If the TTP/EEP is good and the baby does well, we will leave the Valve on for approximately 10 minutes for the initial trial and slowly increase the wear time. If a baby is not able to use the PMV and has a cuff that is inflated, we will then consider cuff deflation trials, maybe 10 - 30 minutes during a session. During cuff deflation trials the SLP will target other goals for the session, such as oral stimulation.

When the baby handles cuff deflation, assuming their tracheostomy tube is not too large or their upper airway obstruction is not too severe (eg grade 4 stenosis—complete airway closure), then providing oral stimulation and airflow through the upper airway begins to restore pharyngeal and glottic sensation for the baby. With restored sensation, placement of the PMV becomes easier.

KK: You recently published a study that addresses predictors of success in infants and children. Could you share what the primary points were that you want as take-aways from the study?
LB: Hopefully, the reader takes away that medically complex patients of any age CAN be considered candidates for a PMV trial and advocate for early application. Transtracheal pressure manometry may be critical to assure that the young patient has a patent airway and can adequately exhale through the mouth and nose. Also, educating SLPs and RTs is critical. Education on the PMV is available through many resources (eg Passy-Muir, Inc. offers continuing education credits through live and recorded webinars, in-service education, seminars, and more). Having a task force with SLPs, RTs, and MDs who understand the PMV and the mission is key. In our study, we found that the main predictors of success were TTP < 15 cm H_20 and voicing with PMV application. Also, important to note is that a small number of patients with a TTP <15 did not tolerate the Valve; while on the other hand, and a few with pressures over 15 cm H_20 could use the Valve, so using 15 cm H_2O is a guide and a;; decisions are patient specific.

KK: Can you share one patient story that particularly had an impact on you?
LB: There is not one patient, every single PMV trial impacts me. When the PMV is placed on an infant for the first time and the Mom or Dad hears the baby cry, they cry, we cry. Imagine having a baby and not being able to hear them cry in the middle of the night to let you know they need something. Imagine knowing that your child is in distress because you cannot hear him/her cry, even if you are in the same room, because an infant with a tracheostomy tube cannot provide audible cues. Providing or restoring an infant's ability to coo, cry, and have vocal play for the first time is absolutely profound to the family.


Enjoying an afternoon in the swing with the joy of laughter.

KK: What are a few primary points of education that you provide to parents and caregivers about a young child with a tracheostomy?
LB: Advocate, question, research, and ask. Your baby with a tracheostomy may be able to do the things that a baby without a tracheostomy can do. Consider the skills that infants go through during development and ask how your baby can do them, such as tummy time, feeding, sitting up, walking, and more. If a parent, participate with the therapists to learn how to carryover new skills your child has achieved and constantly set new goals.

KK: What advice would you give to parents or caregivers who have an infant or young child with a tracheostomy?
LB: The tracheostomy (with or without ventilator-dependence) can be terrifying at worst and inconvenient at best. With proper training and support, you may do things with your baby that every other parent or caregiver can do.

KK: What advice would you give to other clinicians about working with infants and young children with tracheostomies?
LB: Call, email, ask. Seek education. For CHOA, I scheduled in-services from Passy-Muir at least once per year. I called the Clinical Specialists at Passy-Muir regularly until I had a handle on using a Valve in-line and with transtracheal manometry. Use your resources, such as Passy-Muir and clinicians with experience.

In summary, when development is complicated by medical conditions that require a tracheostomy, the way the systems interact are compromised even further. Additionally, research has implicated that a long-term tracheostomy may impact parent-child bonding and the ability to express wants and needs due to the lack of access to vocal and verbal communication.[9] Because of these potentially negative effects on crucial development, it is imperative to provide the pediatric population with a closed system that normalizes the physiologic factors that

impact their development. The primary consideration during assessment is that the patient has a patent airway, meaning the patient can exhale around the tracheostomy tube and out through the mouth and nose. Having a qualified team, familiar with airway management, is a key component of successful Valve use and early intervention. With early intervention in this patient population, whether on a ventilator or not, health professionals provide improved access to functions necessary for development. Delays and limitations may be mitigated by using a Passy Muir Valve to provide a more normalized use of the upper airway.

Abbreviations

1 TTP – use of a manometer to measure the pressure occurring within the airway when the tracheostomy tube is occluded, such as when the PMV is being used.
2 PEEP – Positive End-Expiratory Pressure, PIP – Peak Inspiratory Pressure, FiO2 – concentration of inhaled oxygen
3 NICU – Neonatal Intensive Care Unit; PICU – Pediatric Intensive Care Unit; TICU – Technology dependent Intensive Care Unit

References

1 NIDCD. (2020). Speech and language developmental milestones. Retrieved from https://www.nidcd.nih.gov/health/speech-and-language
2 Massery, M. (2014). Expert interview: The role of the Passy-Muir valve in physical therapy. *Talk Muir* (3 Feb. 2014), 2-4.
3 Massery, M., Hagins, M., Stafford, R., Moerchen, V., & Hodges, V. W. (2013). Effects of airway control by glottal structures on postural stability. *Journal of Applied Physiology*, *115*(4), 483-490.
4 Gross, R. D. (2009). Subglottic air pressure and swallowing. *Perspectives on Swallowing and Swallowing Disorders (Dysphagia SIG 13)*, *18*(1), 13-19.
5 Gross, R. D., Atwood, C. W., Grayhack, J. P., & Shaiman, S. (2003a). Lung volume effects on pharyngeal swallowing physiology. *Journal of Applied Physiology*, *95*(6), 2211-2217. doi:10.1152/japplphysiol.00316.2003
6 Cowell, J., Schlosser, D., & Joy, P. (2013). Language outcomes following infant tracheostomy. *Asia Pacific Journal of Speech*, *Language*, *and Hearing*, *5*(3), 179 - 186. https://doi.org/10.1179/136132800805576942
7 O'Connor, L. R., Morris, N. R., & Paratz, J. (2019). Physiological and clinical outcomes associated with use of one-way speaking valves on tracheostomised patients: A systematic review. *Heart Lung*, *48*(4), 356-364. doi: 10.1016/j.hrtlng.2018.11.006
8 Brooks, L., Figueroa, J., Edwards, T., Reeder, W., McBrayer, S., and Landry, A. (2019). Passy Muir Valve tolerance in medically complex children: Are there predictors for success. *The Laryngoscope*, *00*, 1 – 8. doi: org/10.1002/lary.28440
9 Lieu, J.E., Muntz, H.R., Prater, D., and Stahl, M.B. (1999). Passy-Muir valve in children with tracheotomy. *International Journal of Pediatric Otorhinolaryngology*, *50*(3), 197-203. doi:10.1016/s0165-5876(99)00245-1

Fecal pH: A Window Into The Infant Gut Microbiome

Tracy Shafizadeh, PhD

The gut microbiome plays an active role in human immune function and metabolism, and the composition of the gut microbiota is a factor in overall health or disease. This active role begins the first day of life, as the infant gut microbiome plays a particularly important role in digestion of human milk as well as early immune programming.[1,2] The organisms that comprise the infant gut microbiome are initially acquired at birth and differ dramatically depending on birth mode and infant diet.[3,4] Additionally, hospitalized infants are known to acquire gut microbes from the hospital environment, including pathogens linked to negative health outcomes such as necrotizing enterocolitis and late onset sepsis.[5] In clinical practice, a detailed compositional analysis of the infant gut microbiome is often unavailable. However, data now show that fecal pH is directly linked to the composition of the gut microbiome and may be a useful tool to evaluate infant gut dysbiosis.

The Infant Gut Microbiome and Fecal pH

It is estimated that many hospitalized infants are dysbiotic, a term that is used to describe an overgrowth of pathogenic bacteria in the gut. Pathogenic and opportunistic bacteria have greater potential to colonize and thrive in environments with elevated pH, 5.5 and above. Conversely, an abundance of protective *Bifidobacterium* in the infant gut has been correlated with a lower pH, ~5.0, creating an environment that is inhospitable to pathogen growth.[6] The infant-specific bacterial species *Bifidobacterium longum* subspecies *infantis* (*B. infantis*) is known to thrive in the breastfed infant gut, where it efficiently converts human milk oligosaccharides (HMOs) present in breastmilk into lactate and acetate, effectively lowering the colonic pH to ~5.0.[7] When the colonic environment is maintained at a more acidic pH, pathogen growth is suppressed, a natural mechanism called colonization resistance.[8]

Reestablishing *B. infantis* Restores Colonization Resistance to the Infant Gut

As most hospitalized infants are found to be dysbiotic due to C-section delivery, premature birth, and exposure to antibiotics, intervention is often needed. When *B. infantis* is missing in the infant gut, clinical studies show that there is elevated pathogen abundance, higher levels of antibiotic resistant bacteria, increased breakdown of the colonic mucin layer and significantly higher levels of enteric inflammation.[7,9,10,11] However, when *B. infantis* colonizes the infant gut during the first months of life, dramatic beneficial effects are observed in both the microbiome composition as well as intestinal biochemistry, resolving the negative effects observed in its absence. As described above, *B. infantis* is uniquely adapted to metabolize HMO, and in turn, prevents the loss of these breastmilk components through fecal excretion. In a recent intervention trial, breastfed term infants who were fed and subsequently colonized with an activated strain, *B. infantis* EVC001 (Evivo), showed a 10-fold reduction in fecal excretion of HMO compared to breastfed infants who were lacking this bacterium.[7] The metabolism of HMO by *B. infantis* EVC001 in the infant gut leads to a subsequent production of lactate and acetate, which serve as fuel for the colonocytes, as well as reduce the pH of the intestinal environment. In the same study, lower colonic pH was associated with reduction of potential gut pathogens as much as 80% compared to breastfed controls. Taken together, colonization of *B. infantis* EVC001 in the infant gut is thought to create a functional and protective environment, reducing the abundance of pathogenic bacteria, and maximizing the utilization of breastmilk nutrients.

Published literature shows a trend of increasing infant fecal pH over the last 100 years, correlating with a loss of *Bifidobacterium* in the infant gut.[6] Infant fecal pH above 5.5 suggests a loss of colonization resistance, leading to functional changes that include increased pathogen abundance, degradation of the gut mucosal barrier, and enteric inflammation. Based on this growing body of evidence linking infant gut microbiome composition, fecal pH and health outcomes, LabCorp of America national diagnostic lab has recently recognized the need for an infant-specific fecal pH reference range and updated the range accordingly to pH 4.5-5.5 for infants 0-6 months of age. Therefore, this simple, non-invasive clinical test provides a window into gut microbiome composition, and may be considered as a tool in detecting infant gut dysbiosis.

Dr Tracy Shafizadeh is a nutritional scientist and the Director of Scientific Communications at Evolve BioSystems.

References

1 Zivkovic, Angela M., et al. "Human milk glycobiome and its impact on the infant gastrointestinal microbiota." Proceedings of the National Academy of Sciences 108. Supplement 1 (2011): 4653-4658.

2 Olin, A.; Henckel, E.; Chen, Y.; Lakshmikanth, T.; Pou, C.; Mikes, J.; Gustafsson, A.; Bernhardsson, A.K.; Zhang, C.; Bohlin, K.; et al. Stereotypic Immune System Development in Newborn Children. Cell 2018, 174, 1277–1292.e14.

3 Duar, R.M.; Kyle, D.; Tribe, R.M. Reintroducing B.infantis to the Cesarean-born neonate: An ecologically sound alternative

to “vaginal seeding”. FEMS Microbiol. Lett. 2020, 367, fnaa032.
4 Ferretti, P.; Pasolli, E.; Tett, A.; Asnicar, F.; Gorfer, V.; Fedi, S.; Armanini, F.; Truong, D.T.; Manara, S.; Zolfo, M.; et al. Mother-to-Infant Microbial Transmission from Different Body Sites Shapes the Developing Infant Gut Microbiome. Cell Host Microbe 2018, 24, 133–145.
5 Brooks, Brandon, et al. “Strain-resolved analysis of hospital rooms and infants reveals overlap between the human and room microbiome.” Nature communications 8.1 (2017): 1-7.
6 Henrick, Bethany M., et al. “Elevated fecal pH indicates a profound change in the breastfed infant gut microbiome due to reduction of Bifidobacterium over the past century.” MSphere 3.2 (2018).
7 Frese, Steven A., et al. “Persistence of supplemented Bifidobacterium longum subsp. infantis EVC001 in breastfed infants.” MSphere 2.6 (2017): e00501-17.
8 Duar, Rebbeca M., David Kyle, and Giorgio Casaburi. “Colonization Resistance in the Infant Gut: The Role of B. Infantis in Reducing pH and Preventing Pathogen Growth.” High-throughput 9.2 (2020): 7.
9 Casaburi, Giorgio, et al. “Early-life gut microbiome modulation reduces the abundance of antibiotic-resistant bacteria.” Antimicrobial Resistance & Infection Control 8.1 (2019): 131.
10 Karav, Sercan, Giorgio Casaburi, and Steven A. Frese. “Reduced colonic mucin degradation in breastfed infants colonized by Bifidobacterium longum subsp. infantis EVC001.” FEBS open bio 8.10 (2018): 1649-1657.
11 Henrick, Bethany M., et al. “Colonization by B. infantis EVC001 modulates enteric inflammation in exclusively breastfed infants.” Pediatric research 86.6 (2019): 749-757.

Thresholds for Oximetry Alarms and Target Range in the NICU

Thomas E Bachman[1,2*], Narayan P Iyer[3], Christopher J L Newth[4], Patrick A Ross[4] and Robinder G Khemani[4]

Abstract

Background: Continuous monitoring of SpO_2 in the neonatal ICU is the standard of care. Changes in SpO_2 exposure have been shown to markedly impact outcome, but limiting extreme episodes is an arduous task. Much more complicated than setting alarm policy, it is fraught with balancing alarm fatigue and compliance. Information on optimum strategies is limited.

Methods: This is a retrospective observational study intended to describe the relative chance of normoxemia, and risks of hypoxemia and hyperoxemia at relevant SpO_2 levels in the neonatal ICU. The data, paired SpO_2-PaO_2 and post-menstrual age, are from a single tertiary care unit. They reflect all infants receiving supplemental oxygen and mechanical ventilation during a 3-year period. The primary measures were the chance of normoxemia (PaO_2 50-80 mmHg), risks of severe hypoxemia ($PaO_2 \leq 40$ mmHg), and of severe hyperoxemia ($PaO_2 \geq 100$ mmHg) at relevant SpO_2 levels.

Results: Neonates were categorized by postmenstrual age: < 33 (n = 155), 33-36 (n = 192) and > 36 (n = 1031) weeks. From these infants, 26,162 SpO_2-PaO_2 pairs were evaluated. The post-menstrual weeks (median and IQR) of the three groups were: 26 (24-28) n = 2603; 34 (33-35) n = 2501; and 38 (37-39) n = 21,058. The chance of normoxemia (65, 95%-CI 64-67%) was similar across the SpO_2 range of 88-95%, and independent of PMA. The increasing risk of severe hypoxemia became marked at a SpO_2 of 85% (25, 95%-CI 21-29%), and was independent of PMA. The risk of severe hyperoxemia was dependent on PMA. For infants < 33 weeks it was marked at 98% SpO_2 (25, 95%-CI 18-33%), for infants 33-36 weeks at 97% SpO_2 (24, 95%-CI 14-25%) and for those > 36 weeks at 96% SpO_2 (20, 95%-CI 17-22%).

Conclusions: The risk of hyperoxemia and hypoxemia increases exponentially as SpO_2 moves towards extremes. Postmenstrual age influences the threshold at which the risk of hyperoxemia became pronounced, but not the thresholds of hypoxemia or normoxemia. The thresholds at which a marked change in the risk of hyperoxemia and hypoxemia occur can be used to guide the setting of alarm thresholds. Optimal management of neonatal oxygen saturation must take into account concerns of alarm fatigue, staffing levels, and FiO_2 titration practices.

Background

Shifts in SpO_2 exposure have a profound impact on neonatal outcomes. Control of exposure is associated with the selection of a desired target range, selection of alarm limits as well as nursing compliance with good practices. Manual titration of FiO_2 to address unstable SpO_2 is an arduous task. Infants in the NICU typically spend only about half the time in the desired range, and there is significant variation among centers.[1] Nursing intervention is driven by high and low SpO_2 alarms, probably more than the prescribed target range. Oximeter alarms are notorious for false positives and are associated with alarm fatigue.[2-4] A persistent low alarm necessitates the need for increased supplemental oxygen to minimize the impact of transient hypoxemia, usually a result of respiratory instability. In contrast, high alarms usually signal the need to titrate the oxygen down following recovery from a marked desaturation. If the alarm limits are too narrow or the response to aggressive, troublesome swings between hypoxemia and hyperoxemia can occur. Further there is little evidence supporting guidelines and general practice with regard to selection of SpO_2 alarm limits. Even consensus international guidelines for extremely preterm infants are not consistent. European Guidelines report there is weak evidence to support setting the alarms close to the desired target range.[5] Clearly doing so increases the frequency of false alarms and the potential for alarm fatigue.[3,6]

The most recent guidelines from the American Academy of Pediatrics, in contrast, suggest looser low alarms are more appropriate.[7] They further suggest that SpO_2 alarm limits and target range should not only be decoupled, but also take into account the infant's maturity. Neither guideline integrates the possible impact of differences in averaging period, alarm delay or differences in devices.

In the last two decades studies have focused on the intended SpO_2 target ranges for the extremely premature with a resulting evolution of the standard of practice.[1,8] The most recent very large studies suggest a higher, narrower target range might be preferred for extremely preterm infants.[5,9] This perspective is, however, far from a consensus.[8,10-13] Evaluations of the optimal SpO_2 exposure for more mature infants are lacking. The risks

1Department of Biomedical Technology, Faculty of Biomedical Engineering, Czech Technical University in Prague, Kladno, Czech Republic. 2Lake Arrowhead, USA. 3Fetal and Neonatal Institute, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA. 4Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA. Received: 12 December 2019 Accepted: 23 June 2020.

associated with hypoxemia in near term infants are appreciated; however concerns about hyperoxemia have until recently been limited, at least compared to the extremely preterm.

We have developed an extensive SpO_2-PaO_2 database from our NICU and previously reported on the magnitude of the change of risk of severe hypoxemia and hyperoxemia across different SpO_2 ranges.[14] The aim of this analysis was to see if specific SpO_2 levels for selection of high and low alarms and target ranges could be identified based on the difference in the risk of hypoxemia and hyperoxemia and further to determine to what degree these thresholds might change depending on infant maturity.

Methods

This is a prospectively defined analysis with the aim of describing arterial oxygenation levels (PaO_2) associated with various possible SpO_2 alarm limits and target ranges. The study is based on the paradigm that high and low SpO_2 alarm limits should consider the risk of hypoxemia and hyperoxemia independent of the desired SpO_2 target range and further consider infant maturity.[7]

This study reflects infants in the Neonatal and Infant Critical Care Unit (NICCU) of Children's Hospital Los Angeles. It is a tertiary care referral center affiliated with the Keck School of Medicine of the University of Southern California. The 58-bed NICCU receives transfers from the greater Southern California area. The bioethics review organization at Children's Hospital Los Angeles (CHLA-17-00236) has waived the need for informed consent for aggregate data analysis studies and specifically approved this project.

In a previous publication we described the development of a SpO_2-PaO_2 database of infants receiving mechanical ventilator support with supplemental oxygen between August 2012 and July 2015.[14] The database links arterial blood gas measurements in laboratory records with simultaneous SpO_2 data from the patient monitor system. The SpO_2 level is the mean of four 30-s readings coincident with the arterial sample. The gestational age from medical records for each infant, along with the date of measurement permitted calculation of post-menstrual age for each sample. The oximeter in the patient monitoring system used Masimo SET technology (Masimo Corporation Irvine, California), with 10 s averaging. Continuous monitoring of SpO_2 is by practice post-ductal, pre-ductal assessments are conducted with another oximeter. Arterial samples were collected when clinically indicated. Umbilical catheters are used in most infants in their first week of life. As a matter of practice after that right radial lines are preferred, but when not possible left radial or posterior tibial lines are placed.

These study parameters were prospectively defined. Normoxemia was defined as PaO_2 between 50 and 80 mmHg. Other oxemic levels were defined as severe hypoxemia (PaO_2 ≤ 40 mmHg) and severe hyperoxemia (PaO_2 ≥ 100 mmHg), We also evaluated levels below and above normoxemia (PaO_2 < 50, > 80 mmHg). The selection of the severe thresholds was consistent with our previous publication. Also a consensus of the investigators, the potential ranges of SpO_2 alarm limits were 85-89% and 95-98% and SpO_2 target ranges within the envelop of 88-95%. The endpoints were the chance of normoxemia, and the risk of the 4 oxemic levels. Based on our previous work, we hypothesized that infant maturity would significantly impact the chance of normoxemia and risk of severe hyperoxemia and but not of severe hypoxemia. We used post-menstrual age (PMA) as the metric of maturity. PMA values were categorized into three groups. These were < 33 weeks, 33-36 weeks and >36 weeks PMA. We felt that categories would be of more use clinically than a continuous effect. On a post hoc basis we also explored the impact of postnatal age.

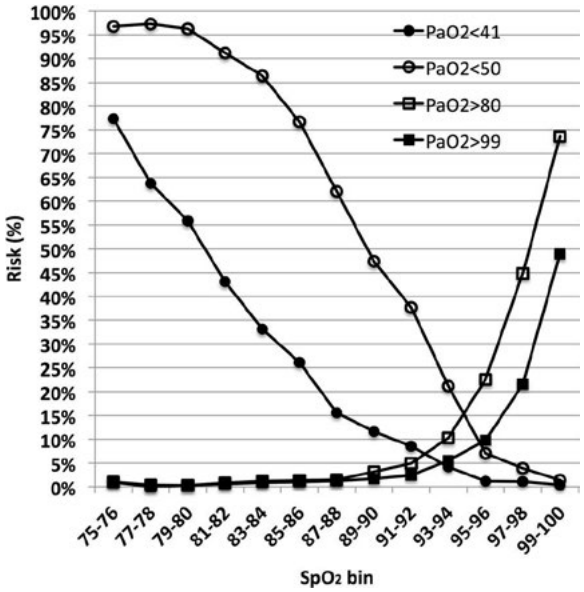

Fig. 1 Risk of Hypoxemia and Hyperoxemia at different levels of SpO_2. Circles represent hypoxemia (solid PaO_2 < 41 mmHg, open < 50 mmHg). Squares represent hyperoxemia (solid PaO_2 > 99 mmHg, open > 80 mmHg)

Our primary measure was the risk or chance of each of these oxemic categories within the relevant SpO_2 range. For the power analysis we assumed a baseline of relevant risk or chance of 25%, and considered sample sizes of PaO_2 values for both 150 and 300 in an adjacent SpO_2 bins. The range of 150-300 was selected as this was consistent with the numbers of observations in the smaller maturity categories at the SpO_2 extremes. Based on this, we determined that there would be an 80% chance, at the $p < 0.05$ level, that we could detect a reduction to 12% with 150 observations and to 15% with 300 observations.

We treated each SpO_2-PaO_2 pair as an independent observation. We deemed consideration of within patient effects as not only impractical because of the large number of patients, but also inappropriate because of intrapatient sample variability of temperature, pH, $PaCO_2$ and transfusion timing. Descriptive presentations of continuous data are shown as median and IQR, and of proportions as percent. The primary variables are presented as percentage along with their 95% confidence intervals of the proportion. Comparison of continuous variables used the Kruskal-Wallis test with Dunn's procedure for pairwise comparisons. Comparisons of proportions were evaluated using the chi-square test, with Maracuilo's procedure for pairwise comparisons. The impact of maturity on each of the three oxemic category parameters was tested by including maturity-category with SpO_2, as independent variables, in a logistic regression equation with oxemic risk or chance as the dependent variable. For the exploratory analysis of the effect of postnatal age, we added age to this logistic regression model. A two-tailed $p < 0.05$ was considered statistically significant for

Table 1 Description of Maturity Category Cohorts

Maturity category	< 33 PMA	33–36 PMA	> 36 PMA	*p*
Subjects (n)	155	192	1031	na
Observations (n)	2603	2501	21,058	na
0bservations/subject (n)	12 (4–22)	9 (4–17)	11 (4–29)	< 0.01
GA (weeks)	26 (24–28)	34 (33–35)	38 (37–39)	< 0.001
PMA (weeks)	28 (26–31)	35 (34–36)	40 (39–43)	< 0.001
Postnatal age (weeks)	2.1 (1.0–3.7)	1.1 (0.4–2.3)	2.0 (1.0–6.3)	< 0.001
FiO_2 (%)	45 (30–70)	50 (35–83)	45 (35–70)	< 0.001
SpO_2 (%)	93 (86–97)	96 (91–100)	97 (87–100)	< 0.001
PaO_2 (mmHg)	55 (45–71)	69 (50–100)	75 (47–112)	< 0.001
$PaO_2 \leq 40$ (%)	15%	12%	15%	< 0.001*
PaO_2 50–80 (%)	43%	33%	24%	< 0.001*
$PaO_2 \geq 100$ (%)	10%	25%	32%	< 0.001*
PaO_2/FiO_2	130 (81–192)	161 (90–240)	167 (93–263)	< 0.001
$PaCO_2$ (mmHg)	45 (39–52)	45 (39–53)	45 (40–52)	ns
pH	7.34 (7.28–7.40)	7.36 (7.30–7.41)	7.39 (7.34–7.43)	< 0.001

Statistical comparisons (Kruskal-Wallis and chi-square* as appropriate) among the 3 maturity categories are shown in Table

all comparisons. Statistical tests were conducted with XLSTAT v19.02 (Addinsoft, Paris, France).

Results

Our data included 26,162 SpO_2-PaO_2 observations of infants receiving supplemental oxygen and respiratory support over a 3-year period. Figure 1 provides a graphic overview of the risk of hypoxemia and hyperoxemia across SpO_2 levels between 75 and 100%. The risk of each rises dramatically as SpO_2 moves from a nominal target range. Even when moving within the latter the trade off between hypoxemia and hyperoxemia is obvious. It is also of note that the difference in risk of severe hypoxemia and a PaO_2 < 50 mmHg, is much larger than the difference between severe hyperoxemia and a PaO_2 > 80 mmHg.

For analysis these observations were divided into three groups according to post-menstrual age (PMA). Details characterizing the 3 groups are shown in Table 1. There were 2603 observations from 155 infants less than 33 weeks PMA, 2501 observations from 192 infants between 33 and 36 weeks PMA and 21,058 observations from 1031 infants greater than 36 weeks PMA. The number of observations per infant was similar among the three groups. The gestational age and postmenstrual age were consistent with the 3 maturity categories. The median SpO_2 and PaO_2 levels were lower in the group less than 33 weeks PMA. This group also included a higher share of measurements in normoxemia and less in severe hyperoxemia.

The chance of normoxemia was dependent on SpO_2 ($p < 0.001$) but not PMA. The chance of normoxemia across the range of 88-95% SpO_2 was 65% (64-67 95% CI). The actual chance of normoxemia for 4 different overlapping SpO_2 target ranges are shown in Table 2, and were different, specifically slightly lower in the lower ranges ($p < 0.001$). The PaO_2 levels for each are also shown in the table and the differences between them are statistically significant ($p < 0.001$). Higher target ranges increase the possibility of higher levels of PaO_2, but decrease the possibility of lower levels. The variation (interquartile range) of PaO_2 levels among the 4 is similar.

The risk of hypoxemia (PaO_2 < 50 and < 41 mmHg) was independent of PMA but not SpO_2 ($p < 0.001$). The risks at different potential alarm levels are shown in Table 3. The risks are not different at settings of 89, 88, and 87% SpO_2 for either PaO_2 < 50 mmHg or < 41 mmHg. They were both markedly higher at 86 and 85% SpO_2. ($p < 0.01$) At these levels the risk of severe hypoxemia (< 41 mmHg) was marked; at 86% SpO_2 (risk: 20% (16-24, 95% CI)) and at 85% SpO_2 (risk: 25% (21-29, 95% CI)). The changes in risks are consistent with the changes in the PaO_2 also shown in the table. The variation (interquartile range) of PaO_2 levels is similar.

The risk of hyperoxemia (PaO_2 > 80 and > 99 mmHg) was significantly different among the 3 PMA categories ($p < 0.001$) and within each category among the SpO_2 levels ($p < 0.001$). The actual risks at different potential alarm levels are shown in Table 4 for each maturity category. The potential point of marked increase in the risk of a PaO_2 > 80 and > 99 mmHg were different for the three maturity categories. With regard to severe hyperoxemia, for those < 33 weeks it was a reading of 98% SpO_2 (risk: 25% (18-33, 95% CI)), which was significantly higher than at 95 and 96% SpO_2 ($p < 0.05$). It was a SpO_2 reading of 97%

Table 2 Chance of Normoxemia at Potential SpO_2 Target Ranges

Target Range	88–92 SpO_2	89–93 SpO_2	90–94 SpO_2	91–95 SpO_2	*p*
n	2357	2946	3716	4584	
Chance 50–80 (%)	59% (57–61%)	63% (61–65%)	67% (65–68%)	68% (67–70%)	< 0.001
PaO_2 (mmHg)	53 (47–61)	55 (48–64)	58 (51–68)	62 (53–73)	< 0.001

Normoxemia defined as PaO_2 of 50–80 mmHg. Chance shown as a percentage (95% CI of proportion), differences evaluated with chi-square test. PaO_2 levels show as median (IQR) differences evaluated with Kruskal-Wallis test

Table 3 Risk of Hypoxemia at Potential Low SpO_2 Alarm Limits

	89% SpO_2	88% SpO_2	87% SpO_2	86% SpO_2	85% SpO_2	*p*
n	279	251	331	389	444	
Risk < 50 (%)	46% (40–50%)	49% (40–55%)	50% (45–56%)	74% (70–78%)	71% (66–75%)	< 0.001
Risk < 41 (%)	13% (9–17%)	10% (06–14%)	11% (8–15%)	20% (16–24%)	25% (21–29%)	< 0.001
PaO_2 (mmHg)	51 (44–57)	50 (44–54)	49 (44–55)	46 (42–50)	46 (40–50)	< 0.001

Severe hypoxemia defined as PaO_2 of < 41 mmHg. Risks shown as a percentage (95% CI of proportion), differences evaluated with chi-square test. PaO_2 among all levels presented as median (IQR), with differences in evaluated with Kruskal-Wallis test

for those 33-36 weeks (risk: 20% (14-25%, 95% CI)), which was not significantly higher than 95 and 96%. A reading of 96% for those > 36 weeks (20% risk: (17-22, 95% CI)), and the difference between all pairs was statistically significant ($p < 0.001$). A point of demarcation for the risks of $PaO_2 > 80$ mmHg is 1 SpO2 level lower for each of the 3 PMA categories. The changes in risks are consistent with the changes in the PaO_2 levels also shown in the table. The variation (interquartile range) of PaO_2 levels is similar except at 98% SpO_2, which is wider.

Our exploratory analysis determined that postnatal age was an independent predictor of chance of normoxemia ($p < 0.001$) and risk of severe hyperoxemia ($p < 0.001$), but not severe hypoxemia. With increasing age the chance of normoxemia increased while the risk of hyperoxemia decreased. However the size of the effect predicted by the regression equation was quite small; that is changes of +0.7% (normoxemia) and –0.6% (severe hyperoxemia) for each week of age.

Discussion

We evaluated a large database of neonatal SpO_2-PaO_2 observations paired with infant postmenstrual age. Our aim was to provide additional guidance to support the selection of SpO_2 alarm levels and target ranges for neonates receiving supplemental oxygen. We identified a SpO_2 range consistent with normoxemia, and showed how a target range could shift depending on a preference for avoiding higher or lower levels of PaO_2. We showed that the risk of hyperoxemia and hypoxemia increases exponentially as SpO_2 moves toward extremes. We found that the risk of severe hypoxemia does not become marked until a level well below common low alarm settings. Finally we found that the risk of severe hyperoxemia becomes marked at different levels depending on postmenstrual age and importantly at thresholds not consistent with standard practices. This report is, to our knowledge, the first to document these perspectives. We evaluated four overlapping target ranges, each 4 wide with mid points of 90, 91, 92, and 93% SpO_2. Our data showed that there was a similar chance of normoxemia across these potential target ranges, but slightly favoring the higher target ranges. This consistency also suggests that a wider target range, even 88-95% SpO_2, would maintain a similar chance of normoxemia, but could be easier to maintain. A wider range at the low end has been suggested for extremely preterm infants,[10,11] in contrast to the European guidelines that recommend a higher target range.[5] Two recent reports of practices in Europe and the US reported that most target ranges were within this wider envelop, though more often narrower than seven but rarely 4 or less.[1,8]

Our analysis did not identify an effect related to maturity associated with normoxemia as we had expected. However our hypothesis was based on risk data of extreme PaO_2 levels (< 41 and > 99 mmHg) at SpO_2 levels between 90 and 95%, which is different from our normoxemia criteria (PaO_2 50-80 mmHg).

Table 4 Risk of Hyperoxemia at potential High SpO_2 Alarm Limits by Maturity Category

	95% SpO_2	96% SpO_2	97% SpO_2	98% SpO_2	*p*
PMA < 33					
n	175	154	150	126	
Risk > 80 (%)	18% (12–23%)	12% (7–18%)	37% (30–45%)	45% (34–54%)	< 0.001
Risk > 99 (%)	7% (3–11%)	4% (1–7%)	14% (8–20%)	25% (18–33%)	< 0.001
PaO_2	63 (54–73)	62 (54–73)	71 (60–88)	80 (63–100)	< 0.001
PMA 33–36					
n	156	172	190	225	
Risk > 80 (%)	28% (0.21–0.35)	26% (19–32%)	0.43 (36–50%)	0.61 (54–67%)	< 0.001
Risk > 99 (%)	10% (6–15%)	13% (8–18%)	20% (14–25%)	34% (28–40%)	< 0.001
PaO_2	68 (61–81)	70 (62–81)	79 (67–92)	86 (73–108)	< 0.001
PMA > 36					
n	959	1156	1483	1729	
Risk > 80 (%)	28% (25–31%)	42% (39–45%)	56% (53–58%)	70% (68–72%)	< 0.001
Risk > 99 (%)	14% (10–14%)	20% (17–22%)	28% (26–30%)	42% (41–45%)	< 0.001
PaO_2	70 (61–83)	76 (65–93)	84 (70–103)	94 (78–124)	< 0.001

Severe hyperoxemia defined as > 99 mmHg. Differences in risk evaluated with chi-square test. PaO_2 presented as median (IQR) with differences evaluated with Kruskal-Wallis test. PaO_2 pairs within each maturity category are also statistically different ($p < 0.001$) except the difference between 95 and 96% SpO_2 in both the < 33 weeks and 33–36 weeks groups

Further the information about likely PaO_2 values, consideration of which might align with maturity, ought to be useful in selecting a target range within these boundaries.[11] A clinical aversion to higher or lower PaO_2 levels is reasonable. The consideration of a trade off of high and low oxygen exposure is supported by a landmark evaluation comparing the long term outcomes of nearly 5000 extremely preterm infants randomized to one of two SpO_2 target ranges (85-89% or 91-95%).[9] It found the high range was associated with increases in severe retinopathy of prematurity and more likely need for supplemental oxygen at 36 weeks PMA, but lower levels of necrotizing enterocolitis and death.

Alarm fatigue in the NICU is a serious problem. Pulse oximetry, while an essential tool, generates the most false alarms and is the alarm least likely to be associated with an actionable nursing intervention.[2,3,15] It is not uncommon with unstable infants to experience a SpO_2 alarm every few minutes, while an intervention is often only warranted every 5-10 min. Faced with this dilemma nurses have been shown to disregard alarm policy.[1] Attention to selection of reasonable alarm settings (delay, and level) as well as sensor/probe integrity, can impact the frequency of alarms not needing intervention.[16,17] However setting alarms, whether by policy or practice, to avoid excessive frequency must also consider the risk of missing or delaying response to important events. Policy and practice must balance the need to find an acceptable medium to balance the risks associated with each. Our data provide SpO_2 thresholds that are associated with marked hyperoxemia and hypoxemia. It is reasonable to consider a buffer zone between the alarm setting and the level of SpO_2 concern. In addition, many events are short and it is standard practice to set the alarm delay to avoid these transient events not needing intervention. Correspondingly it seems appropriate to set a longer alarm delay when the buffer zone is wider.

Our data indicate that the risk of hypoxemia is not related to maturity and is not marked until the SpO_2 is at 86% or 85%, at which point the risk is increasing exponentially. In contrast we found no relevant difference in risk at levels between 87 and 89%. Setting the low alarm between 87 and 89% SpO_2 would create a buffer but at the expense of increased false alarms and alarm fatigue, without a compensating longer alarm delay. A recent analysis has determined that episodes that are significantly lower (< 80% SpO_2) and prolonged (> 60 s) are related to bad outcomes.[18] However, we speculate that episodes of SpO_2 with a nadir between 87 and 89% even if prolonged, would not have a clinical impact, because of the low risk of severe hypoxemia. Finally, based on an audit of extremely preterm infants in 83 NICUs, Hagadorn et al. reported good compliance with low SpO_2 alarm unit guidelines, but provided no related details on the actual settings.[1]

In preterm infants we found the risk of hyperoxemia did not become marked until SpO_2 reached 97-98% in those < 33 weeks PMA and those 33-36 weeks PMA. This is higher than the most recent recommendations for setting the high SpO_2 alarm around 95% in extremely preterm infants.[5,7,10] Such a lower setting could be appropriate with two difference rationales. It could be considered an appropriate buffer zone. But it certainly would increase false positive alarms, without a compensating longer alarm delay. It might also be appropriate if the goal was to avoid PaO_2 levels approaching 80 mmHg, in alignment with a lower target range. Consistent with this likely excessive false positive rate from tighter high alarms, Hagadorn reported only 63% compliance with high SpO_2 alarm unit guidelines.[1]

In contrast to preterm infants, we found that the risk of hyperoxemia, PaO_2 > 80 and > 99 mmHg, in infants > 36 weeks PMA was marked at a SpO_2 of 96%. While reports of guidelines are sparse,[19,20] it is our impression that upper alarms for near term populations are often set much higher than 96%. This practice provides no buffer zone and certainly increases false negatives that could increase clinical risk of hyperoxemia. The concern about the risks associated with hyperoxemia in near term infants is less prevalent than in preterms. Nevertheless, hyperoxemia in children and adults has been associated with morbidity and mortality,[21,22] and it is reasonable to project these risks to near term infants.

The shift of the oxy-hemoglobin dissociation curve with increasing maturity that one would anticipate, was evident in high levels of SpO_2 but not at moderate and low levels. While the predicted shift in the SaO_2-PaO_2 relationship is characterized in a shift of P50, it is understandable that the smaller predicted shifts in SpO_2 at lower levels would be muted. The lack of precision and bias of the pulse oximeter, especially in these ranges, as well as other factors such as local perfusion are documented.[23] The transition from fetal to adult hemoglobin is quite predicable over a couple months of life in healthy neonates, but we did not identify a meaningful impact associated with postnatal age. However the transition from fetal hemoglobin is affected by treatment and disease severity. Transfusions have a marked effect.[24-26] Our study population, all transferred for a higher level of care, commonly were transfused. Accordingly, transfusion naive infants would be shifted more to the left.[14] Such a shift would reduce the risk of hyperoxemia.

This study's design has several limitations. First the PaO_2 thresholds we used for hypoxemia, normoxemia and hyperoxemia, while generally accepted, have not been validated with regard to outcome risk. It is unlikely they ever will be. There is a need for and a growing body of data correlating SpO_2 exposure and outcomes. Of particular interest is a pending analysis of the impact of the actual, rather than assigned, SpO_2 exposure in the NeOProM population.[9] We speculate that these interpretations will be easier with a better understanding of the relationship between PaO_2 and SpO_2. Other factors such as small for gestational age and hemoglobin level as well as cerebral and intestinal oxygenation are also relevant. Second, the study is observational. The location of the SpO_2 sensor and site of arterial sampling were not controlled. It is likely that some of the paired comparisons do not reflect pre-ductal assessment. This could increase the variance, but we do not think this would have a relevant effect on the bias of the risk (median values). Third, we categorized the hyperoxemic risk into three PMA groups. These are reasonable groupings, but it is probable that the effect is somewhat continuous with increasing maturity, but certainly not strictly categorical.

Whether using these results to design research or to evaluate unit guidelines, several generalizability issues should be considered. The first is comparabilty to our study population. Our unit is referral based, with all infants transferred in for tertiary care. After intervention and recovery infants are often returned when they only need low levels of inspired oxygen and minimal pressure support. As reported their supplemental oxygen requirements are quite high. Also previously noted, as

a result of transfusions, their oxy-hemoglobin relationship is shifted to right. Illustrative of this, in our least mature cohort we identified an incidence of severe hyperoxemia more than 10 times higher than that reported in a more traditional inborn population during the first week of life.[27] Another important consideration is the averaging and alarm delay settings on the oximeter. One large study confirmed the clinical relevance of these settings.[28] They documented a marked decrease in the incidence of severe hypoxemic events with increasing averaging time, and also demonstrated that it was associated with increased duration of episodes. They recommended using shorter averaging times and longer delays. Finally the oximeter measurement itself must be considered. Our data reflect a good bit of scatter in the PaO_2 at each SpO_2 level. Sources of the scatter seen with SpO_2 monitoring are well described.[13,29] Consideration of differences in oximeter brands, and models should be considered as well. Our group previously reported no difference in bias between the Massimo and Nellcor devices across the range of saturations in the PICU, but did identify a problem with the use of inappropriate sensors.[23] Of more potential relevance, a difference between the Massimo and Nellcor oximeters has been reported in the SpO_2 range of 87-90%.[30] While this difference is within the device's 3% accuracy specifications, it might well effect a decision about selecting a lower target range, or the low SpO_2 alarm setting.

Conclusion

We provide quantification of the rate at which the risk of hyperoxemia and hypoxemia increase exponentially as SpO_2 moves towards extremes, and how it is affected by maturity. Postmenstrual age influences the threshold at which the risk of hyperoxemia became pronounced, but PMA did not alter the threshold for hypoxemia or normoxemia. The thresholds at which a marked change in the risk of hyperoxemia and hypoxemia occur can be used to guide the setting of alarm thresholds. These findings support reconsideration of common alarm treshold practices. In extreme preterm infants, but not in more mature infants, high SpO_2 alarms may be set higher than 96%. Likewise low SpO_2 alarms may be set lower than 89%. SpO_2 targeting ranges may be selected within the range of 88-95% SpO_2. Optimal management of neonatal oxygen saturation must take into account concerns of alarm fatigue, staffing levels, and FiO_2 titration practices. Integration of these factors should be evaluated in quality improvement programs.

Abbreviations

FiO_2: Fraction of inspired oxygen; SpO_2: Arterial oxygen saturation measured noninvasively; NICU: Neonatal intensive care unit; PaO_2: Arterial partial pressure of oxygen (mmHg); $PaCO_2$: Arterial partial pressure of carbon dioxide (mmHg); PMA: Post-menstrual age (weeks)

Authors' contributions

TB was responsible for the conception of the study, the data analysis and initial draft of the manuscript. CN and NI collected the data. The authors (TB, NI, CN, PR, RK) critically reviewed and approved the manuscript and agree to be accountable for all aspects of the project.

Availability of data and materials

The data sets generated and analyzed during this study are not currently publically available, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The bioethics review organization at Children's Hospital Los Angeles (CHLA-17-00236) has waived the need for informed consent for aggregate data analysis studies and specifically approved this project.

References

1. Hagadorn JJ, Sink DW, Buus-Frank ME, et al. Alarm safety and oxygen saturation targets in the Vermont Oxford network iNICQ 2015 collaborative. J Perinatol. 2017;37:270-6.
2. Bitan Y, Meyer J, Shinar D, Zmora E. Nurses' reactions to alarms in a neonatal intensive care unit. Cogn Tech Work. 2004;6:239-46.
3. Ketko A, Martin C, Nemshak M, et al. Balancing the tension between hyperoxia prevention and alarm fatigue in the NICU. Pediatrics. 2015;136(2): 496-504.
4. Johnson KR, Hagadorn JJ, Sink DW. Alarm safety and alarm fatigue. Clin Perinatol. 2017;44:713-28.
5. Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants- 2019 update. Neonatology. 2019;114(2):432-50.
6. Lansdowne K, Strauss DG, Scully CG. Retrospective analysis of pulse oximeter alarm settings in an intensive care unit patient population. BMC Nurs. 2016;15:36.
7. Cummings JJ, Polin RA. Committee on fetus and newborn. Oxygen targeting in extremely low birth weight infants. Pediatrics. 2016;138(2): e20161576.8.
8. Huizing MJ, Villamor E, Vento M, Villamor E. Pulse oximetry saturation target for preterm infants: a survey among European neonatal intensive care units. Eur J Pediatr. 2017;176(1):51-6.
9. Askie LM, Darlow BA, Finer N, et al. Association between oxygen saturation targeting and death or disability in extremely preterm infants in the neonatal oxygenation prospective meta-analysis collaboration. JAMA. 2018; 319(21):2190-201.
10. Sola A, Golombek S, Montes-Bueno MT, et al. Safe oxygen saturation targeting and monitoring in preterm infants: can we avoid hypoxia and hyperoxia? Acta Paediatr. 2014;103:1009-18.
11. Cayabyab R, Arora V, Wertheimer F, et al. Graded oxygen saturation targets and retinopathy of prematurity in extremely preterm infants. Pediatr Res. 2016;80(3):401-6.
12. Raffay TM, Walsh MC. Pulse oximetry targets in extremely premature infants and associated mortality: one-size may not fit all. J Nat Sci. 2018;4(6):e508.
13. Cummings JJ, Lakshminrusimha S. Oxygen saturation targeting by pulse oximetry in the extremely low gestational age neonate: a quixotic quest. Curr Opin Pediatr. 2017;29(2):153-8.
14. Bachman TE, Newth CJL, Iyer NP, et al. Hypoxemia and hyperoxemic likelihood in pulse oximetery ranges: NICU observational study. Arch Dis Child Fetal Neonatal Ed. 2019;104(3):F244-79.
15. Bonafide CP, Localio AR, Holmes, et al. Video Analysis of Factors Associated With Response Time to Physiologic Monitor Alarms in a Children's Hospital. JAMA Pediatr. 2017;171(6):524-31.
16. Warakomska M, Bachman TE, Wilinska M. Evaluation of two SpO2 alarm strategies during automated FiO2 control in the NICU: a randomized crossover study. BMC Pediatr. 2019;19(1):142.
17. Johnson KR, Hagadorn JJ, Sink DW. Reducing alarm fatigue

in two neonatal intensive care units through a quality improvement collaboration. Am J Perinatol. 2018;35(13):1311-8.
18. Poets CF, Roberts RS, Schmidt B, et al. Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. JAMA. 2015;314:595-603.
19. Austin N. Practical recommendations for oxygen saturation targets for newborns cared for in neonatal units. New Zealand: Newborn Clinical Network Clinical Reference Group; 2017.
20. Pilgrim S. Monitoring of oxygen saturation levels in the newborn in midwifery setting. Clinical Guidelines. 2018;NHS 04220.
21. Numa A, Aneja H, Awad J, et al. Admission hyperoxia is a risk factor for mortality in pediatric intensive care. Pediatr Crit Care Med. 2018 Aug;19(8): 699-704.
22. Aggarwal N, Brower R, Hager D, et al. Oxygen exposure resulting in arterial oxygen tensions above the protocol goal was associated with worse clinical outcomes in acute respiratory distress syndrome. Crit Care Med. 2018;46(4): 517-24.
23. Ross PA, Newth CJL, Khemani R. Accuracy of pulse oximetry in children. Pediatrics. 2014;133:22-9.
24. Bard H, Lachance C, Widness JA, Gagnon C. The reactivation of fetal hemoglobin synthesis during anemia of prematurity. Pediatr Res. 1994;36(2): 253-6.
25. De Halleux V, Truttmann A, Gagnon Bard H. The effect of blood transfusion on the hemoglobin oxygen dissociation curve of very early preterm infants during the first week of life. Semin Perinatol. 2002;26(6):411-5.
26. Shiao SY. Effects of fetal hemoglobin on accurate measurements of oxygen saturation in neonates. Perinat Neonatal Nurs. 2005;19(4):348-61.
27. Quine D, Stenson BJ. Arterial oxygen tension (PaO2) values in infants <29 weeks of gestation at currently targeted saturations. Arch Dis Child Fetal Neonatal Ed. 2009;94:F51-3.
28. McClure C, Jang SY, Fairchild K. Alarms, oxygen saturations, and SpO2 averaging time in the NICU. J Neonatal Perinatal Med. 2016;9(4):357-62.
29. Lakshminrusimha S, Manja V, Mathew B, Suresh GK. Oxygen targeting in preterm infants: a physiological interpretation. J Perinatol. 2015;35(1):8-15.
30. Johnson ED, Boyle B, Juszczak E, et al. Oxygen targeting in preterm infants using the Masimo SET radical pulse oximeter. Arch Dis Child Fetal Neonatal Ed. 2011;96:F429-33.

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Probiotics Receive Conditional Recommendation

Babies born preterm—before 37 weeks of gestation—account for approximately 15 million births worldwide each year, according to the World Health Organization. This extremely vulnerable population of infants are at risk for multiple complications, including susceptibility to NEC, a serious disease that causes tissue damage to the intestines resulting from bacteria invading the intestinal walls. The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) working group on probiotics and prebiotics conducted an extensive review of the clinical evidence surrounding probiotic use in the NICU. The working group published guidelines conditionally recommending specific strains of probiotics, including the combination of B.infantis (BB-02), B.lactis (BB-12), and S.thermophilus (TH-4), as it might reduce NEC stage 2 or 3 in preterm infants (low certainty of evidence), provided all safety conditions are met. The safety conditions include use of strains without transferable antibiotic resistance genes, correct strain identity and lack of product contamination that were manufactured in accordance with good manufacturing practices (GMPs). The authors note that only a limited number of strains have shown clinical effectiveness in this patient population. The guidelines also highlight the importance of assessing the safety in overall product manufacturing. This includes understanding a probiotic's potency, stability and purity. Preterm infants are deprived of adequate time in utero for growth of critical organs, including the digestive system where 70% of the immune system resides. In addition to an underdeveloped digestive system, preterm infants can experience imbalances in gut bacteria. The use of probiotics in this population may reduce the incidence of NEC. Currently ~20% of NICUs in the United States use probiotics when treating and caring for preterm infants. "A high-quality probiotic that has been studied in preterm infants would equip clinicians in the NICU with the ability to mitigate some of the risks associated with preterm births, including necrotizing enterocolitis, that can affect these babies," said Dr Karyn Wulf, MD, MPH, Pediatric Medical Director at Abbott. "The ability for medical professionals to provide best-in-class care using nutrition allows them to proactively support a strong start in life."

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