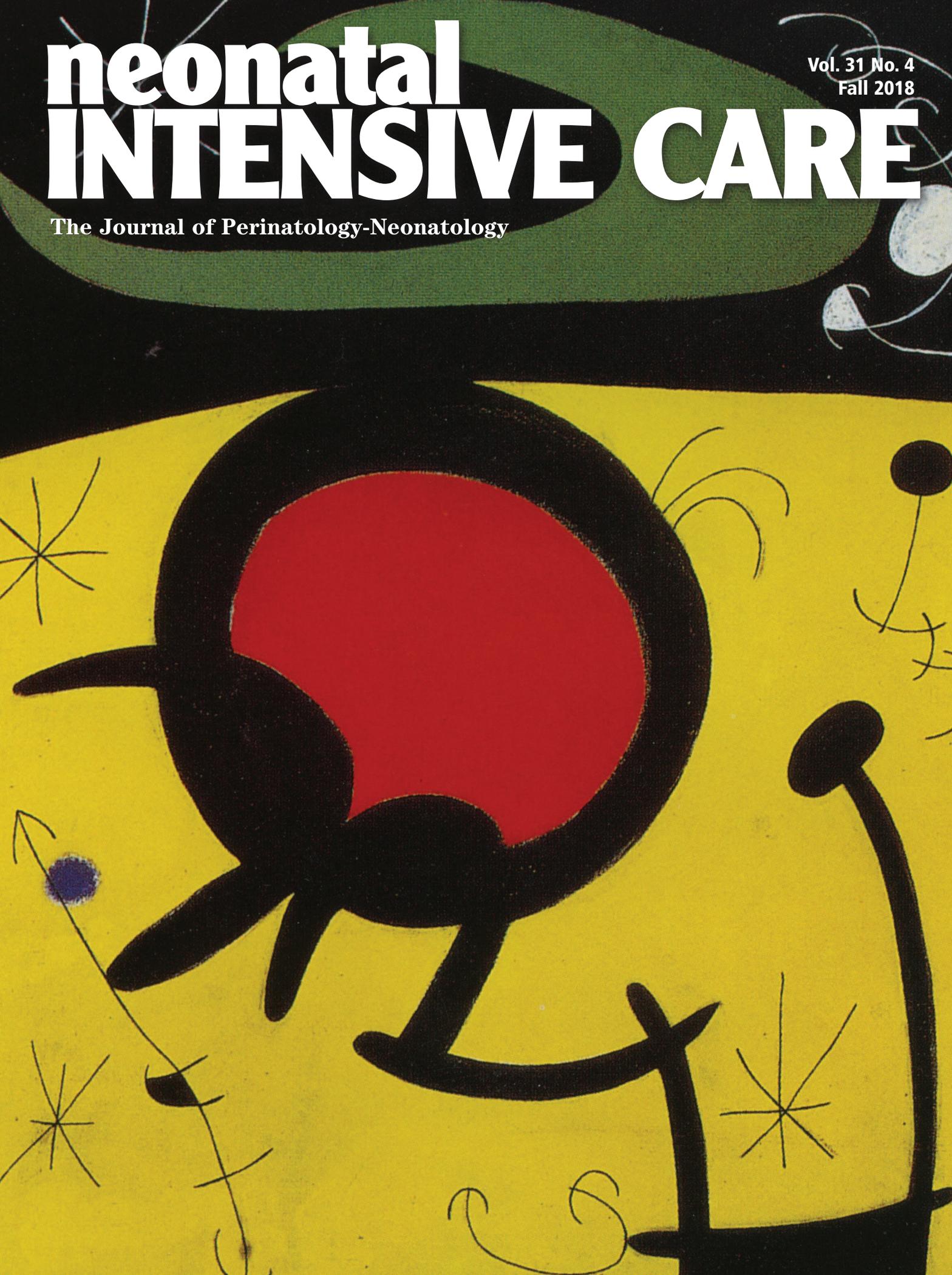


# neonatal INTENSIVE CARE

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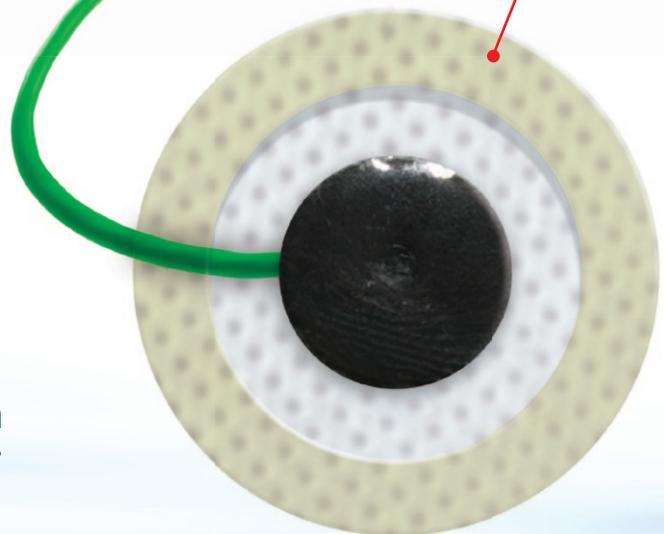


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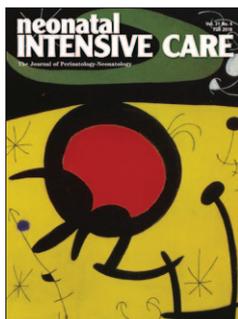


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## Mandatory Newborn Screening for Critical Heart Defects Saves Lives

The need to mandate critical congenital heart disease (CCHD) screening in US newborns was initially questioned, but a new study shows that infant CCHD deaths fell by about a third in states that adopted mandatory screening. Further, overall heart-defect deaths declined in these states by a fifth, while neither outcome was significantly reduced with voluntary policies or as-yet implemented mandates. “This research suggests that every country and every state should have a mandatory screening policy given that the procedure is very affordable and we can expect a substantial impact on infant mortality,” principal investigator Dr Rahi Abouk (William Patterson University, Wayne, NJ) said when interviewed. The study was published in the *Journal of the American Medical Association*. About one in every four US babies born with a congenital heart defect has a CCHD, or a heart defect serious enough to require surgery or other procedures in the first year of life, according to the Centers for Disease Control and Prevention (CDC). CCHD screening, performed with pulse oximetry, was added to the US Recommended Uniform Screening Panel for newborns in 2011, but not without debate over whether a public-health mandate was necessary or whether the test should simply be added to usual newborn care. “I think there were some people who thought this would be helpful but it would be more of an early detection and early implementation of therapy as opposed

to really saving lives,” Dr Stephen Daniels (Children’s Hospital Colorado, University of Colorado School of Medicine, Aurora), who was not involved with the study, said. “What this study shows is that when you don’t have screening in place, cases are missed and the outcome can be bad; screening improves this outcome. And I think that is a very important message.” Using the National Center for Health Statistics period-linked birth/infant death data set from 2007 through 2013, the researchers compared early deaths (age 24 hours to <6 months) due to 12 CCHDs or other/unspecified cardiac causes in eight states with mandatory screening, five states with voluntary screening, and nine states with mandatory screening enacted but not implemented by June 1, 2013. Compared with states without mandatory screening policies, the mean adjusted relative decrease in CCHD deaths with mandatory screening was 33.4%, with an absolute decline of 3.9 deaths per 100,000 births. For other/unspecified cardiac deaths, the relative decrease was 21.4% and absolute decline 3.5 deaths/100,000. In the five states that enacted voluntary screening policies, the absolute decrease in CCHD deaths was 0.6/100,000 and 1.0/100,000 for other cardiac deaths.

## Low-cost, Handheld Device Reliably Detects Neonatal Jaundice

Total serum bilirubin (TSB) levels measured with a battery-powered handheld device reliably detected neonatal jaundice in a small pilot study in Malawi, researchers say. “Jaundice affects more than half of newborns, and clinicians know how to treat it,” according to Dr Rebecca Richards-Kortum of Rice University in Houston, Texas. “The reason babies still die or suffer severe brain damage due to jaundice is because clinicians in places like sub-Saharan Africa do not have the tools to monitor and cure their patients,” she said. “Low-cost treatments are beginning to become available in Africa, but current diagnostics are still far too expensive for most African hospitals. We created a rapid, low-cost, point-of-care bilirubin reader to address this,” she explained. “It’s called BiliSpec, and each test requires 2-3 drops of blood, can be completed in 1-2 minutes, and costs about five cents.” “This, our first clinical study, found that BiliSpec was very close to meeting Clinical Laboratory Improvement Amendments (CLIA) accuracy standards, and we have funding from USAID and others to conduct a larger multisite follow-up study,” she

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said. Dr Richards-Kortum and her colleagues first assessed the device's performance using blood from normal volunteers spiked with differing amounts of bilirubin. The results correlated well with a reference laboratory bilirubinometer, they explain in Proceedings of the National Academy of Sciences USA, online. They then used the device to measure total serum bilirubin in 94 samples obtained by heel-prick from 68 neonates in a hospital in Malawi. The concentrations correlated well ( $r=0.996$ ) with the CLIA reference standard, with concentrations ranging from 1.1 mg/dL to 23.0 mg/dL in the infants' samples. "All samples measured by BiliSpec were within 3.0 mg/dL of the laboratory standard," the authors state.

### Syringe Added to Device Portfolio

NeoMed has announced it has added the 100 mL syringe to its portfolio of characterized syringes for use in the Medfusion v6 3500 Enteral Ready Pump. NeoMed's 100 mL syringe and the Medfusion Enteral Ready Pump are designed to serve as a single solution for the higher volume nutrition delivery needs of NICU and PICU patients. With the addition of the newly characterized 100 mL syringe, NeoMed now offers 65 syringe configurations in sizes ranging from 6 mL to 100 mL for use in the Medfusion Enteral Ready Pump. The 100 mL syringe has significantly lower priming volume compared to giving sets used with bags and may help reduce the number of syringes needed to administer a single large volume feed. Furthermore, the 100 mL features an off-center tip, solid polypropylene plunger, and hands-free tip cap, designed to help maximize nutrition delivery while enhancing aseptic technique. NeoMed has partnered with Smiths Medical to provide an enteral ready pump. Once installed, the NeoMed Enteral Library can be used for both Legacy and NeoConnect

syringes. This enteral pump solution adheres to the Joint Commission's recommendation, which states, "Use distinctly different pumps for IV applications" and "Do not use IV tubing or pumps for enteral feeding." Orange and purple faceplate options are available to color coordinate with NeoMed's Enteral Safety System, offering visual distinction from common parenteral or IV lines. Vice President of Business Development, Marc Waldman, stated, "Optimal nutrition delivery always remains at the forefront of our product design. It is our hope that the 100 mL syringe will replace costly feeding bags that may not deliver maximum macronutrients, micronutrients, and lipids to the patients that need them most." Vice President of Engineering and Product Development, Ben Davis, said, "We are so pleased to now offer the largest enteral syringe that is available for use with Medfusion pumps. Previously, 60 mL was the largest volume that could be administered on a Medfusion pump using a single syringe. Now, a volume of up to 100 mL can be administered with a single syringe on the same pump."

### Drop in Pre-term Births Linked to Plant Closures

The shuttering of eight oil- and coal-fueled electric plants in California was associated with a sizeable decrease in preterm births among women living nearby, researchers say. Their study took advantage of a "natural experiment" when six oil-fueled electricity-generating plants and two coal-powered plants were retired. Using data collected from 2001 to 2011, they found that preterm birth rates among women exposed to the highest amounts of pollution from the plants fell from 7% to 5.1% after the plant closures. Burning oil and coal emits pollution particles, some small enough to penetrate into the lungs and the bloodstream. It also releases sulfur dioxide and nitrogen oxide gasses as well as benzene, lead, mercury and other harmful substances into the air, the study authors note. Many studies have linked air pollution with premature delivery. But it's often difficult to tease apart the influences of pollution, neighborhood, socioeconomic status and race on health conditions, the study team noted. To gauge pregnant women's exposure to pollutants from nearby power plants, the researchers analyzed environmental air monitoring data from two years before through one year after each plant was closed. They also had access to address records for 57,000 births that took place within 20 kilometers (12.4 miles) of the plants. Overall, about 6% of births were preterm. Women living within 5 km (about 3 miles) of a plant showed the biggest drop in preterm births after a plant closure. The improvement was greatest among non-Hispanic Asian and black women and did not differ by maternal education level. The researchers also looked at preterm birth rates around eight power plants that had not closed and found no differences during the same years. The new study "is the opposite of our normal work; instead of studying the problem we could evaluate a solution," lead author Joan Casey, of the University of California, Berkeley School of Public Health, said. Because there were still 380 active coal power plants in the U.S. in 2016, this means there is room for additional closures and potential health benefits, Casey said. "In addition to reducing greenhouse gas emissions, our study shows one potential additional reason to move towards renewables," she added.

### Obesity Links Studied in Pregnant Women

Women with psychiatric illness who become pregnant are more likely to have adverse obstetric outcomes if they are obese, new research suggests. Among women with psychiatric disorders, obesity was associated with a significantly higher risk for major malformations, as well as gestational diabetes, compared to

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control persons of normal weight, Marlene P. Freeman, MD, Massachusetts General Hospital, Boston, told Medscape Medical News. "Women with psychiatric disorders represent an at-risk population for pregnancy. They also have a higher rate of obesity than the general population, and we know that obesity also increases the risk of obstetrical and neonatal complications. But that is a factor that we can potentially address in terms of decreasing risk," she said. The findings were presented here at the American Society of Clinical Psychopharmacology (ASCP) 2018 annual meeting. The investigators prospectively collected data from pregnant women aged 18 to 45 years who were enrolled in the Massachusetts General Hospital National Pregnancy Registry for Psychiatric Medications. The data related to the patients' conditions during the patient's during pregnancy until 6 months post-partum. Of the 584 participants, 252 were of normal weight, 170 were overweight, and 162 were obese. The unadjusted odds ratio of major malformations in infants born to obese vs normal-weight mothers was 3.19 (95% confidence interval [CI], 0.79 - 12.95). Obese and overweight women were at significantly higher risk for gestational diabetes. In obese women, the odds ratio (OR) was 3.81 (95% CI, 1.29 - 7.84; P = .009); in overweight women, the OR was 3.4 (95% CI, 1.49 - 7.76; P = .004). Among obese women, there was a trend for higher rates of hypertension (P = .2) and cesarian delivery (P = .055), compared with normal-weight women. Other outcomes, including preeclampsia, stay in the neonatal intensive care unit, and preterm birth, did not differ significantly between the groups.

of urinary tract infection (UTI) among infant boys with hydronephrosis, researchers in Washington say. Dr John Ellison of Seattle Children's Hospital analyzed outcomes of 5,561 infant boys with hydronephrosis, including 2,386 (43%) who underwent newborn circumcision by four weeks of age and 3,175 (57%) who remained uncircumcised. They also studied 11,120 healthy baby boys, of whom 52% were circumcised by four weeks of age. As reported online June 7 in Pediatrics, the median age at circumcision was 2 days among healthy boys and 9 days among boys with hydronephrosis. Less than one percent of boys with hydronephrosis underwent circumcision at the time of surgery to correct hydronephrosis. Antibiotic prophylaxis was given to 3.7% of boys with hydronephrosis, with similar rates of use among circumcised and uncircumcised infants. By the time they were a year old, UTIs had occurred in 12% of boys with hydronephrosis and 1% of healthy boys. On multivariate analysis, circumcision was associated with a significantly decreased risk of UTI both for boys with hydronephrosis (OR 0.36) and those without (OR 0.32). To prevent one UTI, 10 boys with hydronephrosis would need to undergo circumcision compared with 83 healthy boys.

Among specific hydronephrosis diagnoses, circumcision was associated with a reduced risk of UTI for boys with isolated hydronephrosis (OR 0.35), vesicoureteral reflux (OR 0.35), and ureteropelvic junction obstruction (OR 0.35). Dr Craig Peters, Chief, Pediatric Urology at Children's Health in Dallas and a professor at UT Southwestern, said, "There does seem to be a significant reduction in the risk of UTI with circumcision in those boys. We need to be careful about assuming that all boys with hydronephrosis should be circumcised, however. There is great variation in the severity of hydronephrosis and the causes.

#### Circumcision Associated with Lower Rate of UTI

Circumcision is associated with a significantly lower rate

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The authors were able to separate out some basic diagnoses, but not the severity of the different conditions. The severity is associated with the risk of UTI, so it may be that the benefit of circumcision is limited only to those with the more severe forms of the condition.”

### Genesis of Schizophrenia May Lie in the Placenta

An interaction between gene expression in the placenta and obstetric or neonatal complications may increase schizophrenia risk, new research suggests. Investigators found that the expression of schizophrenia risk genes is particularly enriched in the placenta from male offspring, which may explain the higher incidence of the disease in men. The results underline the importance of the placenta in schizophrenia risk and perhaps in risk for other male-dominated disorders, such as autism and attention-deficit/hyperactivity disorder, Daniel R. Weinberger, MD, director and CEO, Lieber Institute for Brain Development, and professor of neurology, psychiatry, and neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland, said. “It’s clear that the placenta, at a basic molecular level, mediates some genetic risk for developmental behavioral disorders,” Weinberg said. Yet the placenta remains “profoundly neglected. It’s the only organ taken out of a human body that does not routinely get sent to the laboratory for examination but is typically thrown out,” he said. Both genetic and environmental factors affect schizophrenia risk. But researchers have long wondered how these risks are related. “The question is, are they independent risk factors, or are they risk factors that actually exaggerate each other’s effects, which is the principle of the gene-environment interaction?” said Weinberger. To examine the interaction of genomic and environmental risks, the researchers

used a number of large samples. The “discovery” sample included 501 unrelated white US adults (234 with schizophrenia, and 267 healthy persons) who were participants in the Clinical Brain Disorders Branch Sibling Study of Schizophrenia at the National Institute of Mental Health. The study also included more than 2000 unrelated adult individuals in four replication samples from Italy, Germany, and Japan. Two were composed of only patients with schizophrenia, and two were composed of schizophrenia patients and control persons. Researchers calculated the cumulative polygenic risk score (PRS) for each participant. This is a measure of genomic risk, calculated as the weighted sum of risk alleles for schizophrenia from recent genome-wide association studies (GWASs). Initially, they selected relevant genes mapping to the PRS1 loci. According to Weinberger, on the basis of GWAS significant alleles, PRS1 had a significance of  $P < 5 \times 10^{-8}$ . The investigators examined the interaction between PRS and early-life complications (ELCs), which are conditions occurring during pregnancy, labor, delivery, and the neonatal period that are potentially harmful to the offspring.

### Russian Researcher Honored

Professor G. M. Saveleva, from Russian Federation, is the 2018 recipient of Fetal Research Fund award. Saveleva, the matriarch of women’s health in Russia, became the 2018 recipient of the Fetal Research Fund’s distinguished achievement award. Born in 1928, Saveleva is the longest-serving chairwoman in obstetrical history at the Russian National Research Medical University. She became the department head in 1971 and remains in this position until today. Saveleva made significant contributions to the field of obstetrics and gynecology and fetal

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1. Shankaran, Seetha, et al. “Outcomes of Safety & Effectiveness in a Multicenter Randomized, Controlled Trial of Whole-Body Hypothermia for Neonatal Hypoxic- Ischemic Encephalopathy.” *Pediatrics* 122 (2008): 790-799.  
2. Zanelli, S.A., et al. “Implementation of a ‘Hypothermia for HIE’ program: 2-year experience in a single NICU.” *Journal of Perinatology* 28 (2008): 171-175.

medicine. Her major research interests include fetal assessment in pregnancy and labor, fetal physiology, newborn resuscitation, gynecologic laparoscopy and hysteroscopy, among many others. She authored and co-authored 17 books and over 500 peer-reviewed manuscripts. She is one of the pioneers who introduced neonatal head cooling to improve neurologic outcomes in hypoxic neonates, which has become state of the art in the field today.

### Very Obese Women: Lose Weight in Pregnancy for Healthy Baby

Existing guidelines for weight gain and loss during pregnancy require adjustment to optimize outcomes in underweight and very obese women, and their babies, shows a large study from the French island of La Réunion. The authors, led by Pierre-Yves Robillard, MD, from Centre Hospitalier Universitaire Sud Réunion, note that the US Institute of Medicine (IOM) 2009 recommendations are adequate for normal and overweight women, but based on these new findings, are not appropriate for thin and obese women. Specifically, their analysis of over 52,092 full-term births found that a thin woman (with a body mass index [BMI] of 17 kg/m<sup>2</sup>) should gain 21.6 kg (48 lbs) during pregnancy (instead of 12.5–18 kg as recommended), obese woman (with a BMI of 32 kg/m<sup>2</sup>) should gain 3.6 kg (instead of 5–9 kg), and a very obese woman (with a BMI of 40 kg/m<sup>2</sup>) should actually strive to lose 6 kg (13 lbs). Knowing the optimal gestational weight gain among the annual 135 million pregnancies worldwide is considered to be one of the holy grails of healthcare, note the authors in their introduction. This observational study goes some way to tackling the lack of consensus regarding the optimal gestational weight gain for different maternal BMI categories. The results were published in the May issue of *Heliyon*.

“Women want to know what their optimal weight gain should be to have their baby as safely as possible, and their maternity care providers want to know what advice they can give women throughout their pregnancy,” said Robillard in a press release. The observational study had two key aims: firstly, to determine the maternal BMI range associated with a balanced risk of giving birth to a smaller or larger baby (10% small for gestational age [SGA] newborns, 10% large for gestational age [LGA]); and secondly, to investigate the interaction between maternal pre-pregnancy BMI, gestational weight gain, and neonatal birthweight

centiles. Data were drawn from 16.5 years (2001–2017) of live-birth records at the university’s maternity unit. All consecutive singleton live births (37 weeks plus) were included.

### Naps During Pregnancy May Be Linked With Healthier Birth Weight

Pregnant women who nap regularly may reduce their baby’s risk of low birth weight, a study from China suggests. “Low birth weight is one of the feared outcomes of pregnancy, and novel insight into risk factors is welcome,” said Dr Ghada Bourjeily, a sleep researcher at Brown University’s Warren Alpert Medical School in Providence, Rhode Island, who wasn’t involved in the study. “Sleep, its quality, and duration are emerging as risk factors for various perinatal complications,” Bourjeily said in an email. Low birth weight (i.e., less than 5.5 pounds or 2500 grams) is associated with adverse health outcomes in childhood and adulthood, including respiratory illnesses, diabetes and hypertension. In the U.S., about 8% of babies are born at low birth weights, according to the Centers for Disease Control and Prevention. Lulu Song of the Huazhong University of Science and Technology in Wuhan and colleagues analyzed information from more than 10,000 women who were participating in the 2012-2014 Healthy Baby Cohort study in China. The group included 442 women who had low birth weight babies, the authors reported. Compared to mothers who reported no napping, women who took naps of roughly an hour to an hour and a half were about 29% less likely to have a baby with low birth weight. The frequency of napping also seemed to play a role: women who napped on five to seven days per week were 22% less likely to have a baby with low birth weight. The study can’t prove that pregnant mothers’ nap habits affect babies’ birth weight.

### Reject of Hyperbilirubinemia Drug for Newborns: FDA

Federal advisers dealt a setback to the developers of the experimental medicine stansporfin for newborns who cannot quickly clear bilirubin and thus risk developing jaundice, by a 21-3 vote recommending rejection of manufacturer Mallinckrodt’s application for approval of the drug. The US Food and Drug Administration (FDA) posed a pivotal three-part question on stansporfin at a joint meeting of the Gastrointestinal Drugs Advisory Committee and the Pediatric Advisory Committee. Twenty-one panelists voted no to the first part,

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saying that the overall risk-benefit profile of stannosporfin does not support its approval. Another three panelist voted in support of approval if a Risk Evaluation and Mitigation Strategy (REMS) were in place. None of the panelists voted in support of a third option, which backed approval of the drug without a REMS. Stannosporfin is a tin metalloporphyrin that's meant to reduce the production of bilirubin in infants at risk for severe neonatal hyperbilirubinemia. That approach sets it apart from the phototherapy that's now used to treat excess bilirubin in the bloodstream and skin of infants, the company said. It also could replace the current practice of exchange transfusions of blood or plasma to treat the condition, according to the FDA. Neonatal jaundice is considered a common condition for newborns, with yellowing of the skin and the whites of the eyes seen in the first few days after birth. It does not require treatment in most cases, but untreated hyperbilirubinemia can lead to significant morbidity and premature mortality, Mallinckrodt said. The application for stannosporfin rested predominantly on results from what the company identified as the pivotal trial, known as Study 204. This randomized phase 2B study had an initial enrollment of 91 babies who were given the drug at either a single 3.0 mg/kg or a 4.5 mg/kg intramuscular injection, compared with a placebo arm. The babies in this test also received phototherapy. Panelists and FDA staff were clearly uncomfortable with the bid for approval of the drug without data from a third and final stage of testing usually done before seeking US approval of medicines.

### **Gestational Diabetes Tied to Hypoglycemia**

Babies born to mothers with gestational diabetes are at high risk of hypoglycemia and should be screened for the condition within the first 12 hours of life, researchers say. "Some guidelines recommend screening all neonates born after a pregnancy complicated by gestational diabetes mellitus, while others recommend screening only those with abnormal birth weight or insulin-treated gestational diabetes mellitus," said Dr Leon de Wit from University Medical Center at Utrecht University in the Netherlands. "In this study, we show that low-risk neonates are as equally prone to hypoglycemia as high-risk neonates," he said. Dr de Wit and colleagues studied 506 term neonates born to mothers with gestational diabetes from 2013 through 2015. Gestational diabetes was controlled by diet (77.5%) or with insulin (22.5%). Neonatal blood glucose levels were measured at 1, 3, 6, 12 and 24 hours after birth. Neonatal hypoglycemia was defined as severe if the blood glucose level was less than 36 mg/dL, and as mild if it was between 36 mg/dL and 47 mg/dL. Whether the mother's disease was controlled by diet or insulin, rates of mild hypoglycemia were similar (33% vs. 35%, respectively;  $P=0.66$ ), as were rates of severe hypoglycemia (20% vs. 21%,  $P=0.79$ ). Overall, 17.2% of newborns were above the 90th percentile for birth weight. Although these infants had the highest risk for hypoglycemia, 78.6% of neonates with hypoglycemia had a birth weight <90th percentile. More than 95% of all hypoglycemia occurred within 12 hours after birth.

### **No Evidence Placentophagy Harms Neonates**

Placentophagy is not associated with worse outcomes in neonates, new research suggests. And most of the more than 7,000 women in the study who consumed their placentas said they did so in order to prevent postpartum depression, Dr Daniel Benyshek of the University of Nevada, Las Vegas, and his colleagues found. Placentas have been used in Chinese medicine to treat ailments in both men and women for thousands of years, but maternal placenta consumption first emerged in

the 1970s, as part of the home-birth movement, Dr Benyshek, an anthropologist and the new study's first author, said. While nearly all terrestrial mammals eat their placentas, Dr Benyshek noted, in a search through 180 communities he and his colleagues found no evidence for placentophagy as a traditional practice among humans. Benefits claimed for placentophagy include improved energy and lactation, in addition to preventing postpartum depression, the authors note in their report in *Birth*. However, they add, little research has been done on the practice and its benefits. A case of group B *Streptococcus* in an infant that was traced to his mother's placenta capsules has also raised concerns about risk. Dr Benyshek and his colleagues looked at medical records for more than 23,000 women who planned to have a community birth, 31.2% of whom reported consuming their placenta. Capsules were the most common form of placenta consumption, chosen by 85.7% of the placentophagic women. Women from New England were significantly less likely to consume their placentas than were women living in a West Coast state (adjusted odds ratio, 0.52). Primiparas (aOR, 1.65), women with a history of anxiety or depression treated with drugs or hospitalization (aOR, 1.72), those with anxiety or depression not treated with drugs or inpatient stays (aOR, 1.75) and those who planned to deliver at home rather than at a birth center (aOR, 2.21) were also significantly more likely to consume their placenta. There were no differences in hospitalization, neonatal intensive unit admission or neonatal deaths in the first six weeks of life between infants born to mothers who consumed their placenta and those who did not. There was also no difference in outcomes depending on whether the placenta was eaten raw or cooked. "Maternal health care providers need to acknowledge that a large number of women are engaging in placentophagy," Dr Benyshek said. While his study looked only at women who had planned community births, he added, women who have hospital births deliver in the hospital are also asking for their placenta to be released. He estimated that the number of women practicing placentophagy is definitely "in the 10s of thousands." He and his colleagues conclude: "We recommend that maternity care providers discuss the range of clinically proven treatments for postpartum mood disorders, in addition to the currently available evidence regarding the safety of various placentophagy preparation techniques."

### **Adult Survivors of Preterm Birth Have Smaller Airways**

The airways of adult survivors of preterm birth are smaller than those of their peers born full-term, which may help to explain their worse lung function, according to findings published in *Experimental Physiology*. Airway obstruction at rest is a "hallmark finding" in adults who had been born prematurely, Dr Joseph W. Duke of Northern Arizona University in Flagstaff, who helped conduct the study, noted. On average, he added, premature birth is associated with a 20% to 30% reduction in lung function, with expiratory flow limitation (EFL) and reduced inspiratory volume during exercise. Dr Duke and his team used dysanapsis ratio (DR), an indirect measure that accounts for maximal flow, static recoil and vital capacity, to compare airway size in three groups of adults (mean age, 22 years): 14 who had been born at least eight weeks premature and had bronchopulmonary dysplasia (BPD), 21 born at least 8 weeks premature without BPD, and 24 term-born controls matched by age, sex and height. DR was 0.16 for the preterm adults without BPD, 0.10 for the BPD group, and 0.22 for the controls. DR correlated significantly with both peak expiratory airflow at rest ( $r=0.42$ ) and expiratory flow limitation during exercise ( $r=0.60$ ). The researchers used two different equations to measure DR,

with consistent results: DR was significantly smaller for the preterm adults with or without BPD than for the controls, and those with BPD had significantly smaller DR than those without BPD. Given the findings, standard treatments for asthma and chronic obstructive pulmonary disease, which work by dilating the airways, may not be effective in these patients, Dr Duke noted. "We need to do some studies looking at these traditional medicines to reverse airflow obstruction and see what effect, if any, they have on adult survivors of preterm birth," he said. He and his colleagues conclude: "The data in the present study suggest that smaller than normal airways explain, at least in part, the lower expiratory airflow rate in PRE (i.e., without BPD) and BPD. The present findings add important information to our understanding of the cardiopulmonary physiology of PRE and BPD."

### Filtered Blunt Needle Released

NeoMed announced the release of the ENFit filtered blunt needle. Commonly used with oral/enteral medications such as caffeine, the blunt needle features an ENFit connection, allowing ENFit syringe users to draw up oral/enteral medications from manufacturers' vials, ampules, and other containers. The blunt needle is packaged sterile and features a 5µm filter for filling from glass ampules. The 18 gauge stainless steel needle with an angled tip allows for easy penetration through a vial's rubber membrane. The needle comes assembled with a protective sheath and is 38 mm long for easy use with most vials. "As a leading manufacturer and supplier of ENFit products and accessories, we are proud to continue that philosophy by releasing the ENFit blunt needle. The release of this product demonstrates our ability to recognize market demand and respond to our customers' needs," stated NeoMed President, Aaron Ingram. NeoMed's Vice President of International Operations, Hilary Sherman, added "One of the main objectives of our ENFit portfolio is to offer products that minimize process change when switching to ENFit. The blunt needle is an important component in facilitating that goal." For ordering information, contact your local sales representative, visit [www.neomedinc.com](http://www.neomedinc.com), or call 888-876-2225.

### Traffic Pollution Tied to Low-Birth-Weight Risk

Air pollution, but not traffic noise, appears to be linked to an increased risk of having low-birth-weight babies, reports a new study from the UK. Previous studies have tied road traffic air pollution to low birth weight. Road traffic produces noise as well as pollution, but studies of noise pollution have had conflicting results, say the authors. "We know that noise is associated with adverse health effects, e.g. sleep disruption, increased blood pressure, and cardiovascular disease, so it could plausibly have an impact on mothers' health in pregnancy and the health of unborn babies," study leader Dr Rachel Smith Smith at the School of Public Health of the Imperial College in London said. Smith's team wanted to investigate the effect of exposures to both traffic-related air and noise pollution during pregnancy on babies' birth weight. "We found increased risk of babies being born with low birth weight or small for gestational age, at term, to mothers with higher exposure to air pollution from road traffic during pregnancy. We did not see an independent effect of road traffic noise on birth weight," she said. Smith and colleagues used national birth registers to identify over 540,000 live, single, full-term births occurring in the Greater London area between 2006 and 2010. Specifically, the study team was interested in low birth weight (<5.5 pounds) and being born small for gestational age. Mothers' home addresses at the time

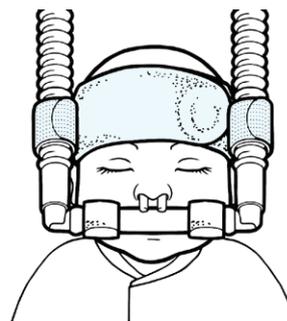


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of birth were used to estimate the average monthly exposure to traffic-related pollutants including nitrogen dioxide, nitrogen oxides, and fine particulate matter, or PM2.5. The researchers also estimated average day and night-time road traffic noise levels. Increases in traffic-related air pollutants, especially PM2.5, were associated with 2% to 6% increased odds of having a low birth weight baby and about 1% to 3% increased odds of a baby being small for gestational age, even after taking road traffic noise into account.

### **Preemies and Underweight Babies More Likely to Develop ADHD**

Babies who are born too soon or arrive weighing too little are about three times more likely to develop attention deficit hyperactivity disorder (ADHD) than full-term, healthy-sized infants, a research review suggests. Researchers examined data from 12 previous studies with a total of 1,787 participants and found that even among these high-risk babies, the odds of ADHD increased as babies spent fewer months in the womb and were born at even tinier sizes. “There is robust evidence that very preterm or very low birth weight individuals have an increased risk of ADHD,” said senior study author Dr Carlos Renato Moreira-Maia of the Federal University of Rio Grande do Sul in Porto Alegre, Brazil. It’s possible that the stress of the early birth or premature development of vital organs and systems in the body might lead to inflammation and hormonal changes that contribute to ADHD, Moreira-Maia said. Many factors including mothers’ medical histories as well as smoking, eating and drinking habits during pregnancy can influence the odds of preterm birth or an underweight infant, and these things might also contribute to ADHD in kids, Moreira-Maia added. “The reasons for increased vulnerability to ADHD in preterm/low birth weight individuals remain unknown,” Moreira-Maia said. The study focused on preterm infants delivered before 32 weeks’ gestation or weighing less than 1,500 grams (3.3 pounds) at birth. In the weeks immediately after birth, preemies often have difficulty breathing and digesting food. They can also encounter longer-term challenges such as impaired vision, hearing and cognitive skills, as well as social and behavioral problems. The researchers also looked at data on healthy babies who were born weighing at least 2,500 grams (5.5 pounds) or arrived after 37 weeks’ gestation and they also considered smaller, earlier arrivals. Compared with these healthy babies, infants born at less than 32 weeks’ gestation or weighing less than 1,500 grams (3.3 pounds) were more than twice as likely to develop ADHD, researchers report. When babies were born at less than 28 weeks’ gestation or weighing less than 1,000 grams (2.2 pounds) their odds of ADHD were more than four times higher than healthy infants, the study also found. One limitation of these results is that all but one of the smaller studies in the analysis was done in a high-income country, which means the results may not reflect what might happen in lower-income nations, the authors note.

### **Cervical Pessary May Prevent Spontaneous Preterm Birth**

Use of a cervical pessary may prevent spontaneous preterm birth in women with a shortened cervix in comparison to women who did not use the device, a study found. This randomized controlled trial “showed that in asymptomatic women with singleton pregnancies without prior spontaneous preterm birth but with a transvaginal ultrasound cervical length of 25 mm or less, use of a cervical pessary resulted in a statistically significantly lower rate of spontaneous preterm birth than no

pessary,” write the authors of the study. Researchers from the University of Naples Federico II, Naples, Italy, enrolled 300 women (age 18 to 50 years) between March 1, 2016, and May 25, 2017. They randomly assigned the women to receive a cervical pessary (intervention group) or no pessary (control group). The women were at 18 weeks 0 days to 23 weeks 6 days of gestation at the time of randomization. Women were evaluated every month until delivery, and all women with cervical length of 20 mm or less were prescribed vaginal progesterone suppositories (200 mg/day) until 36 weeks 6 days of gestation. Among women in the intervention group, the pessary was removed during the 37th week of gestation or earlier if indicated. The researchers found that 7.3% (11 of 150) of women in the pessary group experienced spontaneous preterm birth at less than 34 weeks of gestation compared with 15.3% (23 of 150) of women in the control group (between-group difference, -8.0 percentage points; 95% confidence interval [CI], -15.7 to -0.4 percentage points). Although no differences in pelvic discomfort were reported between the two groups, the authors note that women in the pessary group had a higher rate of new vaginal discharge (86.7% vs 46%; between-group difference, 40.7 percentage points; 95% CI, 30.1 - 50.3 percentage points). No injuries due to insertion or removal of the device were reported. Acknowledging “the exploratory nature of the secondary outcomes,” the researchers also reported longer gestational age at delivery, higher birth weight, and lower incidence of a composite of adverse neonatal outcomes among women in the pessary group.

### **Buprenorphine Use, Methadone Dose Affect Neonatal Outcomes**

For infants of mothers who were treated for opioid use disorder with buprenorphine, rates of neonatal abstinence syndrome (NAS) were found to be lower compared to infants whose mothers were treated with methadone, new research shows. In addition, use of methadone at doses higher than 50 mg was associated with a significantly higher risk for NAS. “If the baby is exposed to more than 50 mg in the mother during the pregnancy, they are three times more likely to develop NAS, which has plenty of adverse implications for the baby and the mother,” first author Raghavendra Parige, MD, of the Australian National University Medical School and ACT Health, in Canberra, told Medscape Medical News. The findings were presented here at the American Academy of Addiction Psychiatry (AAAP) 28th Annual Meeting. The observational study included 218 pregnant women treated with methadone or buprenorphine and their newborns, who were delivered at a single center between January 2001 and December 2016. Among the mothers, 194 were treated with methadone and 24 with buprenorphine. Fewer patients were treated with buprenorphine because methadone is still widely considered the standard of care for opioid use disorder. Overall, 54% (n = 118) of the neonates developed NAS, defined using the modified Finnegan Neonatal Abstinence Scoring System (FNASS) as a score of 8 or higher on three consecutive scores or 12 or higher on two consecutive scores. In the methadone group, 56% (n = 109) of infants were born with NAS, compared to 37% (n = 9) in the buprenorphine group. When the methadone group was stratified into low-dose (7.5 - 50 mg) and high-dose (51 - 170 mg) groups, the results showed a significant increase of NAS in the high-dose group (n = 89; 64%) in comparison with the low-dose group (n = 20; 36%; P = .001). “Most previous studies have shown no correlation between the dose of methadone and incidence of NAS, so it is interesting that we found this dose-related association,” said Dr Parige.

*Continued on page 14...*

# EXECUTIVE PREVIEW OF NANN CONVENTION

## Catapult Products

Booth 620

### What products do you plan to exhibit at NANN?

Catapult Products is excited to exhibit the TurtleTub bathing system including a custom bath tub for hospital use, bathing packs, individual liners, a bathing cart, and a mesh liner for tub storage.

### What's new this year? Tell us about your latest products or future plans.

We now offer a bathing cart, so the TurtleTub can store easily and move between patient rooms.

### What educational or training materials will be available?

We have a clinician and a developer available to demonstrate how to do a swaddle bath with the TurtleTub system. We have educational brochures in the booth and we offer training videos online. We strive to provide the latest research to answer questions regarding infant bathing.

### Why should our readers stop by your display?

The benefits of infant swaddle bathing and immersion swaddle bathing are research based. The TurtleTub bathing system enables hospital caregivers to bathe their infants in the most evidenced-based, appropriate way.

## Fisher & Paykel Healthcare, Inc.

Booth 515

### What products do you plan to exhibit at NANN?

- Optiflow™ Junior 2
- Bubble CPAP
- Flexitrunk CPAP and NIPPV/NIMV interface
- Neopuff Resuscitator

### What's new this year? Tell us about your latest products or future plans.

Optiflow™ Junior 2 is our newest nasal cannula specifically designed for the delicate anatomy and flow requirements of your smallest patients on Nasal High Flow therapy. It uses new Waveflex™ technology for better fit, prong stability, easier readjustment and offers sizes to fit a wider range of patients, while retaining all the benefits of the original Optiflow Junior. It's the next generation of care.

### What educational or training materials will be available?

- Videos showing the application of nasal high flow in real-world clinical situations.
- Clinical summaries outlining the latest clinical data and application of high flow and CPAP in the neonatal respiratory care continuum.

### Tell us about any speakers or in-booth promotions.

We will be discussing the latest Neonatal research on Nasal High Flow and CPAP, why a low resistance CPAP interface should be used, and what types of flow constitute "high" flow therapy.

### Why should our readers stop by your display?

To see the difference it makes to use interfaces designed to accommodate high levels of humidity without persistent rainout.

## COMPANY PROFILE

### Neo Medical Inc.

The Neo-Magic line of vascular devices and accessories are designed specifically for neonatal and older pediatric patients. Our ever-expanding product offering includes PICC lines, Extended Dwell PIV's and the most comprehensive offering of introducer options and accessories available.

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### Modified Seldinger Technique (MST) 30 gage introducer

**Kit:** The MST was designed specifically to access neonate and infants. This introducer has eliminated the need for multiple restarts and introducers in over 3,700 cases annually. Placement on the first stick is exceeding 85% success rates.

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**In-service Education:** All of Neonatal products have in-service support available.

**New Technology:** At Neo Medical we believe that vascular introducers are equally important to any catheter development. We are currently working on several projects that will bring novel and less traumatic insertion processes. We are anticipating an end of year launch of this product system.



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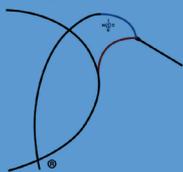
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*News...continued from page 12*

"We have come to the conclusion that the watershed dose of methadone for NAS is 50 mg." No significant differences in NAS were seen in relation to buprenorphine dose, and there were no differences in the groups in terms of gestational age, preterm delivery, birth weight, head circumference, or maternal heroin use.

### Fracking Linked to Low Birthweight, Worse Infant Health

Infants born to mothers who lived within 3 km of a hydraulic fracturing (fracking) site had lower birth weight and worse infant health, a study has found. Effects were largest in infants whose mothers lived within 1 km of a fracking site and dissipated at distances greater than 3 km. "For mothers living within 1 km, we find a 25% increase in the probability of low birth weight (birth weight < 2500 g) and significant declines in average birth weight and in an index of infant health," the researchers write. "There are also reductions in infant health for mothers living within 1 to 3 km of a fracking site, but the estimates are about one-third to one-half of the size of those within the 0- to 1-km band. There is little evidence of health effects at further distances, suggesting that health impacts are highly local." Janet Currie, PhD, from Princeton University, New Jersey, and the National Bureau of Economic Research, Cambridge, Massachusetts, and colleagues published their findings online in *Science Advances*. The researchers analyzed vital statistics records from more than 1.1 million births that occurred in Pennsylvania during 2004 to 2013. They compared infants of mothers living at increasing 1-km intervals from active fracking sites and infants born both before and after the initiation of fracking at each site, looking at birth weight and an index of infant health outcomes including prematurity (gestation less than 37 weeks) and the presence of any congenital anomalies or other abnormal conditions.

"[O]ur models control for mother fixed effects. Estimates of fracking-independent aspects of maternal health in these models are controlled by comparing the health of fracking-exposed and unexposed siblings born to the same mother," the researchers note. Fracking involves forcing water and other chemicals into shale rock to fracture it so that gas or petroleum trapped in the rock can be drawn out. "Whereas much of the previous research has focused on water pollution, several recent studies address the possible effects of chemicals that have been found in both 'fracturing fluid' (the fluid that is forced into the shale in order to fracture it) and in air emissions near fractured gas wells," the authors explain. The investigators estimate that about 29,000 infants were born in the United States to mothers residing within 1 km of a fracking site between July 2012 and June 2013, or approximately 0.7% of US infants born during that period. Other research using large administrative databases has consistently found an association between low birth weight and infant mortality, asthma, attention deficit hyperactivity disorder, lower test scores and schooling attainment, lower earnings, and increased rates of social welfare program involvement.

# In Search Of The 'Best Practice' For Central And Peripheral Line Blood Drawing In The Neonatal And Pediatric ICU

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with NeuroNICU educator Shannon Tinkler, RN, BSN, RNC-NIC, and clinical nurse specialist Michelle D Rhein, MSN, RN, CNS, RNC-NIC, of Stanford Children's Health/Lucile Packard Children's Hospital, Stanford about the Hummi Micro Draw Device.

**Neonatal Intensive Care:** How long have you been using the Hummi Micro Draw system?

**Michelle D Rhein:** We have been using the Hummi Micro Draw device for over 5 years at different institutions.

**NIC:** How would you rate the ease of adoption and use when using the Hummi system for drawing blood in the NICU vs others you have tried?

**MR:** Onsite training and clinical support was superb and allowed for easy adoption in the clinical setting. Since previously there was no dedicated system for closed blood draw, the clinicians were appreciative of having a product designed specifically for this purpose, instead of having to piece together different components to achieve a closed system.

**NIC:** What clinical improvement does the Hummi system provide for your premature infant population vs other methods of drawing blood you have used?

**MR:** The Hummi provides a closed system for drawing blood which decreases the exposure for infection by eliminating the use of multiple stopcocks and exposure induced by opening the line. The Micro Draw System minimizes the amount of blood displaced when sampling arterial lines. Clinically, it is important to remove only the blood necessary for waste and sample, as we know there are detrimental effects on cerebral oxygenation when larger blood volumes are withdrawn.

**NIC:** Since the Hummi system is a closed system in use, have you seen an impact in your infection (CLABSI) rates since you began using the Hummi closed system?

**MR:** In a quality improvement effort to reduce our CLABSI rates, we implemented many changes simultaneously, including the Hummi Micro Draw device. While we have seen a reduction in our CLABSI rate in this reporting period, it cannot be attributed solely to implementation of the Hummi, but has been a valuable asset in elimination of stopcocks as recommended by the CDC and NANN.

**NIC:** What type of catheter blood draws are you doing routinely with the Hummi closed system? Peripheral? Umbilical? PICC? Other types of Central Lines? Blood Culture?

**MR:** We are using the Hummi to withdraw samples from umbilical venous and arterial lines, peripheral arterial lines, and

double lumen PICC catheters (we don't draw from PICC lines less than 2.6 Fr). We do not use the Hummi for blood cultures on these lines, we have a separate process for sterile blood culture samples.

**NIC:** Overall blood and fluid volume movement when drawing blood in the premature infant is very important. How does the Hummi system meet your needs for hemodynamic stability when drawing blood in the premature infant?

**MR:** Changes in cerebral blood volume and oxygenation are blunted by reduction in sample volume (Roll, et al., 2006 & Hüning, et al., 2007). The Hummi micro draw blood system enables clinicians to displace the minimal amount of blood necessary to ensure hemodynamic stability and limit changes to cerebral oxygenation during umbilical sampling.

**NIC:** Do you find the training and support materials provided by the manufacturer and distributor of the Hummi system to be of help to you and your staff when learning to use the system?

**MR:** The training and support materials were very helpful in justifying change in practice to the staff. The support provided by the vendor was outstanding. The vendor was present at multiple skills days, with a realistic hands-on model and demonstration that the nursing staff felt was valuable, and helped adequately prepare them for adoption of the Hummi into practice. The nurses and staff also valued the evidence provided that supported the Hummi micro draw device as a best practice.

**NIC:** Would it be of benefit to your patient care from an infection control aspect, if the Hummi system was available to you in a fully assembled manner fully integrated into your umbilical catheter?

**MR:** Yes, if the Hummi system was available prefabricated, it would eliminate the chance of incorrect set-up and allow for seamless integration into the workflow. A prefabricated system would reduce the number of connections when setting up a fluid administration set, therefore eliminating potential contamination sites.

**NIC:** How would you rate your overall satisfaction clinically with the Hummi Micro Draw system?

**MR:** Overall, the Hummi Micro draw device is phenomenal, and when paired with the outstanding customer service and issue resolution, we highly recommend the device to everyone searching for a closed draw system for the NICU.

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

# Obstetrical Ultrasound and Autism Causation, Association, or Myth?

BM Petrikovsky, MD, PhD, Y Nemova, MD, M Petrikovsky\*

Autism spectrum disorder (ASD) can often be a frustrating problem for both families and healthcare providers. There are numerous speculations about the cause of ASD, most of which are unfounded. Some common theories include: vaccinations, toxic nutrients, maternal obesity, prenatal fever, use of oxytocin for induction of labor, among others.<sup>1</sup> Most of the claims explaining the ‘epidemic’ of autism are based on combined statistics obtained from various centers.<sup>1</sup> The report from the Department of Developmental Services from California has been widely quoted as evidence for the epidemic of autism.<sup>2</sup> ASD rates in recent surveys are substantially higher than 30 years ago. This increase may reflect the adoption of a broader concept of autism, changes in diagnostic criteria, and improved identification of patients with autism attributable to better medical services.<sup>3,4</sup>

Currently, there are no prenatal tests available for autism. In the past, autism was diagnosed only in children with severe language and social impairments, as well as in those exhibiting unusual and repetitious behaviors. Lately, the definition of ASD has gradually expanded to less-severe conditions. Approximately, 1 out of every 59 children in the US were identified as having autism in 2014 (Centers for Disease Control and Prevention report). Caucasian children are diagnosed with autism more often than African American or Hispanic children. The gap between Caucasian and Hispanic children diagnosed with autism has decreased from 50 percent to 20 percent.

Recently, Rosman et al.<sup>5</sup> studied whether there is a relationship between the frequency, timing, and duration of prenatal ultrasonography and autism. The data collected from each ultrasound examination included gestational age, time of exposure to ultrasound, time-weighted mean depth, frame rate (number of ultrasound pulses per second), soft tissue thermal index, time of Doppler use, and the length of time of using 3-dimensional (3-D) imaging. The authors evaluated ultrasound exposure by trimester, as defined by the American Congress of Obstetrics and Gynecology (ACOG) as gestational age no greater than 13 weeks 6 days (first trimester), 14 weeks 0 days to 27 weeks 6 days (second trimester), and at 28 or more weeks (third trimester). They concluded that the ASD group had a greater mean depth of ultrasonographic penetration than the control group in the first trimester (12.5 cm) vs. (11.6 cm) [95% CI].

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Ultrasound has traditionally been considered safe during pregnancy. A large cohort study of infants found that those exposed to ultrasound have increased odds of being left-handed, a finding that was confirmed in subsequent meta-analyses.<sup>6,8</sup> These studies suggest that ultrasound exposure can influence cerebral hemispheric specialization. Animal studies have shown that ultrasonography may have an adverse effect on the developing brain.<sup>9,10</sup> In mice, exposure to the ultrasound in utero caused a failure in the neurons to acquire their normal cortical position. ACOG recently declared: “ultrasound energy delivered to the fetus cannot be assumed to be completely innocuous, and the possibility exists that such biological effects may be identified in the future.” In another recent statement, ACOG has endorsed the “prudent use” of ultrasound in obstetrics, discouraging its use for nonmedical purposes, e.g., solely to create keepsake photographs or videos.<sup>12</sup> The AIUM also advocates the responsible use of ultrasound during pregnancy. Although there are currently no confirmed detrimental biological effects from an ultrasound during pregnancy, the possibility exists that such biological effects may be eventually identified. Doppler studies pose the highest risk of thermal effects on the fetus and may cause a substantial temperature increase in the fetal brain.<sup>13</sup> ACOG claims that there are no clear clinical benefit of 3-or 4-D imaging and suggests that conventional 2-D ultrasonography be the recommended standard of care.<sup>11</sup> Most of the ACOG guidelines follow the ALARA (as low as reasonably achievable) principle during pregnancy, but even the ALARA principle does not provide any specific, evidence-based limit for safe use.

On the other hand, a World Health Organization (WHO) study reviewed 6,717 citations obtained from a systematic search of MEDLINE and the Cochrane Central Register of controlled trials electronic databases between 1950 and 2007. The final analysis included 61 publications on short and long-term effects of in utero exposure to ultrasound from 41 different studies: 16 controlled trials, 13 cohort studies, and 12 case-control studies. The outcome include analysis of low birth weight, preterm birth, low Apgar scores, need for neonatal resuscitation, presence of seizures, admission to a neonatal intensive care unit, perinatal mortality, childhood growth, neurologic development, behavioral scores, hearing and visual impairment, cognitive function, attention deficits, and motor skills, among others. The only finding was the previously reported weak correlation between ultrasound exposure and left-handedness in males.<sup>8</sup> If we assume the assertion of an increased recent prevalence of autism to be adjusted for the purposes of the study, then it is fair to state that

the increased prevalence of ASD parallels the increased use of ultrasound during pregnancy. At the same time, there has been an increased use of cell phones and personal computers over the same time period.<sup>14</sup> It is unclear if this rise in autism is due to an increase in diagnoses or an increase in its prevalence. Some researchers argue that physicians are doing a better job at diagnosing autism, particularly in minority populations. Therefore, if an association between prenatal ultrasonography and autism exists, it doesn't necessarily imply causation. The question remains, however, what is the current status of the problem and what further steps are warranted? The continued lack of scientific data may result in conspiracy theories and the risk of creating unjustified public fear.<sup>14</sup> On the basis of the current information, we conclude that currently, there is no credible evidence that a cause-effect relationship exists between in utero exposure to ultrasound and development of ASD.

**Current Recommendations.** Ultrasound use should be restricted to medical indications and performed by trained professionals.<sup>14</sup> In the meantime, certain measures, in light of ACOG and AIUM recommendations can be considered, e.g., establishing time limits for performing 1st, 2nd, and 3rd-trimester ultrasound examinations. In our experience, computer-assisted detection of fetal abnormalities shortens the timing of fetal ultrasound exposure without compromising its diagnostic accuracy.<sup>15</sup> This software works by overlapping various sonographic features of fetuses we are studying over analogous features from the database containing various genetic abnormalities and other fetal syndromes. We recently published a study on the duration of ultrasound examinations performed by radiologists as compared to maternal-fetal medicine (MFM) specialists (a total of 10,000 scans). A wide variety in the duration of sonographic examinations had been observed. It appears that MFM specialists take more time performing sonographic examinations than radiologists. The reported data can be utilized in developing timing guidelines for obstetrical sonography.<sup>16</sup>

In conclusion, until further research eliminates any association between obstetrical ultrasound and autism, caution should be exercised to avoid extended exposure to ultrasound.

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# A Survey Report On 24-Hour In-House Calls For Attending Neonatologists

Shabih Manzar, MD

During training, the medical residents are required to take 24-hour in-house calls. Accreditation Council for Graduate Medical Education (ACGME) has gone through changes in the call requirements from 24 hours to 16 hours and now back to 20 hours.<sup>1</sup> The idea behind cutting back the hours was sleep deprivation that has been shown in studies.<sup>2,4</sup> During training, continuing of care is an important component of learning, thus presence in the hospital for longer hours is required but with an 80-hour cap on clinical hours so that they can have a work-family life balance, which has been addressed in the whole issue of JAMA.<sup>5</sup>

It is expected that after the completion of training, passing boards and becoming an attending, the on-call hours should be reduced. In Canada, the practice of 24-hour call has been questioned extensively.<sup>6,8</sup> However, in certain specialties in-house presence of a physician is mandatory at all times. The field of neonatology is a good example. In recent years, many states have mandated for the designated level 3 neonatal intensive care unit (NICU) the presence of a skilled health care provider on-site for 24 hours. The issue that which hospital and physician hiring companies face is staffing the level 3 NICU 24/7. Many models are in place. Some centers were able to recruit enough mid-level providers while attending physicians support them on-call working as a think tank, assisting in decision making and driving in if needed. While other institutions hired physicians to be in the hospital 24 hours all by themselves. These 24-hour in-house calls have a high potential for sleep deprivation comprising quality care of the sick neonates.

To get the feedback on this issue we conducted a survey including multiple responders that are involved in establishing the neonatal practice including recruiters to physicians. The survey was emailed to 25 known recipients while it was also posted on professional website for others to fill in.

The survey had 10 questions (Appendix 1). Forty percent responded to the survey. The results of the survey are depicted in Appendix 2.

## Discussion

Among the responders 83% were physicians and 50% are already engaged in 24-hour in-house calls. That makes the survey very

pertinent to the target audience. In managed care it has been speculated that having physicians in the hospital 24 hours may affect the outcome. The survey response to that question was 50-50. More studies are needed to address this question in detail. The majority of the responder agrees that 24-hour in-house call is unhealthy and results in more burn out.

An interesting observation was noticed in response to question 3 and 6. Fifty percent of the responders disagreed to splitting the call in 12 hours. They might favor 8:16 hour ratio. The other interesting observation was that one-third favored not abandoning the 24-hour in-house call. The Physician: mid-level provider (MLP) difference is expected in care of the neonate. MLP are mostly shadowed by the on-call physician while in 'physician 24 hrs call model' physicians are usually all by themselves. That's why we see a 50% responders agreeing to the difference. And lastly 83 percent agrees that 24-hour mandated in-house call requirement should be reviewed by states and hospitals.

In conclusion, the survey results highlight that physicians should have a flexible schedule and strategies should be adopted to minimize their fatigue and burn out. More studies are needed to look at variables important in patient care namely patient satisfaction, continuity of care, quality, outcome and physician burn out.

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### Appendix 1: Survey Questions

1. Do you think 24-hr in-house call affects patient's outcome?
2. Do you think 24-hr in-house call will result in more burn out?
3. Calls should be split into 12-hr shifts, 24-hr is too long
4. 24-hr in-house call is not physiological and therefore unhealthy
5. The impact of 24-hr, in-house call is different between physicians and mid-level providers
6. State and Hospital should review the mandated 24-hr in-house call requirement for health care providers.
7. Except during training, 24-hr in-house calls should be abandoned.
8. Are you satisfied with the current physician: mid-level provider's ratio in your hospital?
9. What is your area of expertise?
10. Are you currently doing 24-hr in-house calls?

### Appendix 2: Results and analysis of survey

1. Do you think 24-hr in-house call affects patient's outcome?  
*Yes 50%, No 50%*
2. Do you think 24-hr in-house call will result in more burn out?  
*Yes 80%, No 20%*
3. Calls should be split into 12-hr shifts, 24-hr is too long  
*Strongly agree 33%, Neither 16.6%, Disagree 16.6%, Strongly disagree 33.3%*
4. 24-hr in-house call is not physiological and therefore unhealthy  
*Strongly agree 50%, Agree 16.7%, Disagree 33.3%*
5. The impact of 24-hr, in-house call is different between physicians and mid-level providers  
*Strongly agree 16.67% %, Agree 33.3%, Neither 33.3%, Strongly disagree 16.67%*
6. State and Hospital should review the mandated 24-hr in-house call requirement for health care providers.  
*Yes 83.3%, No 16.6 %*
7. Except during training, 24-hr in-house calls should be abandoned.  
*Strongly agree 16.67%, Agree 33.3%, Neither 16.6%, Strongly disagree 33.3%*
8. Are you satisfied with the current physician: mid-level provider's ratio in your hospital?  
*Very satisfied 50%, Neither 16.67%, Dissatisfied 33.3%*
9. What is your area of expertise?  
*Physician 83%, Others 16.67%*
10. Are you currently doing 24-hr in-house calls?  
*Yes 50%, No 50%*

# Predictions for Mother's Own Milk Feedings at NICU Discharge

Carol Chamblin, DNP, APN, RN, IBCLC

## Introduction

The American Academy of Pediatrics recommends exclusive breastfeeding for infants for the first six months of life and continued breastfeeding for one year or longer (AAP, 2012). Breast milk has many health benefits for infants, including decreased rates of respiratory infections, asthma, ear infections, and gastrointestinal illnesses. For preterm infants in the neonatal intensive care unit (NICU), breast milk feeding has decreased the risk of necrotizing enterocolitis by 77% (AAP, 2012).

Although rates are going up, according to the latest Centers for Disease Control and Prevention (CDC) report (2016), 81.1% of women initiate breastfeeding their infants. Breastfeeding exclusivity and duration rates decline rapidly, and only 22.3% of infants are exclusively breastfeeding at six months after birth (CDC, 2016). The Surgeon General's Call to Action to Support Breastfeeding addresses the necessity for health care providers to be educated about delivering evidence-based lactation care and support (U.S. Department of Health and Human Services, 2011).

## Anatomy and Physiology

The anatomy and physiology of the lactating breast begins its development during pregnancy (Neville, M. & Morton, J, 2001). Progesterone levels elevate and the ductal lobules within the breast increase in number and size. During pregnancy, secretory differentiation occurs as fat globules increase in size in the cells of the mammary gland, referred to as stage I Lactogenesis. High levels of circulating progesterone during pregnancy inhibit the release of prolactin. At the time of birth, progesterone levels drop upon delivery of the placenta, and the onset of copious milk secretion occurs, referred to as stage II Lactogenesis. As prolactin secretion takes place by either the newborn's suckle at breast, or in the absence of direct breastfeeding, the effective use of a hospital-grade (multi-user) breast pump, milk removal occurs and milk secretion is maintained. Failure of efficient milk removal at this time can lead to breast involution and insufficient milk volume.

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Carol Chamblin has spent over 30 years caring for mothers and infants in pediatrics, lactation, PICU and NICU settings. She became certified as an International Board Certified Lactation Consultant in 1995. Her successful private practice specializing in lactation-related care began over 17 years ago. In 2010 Carol extended her role as an Advanced Practice Nurse in a pediatric office, teaching prenatal breastfeeding classes and providing clinical expertise. Carol earned her Doctor of Nursing Practice (DNP) from Rush University in 2012.

Preterm infants in the NICU demonstrate immature suckling capability for adequate milk removal (Geddes et al, 2017). Recent ultrasound studies indicate that oral vacuum is instrumental in milk removal. For the preterm infant, the degree of vacuum strength is compromised compared to the term infant, and this impacts feeding effectiveness. Until the preterm infant can overcome limitations caused by neurological or developmental immaturity, and respiratory conditions such as immature coordination of suck-swallow-breathing, effective pumping allows a mother to maintain milk expression.

## Early Breast Milk Expression

Research demonstrates improved health benefits for all infants, especially infants weighing < 1500 g at birth, or very low birth weight (VLBW) infants (Parker, L.A. et al. 2012). Decreased morbidity associated with prematurity, feeding intolerances, sepsis and necrotizing enterocolitis are a few examples. Providing the nutrition of exclusive breast milk for premature infants in the NICU can be very challenging for mothers, despite its heightened necessity for this vulnerable population of newborns to receive their mother's own milk (MOM).

Dr. LA Parker at the University of Florida in Gainesville, FL has performed extensive research on the subject of early initiation of breast milk expression on the impact of milk volume (Parker et al, 2012; Parker et al, 2015). Lactogenesis stage II occurs with the change from production of small quantities of colostrum to copious amounts of breast milk. For mothers delivering term infants, this stage takes place after delivery of the placenta with a decrease in progesterone, effective removal of milk from the breast, and ongoing prolactin levels. Preterm delivery and a delay in breastfeeding have been associated with a delay in Lactogenesis II. Mothers of preterm infants may be affected by decreased mammary gland development and decreased exposure to prolactin, cortisol and other hormones that occur during term pregnancy. Delayed lactogenesis can lead to inadequate milk volume and discontinuation of milk expression, or breastfeeding.

Secretory activation, initiation of copious milk secretion, occurs 30-40 hours after birth for the term infant who is capable of efficient milk removal. There are rapid increases in milk secretion at this time such that infant milk transfer increases from less than 100 mL/day on day one post-delivery to between 500-750 mL/day by day 5, and reaching 750-800 mL/day on average by one month (Saint, Smith, Hartmann 1984). Transition from Lactogenesis II to a sufficient milk output at two weeks for exclusive breastfeeding has been termed "coming to

volume” (CTV) by Dr. Paula Meier and her research team at Rush University Medical Center in Chicago, IL (Meier et al, 2016). Once CTV is achieved at two weeks post-birth, some pump-dependent mothers are able to decrease pumping frequency and still maintain adequate milk output (Edwards & Spatz, 2010).

### **Initiate and Maintain Maternal Milk Volume**

Establishment of breastfeeding for the very low birth weight (VLBW) preterm infant is fraught with many obstacles (Parker et al, 2012; Geddes et al, 2017). Often these infants are too ill to directly breastfeed immediately after birth. The method of initial oral feeding is often per feeding tube. A main priority at this time is the initiation and establishment of maternal milk volume. Recent evidence demonstrates expressing breast milk within an hour of delivery has a significant impact on how much milk volume mothers are able to produce at six weeks post-delivery. It has also been demonstrated that there is a strong correlation between the frequency of pumping and milk volume.

Research studies demonstrate mothers of infants in the NICU who are breast pump-dependent experience problems with delayed lactogenesis and inadequate milk volume. Only 29% of mothers of preterm infants were able to provide exclusive mother's own milk throughout the NICU stay in one study (Schanler et al, 2005). Recent studies comparing different breast pump suction patterns and implementation of pumping within 1 hour of birth may reduce the number of mothers who cannot produce enough milk volume (Meier et al, 2010; Meier et al, 2012).

The first two weeks are a critical time for the initiation of an adequate milk supply (Meier et al, 2011). “Milk production is enhanced with pumps that mimic infant suckling patterns in the first few days of life” (Meier et al, 2012). Term infants exhibit an irregular, intermittent suckling pattern of rapid sucking bursts followed by long pauses (Santoro W., Jr. et al, 2010). Dr. Diane Spatz, a renown researcher and Director of the lactation program at Children's Hospital of Philadelphia outfitted all breast pumps in the NICU with Medela® Symphony Plus® breast pumps featuring the Initiation Technology™ to facilitate the removal of colostrum and support the establishment of milk supply. (Fugate et al, 2015). While it is beyond the scope of this article to describe more fully the evidence-based breast pump technology, mothers using this technology had significantly higher milk volumes by day 14 post-delivery.

To facilitate early initiation of pumping, it is the primary responsibility of the nursing staff to educate the mother on pump use and the safe handling of human milk (Fugate et al., 2015). Expressed breast milk needs to be used in the order pumped for the first two weeks to maximize protein intake and immunological properties. NICU mothers are educated to label the bottles of their expressed milk in pumping session order from 1 to 60 (Meier et al., 2011). After these bottles are used, fresh nonfrozen human milk is preferable to frozen milk since immunomodulatory proteins are reduced by the freezing process (Akinbi et al., 2010).

### **Human Milk Oral Care**

Human milk oral care is the process of applying fresh breast milk to an infant's oral mucosa with a swab. Performing this care by mothers of infants hospitalized with congenital diaphragmatic hernia (CDH) was determined to have an impact on mothers to remain motivated to keep pumping and build their milk supplies

(Froh, E. et al, 2015). Though research was performed for infants with CDH, it applies to all infants separated from mothers by hospitalization.

### **Evidence-Based Best NICU Practice**

The ability of mothers to have adequate milk volume to exclusively feed their infants mother's own milk (MOM) feedings from the NICU days through to discharge is based on best practice changes within NICU settings. All of the aforementioned implementation strategies are based on in-depth evidence for optimal lactation care. Between February 2008 and December 2012, 402 VLBW infants and their mothers were involved in a study at Rush University Medical Center to determine predictors of MOM feeding at NICU discharge (Hoban et al, 2018). Findings demonstrated achievement of CTV by postpartum day 14 as the strongest predictor for infants receiving MOM feedings at NICU discharge in breast pump-dependent mothers. Clinical practice incorporating effective pumping technique and technology to prevent low MOM volume should be targeted during the first postpartum week.

### **Revised Baby Friendly Hospital Initiative**

World Health Organization (WHO) and United Nations Children's Fund (UNICEF) published the Ten Steps to Successful Breastfeeding in 1989 for implementation of policies and procedures for facilities providing maternity and newborn services in support of breastfeeding. WHO and UNICEF launched the Baby-Friendly Hospital Initiative (BFHI) in 1991 to motivate facilities offering maternity and newborn services in the implementation of the Ten Steps. The latest revision of the Baby Friendly Hospital Initiative was released in April 2018. A key statement of this publication is: “The first few hours and days of a newborn's life are a critical window for establishing lactation and providing mothers with the support they need to breastfeed successfully.” Breastfeeding is described as a biological norm for healthy moms and newborns. However, interruptions such as necessary medical procedures, and separation of mothers from their infants in the NICU population may pose an increased risk for breastfeeding challenges and the initiation and maintenance of milk supply.

The updated guidance of the Ten Steps continues to cover the protection, promotion and support of breastfeeding healthy term newborns rather than the needs of the sick or preterm infants. However, it does mention that small, sick and/or preterm newborns have their own set of needs and that more specific guidance is available elsewhere. In 2004, Dr. Diane Spatz adapted the Ten Steps for Vulnerable Infants, and as a result, there was an increase in the percentage of infants receiving mother's own milk (MOM) at initiation of feeds and at discharge (Fugate et al., 2015).

The revised Baby Friendly Initiative has several key points inclusive of support for the initiation and maintenance of breast milk in times of common difficulties:

- Practical support for preterm or late preterm infants is critical to establish and maintain milk production
- Mothers of preterm infants often have health problems and need extra motivation and support for milk expression
- Late preterm infants are generally able to exclusively feed at the breast, but are more at-risk for jaundice, hypoglycemia and feeding difficulties, requiring increased vigilance

- Mothers of multiples need extra support
- Mothers need to be taught how to express their breast milk as a means to maintain lactation if separated from their infants
- Mothers must be supported and encouraged to express their own milk as a priority
- Mothers should have adequate space to express milk adjacent to their infants
- For preterm infants unable to breastfeed directly, non-nutritive sucking (pacifier use) may be beneficial until breastfeeding is established

**Spatz Ten Steps for Promoting and Protecting Breastfeeding for Vulnerable Infants (Fugate et al. 2015)**

Step	Description
1	Informed decision
2	Establishment and maintenance of milk supply
3	Human milk management
4	Oral care and feeding of human milk
5	Skin-to-skin contact
6	Non-nutritive sucking
7	Transition to breast
8	Measurement of milk transfer
9	Preparation for discharge
10	Appropriate follow-up

If the amount of milk you are expressing is filling the small containers close to the level of the yellow valves, you should start using the larger containers. Soon you will have enough breast milk to start storing it in the freezer because you will have more milk than your baby will need in the NICU.

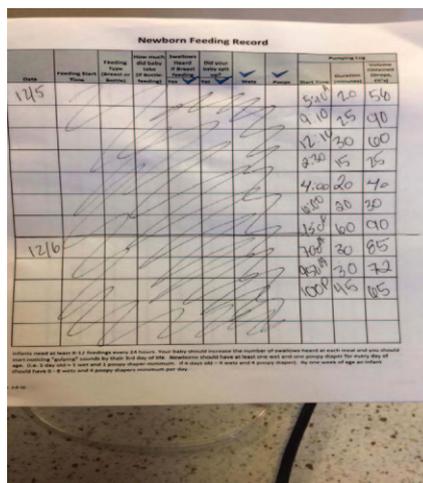
December 5, 2018 — On day seven post-delivery, mom was able to express 10 ounces from 11pm-12N and texted the author to ask if this was a good milk volume.



Breast milk collected, labeled, and stored in refrigerator at home ready for transport to the NICU.

**Case Scenario**

A primiparous 27 year old had preterm labor at 32 weeks gestation and delivered a baby boy who was admitted to the NICU. During this mom's pregnancy, contact with a lactation consultant in private practice was established. Mom signed consent to give permission for information and/or photos of breastfeeding-related nursing care to be anonymously used for professional articles or studies for professional education. Another aspect of the consent covered the use of emailing or texting for non-urgent care and treatment. The following is a partial exchange of texting between mom and the author.



Pumping log of days 7 and 8 post-delivery



Enjoying skin-to-skin

**December 5, 2018**

Mother: New doctor on rotation today and she came in and was like WOW look at all that milk!

Author: Great! Because you have enough breast milk, your baby will tolerate his feedings well. He most likely will gain weight and be discharged earlier than if he was being fed formula.

December 9, 2018 — On day 11 post-delivery, Mom was expressing a little over 600 mLs.

Author: You are doing great! The goal by day 14 is to be expressing 750-850 mL in 24 hrs. You are increasing your milk supply by continuing to pump seven times in 24 hours and are right on track! Do you have any questions about putting your baby to breast next week? You had said yesterday that you were told you would have the opportunity to put your baby to breast.

Mother: Not yet. I'm sure I'll have questions once we try it.

**December 13, 2018**

Mother: We latched and licked today but mostly just spooned my breast milk to Andy. I'm expressing 650-700 mL/24 hours.

**December 16, 2018**

Milk output is 675-820 mL/24 hours

Baby Andy was discharged from the NICU at age six weeks. There were some feeding issues related to anemia which postponed his discharge by a few weeks. Mom had initiated and maintained adequate milk volume by effective pumping. Andy is a robust, healthy five month old and has only been fed MOM.

This mom continues to express her breast milk for her now five month old.



## Conclusion

Initiation and maintenance of adequate milk volume is based on ongoing effective infant suckle at breast, or effective pumping technique for infants in the NICU. Early milk expression using effective breast pump technology within one hour of birth in the absence of an infant at breast significantly alters a mother's ability to achieve a full milk supply by 14 days; known as "coming to volume". Evidence-based NICU practice adheres to the goal of achieving mother's own milk feedings in the NICU and at discharge from the NICU. Many NICU settings do not have unit protocols that support the latest breast pump technology for support of optimal mother's milk volume. There is opportunity for continuous process improvement projects in the area of breast milk feeding and pumping in the NICU population because every preterm infant in the NICU deserves to receive mother's own milk (MOM).

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# Determination of Colonization Profiles in Oro/Nasogastric Tubes in Premature Infants: A Clinical Observational Study

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## Abstract

**Objective:** To determine microbial colonization profiles, and persistence of colonization, in oro/nasogastric tubes (O/NGTs) for premature infants.

**Study Design:** A prospective, observational clinical study.

**Subjects/Setting:** 46 premature infants (< 35 weeks gestation) hospitalized in a 44-bed NICU.

**Methods:** Serial O/NGTs were removed from subjects at 7 days post-insertion and the tube tip was cut and sent for microbial analysis.

**Statistical analysis:** descriptive statistics.

**Results:** Of the 146 samples, 70% grew gram-negative organisms. Of the 46 infants, 23 had persistent O/NGT colonization with gram-negative organisms. For some infants, the same gram-negative organism that was persistent in the O/NGT culture also grew in either the endotracheal tube aspirate culture or the blood culture

**Conclusions:** O/NGTs are quickly colonized with pathogenic gram-negative organisms, and colonization persists despite changing the tube every 7 days. Peak colonization occurs at approximately 33 weeks CGA, which corresponds to the time when NEC typically begins to appear.

## Introduction

Premature infants are born with an immature suck reflex and do not attain full per oral feedings until approximately 35-37 weeks post-conceptual age. During this prolonged period- up to 12 weeks for infants born at 23-24 weeks gestation- they require an indwelling oro/nasogastric tube (O/NGT) for the administration of enteral feedings. The tube is changed at regular frequencies, between 3 and 30 days based on the policy in each neonatal intensive care unit (NICU). The lack of evidence to guide this practice has resulted in significant variation among NICUs for O/NGT "indwelling time". Some manufacturers recommend an indwelling time of up to 30 days, raising concerns among neonatal physicians and nurses regarding infection risk for premature infants.

Premature infants are at high risk for developing infections such as late-onset sepsis (L-OS), ventilator-associated pneumonia (VAP), and necrotizing enterocolitis (NEC), a potentially lethal gastrointestinal infectious/inflammatory disorder.<sup>1-3</sup> Impaired host defense mechanisms, abnormal gastrointestinal colonization, an immature intestinal epithelial barrier, and exposure to environmental (NICU) pathogens place these infants at risk.<sup>1,4-6</sup> Both L-OS and NEC are associated with significant mortality and morbidity, and also adverse neurodevelopmental outcomes.<sup>1,7</sup> Highest at risk are extremely premature infants, who must remain hospitalized in the pathogen-laden NICU environment for 3 to 4 months. During this extended period, they will require numerous O/NGTs that can become colonized with pathogenic bacteria from the NICU. The prolonged presence of an indwelling colonized O/NGT raises concerns about infection risk. Yet there is a lack of adequate empirically-derived evidence to determine a safe and appropriate dwelling time for O/NGTs in the NICU.

In efforts to expand our knowledge base regarding the patterns of microbial colonization in O/NGTs for premature infants in the NICU, we conducted a pilot clinical study. In this study, we collected the O/NGT *tip* to send for culture because we felt that microbial analysis of the intracorporeal portion (the part of the tube that is inside the body) is a better indicator of gastrointestinal colonization, while the extracorporeal portion likely reflects nosocomial organisms in the NICU.

The main impetus for this study followed from a hospital change of vendors that recommended replacement of O/NGTs only monthly in our NICU, without solid safety evidence. Since our standard practice was to change tubes weekly, we chose this as a natural data collection point. The purpose of this study was to prospectively determine the *intracorporeal* microbial colonization profiles, and persistence of colonization, in O/NGTs for a small cohort of premature infants hospitalized in the NICU.

## Materials and Methods

**Design:** A prospective, observational clinical study.

**Settings and Subjects:** The study was conducted in a 44-bed, level 3 NICU in a large teaching hospital. Subjects were premature infants, born at less than 35 completed weeks of gestation, hospitalized in the NICU, and requiring an O/NGT.

**Procedures:** The study was approved by the NorthShore Institutional Review Board (IRB). Eligible infants were identified

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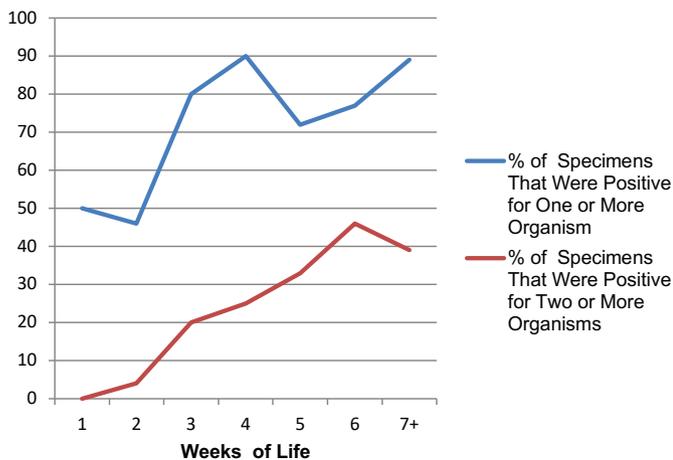


Figure 1. Percent Colonization by Week of Life for All Specimens

within 48 hours of birth and enrolled after informed consent was obtained from one parent. Once the infant was enrolled, the following information was entered into a logbook: infant's name, date of O/NGT placement and removal (exactly 7 days after placement). The O/NGT was placed, as per standard practice, by the bedside nurse using non-sterile gloves. Exactly seven days later, the research nurse followed a strict, standardized procedure to remove the O/NGT without contamination. Using sterile gloves, the O/NGT tip was cut using sterile scissors, so the tip would fall into the sterile specimen container without contamination. The container was capped, labeled and immediately sent to the microbiology lab for culture. Culture was performed by rolling the 2 inch segment of catheter back and forth across the surface of a blood agar plate four times, in order to expose all surfaces of the catheter to the agar. The tip was removed from the inoculated agar plate using sterile forceps and aseptically placed into a tube containing 10 ml of thioglycollate culture broth. The blood agar plate was incubated at 35 degrees Celsius in an atmosphere containing 5% CO<sub>2</sub>. The thioglycollate broth was incubated at 35 degrees Celsius in ambient gas. Incubation extended for a maximum of 48 hours. All pathogens growing on the agar plate or in the broth media were identified by usual laboratory techniques.<sup>8</sup> This entire procedure was repeated every week with each new O/NGT that was placed, until it was no longer needed for feedings. Only tubes with an indwelling time of 7 days were included in the sample. If the O/NGT was accidentally removed by the infant or staff prior to 7 days, the tube tip was considered contaminated and was not sent to the lab.

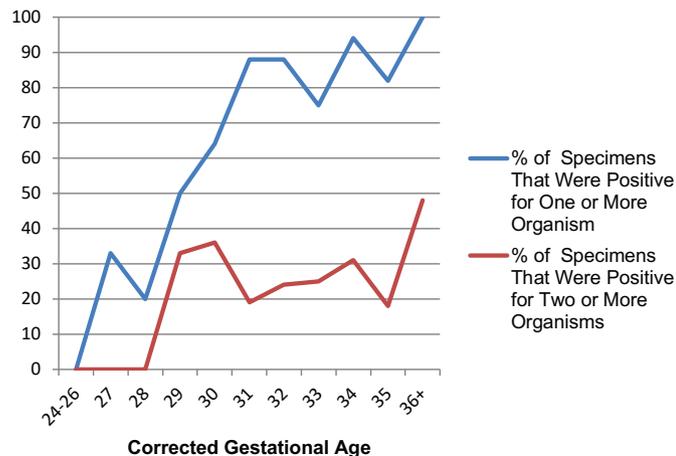


Figure 2. Percent Colonization by CGA for All Specimens

**Statistical analysis:** descriptive statistics were presented as mean, standard deviation, and range for continuous variables, and as frequencies and percentages for categorical variables.

## Results

Forty-six premature infants served as subjects for this study. The mean birth weight for enrolled infants was 1399 grams (SD 479; range 570-2465g) and the mean gestational age was 29 weeks (SD 3; range 23-28 weeks).

A total of 146 O/NGT samples were collected from the 46 infants. Almost 80% of samples grew an organism. The number of samples collected from each infant ranged from 1 to 11, with a mean of 3 per infant. Thirty infants (65%) had at least two samples collected, and 100% of those samples grew an organism. Sixteen infants had only one sample collected, yet 77% of these samples grew an organism.

Table 1 shows O/NGT colonization results for the 146 specimens, and provides a list of organisms together with their frequency distribution. Overall, a large percentage of cultures grew gram-negative organisms (69%; depicted in bold font), whereas 18% grew both gram-positive and gram-negative organisms, 6% grew only gram-positive organisms, 2% grew mixed bacteria, and 23% of specimens had no growth. The most common organisms were *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Klebsiella oxytoca*, and *Escherichia coli*.

The persistence of colonization in O/NGT samples, for each of these five organisms, is depicted in Table 2. For each organism of interest, we determined the number of colonized samples that had a follow-up sample available, and then further determined how many of the follow-up samples were also colonized, with that same organism. For example, for *Klebsiella oxytoca*, there were 15 positive samples that had a follow-up sample available, and of those, 11 were positive on follow-up, demonstrating a persistence rate of 73% for that particular organism.

The percent of colonization in O/NGT samples, by week of life and also by corrected gestational age (CGA) for enrolled infants, is depicted in Figures 1 and 2, respectively. By 4 weeks of life, and/or a CGA of 31 weeks, 90% of O/NGT samples were colonized with one or more organism. Figure 3 shows the percent colonization by CGA for the *five most common organisms*. The highest colonization rates occurred between 30-33 weeks CGA for enrolled infants, with an abrupt peak at approximately 33 weeks CGA.

A further analysis of the data was conducted to determine whether infants who had persistent bacterial colonization of their O/NGTs developed clinical signs of infection. Out of the total sample of 46 infants, 30 had at least 2 cultures done and of these 23 had persistent colonization in their O/NGTs. Gram-negative organisms were found in *all of these cultures*; either alone, in combination with other gram-negative organisms, or in combination with *staph aureus*. Thirteen out of the 23 infants showed clinical signs of infection and required a septic work-up. For 9 out of the 13 infants, the septic work-ups were positive as shown in Table 3. For 5 infants (highlighted in bold font), the same gram-negative organism that was persistent in the O/NGT culture also grew in either the endotracheal tube (ETT) culture or the blood culture. Four out of the five infants were diagnosed with either NEC, L-OS or VAP, with one infant having both NEC and L-OS together.

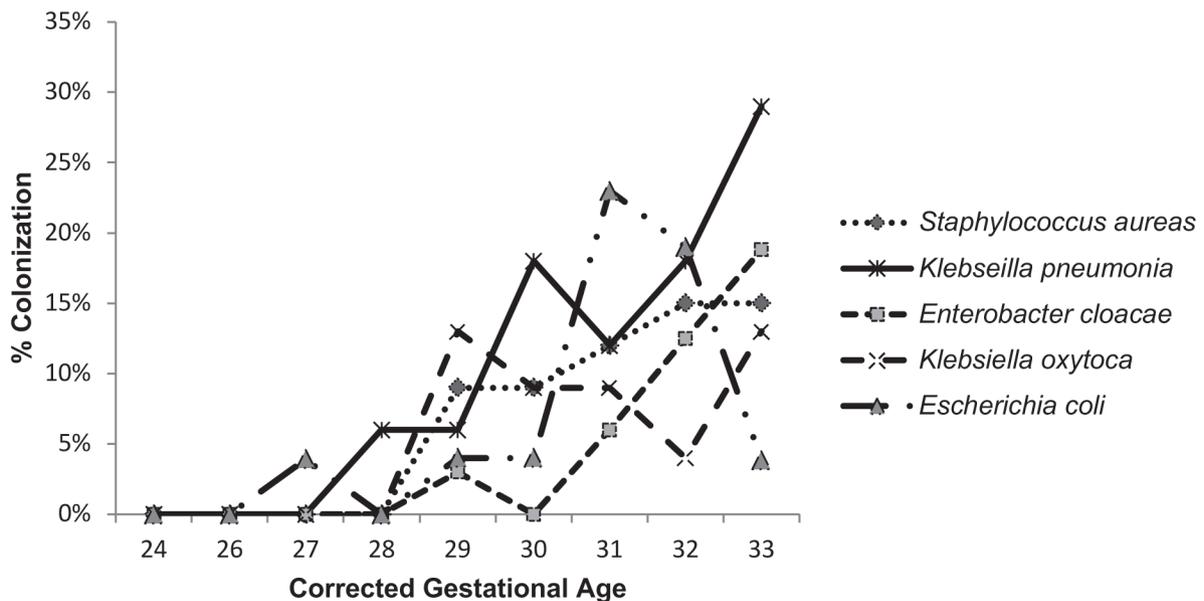


Figure 3. Percent Colonization by Corrected Gestational Age for 5 Most Common Organisms

## Discussion

To our knowledge, this is the first clinical study which sought to prospectively determine the *intracorporeal* colonization profiles and persistence of colonization for O/NGTs in premature infants. Results showed that despite being replaced every 7 days, O/NGTs become colonized quickly with potentially pathogenic gram-negative bacteria. Our data shows that colonization with the same gram-negative organism may become persistent from week to week. The most compelling finding was that colonization increases with post-conceptual age, and increases rather abruptly at around 33 weeks CGA, which is when NEC begins to appear.

Our finding of a microbial pattern with predominantly gram-negative organisms is in agreement with previous studies. In a prospective study involving 50 neonates, the most frequently cultured microorganisms from their O/NGTs included *Enterobacter cloacae* and *Klebsiella pneumonia*.<sup>9</sup> In another prospective study,<sup>10</sup> 129 O/NGTs were collected from two separate NICUs, and results showed that 76% of the O/NGTs were colonized with Gram-negative organisms. The O/NGTs were in place between <6 hours (22%) to >48 hours (13%).<sup>10</sup>

In a recent study<sup>11</sup> investigators sampled the external feeding tube system that connects to the O/NGT. Samples of milk or formula were passed through the external part of the enteral feeding system and then the solution was cultured. The dominant species found were *Staphylococcus epidermis*, *S aureus*, *Enterococcus faecalis*, *E faecium*, *Serratia marcescens*, *Klebsiella pneumonia*, and *Escherichia coli*. The investigators found thick bacterial biofilms inside the external feeding tube and connectors that were used for 24 hours, and noted that these biofilms became more complex in tubes that were used for > 48 hours. The authors concluded that as biofilms age, bacteria (present in these biofilms) can break off in clumps and inoculate the infant's gastrointestinal tract with (NICU) pathogens, when a feeding is administered through the O/NGT.<sup>11</sup>

In another recent study<sup>12</sup> investigators also noted the presence of dense biofilms in both the proximal and distal (intra-gastric) portion of the O/NGT. In this study, a total of 94 O/NGTs were

collected from 34 preterm infants. Each O/NGT was flushed with a 1 ml saline solution, then the (flushed) solution was cultured. Results showed that 89% of the cultures yielded more than 1000 colony-forming units (CFUs) per mL bacteria and over half (55%) grew *Enterobacteriaceae* and/or *Staphylococcus aureus*. This study showed that the O/NGTs from preterm infants in a NICU can yield high densities of potentially pathogenic bacteria, *even within the first 24 hours post-insertion*.<sup>12</sup>

Despite variable methodology, findings from these previous studies concur with ours and show that O/NGTs in the NICU, become quickly colonized with potentially pathogenic organisms; primarily gram-negative bacteria. These opportunistic pathogens likely enter the stomach as a bolus with each enteral feeding.<sup>10</sup> This has important implications for premature infants because they have an immature intestinal mucosal barrier which is vulnerable to injury from pathogens; an initial step in NEC pathogenesis.<sup>4,6</sup> Also, disruption to the mucosal barrier facilitates translocation of pathogens from the gastrointestinal tract to the bloodstream, resulting in bacteremia.<sup>2,13</sup>

A pathogen-predominant gastrointestinal microbiome together with an immature gastrointestinal tract places the premature infant at risk for NEC and L-OS. While the presence of dysbiosis has been linked to NEC pathogenesis, it is not known if a pathogen-colonized O/NGT leads to dysbiosis, and increases the risk for NEC. A small prospective study showed that 57% of neonatal O/NGTs were contaminated with bacteria in significant amounts (mean amount was nearly a million CFU of bacteria) and contamination was associated with poor weight gain, feeding intolerance and possibly NEC in a cohort of 50 premature infants.<sup>9</sup> Ten of the 50 infants had O/NGTs that were contaminated with more than 1,000 CFU of gram-negative bacteria (either *Enterobacter* or *Klebsiella*). Of the 10 infants, 7 were diagnosed with NEC. All 7 infants were formula-fed via the O/NGT and the formula was found to be contaminated with more than 100,000 CFU/mL of gram-negative bacteria. Of the 7 subjects who developed NEC, 4 required surgery, and the intraperitoneal culture taken during the operation grew the same organism that had previously been cultured from the infant's O/NGT.<sup>9</sup> These results suggest a possible link between significant

**Table 1:** Frequency Distribution of Organisms in 146 Oro/Nasogastric Tube Cultures

	Frequency	Percentage
<b>Staphylococcus aureas</b>	34	23.3%
<b>Enterobacter cloacae</b>	32	21.9%
<b>Escherichia coli</b>	26	17.8%
<b>Klebsiella oxytoca</b>	23	15.8%
<b>Klebsiella pneumoniae</b>	17	11.6%
<b>Serratia marcescens</b>	4	2.7%
<b>Enterobacter aerogenes</b>	4	2.7%
<b>Pseudomonas aeruginosa</b>	4	2.7%
<b>Kluyvera species</b>	2	1.4%
<b>Mixed Bacteria</b>	2	1.4%
<b>Gram Negative Rod</b>	2	1.4%
<b>Stenotrophomonas maltophilia</b>	1	0.7%
<b>Klebsiella species</b>	1	0.7%
<b>Citrobacter koseri</b>	1	0.7%
<b>No growth</b>	34	23.3%

The frequencies will not add to 146 and percentages will not add up to 100% inasmuch as most cultures grew more than 1 organism. The percentages here refer to the number of cultures out of 146 that were positive for that organism.

(gram-negative) contamination of neonatal O/NGTs and the subsequent development of NEC however more research is needed in this area.<sup>9</sup>

It is also not known if a pathogen-colonized O/NGT increases the risk for bacteremia, and L-OS. However, in a study involving 698 premature infants, researchers investigated the relationship between gastrointestinal tract colonization (measured by rectal swab surveillance cultures) and subsequent bacteremia.<sup>14</sup> Results showed that 98% of bloodstream infections caused by gram-negative bacilli were preceded by gastrointestinal colonization with the same bacteria species and also the same gentamicin susceptibility profile.<sup>14</sup> Thus, it is plausible that a pathogen-colonized O/NGT can lead to dysbiosis, perhaps through inoculation of pathogens into the stomach with each enteral feeding, as several investigators have suggested.<sup>10-12</sup> The subsequent injury to the immature intestinal mucosa can facilitate translocation of pathogens into the bloodstream.

It is not known whether a pathogen-colonized O/NGT increases the risk for VAP. Researchers have reported a *correlation* between pathogenic organisms in the oropharynx and gastric juices in O/NGT-fed patients, which suggest a *bidirectional transmission of opportunistic pathogens*.<sup>15,16</sup> VAP is a common hospital-acquired infection in critically ill neonates,<sup>3,17</sup> and may occur by aspiration of bacteria that colonizes the oropharynx or

upper gastrointestinal tract of these infants.<sup>17</sup> In our study, for 3 subjects who had persistence of gram-negative colonization in their O/NGTs, the same organism was also isolated in the ETT aspirate culture, and two subjects were diagnosed with VAP. While these findings from our small study cannot show correlation, it is plausible, as previously suggested, that pathogens from bacterial biofilms may enter the stomach as a bolus with each enteral feeding. Bidirectional transmission and subsequent aspiration of these pathogens would lead to VAP.

Our study was not designed, or adequately-powered to determine whether the persistence of bacterial colonization is linked to a higher incidence of NEC, L-OS or VAP. Although we cannot show correlation, the fact that 4 infants who were later diagnosed with NEC, L-OS or VAP had persistent colonization (in their O/NGT) with the same gram-negative organism that was isolated in their blood and/or ETT aspirate culture, is an important finding.

This study was limited by a small sample size and the lack of control over potential confounding variables, including mode of delivery, feeding type and exposure to antibiotics. Nonetheless, this small descriptive pilot study adds to our body of knowledge, demonstrating that (1) O/NGTs are quickly colonized with pathogenic (primarily gram-negative) organisms (2) colonization persists over several weeks despite changing the tube every 7 days and (3) peak colonization seems to occur at approximately 33 weeks CGA which corresponds to the time when NEC typically begins to appear. More research is needed to determine if there is a greater risk for NEC, L-OS or VAP, when O/NGTs are left in place longer than 7 days. Our findings as well as others,<sup>11,12</sup> suggest that the prolonged placement of O/NGTs in premature infants may need to be re-evaluated.

## Conclusions

Results from this pilot study showed that O/NGTs become colonized with potentially pathogenic gram-negative organisms by one week post-insertion, in a small cohort of premature infants hospitalized in the NICU. The O/NGT tip colonization likely reflects gastric pathogens. Gastric colonization with potential pathogens, once established, tends to be persistent despite changing of the O/NGT.

Because of the small sample size and observational design of this study, we did not intend to determine whether there was a statistically significant relationship between O/NGT colonization with pathogens and the development of NEC, L-OS or VAP. Yet, for several subjects, the same gram-negative organism isolated from the O/NGT culture also grew in the blood and/or the ETT culture, and was associated with a later diagnosis of NEC, L-OS or VAP. It is plausible that the O/NGT is likely a portal of entry, and reservoir, for pathogens. Based on our findings and from others, we speculate that indwelling times may potentially

**Table 2:** Persistence Rate for Samples

	Positive Samples	Positive Samples with a Follow-Up Sample	Positive Follow-Up Samples	Persistence Rate	Addition of New Organism in Follow-Up Samples
<b>Staphylococcus aureas</b>	34	18	15	83%	10 (56%)
<b>Klebsiella pneumonia</b>	17	10	8	80%	5 (50%)
<b>Enterobacter cloacae</b>	32	22	17	77%	9 (41%)
<b>Klebsiella oxytoca</b>	23	15	11	73%	6 (40%)
<b>Escherichia coli</b>	26	14	9	64%	7 (50%)



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<sup>1</sup> 2016 GHX market data on single-sterile sales of standalone needleless connectors and single-sterile sales of extension sets with needleless connectors. <sup>2</sup> Tanner J, Neonatal Intensive Care Journal, July-August 2012. Developing a Closed, Intravenous Medication System for a Neonatal Intensive Care Unit.

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**Table 3.** Colonization in Oro/Nasogastric Tube and Culture Results Diagnosis of NEC/Late-Onset Sepsis/VAP

Infant's Gestational Age at birth (weeks)	Oro/Nasogastric Tube		ETT Culture		Blood Culture		Diagnosis of NEC, Late-onset Sepsis or VAP?
	Organism	Positive Cultures/ Cultures done	Organism	Positive Cultures/ Cultures done	Organism	Positive Cultures/ Cultures done	
30	<i>Kluyvera Species</i>	2/3	Not done			0/1	NEC
25	<i>Escherichia coli</i>	1/2	Not done		<i>Escherichia coli</i>	1/1	NEC L-OS
30	<i>Enterobacter cloacae</i>	5/7	Not done		<i>Candida Albicans</i>	1/3	NEC (2 separate episodes)  L-OS
	<i>Serratia marcescens</i>	2/7					
	<i>Klebsiella oxytoca</i>	2/7					
	<i>Staph aureus</i>	1/7					
	<i>Escherichia coli</i>	1/7					
23	<i>Enterobacter cloacae</i>	4/9	<i>Enterococcus species</i>	1/2	CONS	1/5	L-OS
			<i>mixed flora</i>	1/2			
			CONS	1/2			
23	<i>Enterobacter cloacae</i>	5/11	Not done		<i>Enterobacter cloacae</i>	1/5	L-OS
	<i>Staph aureus</i>	2/11					
29	<i>Enterobacter cloacae</i>	2/2	<i>Staph aureus</i>	1/1	<i>Staph aureus</i>	1/1	L-OS
	<i>Klebsiella oxytoca</i>	1/1					
	<i>Klebsiella pneumoniae</i>	1/1					
28	<i>Staph aureus</i>	5/10	<i>Staph aureus</i>	2/5		0/6	VAP
	<i>Enterobacter aerogenes</i>	3/10	<i>Enterobacter aerogenes</i>	3/5			
	<i>Enterobacter cloacae</i>	4/10					
	<i>Klebsiella oxytoca</i>	1/10					
25	<i>Klebsiella pneumoniae</i>	4/4	<i>Klebsiella pneumoniae</i>	2/2		0/2	VAP
27	<i>Klebsiella oxytoca</i>	4/4	<i>Klebsiella oxytoca</i>	1/1		0/2	

contribute to O/NGT colonization and infection risk; therefore we have not changed our practice to replace O/NGT monthly, despite manufacturer's recommendations. Further research is warranted to identify an appropriate indwelling time for O/NGTs in the NICU.

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### Competing interests

The authors declare that they have no competing financial interests in relation to the work submitted.

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# Hypothermia for Neonatal Asphyxia: Past, Present, and Future

G M Savelieva, MD, DSc, L G Sichinava, MD, DSc, R I Shalina, MD, DSc, M A Kurtser, MD, DSc

## Foreword

In the 70's and 80's, I was working on my PhD thesis in fetal physiology at the Russian Research Medical University, and still remember the excitement of the faculty whenever hypothermia research results were presented. It was a group project headed by Professor G. Savelieva, Full Member of Russian Academy of Science. The team included high-risk obstetricians (S Kopshev, L Sichinava, among others), basic science researchers (G Dzhivelegova, the late G Bykova), and a pediatric neurologist (A Burkova). Now, decades later, neonatal hypothermia has become a valuable tool in treating neonatal asphyxia. Today, it is my great pleasure to introduce this review article by Russian researchers discussing the past, present, and future of hypothermia in neonatal medicine.

*BM Petrikovsky, MD, PhD*  
*Professor of Obstetrics and Gynecology*  
*Editorial Board Member*

## Introduction

In adults, induced hypothermia (temperature of 32-34°C) for 12-24 hours improves neurological outcome after cardiac arrest due to ventricular arrhythmias.<sup>1</sup> A reduction of body temperature by 2-3°C (modest hypothermia) following cerebral hypoxia-ischemia reduces the degree of cerebral, metabolic, and biochemical abnormalities.<sup>2-3</sup> The earliest scientific evidence of the possible benefits of hypothermia in animal models were presented by Miller in 1949.<sup>4</sup>

## Past

In 1959, Westin et al.<sup>5</sup> used hypothermia in the treatment of asphyxia neonatorum in the Sabbatsberg Hospital in Stockholm. These authors reported their experience in six cases in which severely asphyxiated infants were resuscitated by either hypothermia or by a transfusion with oxygenated blood.<sup>6-7</sup> Later, hypothermia was used at the Institute of Midwifery, Helsinki, during the period 1961-64 for the resuscitation of 23 severely hypoxic full-term and 6 premature newborns after other resuscitation efforts had proved to be fruitless. Fifteen of the full-term infants and one premature infant survived. Twelve of them have had follow-up examinations at the age of 2-5 years with unexpectedly favorable results.<sup>8</sup>

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## Present

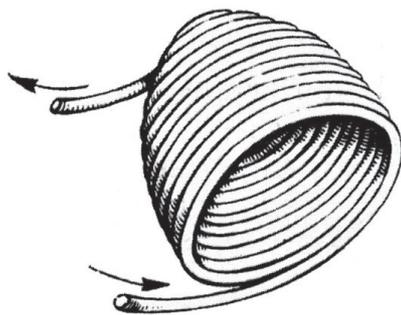
In 1969, our team headed by Professor Savelieva, began using hypothermia to treat asphyxiated newborns at the Pirogov Russian National Research Medical University in Moscow. Our work was inspired by the ideas of Russian cardiac surgeons and anesthesiologists who successfully used local hypothermia during cardiac surgery. This was the first known randomized trial of hypothermia in neonatal medicine. A special piece of equipment known as the cold Cholod-2 was developed for this purpose (Figure 1). The equipment consisted of two communicating two-liter vacuum flasks. One was above the infant and the other below the infant. The flasks were connected to a silicon cap which was applied to the head of the newborn. Chilled water was running continuously through the cap. The temperature of the water was about 4°C. One hundred and sixty-four hypoxic neonates were included in the study group, 33 were placed in the control group (full resuscitation without hypothermia). The neurological outcomes were significantly better in the study group. Inclusion of hypothermia in the resuscitation protocol led to improved acidosis, decreased plasma perfusion, and increased hematocrit. The contraindications to hypothermia were as follows: congenital malformations of the central nervous system and massive bleeding in the brain (subarachnoid, subdural, intraventricular hemorrhage), among others.<sup>9-11</sup> In 2009, we started to use Olympic Cool-Cap equipment and demonstrated that its use was accompanied by a 2-2.5 decrease in severe neurological complications at one year of age.<sup>12</sup> A total body hypothermia has been used since 2016.

Neuronal rescue in hypoxic newborns using induced hypothermia is one of the few therapeutic modalities in neonatology that was studied extensively in animal models. From animal studies, it was noted that brain cooling to approximately 32°C to 34°C for 12 to 72 hours resulted in improved neuropathologic and functional outcomes.<sup>13</sup> Six large randomized clinical trials of hypothermia for neonatal encephalopathy were published from 2005 to 2011.<sup>14-18</sup> In all trials, the infants were at least 35 weeks' gestation at birth; the target temperature was 33.5°C to 34.5°C, and the intervention period was within the first 72 hours of life. The primary outcome measured was the combined rate of death or disability at 18 to 22 months of age. A beneficial effect was noted both in infants who had moderate encephalopathy (RR, 0.67; 95% CI, 0.56-0.81) and those who had severe encephalopathy (RR 0.83; 95% CI, 0.74-0.92). A review by Cochrane Library (evidence-based medicine), which included 11 randomized

controlled trials with a total number of 1505 term and late preterm infants who had moderate/severe encephalopathy, also confirmed the benefits of hypothermia.<sup>17</sup> The reduction in death or major neurodevelopmental disability to 18 months of age in treated infants was 25% overall; 32% for infants who had moderate encephalopathy and 18% for those who had severe encephalopathy.

### Future

It is very difficult to predict the future. However, hypothermia has become a modality with well documented benefits. In a recent interview published in *Neonatal Intensive Care*, J. Beachy suggested that hypothermia should be initiated as soon as possible, within a couple of hours if possible. Regarding the direction hypothermia will take in the next 5-10 years, J. Beachy considered adjunct therapies like EPO and Xenon gas, both of which are already being used in Europe.<sup>19</sup>



The CCH cap (above)

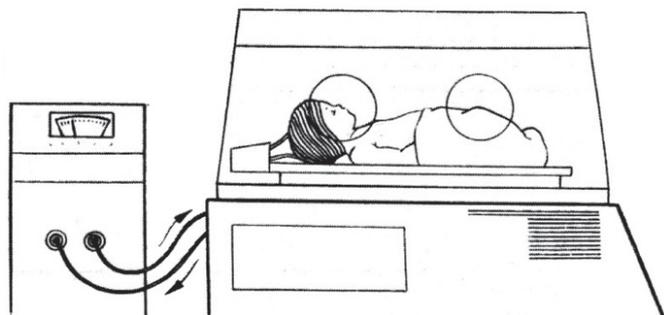


Figure 1. The 'holod-2' device. The cap and intensive care incubator.

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# The Benefits of NIV-NAVA Compared to NIMV

Chris Campbell

When it comes to modes of mechanical ventilation, neurally adjusted ventilatory assist (NAVA) is relatively new. NAVA assists the patient in proportion to the respiratory effort based on the detection of the electrical activity of the diaphragm (Edi) by an array of electrodes built into a modified feeding tube. The Edi is translated into proportional increases in airway pressure in synchrony with, and in proportion to, the patient's respiratory effort. This means patients initiate their own breaths and regulate their own peak inspiratory pressures (PIPs) and inspiratory times (Ti). According to a study by staff at the department of pediatrics at the University of California, the benefits of NAVA are quite significant.

"NAVA, therefore, represents a paradigm shift in ventilatory management, as the standard ventilator settings used in common practice are not used during NAVA," wrote the authors of the research study, *Feasibility and Physiological Effects of Noninvasive Neurally Adjusted Ventilatory Assist in Preterm Infants*.

In the study, the team tested NAVA on infants to see if it was a safe alternative mode of noninvasive support.

## NAVA Testing

In the study, the authors outlined a history of how NAVA has been studied in the past, including its origins with a certain animal that had suffered lung injury.

"The literature has recently been reviewed for older infants<sup>1</sup> and newborns,<sup>2</sup> and practical application has been described by a group with the largest neonatal experience to date.<sup>3</sup> The physiological effects of NAVA have been mainly described in intubated patients. In a retrospective study in intubated preterm infants, there was a reduction in PIP, FiO<sub>2</sub>, and arterial PCO<sub>2</sub> (in infants with baseline PCO<sub>2</sub>>45) on NAVA compared with those on synchronized intermittent mandatory ventilation (SIMV).<sup>4</sup> These authors also performed a prospective, randomized crossover trial<sup>5</sup> that showed a reduction in PIP, FiO<sub>2</sub>, transcutaneous PCO<sub>2</sub> (PtcCO<sub>2</sub>), peak Edi, and respiratory rate on NAVA compared with those on pressure support ventilation (PS). The reduction in the PIP but not in the FiO<sub>2</sub> was confirmed in two randomized crossover studies of intubated preterm infants comparing NAVA with SIMV with PS,<sup>6</sup> and NAVA with IMV or high-frequency oscillatory ventilation.<sup>7</sup> The effectiveness of NIV-NAVA was first demonstrated in rabbits.<sup>8</sup> The first report of

NIV-NAVA in preterm infants was a study performed immediately after extubation<sup>9</sup> that demonstrated an excellent correlation between the PIP and peak Edi in infants both when intubated and after they were extubated, with no correlation between the PIP and Edi on PS. A large clinical experience suggests that NIV-NAVA reduces the need for invasive ventilation.<sup>2</sup> The first systematic study of NIV-NAVA was a randomized crossover study in infants immediately after extubation that demonstrated a reduction in PIP but not in FiO<sub>2</sub> on NIV-NAVA vs. NIV-PS, significantly reduced trigger delay, and asynchrony events, even in the presence of large air leaks.<sup>10</sup>

"We performed a pilot feasibility study in infants on various modes of noninvasive support to introduce NIV-NAVA to our practice. We were able to lower the PIP and FiO<sub>2</sub> in a subset of these infants during NIV-NAVA compared with nasal intermittent mandatory ventilation (NIMV). The resulting data were used to design a randomized, crossover observational study to test the hypothesis that NIV-NAVA could reduce the PIP needed on NIMV while supporting the infant on the same mean airway pressure and overall gas exchange, as determined by pulse oximetry and PtcCO<sub>2</sub>. During both studies, we analyzed detailed recordings of electrocardiogram, oxygen saturation, PtcCO<sub>2</sub>, and infant and caretaker movement using an Acoustic Respiratory Movement Sensor (ARMS). Our secondary outcomes were a comparison of the FiO<sub>2</sub> required to maintain the oxygen saturation in a target range, the character of episodes of desaturation, and infant comfort as reflected in the phasic Edi and the measurements of infant and caretaker movement, as these data have not been described. We chose to study noninvasive support, as it represented the majority of ventilatory assistance in our Neonatal Intensive Care Unit and it had the greatest potential to help neonates recover from respiratory distress syndrome without the need for intubation."

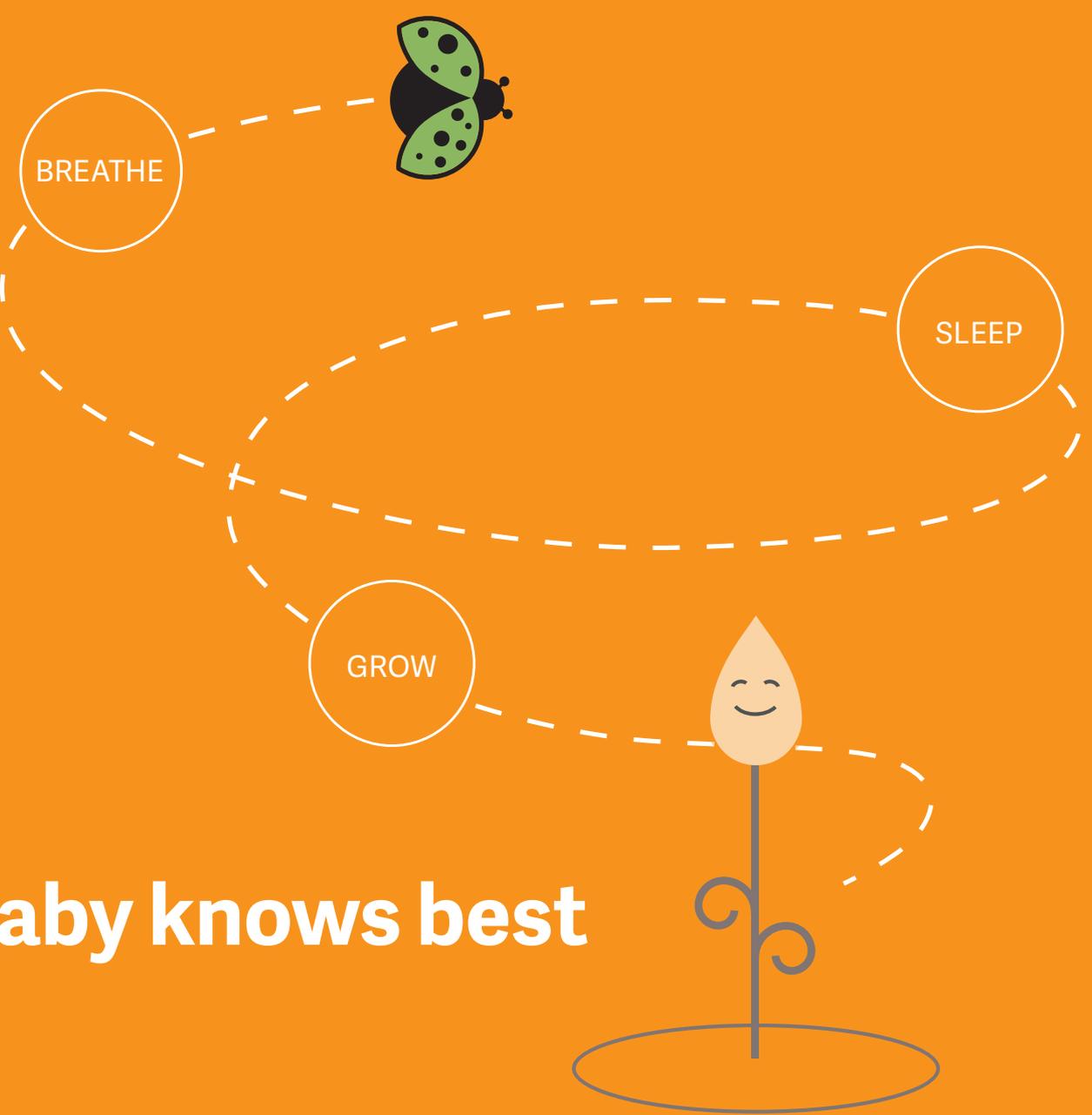
## Study Methods

The pilot study was performed between October 2012 and November 2014, with a subsequent randomized observational study performed between August 2014 and March 2016. Both studies were approved by the Institutional Review Board of the University of California, San Diego under separate protocols. Informed, written parental consent was obtained prior to enrollment.

"Our pilot study was performed in 11 preterm infants, ranging in study weights of 840–2,200 g, who were on NCPAP, NIMV, or high-flow nasal cannula," the authors wrote. "We applied NIV-

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Chris Campbell is the Senior Editor of Neonatal Intensive Care.



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NAVA for 2–4 h on each of 1–5 days during which time the NAVA catheters were in place, and compared the infants' physiological response to NIV-NAVA with that of the other methods. We found that we were able to reduce the PIP of  $33 \pm 12\%$ , ( $P < 0.01$ ,  $N = 10$  recordings) in six infants on NIMV. From this limited data set, a power analysis indicated that this reduction could be verified with 14 crossovers in seven infants ( $\alpha = 0.05$ ,  $\beta = 0.8$ ). We chose to study each infant on 2 days to produce data with more generalizability. We also observed that episodes of desaturation were frequently caused by handling of the infant; so this study was coordinated with the routine nursing care to eliminate handling the infants unless necessary during the NIV-NAVA or NIMV recording periods. Premature infants were eligible for enrollment in the randomized observational study if they were on NIMV and considered clinically stable by the medical team. Infants were excluded if they had congenital airway anomalies, congenital heart disease, neuromuscular disease, feeding intolerance, or gastric or esophageal pathology.

“We compared the mean value of the PIP, saturation histogram data, frequency, depth, and length of episodes of desaturations, peak, tonic and phasic Edi,  $PtcCO_2$ , and infant and caretaker movement from the recording periods in each crossover by the paired t-test or rank-sum test in the case of data that were not normally distributed. The timing intervals were averaged for breaths in each mode in each recording period and compared with their corresponding average within each study day between NIV-NAVA and unassisted breaths by the paired t-test or rank-sum test if the data were not normally distributed.”

## Results

The authors noted the ease that nurses had in using the device, even on such tiny patients.

“We found that nurses, respiratory therapists, and physicians could easily place the Edi catheter in the appropriate position using the positioning window on the Servo-i ventilator. The total time that the Edi catheter was in place for the pilot and randomized studies was 81 patient days. There were no episodes of gastric distention or suctioning malfunction, and Edi catheter did not require repositioning during the time it was in place in both studies.”

The authors also noted that nurses and parents of the infants being tested were pleased with the NAVA results.

“Both nurses and parents of infants subjectively felt that the infants were more comfortable on NIV-NAVA than on NIMV, and fought the ventilator less. This was corroborated by significant reductions in infant movement ( $-42 \pm 9\%$ ,  $P < 0.01$ ) and caretaker movement ( $-29 \pm 8\%$ ,  $P < 0.01$ ) on NIV-NAVA. Caretaker movement was detected in  $< 1.2\%$  of the recording times, indicating that there was little handling of the infants during the recordings. There were no differences in the mean heart rates between NIMV and NIV-NAVA.”

According to the study, the NAVA catheter was used for 81 patient days without complications. NIV-NAVA produced significant reductions (as a percentage of measurements on NIMV) in the following: PIP, 13%  $FiO_2$ , 13% frequency of desaturations, 42% length of desaturations, 32% and phasic Edi, 19%. Infant movement and caretaker movement were reduced by 42% and 27%, respectively. Neural inspiratory time was increased by 39 ms on NIV-NAVA, possibly due to Head's paradoxical reflex.

“We have demonstrated the feasibility of NIV-NAVA with a substantial experience of 81 patient days,” the authors wrote. “The Edi catheter could be placed by the nursing, respiratory therapy, and physician staff with limited experience. With the change to NIV-NAVA, we were able to significantly reduce the PIP and  $FiO_2$  at the same level of gas exchange and mean airway pressure. Short respiratory pauses were reliably detected, and backup breaths were delivered that resulted in a reduction in the frequency and duration of episodes of desaturation. The ventilator returned immediately back to the NAVA mode after providing backup breaths. Infants on NIV-NAVA appeared more comfortable, and had less movement and caretaker intervention, as quantified by the ARMS.”

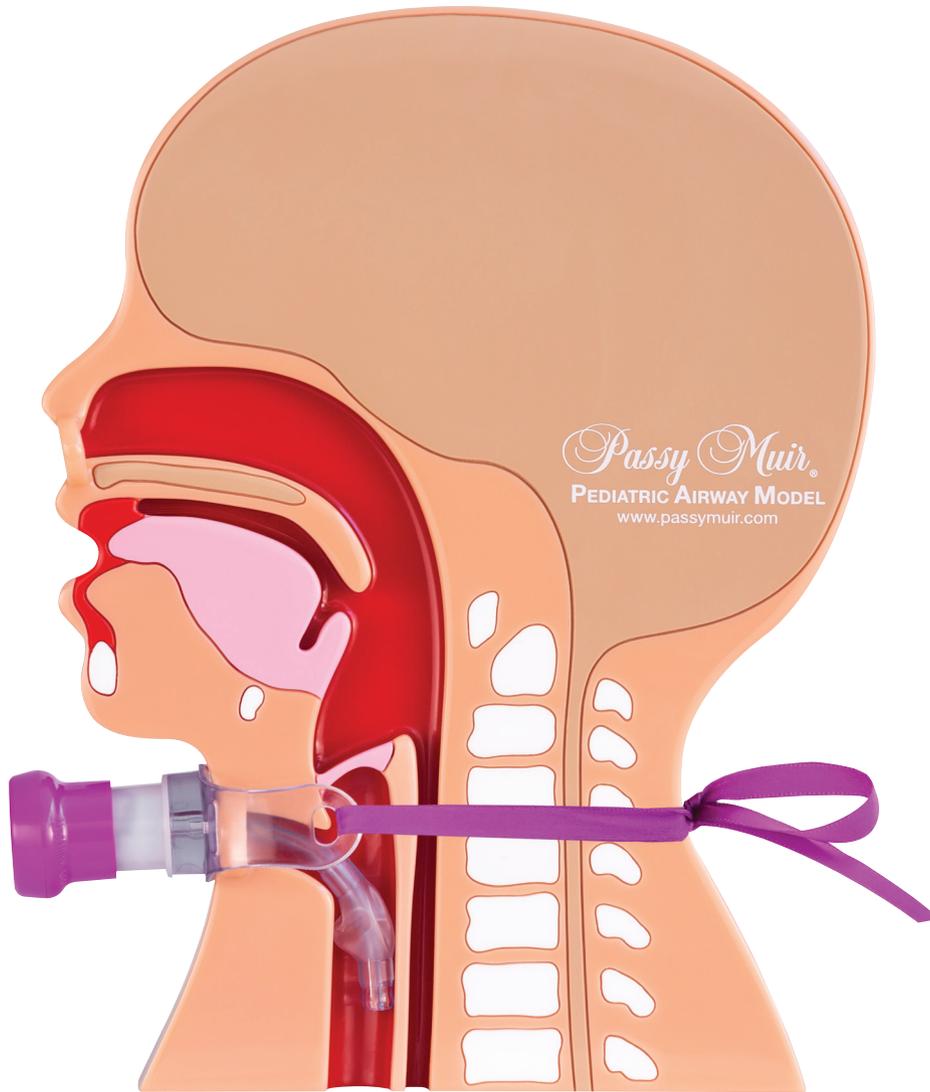
In conclusion, the authors wrote that the “improvements in oxygenation at lower levels of support and the reduction in the frequency and severity of episodes of desaturation, if sustained on NIV-NAVA, could make a difference in the long-term outcomes of BPD or retinopathy of prematurity.

“The safety of NIV-NAVA and its possible longer-term physiological benefits make it a feasible alternate therapy to all current modalities of noninvasive support. A large, randomized clinical trial is needed to determine the effect of NIV-NAVA on important long-term outcomes ... “NIV-NAVA was a safe, alternative mode of noninvasive support that produced beneficial short-term physiological effects, especially compared with NIMV.”

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# Infants and Children Following Tracheostomy and Ventilator Dependence in the Intensive Care Units: Candidacy and Early Intervention with a Bias-Closed, No-Leak Speaking Valve

Laura B Brooks M.Ed, CCC-SLP, BCS-S

Extensive research on the Passy Muir® Tracheostomy and Ventilator Swallowing and Speaking Valve (PMV®) exists within the adult population to support the benefits for voicing, secretion management, physiologic PEEP, swallowing, olfaction, quality of life, speech/language development, weaning and more. However, working with infants and children, who have tracheostomies with or without ventilator support, can be more challenging than adults, and the literature is inadequate for pediatrics (Suiter, 2003). Review of recent literature suggests that about half of all pediatric patients who receive a tracheostomy are younger than 1 year of age (Barbato, Bottecchia, and Snijders, 2012; Lewis, 2003). Early tracheostomy placement provides an opportunity for application of the PMV that may be missed, if the medical team does not have a good understanding of candidacy for Valve use or a practice guideline for PMV application.

Because of the limited research available, it is challenging to have consensus among physicians and clinicians regarding candidacy for Passy Muir® Valve application for medically complex infants and children. This is particularly difficult for infants in the Neonatal Intensive Care Unit (NICU), patients who are ventilator dependent, and individuals with airway compromise (i.e. stenosis, vocal fold paralysis). As a result, there are patients who may be a candidate for Valve placement but are not receiving this intervention due to physician concern for use in what is viewed as a higher risk population. Decreased access to vocalizations from an infant leads to the parents or caregivers missing an opportunity to bond with their baby during reciprocal vocalizing and babbling. Additionally, parents may not be aware of their baby's cry as a sign of stress or the communication of a need.

Therefore, it is critical that all healthcare practitioners have a thorough understanding of the ventilator and the patient's specific settings, including the speech language pathologist (SLP). The team should be knowledgeable regarding how the PMV changes the mechanics of breathing/exhalation when on the ventilator and with the medical comorbidities that may compromise successful PMV application. The medical team and facility should have a practice guideline to ensure consistent practice of PMV application and an understanding of any contraindications.

## Understanding the Ventilator

The PMV was invented for use in-line (for patients who are

ventilator dependent) by a patient who was ventilator dependent. It is a bias-closed, one-way valve that allows inspiratory support from the ventilator and allows 100% of exhalation to occur through the patient's nose and mouth. For best practice, the PMV is typically placed in the ventilator circuit and not directly on the tracheostomy hub. Placement on the hub of the tracheostomy tube may create torque and has the potential to cause erosion, laceration of the skin, and an exacerbation of granulation tissue growth (Keen, Kun, & Davidson Ward, 2017). Because of the variety of hospital and home ventilators and circuits, clinicians and caregivers must understand the differences between them, and the level of support that the patient is receiving from the ventilator.

For example, the Servo and Draeger ventilators may be seen with patients in the intensive care units. These ventilators are precise and most frequently used for higher risk patients who require more ventilator support. Home ventilators, such as the LTV and Trilogy, are more portable, less expensive, and may be used for patients transitioning from the ICU to the acute care floor and then to home. Candidates for home ventilators are children with relatively stable ventilator settings, with lower FIO<sub>2</sub> (<40) and peak inspiratory pressure (PIP) (<40) (Keens et al, 2017).

When working with patients on mechanical ventilation, an understanding of the ventilator settings and patient parameters are essential for all healthcare professionals. There are two primary types of ventilation, pressure controlled or volume-controlled ventilation. The type of ventilation is ordered by the physician depending on the patient's needs. The following terms are some of the common terms related to care of a patient on mechanical ventilation with which the healthcare professional should be familiar:

## Breath Types

- **Volume breath:** ventilator delivers a pre-set volume, regardless of the pressure required to do so. Volume is constant, pressure is variable. (Pressure varies depending on lung compliance/resistance.)
- **Pressure breath:** ventilator delivers a pre-set pressure over a pre-set inspiratory time. Pressure is constant, volume is variable. (Volume varies depending on lung compliance/resistance.)

## Common Modes of Ventilation

- **Pressure Control Ventilation (PC or PC/PS):** ventilator delivers a predetermined # of breaths per minute with a pre-set

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NICU patient with the PMV 007 Aqua valve in-line with mechanical ventilation circuitry. Photo submitted.

pressure over a pre-set inspiratory time. Pressure support may be provided during spontaneous breathing on some ventilators.

- **Assist Control (A/C):** ventilator delivers a predetermined # of breaths per minute using either a specified volume or pressure. All triggered breaths are fully supported.
- **Synchronized Intermittent Mandatory Ventilation with Pressure Support (SIMV/PS):** ventilator delivers a predetermined # of breaths per minute using either a specified volume or pressure. Pressure support is provided during the spontaneous breath.
- **Pressure Regulated Volume Control (PRVC):** ventilator adjusts the pressure delivered during each breath to ensure target volumes are delivered.
- **Pressure support with Continuous Positive Airway Pressure (PS w CPAP):** continuous positive airway is maintained during exhalation, while each spontaneous breath is supported with a set pressure.

#### Ventilator Settings: (what the physician orders)

- **Breath Type:**
  - **Pressure Breaths:** physician orders set pressure.
  - **Volume Breaths:** physician orders set volume.
- **Positive End-Expiratory Pressure (PEEP):** amount of pressure that remains in the lungs at the end of exhalation.
- **CPAP:** continuous positive airway pressure
- **Pressure Support (PS):** positive pressure provided during a spontaneous breath.
- **Respiratory Rate (RR):** number of breaths per minute delivered by the ventilator.
- **Fraction of Inspired Oxygen (FiO2):** The percentage of oxygen the ventilator delivers. For reference, room air has FiO2 of 21%.
- **Tidal Volume (Vt):** volume of gas inhaled with each breath, recorded in cc/ml. Physicians prescribe tidal volume using ideal body weight and lung pathology.

#### Other

- **Peak Inspiratory Pressure (PIP):** The highest level of pressure applied to the lungs during inhalation.
- **End-Tidal Carbon Dioxide (EtCO2):** capnograph measures exhaled CO2. This value can either be found on the ventilator or on a separate machine. EtCO2 readings may indicate the quality of ventilation, cardiac output, and is the gold standard to confirm endotracheal tube placement.
- **Partial Pressure Carbon Dioxide (PaCO2):** measured from an arterial blood sample. Normal values range from 35-45 mmHg.
- **Inspiratory Time/I-Time:** The duration of inspiration in seconds.

#### Indications for the Tracheostomy

When working with this patient population, it is important to understand the patient's indications for a tracheostomy. The disease process and reason for tracheostomy may impact the timing for intervention as it is related to PMV use. With infants and children, several reasons may lead to the need for a tracheostomy. These reasons include neuromuscular deficits, airway obstruction, vocal cord paralysis, severe CNS impairment, craniofacial anomalies, and chronic lung disease (Shaker, and Mutnik, 2012). Often with neuromuscular deficits, patients may have a requirement for prolonged ventilatory support or even have vent dependency. These diagnoses include, but are not limited to, chronic obstruction within the airway, such as Choanal Atresia, Subglottic stenosis, tracheomalacia, laryngomalacia, and bronchomalacia; vocal cord paralysis, leading to chronic aspiration or poor pulmonary toileting with an inability to clear secretions; severe CNS impairment, such as seen with Arnold Chiari, Werdnig - Hoffman, and Congenital Hypoventilation Syndrome; Craniofacial anomalies, such as Pierre Robin Sequence, Treacher Collins, Beckwith - Wiedemann, and CHARGE Syndrome; and Chronic Lung Disease, such as BPD (Shaker and Mutnik, 2012). Timing of interventions and establishing access to the upper airway for communication, speech-language development, cough, and other pulmonary functions is crucial. Early intervention and use of a PMV provides benefits which may assist in the recovery process.

If the patient has neurologic indications for a tracheostomy, the lungs are healthy, but the muscles are weak, thus these patients generally do not require frequent changes in ventilator settings (Keen et al, 2017). For patients with upper airway anomalies requiring a tracheostomy, the ability of the patient to adequately exhale around the tracheostomy tube is a concern and would need to be considered during the evaluation. This diagnosis may even require a Direct Laryngoscopy and Bronchoscopy (DLB) to be performed by the Otolaryngologist. This assessment would address the severity of the obstruction. Because of the wide variety of causes for a tracheostomy, the history provides crucial information that may impact the assessment process.

#### Application of the PMV: How to Maximize Safety and Success

Understanding the value of the PMV application for our patients and the benefits that may be achieved assist with improving patient use and care. However, many patients are underserved due to lack of clinician and physician consensus for understanding the range of benefits and in determining candidacy. Members of the medical team may ask such questions as: is this patient too young? too small? too sick? on too much PEEP? Can the patient tolerate the PMV with any degree of airway obstruction or narrowing?

The benefits for using a bias-closed, one-way valve have been reported in the literature and include access for the infant to communicate via cry/sounds; improved taste and smell; ability to generate subglottic pressure for cough, cry, and swallowing; reduction in the potential for further vocal cord dysfunction; restoration of laryngeal/pharyngeal sensation; and improved secretion management (Hull et al, 2005; Torres, 2004). Abraham (2009) investigated the use of a PMV in children and reported that children wearing a Passy Muir Valve during waking hours normalized secretion management within 2 weeks due to improved sensation of secretions. Benefits also have been reported for reducing time to decannulation and restoring physiologic PEEP, which led to diminished WOB (work of breathing) (Hull et al, 2005; Torres, 2004; Sutt et al, 2016).

Review of the current literature supports safety of PMV application with certain patients, providing for various ages and medical comorbidities. Passy Muir Valves have been used with both pediatric and adult populations, with the PMV being used with infants as young as 1 day old and within the NICU (Torres, 2004; Engelman & Turnage-Carrier, 1997). Some specialists might have concerns that an infant's airway is too small and will not have enough room around the tracheostomy tube (Torres, 2004). However, the concerns related to upper airway patency may be assessed in two different ways: visual observation by the otolaryngologist via DLB and/or testing with manometry. If it is determined initially that the patient's upper airway is not patent via endoscopy or manometry, then the infant should be retested during their admission. Retesting is warranted because an infant or young child may have significant improvement in airway patency secondary to changes in age, weight, and size of the trachea.

Once it is established that the patient is a good candidate and has a patent upper airway, additional criteria is considered. For Valve placement, the following criteria may be considered for patients who are ventilator dependent:

- a. The patient must tolerate cuff deflation. Set the patient up for success by slowly deflating the cuff. Some patients may even require deflation to take place over several minutes to adjust to the change in airflow (Hess, 2014)
- b. PMV in the pediatric population should be trialed following patient's first trach change. The first trach change is often done by the surgeon as the immature stoma poses some risk for damage (Hess, 2014)
- c. The patient must be hemodynamically stable
- d. Contraindications for PMV application:
  - i. Significant upper airway obstruction (eg grade 4 subglottic stenosis )
  - ii. Thick secretions
  - iii. Foam filled cuff, as these cuffs cannot be safely deflated (Hofmann, Bolton, & Ferry, 2008)
  - iv. With the Trilogy ventilators: For the Passive circuit, you can only use a PMV with patients who require pressure ventilation. With an active circuit, you can only use PMV with patients who are volume ventilated
- e. FiO<sub>2</sub> <50%
- f. PEEP < 10 cm H<sub>2</sub>O
- g. PIP/PAP= <40

*\*although some institutions follow the guideline to apply if PEEP is 12 or less.*

It is recommended that the medical team continue to apply humidity through a heated humidifier. However, a heat-moisture exchanger (HME) should not be used with PMV, as no exhaled gas passes occurs through the tracheostomy tube when the valve is in place (Hess, 2014).

When using the Passy Muir Valve during mechanical ventilation, respiratory therapists may make some adjustments under physician direction to improve patient comfort and safety. Some common, simple adjustments may include:

- **Reduction or elimination of PEEP:** The establishment of a closed respiratory system and exhalation through the oronasopharynx, restores physiologic PEEP. This enables the clinician to reduce/eliminate set mechanical PEEP (Sutt et al, 2016). This adjustment may also eliminate any unnecessary continuous airflow within the circuit. Continuous flow in the circuit may make it difficult for the patient to close his vocal cords and may stimulate continuous coughing and autocycling of the ventilator.
- **Volume Compensation:** For patients with inspiratory volume loss, after cuff deflation, additional tidal volume can be provided until baseline peak inspiratory pressure (PIP) is reached. An increase in delivered tidal volume may be a temporary adjustment until strength of the pharyngeal and laryngeal muscles is regained. When considering use of a PMV with mechanical ventilation, factors such as inspiratory support may be managed by insuring the patient achieves baseline Peak Inspiratory Pressures (PIP).
- **Alarm Adjustments:** All alarms on the ventilator must be re-evaluated for appropriate adjustments before, during, and after use of the valve.

Adjusting alarm settings are dependent upon facility policy. Patient safety is the priority and proper management of the ventilator is key. With a good understanding of the ventilator alarms and the changes that the PMV applies to the respiratory system, the members of the care team may advocate for alarm adjustments (ordered by the physician). It is recommended that



**Figure 1.** Pressure testing equipment.

a procedure be in place to identify when settings have been changed. Proper documentation allows for the ventilator to be returned to the appropriate settings when the PMV is removed.

### **Manometry: Measuring Transtracheal Pressure and Ensuring Airway Patency**

To address the issue of the airway and atypical airflow, the step of assessing airway patency with manometry may provide information to the medical team regarding the patient's ability to adequately exhale around the trachea. If there is obstruction and the patient cannot adequately exhale, pressure can incrementally increase with each breath, known as *breath stacking* or *air trapping* (Hess 2005, Hofmann et al, 2008). Additionally, a higher end expiratory pressure reading with manometry may indicate patient discomfort, even if the patient is not breath stacking.

For medically complex infants in the ICUs, initiating Transtracheal Pressure testing as part of every PMV assessment is a helpful tool in providing objective feedback to physicians and the team regarding safety and readiness for valve application. Transtracheal pressure (TTP) testing equipment (see Figure 1) includes a manometer to be applied within the ventilator circuit with O<sub>2</sub> tubing and a Washington Tee piece. Adapters, such as 15 mm or 22 mm, may be added into the circuit as well. The assessment team, typically respiratory and speech pathology, determine how to place the valve with and without the manometer into the circuit.

TTP value is the number at the *end* of exhalation or end expiratory pressure with resting breaths only. The TTP represents the patient's physiologic PEEP, since the placement of the PMV has eliminated the PEEP from the ventilator and restored the patient's physiologic PEEP. An adequate TTP reading gives feedback to the team that the airway is patent, and the patient can adequately exhale around the trachea, out to the mouth and nose.

TTP measurements may be challenging in the pediatric population as any movement or vocalization will increase the pressure and compromise the ability to read it. If an infant is crying, moving, vocalizing, or pushing, the pressures will be increased, and this should not be considered a true read. One option to circumvent behavioral interference is to obtain TTP reading while the patient is sleeping, which provides a reading at rest, and can be done in as little as 20 seconds. However, the team should take into account that despite current literature supporting application of the PMV during sleep (Barraza, Fernandez, Halaby, Ambrosio, Simpser, & Pirezada, 2014), use during sleep is not an FDA listed benefit. Alternatives would be to place the TTP device while the patient is in a drowsy state or distracted by a toy or video.

However, currently, the research studies regarding TTP measurements are not consistent with the recommendation for what Value is deemed acceptable. Research reports different numbers as to what TTP reading demonstrates that the airway is considered patent, and the patient may comfortably and adequately exhale around the tracheostomy tube. One study suggested that a tracheal pressure greater than 5 cm H<sub>2</sub>O during passive exhalation may indicate excessive expiratory resistance (Hess, 2005). Another study indicated that with pressures in the range of 2-6 cm H<sub>2</sub>O the patient would have no difficulty wearing the PMV and would exhale through the

mouth and nose without difficulty; however, the same study also indicated that children with end expiratory pressures up to 10 cm H<sub>2</sub>O could be tolerated with a PMV in place (Utrarachkij, Pongsasongkul, Preutthipan, & Chantarojanasri, 2005). And in yet another study Trotter (1995) reported that patients with end expiratory pressure of 15 cm H<sub>2</sub>O could use the PMV. Due to the inconsistent findings, further research of this area is warranted, especially since TTP measurements provide an objective way of establishing the patency of the upper airway.

When assessing TTP with patients on a ventilator, obtaining accurate TTP readings requires a good understanding of respiratory and ventilator basics such as PIP and PEEP. Due to the increased complication of taking these measurements while a patient is on the ventilator, it may be useful to test via manometry with a closed circuit and adapter as an initial step in order to view the patient's baseline pressures. Generally, the manometer without PMV will read PIP (inhale) to PEEP (exhale) values similar to what is set by the ventilator. For example, if the patient's ventilator is set to a PEEP of 8 and a PIP of 20, the manometer should fluctuate between 8-20 cm H<sub>2</sub>O with each breath, although sometimes the PIP value on the manometer can be slightly lower than the ventilator PIP. So, once the SLP and RT obtain a patient's manometry baseline, the PMV is placed in-line with the manometer and adapters. With resting breaths only, the TTP reading is the value again at the *end* of exhalation. It is important that the clinician does not read the high number as the inhale/PIP and the low number as the exhale/PEEP. In fact, with initial placement the high number can initially be the exhale but then once the patient settles and resting breaths are measured the high number is the PIP or inhale. It is helpful to watch the patient and the manometer, while the RT monitors the ventilator. If the RT provides a verbal indicator of when an inhale or PIP occurs or indicates when the patient should be at the end of exhalation, then proper reading of end expiratory pressure will occur. Watching the infant's chest rise and fall has been helpful as well. Since TTP readings can be impacted by position, patient state, and behavior, the SLP and RT should ensure that the measurements taken occur with true resting breaths to increase accuracy of the readings. With some patients, this may take multiple sessions.

If the TTP measurement is too high, the patient is breath stacking, or the patient seems uncomfortable with exhalation through the nose and mouth, the following should be considered:

- 1) A repeat DLB/endoscopy to examine the airway
- 2) Tracheostomy tube downsizing
- 3) Changing from a cuffed tracheostomy tube to a cuffless (Hess, 2005).

It should be noted airway patency and TTP measurements are just one step in the assessment process. Therefore, it is important that the SLP and RT offer the opportunity to use the valve safely and consistently to progress the patient both with wear times and for improved function (Hull et al, 2005).

In summary, the Passy Muir Valve provides many benefits to infants and families; yet is often overlooked as an option for medically complex babies in the intensive care or acute care units. It is critical that the Speech-Language Pathologist has a thorough understanding of the PMV benefits, instructions for application, and contraindications to help the medical team (Respiratory Therapists, Otolaryngologists, Pulmonologists, Neonatologists, etc) identify candidates for Valve trials.

Education plays a key role in preparing all team members with the knowledge necessary to overcome the barriers to PMV use. Establishing protocols and practice guidelines for PMV use in each facility also provides an opportunity for improving patient care and providing early intervention that may lead to faster weaning and decannulation as appropriate.

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# Empowering NICU Moms to Produce Colostrum

Deb Discenza

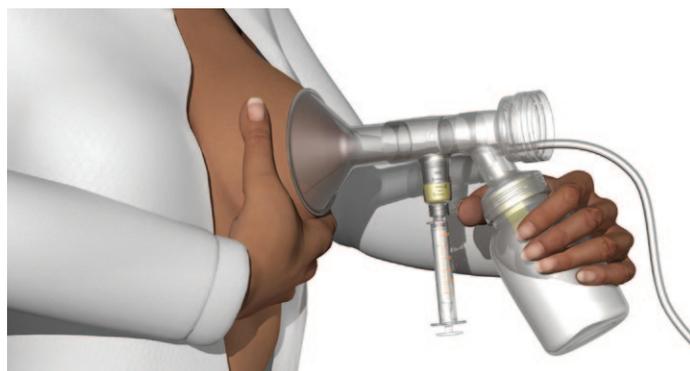
In today's baby-friendly focused Neonatal Intensive Care Units (NICUs) breastfeeding is a discussion that requires definition because of the layered needs of the baby and the mother. Gone are the moments of simply putting the newborn to the breast. Instead breast pumps are used, hand expression provided when necessary and more. With the strong interest in asking a mother to provide colostrum for her infant, NICUs have to make that effort count in terms of collection, amount used and overall experience that could lead to ongoing milk production and ultimately feeding at the breast. Enter Jules Sherman the creator of the colostrum collection device — Primo-Lacto<sup>®</sup>. The research behind this simple yet sophisticated product is a game-changer for the NICU mothers and babies. I sat down with Ms. Sherman to find out more about this innovative device:

**Deb Discenza:** What challenges in the patient experience and the staff experience in the NICU space led to creating Primo-Lacto<sup>®</sup>?

**Jules Sherman:** My own experience in the hospital led to the invention of Primo-Lacto<sup>®</sup>. After my daughter was born by way of vacuum assist (there was a shoulder dystocia) she had a bruised jaw and wouldn't latch properly. I was given a urine cup to hand express into and I thought, "Wow, this is archaic!" I watched the nurses scraping the colostrum off the sides of the cup with a plastic cafeteria spoon and then transferring that to a syringe. Pumping colostrum leads to the material getting stuck in the pump valve. I watched nurses trying to scrape the colostrum out of the pump flange and valve. Later when I joined a mother's group at Stanford, I learned that I was not the only one who had issues breastfeeding in the hospital and at home. Other mothers and the group's lactation consultants validated the need.

**DD:** What is the older method for colostrum collection and how does that impact user experience, patient health, overall costs of the unit and payers of healthcare?

**JS:** Well, every hospital has different work-around methods, but as I stated above, pumping and hand expression into any kind of clean container is the norm. Transferring colostrum from a capturing container to a feeding container (usually a syringe)



Hand-Expression. Photo illustration submitted.

increases the potential for contamination and infection to the neonate, so I was interested in creating a closed system for colostrum collection with Primo-Lacto<sup>®</sup>. The PL pump adapter intercepts the colostrum before it has a chance to go into the pump valve and redirects the colostrum directly into an enteral syringe. There are two designs for Primo-Lacto<sup>®</sup>: One set that fits slip fit enteral syringes and another that fits the new ENFit<sup>®</sup> enteral syringes.

**DD:** In the studies leading up to the release of the product what was the response of the users (nurses and mothers) in using the product?

**JS:** With the help of a grant from the New England Pediatric Device Consortium (NEPDC) I had the opportunity to run clinical focus groups prior to creating molds and running the clinical trial in hospitals with patients. I went to seven hospitals and at each hospital I placed the 3D printed prototypes on the table with the pump parts and syringes and all the nurses/LCs would understand how it was used immediately. I hardly had to explain anything because it's a very intuitive system. The response was always something like, "of course, why hasn't this existed already?" This encouraged me to apply for two more grants, a full seed from the NEPDC and a grant from The National Capital Consortium For Pediatric Surgical Innovation (NCC-PDI Award) at Children's National Hospital in DC. These grants allowed me to run the clinical study at three different hospitals: Sharp Mary Birch, John Muir and Indiana Memorial of South Bend. I received interim feedback after about 30 mothers were tested. I presented the data at the Stanford Nursing Symposium in 2016. You can see the interim results at <https://bit.ly/2LhWLVg>. I was testing for ease of use (nurse and mom) as well as percent of colostrum lost and the nurse's time

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Deb Discenza is the proud mother of Becky, who was born at 30 weeks and is now 14 years old. Deb is the head of PreemieWorld LLC ([www.PreemieWorld.com](http://www.PreemieWorld.com)), co-author of The Preemie Parent's Survival Guide to the NICU, and the founder and leader of the 42,000+ member Inspire Preemie Community (<http://preemie.inspire.com>).



The ENFit® syringe is shown being used with the NeoMed DoseMate® attachment, making it easier to feed the infant directly from an ENFit® syringe.



to collect. Final study results will be published soon in a peer reviewed journal. One thing I learned while actively trying to sell the device is that some breast pump companies don't care about hand-expression, they only care about pump expression, so they were only interested in the adapter. Pump companies are in the business of selling pumps, so it's no surprise that they don't particularly want to encourage hand expression even though incorporating this technique is best practice. I was thrilled to find a company (Lansinoh®) to acquire the two-part system (pump adapter and hand-expression funnel), as they understand alternating between pump/hand expression is proven to help moms in the early days of lactation. Primo-Lacto® will be distributed worldwide through Lansinoh® starting May 2018. Lansinoh will offer a full two-part system kit and a hand expression only kit. The kits will come in slip-fit and ENFit® connector designs so they can fit either syringe style.

**DD:** How do you see this product helping baby-friendly hospitals positively impact breastfeeding rates?

**JS:** By making collection easier we will see more mother successful at collecting their colostrum and experiencing less frustration with the process. In addition, by improving the

quantities collected, we will see improved outcomes for babies. Handing a mom a urine cup to hand express into is not respectful and does not elevate the process of collection/feeding. Using a pump that traps colostrum in the valve is not helpful either. Pumps are not designed for the viscous quality of colostrum. Primo-Lacto® solves the pump colostrum collection conundrum with a simple adapter and hand-expression funnel. I created the PL kit to be a two-part closed system. There are two breast pump adapters (for double pumping) and one hand expression funnel in every full kit. Lansinoh will also be offering a separate kit just for hand-expression (only the funnel). The research clearly shows that HOP (hands-on pumping) and direct hand expression yields the most colostrum and the fattiest colostrum.<sup>1</sup> I want to encourage mothers to alternate between both techniques.

Besides helping mothers in modern hospitals, we will sell Primo-Lacto to low-resource clinics in developing nations. Since Primo-Lacto® can be used with hand-pumps, and of course for hand-expression, the product may be utilized everywhere for mothers who have preterm babies or babies who are having trouble latching on.

**DD:** Are there any health risks to using this product?

**JS:** No.

**DD:** You created a clinical study around this product. Can you tell us the outcome of that research?

**JS:** From the patient perspective, ease of use and confidence were better with the colostrum collection system for both hand-expression and pump-expression. For nurses, ease of use was better and percent of colostrum lost was less with the colostrum collection system for both hand-expression and pump-expression. There was a 75% increase of colostrum collected while using the hand-expression funnel + syringe, and a 45% increase of colostrum collected while using the pump adapter + syringe (as opposed to standard practice). The collection times were not significantly different. Themes common for standard hospital practice included difficulty with colostrum collection and wasted colostrum. Themes common for pump with Primo-Lacto® and the PL hand expression funnel included greater colostrum collection and ease of use.

With a product like Primo-Lacto® coming to market, I find, as a parent, that this will increase some form of breastmilk helping NICU infants across the unit. As a parent seeing the effects of colostrum on my own daughter born prematurely, I can tell you the incredible feeling is akin to winning the lottery. Neonatology should focus on whatever win can be had to help that NICU infant and to properly support the mother into making smart choices without guilt or bullying. It is my belief that Primo-Lacto® can be that game-changer.

### **Issued Patents**

US8979819, US8998879, US9782526, and recent notice of allowances, to be issued soon: US20150065996, US20150148783, US20170095600.

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# Enlightenment: Using Phototherapy Properly

Shabih Manzar, MD

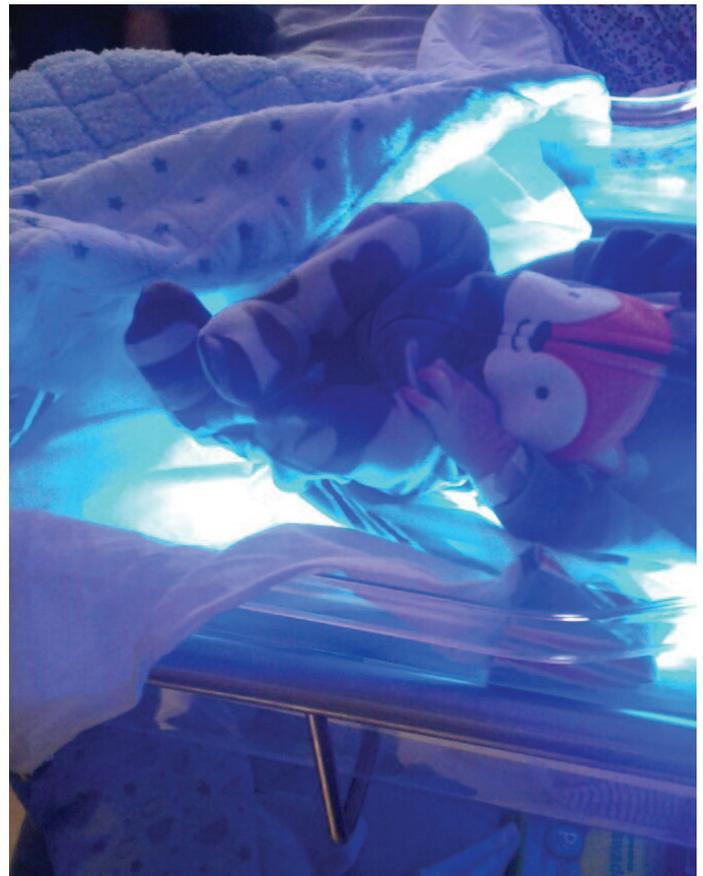
Hyperbilirubinemia is a common problem in newborn infants. Almost all newborn infants manifest jaundice in the first few days of life. In the absence of risk factors, most of the cases of hyperbilirubinemia can be managed conservatively. There are resources available that can guide the clinician on the plan of action and need for phototherapy in newborn infants.<sup>1,2</sup> To encourage maternal bonding and save on the hospital cost, home phototherapy could be used in certain cases.<sup>3</sup> In hospitals that have room-in facilities prior to discharge or that follow a couplet model or family integrated model, phototherapy could be used in a family room. But the use of room phototherapy could have potential errors.

As depicted in the picture (Figure 1) the infant was essentially not receiving any phototherapy. He was dressed completely and the only bare area of skin exposed were the hands. This could happen if parents are not told completely about the use of phototherapy. With proper nursing supervision the chances of this occurring is minimal. However, no assumption should be made as parents could be of different intellect.

It is therefore essential for the medical staff to explain the logistics of phototherapy when room or home phototherapy is used. Explain to the parents the need for and actions of phototherapy, particularly in relation to the need for skin surface to be exposed to the phototherapy light. Potential complications of phototherapy and the need for protective eye coverings during phototherapy treatment should be explained. The need for measuring the transcutaneous or serum bilirubin should also be explained.<sup>4</sup>

A simple checklist should be followed:<sup>5</sup>

- Place infant in bassinet with diaper on and eye protection in place.
- Position phototherapy device at bedside with lights set at recommended distance from the infant (~30 cm for overhead light). For fluorescent and LED lights, this is as close as possible to the infant's skin, typically less than 10 cm. If using a halogen spot light, the light should be kept at the manufacturer-recommended distance to avoid overheating.
- Turn on the phototherapy lights.
- Direct light towards the infant with exposure of maximal surface area. If halogen spotlights are used, more than one



**Figure 1.** Picture showing inappropriate use of phototherapy

light may be required to cover the entire infant with light. This is typically done with one light directed at the chest and head, with the second directed at the abdomen and legs.

- Bilirubin check (serum or transcutaneous) should be done within 24 hours.

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- 5 <https://emedicine.medscape.com/article/1894477-technique>

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# ***B. infantis* Colonization Creates A Protective Environment In The Infant Gut**

Tracy Shafizadeh, PhD

## **The Infant Gut Microbiome**

The gut microbiome plays an active role in human immune function, metabolism and neurological processes, and the composition of the gut microbiota is a factor in overall health or disease. The infant gut microbiome plays a particularly important role in human health, as it is directly involved in early immune programming and metabolic function.<sup>1</sup> The organisms that comprise the infant gut microbiome are initially acquired at birth, and differ dramatically depending on birth mode and infant diet.<sup>2,3</sup> Vaginally delivered infants are exposed to maternal vaginal and colonic microbes, allowing for rapid colonization of *Bifidobacterium* and *Bacteroides* in the breastfed infant. However, infants delivered by Cesarean-section are not exposed to the same maternal microbes as vaginally delivered infants, and are instead rapidly colonized with bacteria commonly found on the skin and the environment such as *Escherichia*, *Staphylococcus*, *Streptococcus* and *Clostridium*. This C-section associated gut dysbiosis has been linked to both acute and chronic disorders, such as colic, eczema, asthma, allergy, obesity and T1D.<sup>4</sup>

In addition to birth mode, infant diet plays a significant role in shaping the infant gut microbiome, as breastmilk is known to contain specific carbohydrates, called human milk oligosaccharides (HMO), that are indigestible by the infant and instead serve as food for gut microbes. The ability to metabolize HMOs differs among bacterial species, and the infant-adapted *Bifidobacterium longum* subsp. *infantis* (*B. infantis*) has been well documented to provide maximum utilization of HMO.<sup>5</sup> Alternatively, infant formula does not provide an equivalent food for the gut microbiota, and therefore does not support the colonization of known protective gut microbes found in the breastfed infant.<sup>6</sup>

## **Protective Effects of *B. infantis* Colonization**

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. As described above, *B. infantis* is uniquely adapted to metabolize HMO, and in turn, prevents the loss of this breastmilk component through fecal excretion. In a recent clinical study, breastfed infants who were colonized with *B. infantis* showed a 10-fold reduction in fecal excretion of HMO compared to breastfed infants who were lacking

*B. infantis*.<sup>7</sup> This reduction in HMO excretion was further associated with improved stooling patterns, where *B. infantis* colonized infants showed significantly fewer loose, watery stools compared to controls infants.<sup>8</sup> The metabolism of HMO by *B. infantis* 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, inhibiting growth of potential gut pathogens such as *Escherichia coli* and *Clostridium difficile*.<sup>9</sup>

In fact, in a recent clinical study breastfed infants fed *B. infantis* EVC001 (commercially available as Evivo<sup>®</sup>) showed a **93% reduction in potentially pathogenic bacteria**, along with an **85% reduction in pathogen associated virulence factors**, compared to breastfed controls.<sup>10</sup> Taken together, colonization of *B. infantis* in the infant gut is thought to create a protective environment, reducing the abundance and virulence of pathogenic bacteria and maximizing the utilization of breastmilk nutrients.

## **Restoring the Dysbiotic Infant Gut with *B. infantis***

Although the infant gut microbiome is expected to be colonized by *B. infantis* during the first months of life, modern medical and dietary practices such as C-section delivery, antibiotic use and formula feeding over the past century have disrupted the transfer of *B. infantis* from mother to infant at birth, and have led to a generational loss of *B. infantis* from the infant gut microbiome.<sup>9</sup> Clinical studies have now shown a marked increase in the abundance of potentially pathogenic bacteria in infants who are missing *B. infantis*, and this loss of a protective intestinal environment could have a profound impact on real time infection risk, as well as long term predisposition for auto-immune and inflammatory disorders later in life. Probiotic restoration of *B. infantis* to the infant gut microbiome has now been clinically demonstrated.<sup>7</sup> In this study, exclusively breastfed infants fed *B. infantis* EVC001 daily for 21 days showed stable and persistent *B. infantis* colonization throughout the supplementation period, as well as a full month after supplementation had ceased, as long as infants continued to consume breastmilk.

As we continue to better understand the critical role of the infant gut microbiome in establishing long term health trajectory, these data provide evidence that resolution of infant gut dysbiosis is possible, and stable restoration of *B. infantis* leads to significant and protective effects in the infant gut.

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# Correlation Between Serum Vitamin D Level and Neonatal Indirect Hyperbilirubinemia

Shahrokh Mehrpishah<sup>1</sup>, Azadeh Memarian<sup>2\*</sup>, Abolfazl Mahyar<sup>3</sup> and Negin Sadat Valiahd<sup>3</sup>

## Abstract

**Background:** Considering the significant prevalence of Neonatal Indirect Hyperbilirubinemia (NIH) and its irreversible neurological complications, identifying the factors involved in the prevalence of neonatal jaundice is essential. The present study was conducted to determine the relationship between serum vitamin D levels and the prevalence of NIH in infants admitted to Qods Hospital of Qazvin in Iran in 2015–16.

**Methods:** In this case-control study, 30 term infants with NIH (the case group) were compared with 30 healthy, non-icteric, term infants (the control group) in terms of serum levels of 25-hydroxyvitamin D. The results were analyzed and compared between the two groups using t-test and the Chi-square test.

**Results:** The mean and standard deviation of serum 25-hydroxyvitamin D levels were  $10.76 \pm 8.6$  ng/dl in the case group and  $14.88 \pm 11.38$  ng/dl in the control group. There were no significant differences between the two groups ( $P = 0.11$ ).

**Conclusion:** The results suggest the lack of a relationship between vitamin D levels and NIH. However, further prospective studies are needed to conclude that vitamin D has no role in the pathogenesis of NIH.

**Keywords:** Infant, Vitamin D, Hyperbilirubinemia, Neonatal

## Background

Neonatal indirect hyperbilirubinemia (NIH) is a prevalent issue among newborns [1]. NIH may have some detrimental complications such as long term neurologic deficits and death [2]. Any problem which rises bilirubin production and decreases conjugation can cause NIH [3]. Some of the causes of neonatal jaundice include blood group incompatibility, sequestration, G6PD deficiency, polycythemia and infections, while in most cases, there are no known causes [4]. Recent studies have shown the presence of vitamin D receptors in some of the cells derived from different tissues such as the liver, pancreas, brain and prostate as well as on the surface of immune cells, including lymphocytes and macrophages [5, 6]. Moreover, vitamin D

activation occurs through 25-hydroxylation in the liver followed by 1-hydroxylation in the kidney [7, 8]. This metabolite can also be synthesized in various cells, including monocytes, skin cells and the placenta during pregnancy [9]. The liver tissue is not only involved in vitamin D synthesis, but also plays a key role in converting indirect bilirubin to direct bilirubin [10]. The metabolisms of bilirubin and vitamin D happen in two separate paths, but they may affect each other since one stage of their synthesis takes place in liver. The 25-hydroxylation stage, one of the main phases of vitamin D synthesis, takes place in the liver, as well as bilirubin conjugation [11]. So far, few studies have examined the relationship between hyperbilirubinemia and neonatal serum vitamin D [12, 13]. Given the high prevalence of jaundice and the importance of identifying its risk factors, understanding the relationship between these two can play a positive role in the diagnosis and treatment of neonatal jaundice. The present study was therefore conducted to investigate the relationship between serum vitamin D levels and hyperbilirubinemia in infants admitted to Qods Hospital in 2015–16.

## Methods

In this case-control study, 30 eligible infants with hyperbilirubinemia were compared with 30 healthy infants admitted to Qods Hospital in Qazvin, Iran, after obtaining a written consent from their parents. Hyperbilirubinemia was determined by bilirubin test that determine the bilirubin level in blood. Increasing of the bilirubin level more than 5 mg/dl was considered as hyperbilirubinemia. The infants were examined in terms of serum 25-hydroxyvitamin D level over 1 year. The term infants with a gestational age of 37–42 weeks and a postnatal age of three to 10 days, weighing 2500–4000 g and with no evidence of apparent anomalies, congenital anomalies, hematoma or symptoms suggesting infections as confirmed by a physician entered the study. Moreover, the infants with Rh or ABO incompatibility and with urinary infection, hypothyroidism, and children with direct or conjugated bilirubin  $> 0.8$  were excluded from the study. The two groups were homogenized in terms of confounding and underlying variables such as age, gender, birth weight, gestational age, type of delivery, type of nutrition, place of residence, vitamin D supplementation during pregnancy, the mothers' disease history, the mothers' medication history, the families' socioeconomic status, the mothers' and the infants' 25-hydroxyvitamin D level and the infants' Ca (calcium), P (phosphorus), ALP (Alkaline phosphatas) and Mg (magnesium) levels. Infants whose mothers had a history of liver, kidney, thyroid and metabolic diseases such as diabetes or consumed a

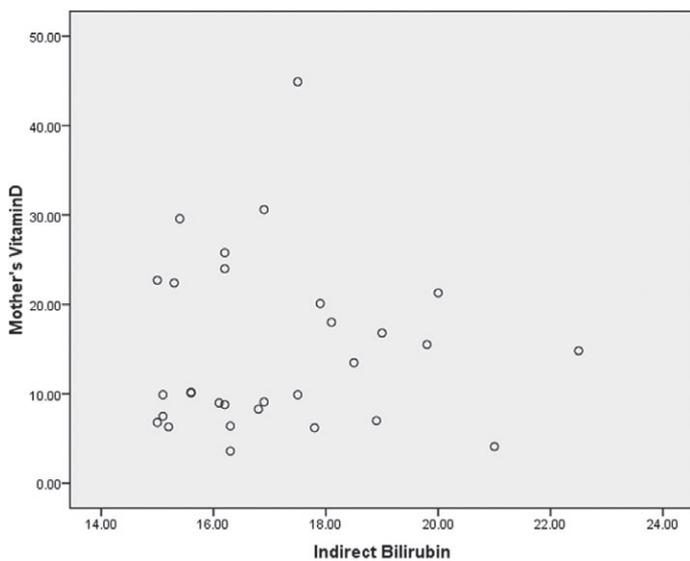
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**Table 1.** A comparison of the mean demographic variables between the infants in the case and control groups and their relationships.

Variables	Study group (n = 30)	Control group (n = 30)	P
Male/Female (n)	17/13	15/15	0.605
Postnatal age (day)	5.6 ± 1.75 (3–10)	6.26 ± 1.87 (3–10)	0.160
Birth weight (gr)	3266 ± 365 (2700–3950)	3287 ± 326 (2850–3820)	0.815
Postnatal weight (gr)	3215 ± 378 (2500–4100)	3244 ± 330 (2800–3800)	0.753
Head circumference (cm)	34.9 ± 1.01 (33–37)	34.98 ± 1.06 (33–37)	0.757
Height (cm)	50.43 ± 1.75 (46–53)	50.00 ± 1.41 (47–52)	0.297
Gestational age (week)	38.2 ± 1.3 (37–40)	38.4 ± 0.7 (37–40)	0.910
Delivey type: SVD/ C/S (n)	19/11	16/14	0.432
Breast feeding [n (%)]	30 (100)	30 (100)	0.321

SVD: Spontaneous vaginal delivery; C/S: Cesarean section  
T-test and frequency and percentage are the tests used in this table

specific medication such as anticonvulsants were excluded from the study. The hospitalized icteric infants who were candidates for phototherapy based on the American Academy of Pediatrics entered the study after undergoing the required tests and the rejection of hemolytic icterus, sequestration, polycythemia and infections by a neonatologist. The infants' weight, height and head circumference were measured by standard methods (the infants were weighed with a Seca weighing scale with a precision of 500 g). To measure serum 25-hydroxyvitamin D levels, 3 cm<sup>3</sup> of blood was taken from the infants, its serum was separated, and stored in a freezer at -20°C until the test time. Considering the potential impact of phototherapy on serum vitamin D levels, the first serum sample of the icteric infants before the phototherapy was used for the tests. The 25-hydroxyvitamin D test was performed with the ELISA method (EIA or enzyme immunoassay), an ELISA Reader device called Awareness (made in the US), kits with a 2.7 ng/ml sensitivity and a batch number



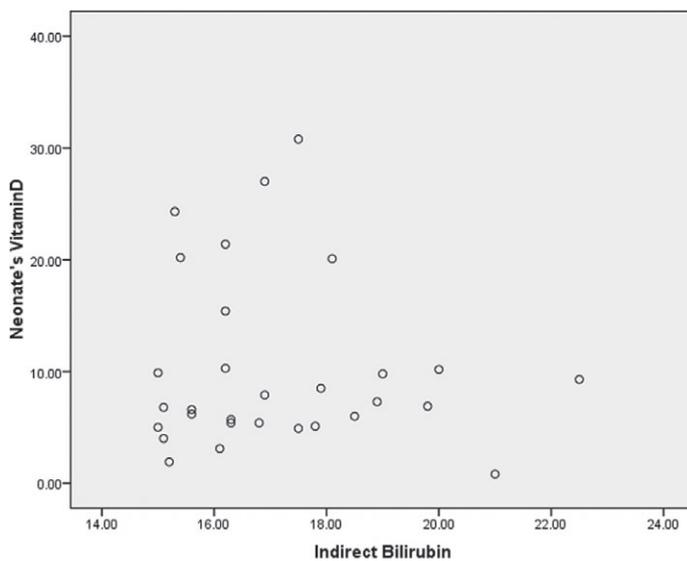
**Fig. 1** The relationship between serum vitamin D levels in the mothers and the infants' indirect bilirubin levels: Indicates the lack of a relationship and correlation between the two variables (Pearson's Correlation Coefficient = 0.97).

= 34,408, 33,737 (made by IDS in Germany) at the laboratory of Qods Hospital. All the biochemical and bilirubin tests were performed using photometry with an Auto Analyzer (Prestige 24i model, made in Japan), and the Ca level was measured with the help of Cresolphthalein Complexone, P with a UV test, ALP using the DGKC's (German Society for Clinical Chemistry's) method, Mg with Xylidyl Blue and total bilirubin with 2,4-dichloroaniline DCA. Based on the available sources of data, serum 25-hydroxyvitamin D levels were categorized as follows [14]: Very severe vitamin D deficiency = Less than 5 ng/ml, Severe vitamin D deficiency = 5–10 ng/ml, Vitamin D deficiency = 10–20 ng/ml, Suboptimal vitamin D provision = 20–30 ng/ml, Optimal vitamin D level = 30–50 ng/ml Upper normal = 50–70 ng/ml.

Data were statistically analyzed in SPSS-16. The frequency percentage, mean and standard deviation were used for the descriptive analysis of the data. The t-test was used to compare the two groups in terms of the mean quantitative variables and the Chi-squared test to compare them in terms of the mean qualitative variables. Data was statistically significant at P < 0.05.

## Results

In this study, 60 term infants admitted to Qods Hospital of Qazvin were examined in two groups, including 30 infants with hyperbilirubinemia who were candidates for phototherapy in the case group and 30 healthy infants without jaundice in the control group. None of the subjects withdrew from the study, and the number of patients in each of the case and control groups remained the same until the very end. All the infants were breastfed and none had started receiving supplementation with formula. The mothers' type of clothing was similar in the two groups. All the infants were cared for by their mothers and they were all Iranian in ethnicity. The infants were compared between the two groups in terms of demographic variables, including gender, age, birth weight, weight at the time of the visit (postnatal weight), height, head circumference, gestational age and type of delivery. No significant differences were observed between the two groups (Table 1); (P > 0.05). There were no significant differences between the two groups in terms of maternal variables such as the mothers' age, BMI, vitamin D supplementation during pregnancy, number of deliveries



**Fig. 2** The relationship between serum vitamin D levels and indirect bilirubin in the infants: Indicates the lack of a relationship and correlation between the two variables (Pearson's Correlation Coefficient = 0.64).

**Table 2.** Comparison of the mean demographic variables between the mothers in the case and control groups and their relationships

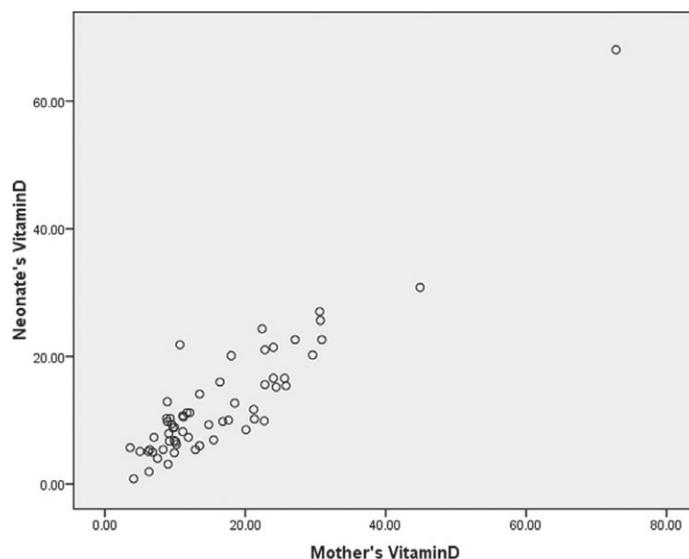
Demographic characteristics of the mothers' cases and controls [mean ± SD (min-max)]			
	Study group (n = 30)	Control group (n = 30)	P
Mother age	27.13 ± 4.45 (17-33)	26.63 ± 6.85 (15-42)	0.739
Mother BMI	27.63 ± 4.41 (21.9-36.7)	25.41 ± 3.04 (21.5-33.6)	0.280
Abortion's number	11	8	0.584
Delivery number	60	66	0.665
Mothers' vitamin D use:			
Regularly [n (%)]	4 (13)	3 (10)	0.247
Irregularly [n (%)]	3 (10)	8 (27)	
None [n (%)]	23 (77)	19 (63)	

T-test and frequency and percentage are the tests used in this table  
 BMI: Body mass index

and number of abortions (Table 2); ( $P > 0.05$ ). There were no statistically significant differences between the two groups in terms of socioeconomic status, including the number of children, household size, the bedroom/household size ratio, family income, place of residence (urban/rural), the mother's occupation and education and the father's occupation and education ( $P > 0.05$ ). The icteric infants had a mean hemoglobin of  $16.63 \pm 1.61$ , a mean hematocrit of  $48.05 \pm 4.8$ , a mean total bilirubin of  $17.55 \pm 2$ , and a mean indirect bilirubin of  $17.12 \pm 1.92$ . In the case group, 22 infants (73.3%) were hospitalized at Qods Hospital for phototherapy for 2 days, six infants (20%) for 3 days, one infant (3.3%) for 4 days and one infant (3.3%) for 5 days. The signs of jaundice appeared in the infants in the case group three to 7 days after birth and the time of blood sampling for measuring the vitamin D level was three to ten days after birth in both groups and the two groups were thus similar in terms of the time of taking the blood samples. There were no significant relationships between the two groups in terms of laboratory parameters such as Ca, P, Mg and ALP (Table 3); ( $P > 0.05$ ). The mean serum vitamin D level in the mothers was  $14.72 \pm 9.60$  in the case group and  $17.71 \pm 12.66$  in the control group, suggesting the lack of a statistically significant relationship (Fig. 1); ( $P = 0.119$ ). Finally, the two groups were compared in terms of serum vitamin D level in the infants (i.e. the main objective of the study). The mean serum vitamin D level was  $10.76 \pm 8.60$  in the icteric infants (the cases) and  $14.88 \pm 11.38$  in the healthy infants. Although the mean serum vitamin D level was lower in the infants with indirect hyperbilirubinemia than in the healthy infants, no significant differences were observed between the two groups and serum vitamin D level was not significantly related to neonatal jaundice (Figs. 2 and 3); ( $P = 0.119$ ).

## Discussion

The study found no relationships between serum vitamin D levels in infants and the prevalence of Neonatal Indirect Hyperbilirubinemia (NIH). Although the mean serum vitamin D level was lower in the infants with NIH compared to the healthy infants, no significant differences were observed between the two groups and serum vitamin D level was not significantly related to the prevalence of NIH [15]. About two-thirds of newborns develop clinical neonatal jaundice (serum bilirubin level  $> 5$  mg/dl) and more than 97% of term and preterm infants develop biochemical hyperbilirubinemia (serum bilirubin level  $> 1$  mg/dl); [16, 17]. Clinical guidelines recommend identifying the causes of hyperbilirubinemia and adopting effective prevention strategies [18]. Identifying the treatable etiology of hyperbilirubinemia and preventing its prevalence, which



**Fig. 3** The relationship between serum vitamin D levels in the infants and the mothers: Indicates the lack of a relationship and correlation between the two variables (Pearson's Correlation Coefficient = 0.00).

comprised the objectives of the present study, are essential. A similar prospective study by M. Mutlu et al. [19] investigated the relationship between vitamin D level and neonatal hyperbilirubinemia in term infants and compared vitamin D levels in infants with pathologic hyperbilirubinemia and healthy infants with normal or physiological levels of bilirubin. The results showed statistically significant differences between the control and case groups in terms of 25-hydroxyvitamin D levels ( $P = 0.01$ ). A significant negative relationship was also observed between vitamin D levels and the parathyroid hormone in the infants ( $P = 0.03$ ). Mutlu's study was conducted over 1 year on infants aged three to ten days and born at a gestational age of 37-40 weeks who had a serum bilirubin level requiring phototherapy (group 1 or the case group) and healthy infants of the same age but without jaundice or with physiological jaundice only (group 2 or the control group). Both groups were examined at identical time periods in terms of their birth weight, gestational age, neonatal age, weight at the visit, type of delivery, gender, type of nutrition, mother's age, mother's type of clothing, place of residence (geographical region), vitamin D supplementation during pregnancy, the mother's disease history and the mother's medication history during the pregnancy, which could affect the level of vitamin D. Infants born to mothers with symptoms of chronic liver disease and kidney disease or those who regularly used anticonvulsants were excluded from the study [19]. Just

**Table 3.** A comparison of the mean laboratory parameters in the case and control groups and their relationships [mean  $\pm$  SD (min-max)]

Variables	Study group (n = 30)	Control group (n = 30)	P
Ca (mg/dL)	9.21 $\pm$ 0.73 (7.7–10.7)	9.30 $\pm$ 0.58 (8.2–10.4)	0.256
P (mg/dL)	5.98 $\pm$ 0.82 (4.6–7.6)	5.73 $\pm$ 0.69 (4.3–7.3)	0.173
ALP (U/L)	409 $\pm$ 102 (247–647)	373 $\pm$ 106 (232–680)	0.895
Mg (mg/dL)	1.95 $\pm$ 0.20 (1.7–2.4)	1.99 $\pm$ 0.16 (1.7–2.3)	0.075
Neonate's 25-OH vit D (ng/mL)	10.76 $\pm$ 8.60 (0.8–30.8)	14.88 $\pm$ 11.38 (5.1–68)	0.119
< 5 ng/mL [n (%)]	5 (17)	0 (0)	
5–10 ng/mL [n (%)]	16 (53)	10 (33)	
10–20 ng/mL [n (%)]	3 (10)	14 (47)	
20–30 ng/mL [n (%)]	5 (17)	5 (17)	
30–50 ng/mL [n (%)]	1 (3)	0 (0)	
50–70 ng/mL [n (%)]	0 (0)	1 (3)	
Mother's 25-OH vit D (ng/mL)	14.72 $\pm$ 9.6 (3.6–44.9)	17.71 $\pm$ 12.66 (5.0–72.8)	0.307
< 5 ng/mL [n (%)]	2 (7)	0 (0)	
5–10 ng/mL [n (%)]	12 (40)	8 (27)	
10–20 ng/mL [n (%)]	7 (23)	12 (40)	
20–30 ng/mL [n (%)]	7 (23)	7 (23)	
30–50 ng/mL [n (%)]	2 (7)	2 (7)	
50–70 ng/mL [n (%)]	0 (0)	1 (3)	

Ca calcium, P phosphate, ALP alkaline phosphatase, Mg magnesium, 25-OH vit D 25-hydroxy vitamin D  
t-test and frequency and percentage tests are used in this table

as in the discussed study, the present study considered all these criteria, with few differences, including examining infants with a gestational age of 37 to 42 weeks and following up on all the infants in the control group until 15 days and eliminating the cases of physiological jaundice from the control group, such that even suspicions about very mild jaundice only in the sclera meant exclusion from the study. The groups were also homogenized in terms of their demographic variables and socioeconomic status. A study by E. Dan-Ierodiaconou et al. (1980) on the effect of phototherapy on vitamin D metabolism examined ten infants with jaundice under phototherapy treatment. The infants' 25-OHD, 24, 25(OH)2D, Ca and P levels were measured before phototherapy and 24 and 48 h after the procedure was over. The mean weight of the infants was 3.4 kg, their mean age 64 h, their mean bilirubin level was 17.1 mg and their mean duration of phototherapy 83 h. The causes of jaundice included G6PD deficiency, Rh incompatibility, blood type incompatibility and unknown factors. For their phototherapy, the infants were placed under seven lamps positioned 60 cm above them and were fed with cow's milk containing no vitamin D. The results of the study showed that the skin of infants with jaundice treated with phototherapy does not convert pro-vitamin D to active vitamin D [20–22]. A similar study by Gillies DR et al. (1984) on the effect of phototherapy in infants with neonatal jaundice on the production of vitamin D measured the 25(OH) VitD level before and 48 h after phototherapy. The results of the study showed no significant increase in active vitamin D levels 48 h after phototherapy [23]. Given the disparities in the results of the discussed studies and the potential impact of phototherapy on serum vitamin D levels, blood samples from the case group were sent to the laboratory for measuring the infants' serum vitamin D level before starting phototherapy in the present study. In Mutlu's study, hemogram, peripheral smear, reticulocyte count, blood group, direct Coombs, bilirubin, free T4, TSH, Ca, P, Mg, ALP, PTH and 25(OH) VitD testing was performed on all the infants. Ca, P, Mg, ALP, PTH, 25(OH) VitD

and blood group testing was performed on all the mothers too. Given the existing imitations, the present study measured only Ca, P, Mg, ALP and 25(OH) VitD in the infants and 25(OH) VitD in the mothers. The objective of the present study was to evaluate the relationship between hyperbilirubinemia and serum vitamin D levels –not to assess the etiology of vitamin D deficiency; as a result, PTH, TSH and free T4 were not measured in this study. Considering the exclusion of infants with physiological icterus, the total and indirect bilirubin levels were not measured in the control group. Hemogram, peripheral smear, reticulocyte count, blood group, direct Coombs and G6PD activity testing were performed in all the icteric infants in the case group and the cases of hemolytic icterus, as diagnosed by the neonatologist, were excluded from the study. Mutlu's research was a case-control study with a one-on-one design that was conducted on 51 infants, since some of the families that were entered into the study withdrew, and 30 infants with hyperbilirubinemia ultimately remained in group 1 and 21 healthy infants remained in group 2. In terms of laboratory parameters, bilirubin levels were significantly higher in group 1 compared to in group 2, while there were no statistically significant differences between the two groups in terms of Ca, P, Mg and ALP in the infants and Ca, P, Mg, ALP, PTH and 25(OH) VitD in the mothers. There was a significant difference between the two groups in terms of serum 25-hydroxy vitamin D levels and a significant negative relationship was also observed between vitamin D levels and PTH. Vitamin D deficiency was reported in 86% of the infants in group 1 and vitamin D inadequacy was reported in 7%. The case group had a significantly more severe degree of vitamin D deficiency compared to the controls, but there were no significant differences between the two groups in terms of vitamin D inadequacy. In the present study, none of the participants withdrew from the study because the parents were given adequate explanations, the physician visits were free and the families incurred no additional costs. The findings of this study showed a statistically significant difference between the

control group and the infants with hyperbilirubinemia in terms of 25-hydroxyvitamin D level. There was also a significant negative relationship between vitamin D level and the parathyroid hormone in the infants. This disparity could be due to the high prevalence of vitamin deficiency D among Iranians, which led to an inadequate mean serum vitamin D level in both groups.

## Conclusion

The result of this study showed no relationships between vitamin D levels and NIH. In spite of a fact that, a larger statistical population was examined in this study compared to previous studies, more extensive research or a cohort study or an animal study is still needed to generalize the result of this study.

## Limitations

A multivariable linear regression model with the infants' indirect bilirubin as the outcome measure controlling for confounders and a regression model with infant Vitamin D as outcome and maternal Vitamin D as exposure to assess relationship would be helpful but unfortunately we weren't able to do it in this study.

## Abbreviations

ALP: Alkaline Phosphatase; G6PD: Glucose-6-Phosphate Dehydrogenase; NIH: Neonatal Indirect Hyperbilirubinemia; PTH: Parathyroid hormone

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## Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

## Authors' contributions

SM and AM conceived and led the design of the study, analyses, and drafting of the article. SM, AM 1, AM 2, and NSV distributed the survey and collected survey responses. AM 1 wrote the first draft of the paper. SM, AM 1, AM 2, and NSV contributed to the discussion of the results, revisions, and approval of the manuscript. AM 2 conducted the extraction of data and data analysis. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The study is approved by ethical committee of Qazvin University of Medical Sciences. Written consent was obtained from the parents of the participants in this study.

## Competing interests

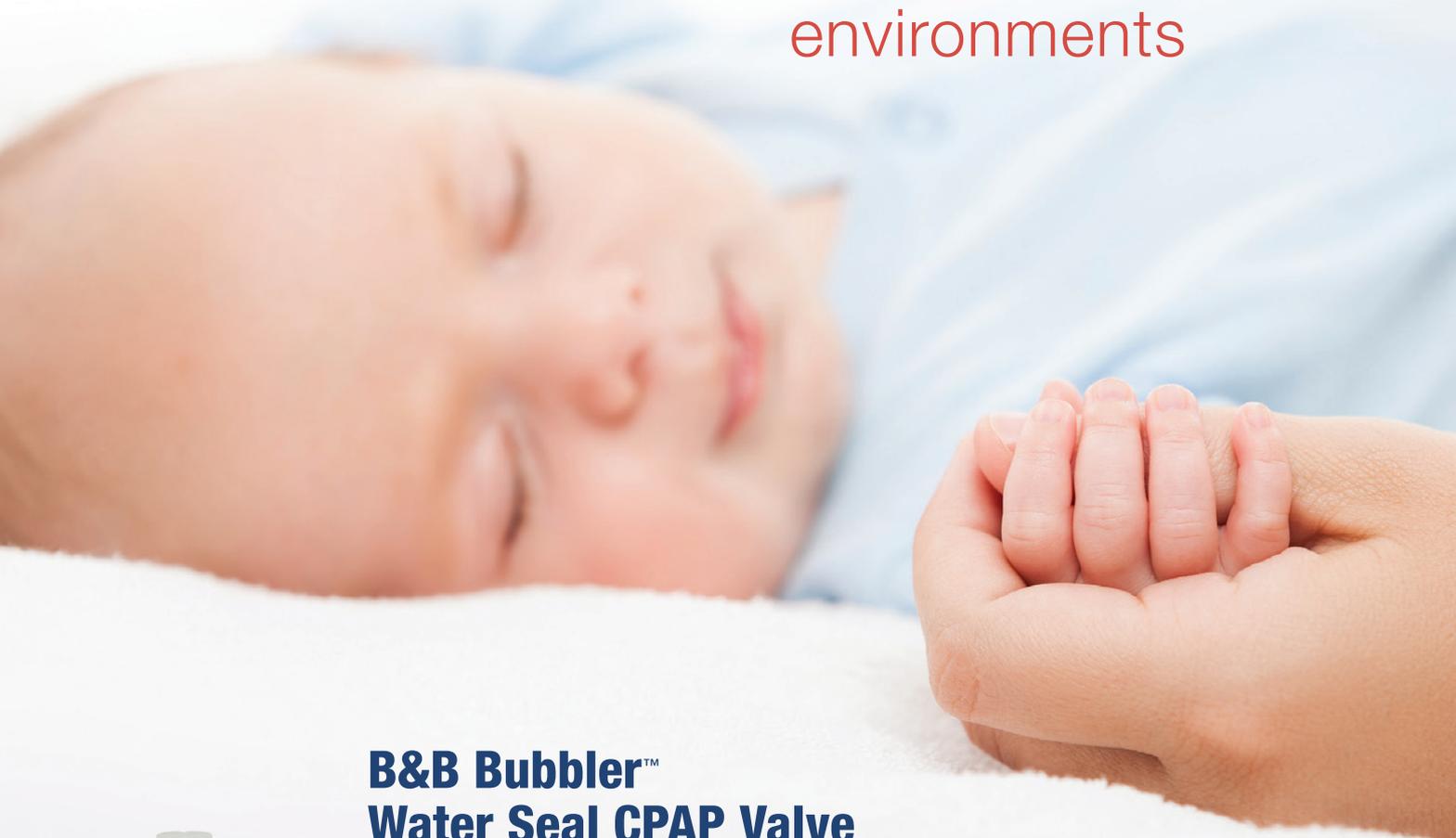
The authors declare that they have no competing interests.

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\* Outcome measures were statistically based on mean weight data.

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