

An abstract painting of a face, rendered in a style reminiscent of Vincent van Gogh's 'Owl' or 'Self-Portrait with Bandaged Ear'. The face is composed of bold, expressive brushstrokes in a variety of colors including red, yellow, blue, green, and purple. The eyes are large and swirling, and the overall composition is dynamic and textured. The title 'neonatal INTENSIVE CARE' is overlaid on the top left, with 'neonatal' in a smaller font and 'INTENSIVE CARE' in a large, bold, white font. The subtitle 'The Journal of Perinatology-Neonatology' is in a smaller, black font below the title. The volume and issue information 'Vol. 25 No. 5 September 2012' is in the top right corner. The content highlights are listed in the bottom left corner.

# neonatal INTENSIVE CARE

Vol. 25 No. 5  
September 2012

The Journal of Perinatology-Neonatology

**NURSING  
BREAST MILK  
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NANN PREVIEW**





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\*A post hoc analysis excluding Retinopathy of Prematurity (ROP); photoreceptor sensitivity assessed by full-field electroretinogram.

**References:** 1. Rubin LP, et al. *Journal of Perinatology* advance online publication, 14 July 2011; doi:10.1038/jp.2011.87. 2. Kanako IN, et al. *Arterioscler Thromb Vasc Biol.* 2007;27:2555-2562. 3. Canfield LM, et al. *Eur J Nutr.* 2003;42:133-141. 4. Schweigert FJ, et al. *Eur J Nutr.* 2004;43:39-44. 5. Patton S, et al. *Lipids.* 1990;25:159-165. 6. Jewell VC, et al. *Proc Nutr Soc.* 2001;60:171-178. 7. Connor SL, et al. *FASEB.* 2008;22:451-454.

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# neonatal INTENSIVE CARE

Vol. 25 No. 5  
September 2012

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## Editorial

### Late Preterm/Early Term

A recent study in BMC Pregnancy and Childbirth discusses a topic worth looking at: "The influence of gestational age and socioeconomic status on neonatal outcomes in late preterm and early term gestation: a population based study."\*

The paper proceeds from the fact that infants born late preterm (34 + 0 to 36 + 6 weeks gestational age) are known to have higher neonatal morbidity than term (37 + 0 to 41 + 6 weeks GA) infants. There is emerging evidence that these risks may not be homogenous within the term cohort and may be higher in early term (37 + 0 to 38 + 6 weeks GA). These risks may also be affected by socioeconomic status, a risk factor for preterm birth.

A retrospective population based cohort of infants born at 34 to 41 weeks of GA was assembled; individual and area-level income was used to develop three socioeconomic (SES) groups. Neonatal morbidity was grouped into respiratory distress syndrome (RDS), other respiratory disorders, other complications of prematurity, admission to a Level II/III nursery and receipt of phototherapy. Regression models were constructed to examine the relationship of GA and SES to neonatal morbidity while controlling for other perinatal variables.

The cohort contained 25,312 infants of whom 6.1% (n = 1,524) were born preterm and 32.4% (n = 8,203) were of low SES. Using 39/40 weeks GA as the reference group there was a decrease in neonatal morbidity at each week of gestation. The odds ratios remained significantly higher at 37 weeks for RDS or other respiratory disorders, and at 38 weeks for all other outcomes. SES had an independent effect, increasing morbidity with odds ratios ranging from 1.2–1.5 for all outcomes except for the RDS group, where it was not significant. The risks of morbidity fell throughout late preterm and early term gestation for both respiratory and non-respiratory morbidity. Low SES was associated with an independent increased risk. Recognition that the morbidities associated with prematurity continue into early term gestation and are further compounded by SES is important to develop strategies for improving care of early term infants, avoiding iatrogenic complications and prioritizing public health interventions.

The authors noted: Risks of neonatal morbidity related to maturity fall with each week of gestation throughout the late preterm period but little is known about how this gradient acts past 36 weeks. A small number of studies have demonstrated persistent risks in early term gestation (defined as 37 to 38 completed weeks) casting doubt on the practice of considering all infants born at 37 weeks GA as a homogenous term group. One example is respiratory distress syndrome (RDS), which has as a relatively low absolute risk at late gestation yet demonstrates a gradient crossing term: 2.3% at 36 weeks, 1.2% at 37 weeks and 0.6% at 38 weeks. Pulmonary immaturity however, is not the only complication of prematurity. Late preterm infants are more likely than term infants to need specialized care in the first few days and experience minor maturity-related morbidity such as poor feeding, hypoglycemia, temperature instability and apnea. More research is needed to examine whether every additional week of gestational age (GA) is associated with an improvement in outcomes in these areas, similar to what is seen with respiratory morbidity. Investigating this gradient is important since mean gestational age at delivery continues to shift to the left, with higher numbers of late preterm and early term deliveries.

Socioeconomic status (SES) is also linked with birth outcomes; lower SES groups demonstrate higher neonatal morbidity and mortality, partially related to their higher rates of preterm delivery. Many infants thus have two interrelated risk factors for morbidity, GA and SES. Understanding the interactions between these two factors is important if we are to develop strategies for decreasing preterm birth and reducing neonatal morbidity. Small decreases in morbidity per infant when many infants are

*Continued on page 52...*



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1. Centers for Disease Control and Prevention. (2003) Guidelines for Environmental Infection Control in Health-Care Facilities. Recommendations of CDC and Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR, 52(RR10):1-42.



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# News

□ September 2012

## TIRED?

Neonatal nurses, if your shift is too long, if you're tired, the NANNP has published its position statement, "The Impact of Advanced Practice Nurses' Shift Length and Fatigue on Patient Safety." Here's some highlights: NANNP recognizes that fatigue, sleep deprivation, and the extended shift lengths or hours that neonatal nurse practitioners (NNPs) often work present potential safety risks for both providers and patients. NANNP recognizes that research addressing sleep deprivation, fatigue, and patient outcome is limited in the nursing profession and, specifically, in NNP practice. In addition, the uniqueness of the patient population and NNP responsibilities further complicate the delineation of strict scheduling limitations. Maximum shift length should be 24 hours, regardless of work setting and patient

acuity. A period of protected sleep time should be provided following 16 consecutive hours of working. The maximum number of working hours per week should be 60 hours. Recent data from an NNP workforce survey conducted by NANNP reveal that among 679 respondents the majority of NNPs work either 24-hour shifts (35%) or shifts with day-night rotation (36%). Day-night rotating shifts tend to be 12 hours. Job satisfaction did not vary with shift length. The highest patient load was associated with night shift or 24-hour shifts. The most common NNP shift length was 24 hours, followed by 12-, 10-, and 8-hour shifts, respectively. NNPs have workflow patterns analogous to those of medical residents or fellows, flight nurses, or air medical staff. The statement concludes: Workplace fatigue remains a critical issue in health care. NNPs should be professionally accountable to ensure they are fit to provide patient care and to be proactive in minimizing patient and personal safety risks. NNPs are encouraged to collaborate with colleagues and employers to create responsible staffing patterns and work models that use strategies designed to reduce the risk of fatigue threats to patient and personal safety. To see the entire position statement, go to [nannp.org](http://nannp.org) and click the appropriate box on the right hand column.

## CODE LAVENDER

That's the internal signal to one hospital's staff that NICU caregivers are hurting. Donna Koehn writes in The Tampa Tribune about a notification instituted at Tampa General Hospital to deal with people who are grieving due to events on the NICU. According to NICU nurse manager Pam Sanders, the program is about not just caring for babies, but caring for those who care for the babies, to help them cope when preemies or very ill

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babies die. The program was initiated when an NICU nurse was murdered. The Tampa Tribune said, "Code Lavender was born in those days, when TGH staff stepped in to help their colleagues. Counselors talked it out with NICU workers [while] pediatric nurses took over the care of the NICU babies. Sanders arranged for the grieving nurses to take time off and made sure food was available for those too stricken to think about cooking."

## DOUBLED

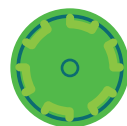
American Medical News (amednews.com) reported that "researchers at the RAND Corp used modeling to project that the count of those trained as nurse practitioners would increase 94% from 128,000 in 2008 to 244,000 in 2025. The subgroup of those providing patient care as nurse practitioners, rather than filling administrative or other roles, will rise 130% from 86,000 in 2008 to 198,000 in 2025. Other research has found significant growth in the number of nurse practitioners and other midlevel clinicians and indicated that more physicians are working with them. According to the annual census by the American Academy of Physician Assistants, 40,469 physician assistants were practicing in 2000, and that number went up 106% to 83,466 in 2010. A data brief by the CDC found that 49% of office-based physicians worked with physician assistants, nurse practitioners and/or certified nurse midwives... The number of physician assistants in the US more than doubled from 2000 to 2010... The Bureau of Labor Statistics projects that the number of jobs for any type of nurse, including NPs, will increase 26%, from 2,737,400 positions in 2010 to 3,449,300 in 2020. Average growth for any occupation in this time frame is 14%. In 2011, the average nurse practitioner earned \$90,583, according to the annual survey by Advance for NPs & PAs, a monthly journal for midlevels."

## NO MORE RISK

According to data presented at the 2012 Digestive Disease Week conference, there is no increased risk of birth defects among newborns of women who take certain biologic (infliximab, adalimumab and certolizumab) or immunomodulator (azathioprine and 6-mercaptopurine) therapy to control their Inflammatory Bowel Disease (IBD). These results are from a national registry of 1100 women from a Crohn's & Colitis Foundation of America sponsored trial. The risk of flaring during pregnancy was found to be the same as in the non-pregnant IBD patient – approximately 33% per year. Research revealed that women with IBD have the same rate of fertility as women of the same age without IBD, unless they have had surgery in the pelvis and that women with IBD have higher rates of complications during pregnancy and should be treated as high-risk obstetric patients. Even women with inactive IBD can have an increased risk of miscarriage, preterm birth, small-for-gestational-age infants, and complications of labor and delivery.

## STONED ON SOAP

Medical Xpress reported that the accuracy of routine urine drug testing of newborns to identify exposure in the womb to marijuana may be interfered with by chemicals in commonly used baby soap and wash products, including those widely used by hospital nurseries. Researchers at North Carolina School of Medicine and UNC Hospitals revealed that soap was behind a lot of false positives for cannabis exposure. The researchers weren't sure why this was happening, but noted that testers should use sophisticated methods like mass spectrometry before possibly intervening with child social services or alleging drug use by the mom.



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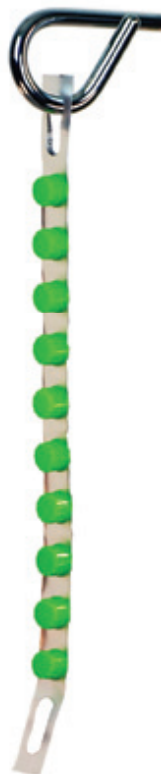
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## SHACKLED

A former inmate is suing the Nevada Department of Correction because she says she was forced to wear shackles while in labor. Raw Story writer David Edwards posted: "Valerie Nabors told [a TV station] that officials at the Florence McClure Women's Correctional Center in North Las Vegas violated state law when they put her in shackles while she was being transported to University Medical Center to give birth. Nabors said that prison guards ignored the advice of an emergency medical technician who cautioned them not to bind her ankles with the shackles." The EMT told the guards that they shouldn't shackle her because she needed to be checked on during the ride. Nabors' ACLU attorney said: "When you shackle a woman at her ankles, making it difficult for medical personnel to check her, you're sending a message that our primary obligation in society is not taking care of women, but to punish them needlessly and I think it's cruel and sadistic. This is not a time when a woman is thinking about escape. This is not a time when a woman is thinking about injuring anyone. This is a time when a woman is trying to get through the process of child birth with dignity and with respect for her health and the health of her child." Raw Story reported: "After giving birth the shackles were again placed on Nabors, who was serving a 12 to 30-month sentence for stealing about \$250 in casino chips... Nabors's lawsuit also alleges that prison officials confiscated her prescribed breast pump after being returned to the facility."

## MINE AND YOURS

Heather Piwowar wrote in the Guardian about restrictions by publishers to text mining, the valuable tool for navigating research across multiple publications. She wrote that text

mining had the potential to create €250bn of annual value to Europe's economy, if researchers were allowed to make full use of it. According to the Guardian, "Unfortunately, in most cases, text mining is forbidden... Academics are prevented from using the most modern research techniques because the big publishing companies such as Macmillan, Wiley and Elsevier, which control the distribution of most of the world's academic literature, by default do not allow text mining of the content that sits behind their expensive paywalls... The restrictions placed by publishers on text mining has led campaigners to view the issue as another front in the battle to make fruits of publicly funded research work available through open access, free at the point of use." Piwowar noted, "The scale of new information in modern science is staggering: more than 1.5m scholarly articles are published every year and the volume of data doubles every three years. No individual can keep up with such a volume, and scientists need computers to help them digest and make sense of the information." She wrote that "the brewing controversy between scientists and publishers over access to scientific information has caught the attention of investors," and she quoted a source who said, "some of the commercial restrictions from publishers seemed not only to be restricting access to the scientific community, but also hindering the work of researchers." Information above is from the Guardian, copyright Guardian News and Media 2012.

## OPEN ACCESS

Chris Wickham writes for Reuters that there's a new open access journal, PeerJ, a low-cost scientific journal with an unusual business model, will add to the pressure on publishers like Reed Elsevier and Axel Springer and stoke the debate over free access to research... The founders of the new journal previously worked for PLoS One and the research database group Mendeley. PeerJ will publish research in biological and medical sciences using a revenue model based on a one-off payment ranging from \$99 to \$259 for lifetime membership per researcher, rather than payment per paper or subscription by readers. As we have noted here before, and as Wickham points out, while much research in journals is behind a paywall, "the content of the research is provided largely for free by scientists and peer-reviewed by unpaid academics, with the journals then sold to those same academics via their university libraries for thousands of dollars per year." The current boycott of Elsevier has 12,000 signatories, but this represents less than 1% of its journals' readership. (Information is from Reuters, with additional reporting by Georgina Prodhan and editing by Ben Hirschler and Roger Atwood.)

## BMC NEWS

The winners of BioMed Central's 6th Annual Research Awards were celebrated recently at the Emirates Stadium, London, UK, honoring the outstanding research that has been made available with open access publishing. Over 100 guests attended the ceremony including leading researchers, shortlisted authors and science journalists from around the world. The winners were selected by internationally renowned judges from over 230 BioMed Central journals that together contain more than 18,000 peer-reviewed open access articles from the last 12 months. The overall winner of the prestigious BioMed Central Research Award was the article "A whole genome screen for HIV restriction factors" published in *Retrovirology* 2011, 8:94, written by Professor Áine McKnight and team... In other BioMed News, the BMC urged all its users to sign the White House open access petition. A "We the People" White House petition was instigated

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to help increase open access within US Federally Funded Research. It was hoped that the petition would demonstrate the wide public support of open access scientific research... BMC introduced the BioMed Central author academy, a free online learning resource for authors on writing and publishing in scientific journals. It includes advice on how to structure and write a good research article and offers help with choosing a target journal and publication ethics. The academy is aimed at authors who are less experienced in writing for English-language international journals, to help increase the chance of successful publication... BMC also announced the addition of subject sections on some of the BMC-series journal websites. For an example, see BMC Public Health. This new functionality both allows for an author to submit to a specific section within a journal, and also offers the community of readers the chance to browse articles in their specific sub-areas of interest. Of course, this is not the only way to find articles – and those who prefer the direct search, or even the general browse, can still do exactly that. Some of the BMC-series journals are not yet using this process, and thus do not yet have sections, but will be moving to this in the coming months. If you are interested in getting involved with any journal, simply contact the Executive Editor via the relevant journal homepage... BioMed Central will be holding the third annual Open Access Africa conference at the University of Cape Town, South Africa, on November 4-5, 2012... The Berlin 10 Open Access Conference will be held at Stellenbosch, South Africa. The Conference will be held at the Wallenberg Research Centre, Stellenbosch Institute for Advanced Study (STIAS) from 7-8 November 2012. Pre-conference workshops will be held on 6 November. The theme of the Conference is Networked scholarship in a networked world: participation in Open Access.

#### LASER IN THE WOMB

Richard Luscombe, in The Guardian, writes about the world's first operation performed using a laser beam on a fetus to remove a tumor. Surgeons at the University of Miami/Jackson Memorial Hospital operated on a growing tumor at the roof of the infant's mouth. The surgery was performed by Dr Ruben Quintero at the University of Miami, who noted that removal of such a tumor had never been tried in utero. He used an endoscope guided by ultrasound, making a minor incision on the mom's abdomen, then using a laser while the mom watched on a screen.

#### BILLED

Harry Bradford reports in the Huffington Post (via The Daily Mail) that after an Arizona mother lost her daughter just minutes after her premature birth, she spent months battling a hospital in Southern California over a nearly \$900 bill that she says she received despite the newborn not receiving any substantial medical care. "She felt strongly that her bill for \$896.73 'didn't make sense,' but it was only after she started working with a local news station that the hospital agreed to waive the costs. The hospital's CEO said he only dropped the charges to zero as a 'courtesy,' insisting that the bill included 'routine daily accommodation charges' and was 'accurate.'"

#### DISTINGUISHED

AWHONN presented its highest honor, the Distinguished Professional Service Award, to Sandra Cesario, PhD, MS, RNC, FAAN, for her contributions to the field of women's health. The award was presented at the AWHONN National Convention in the Washington, DC area and sponsored by Johnson & Johnson. Dr Cesario, a long-time member of AWHONN. She's the PhD Program Coordinator and a tenured professor at the Texas Woman's University's College of Nursing in Houston. For the past year, she has also served as the Interim Director of International Programs for the College of Nursing. An expert in women's health, she has conducted extensive research in ovarian cancer, second stage of labor management, newborn abandonment and design of health care systems. AWHONN also presented the Hill-Rom/Celeste Phillips Family-Centered Maternity Care Research Award to Ruth Lucas, PhD, RNC, for her study entitled, "Maternal assessment of infant breastfeeding behaviors." The purpose of the study is to determine the reliability of weekly maternal assessment of infant breastfeeding behaviors. The award is named for Celeste Phillips, a nurse and internationally recognized leader in family-centered maternity care. Dr Lucas has been a nurse for 26 years and is currently a Trajectories of Chronic Illness and Care Systems Postdoctoral Fellow at Duke University School of Nursing in Durham, NC.

#### SKIN TO SKIN

AWHONN reports: The postpartum period brings physical and mental transitions that may predispose new mothers to depressive symptoms, including mental confusion, despair,



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sadness, anxiety, fear, compulsive thinking, and feelings of inadequacy. These symptoms are of particular concern because infants of mothers with these symptoms are at risk for developmental and emotional difficulties. In an article in the May/June issue of the *Journal of Obstetric, Gynecologic & Neonatal Nursing*, the authors discuss skin-to-skin contact (SSC), in which the infant is placed on the mother's bare chest, dressed only in a diaper, so that frontal body contact of mother and infant is skin to skin. The authors describe benefits to the mother and newborn. In "The Effect of Mother/Infant Skin-to-Skin Contact on Postpartum Depressive Symptoms and Maternal Physiological Stress," Ann Bigelow, PhD; Michelle Power BSc; Janis MacLellan-Peters, RN, MN; Marion Alex, RN, MN, CMN; and Claudette McDonald BScN, RN examine how SSC positively affects maternal and newborn postnatal life. Researchers have found that infants who participate in SSC with their mothers have more stable body temperatures, heart rates, and respiratory rates; healthier gastrointestinal adaptation; improved sleep habits; less crying; better growth; longer rates of breastfeeding; and less pain from routine procedures. Additionally, SSC has been shown to have a positive impact on new mothers' feelings toward and perceptions of their newborns. These women also experience less depression and more empowerment in their roles as parents.

## UNDEREXPOSED

Lack of exposure to amniotic fluid could be the reason that preterm infants are more susceptible to NEC, according to researchers at Children's Hospital of Pittsburgh and the University of Pittsburgh School of Medicine. Feeding amniotic fluid to young mice reduced the risk of NEC in an experimental model. Previous research determined that the molecular switch TLR4 was turned on in intestinal tissue affected by NEC. Healthy infants born at term have relatively low levels of TLR4 in the gut. The researchers posited that unlike in healthy newborns, something goes wrong with the TLR4 response when preemies get colonized with normal gut flora. In the current study, researchers showed that injecting small amounts of amniotic fluid into the intestine of premature mice, or feeding them the fluid, stopped NEC from developing, because the fluid is rich in epidermal growth factor. When the researchers removed it from the fluid or blocked or removed the EGF receptor on intestinal cells, amniotic fluid no longer had a protective effect.

## iPAD YOU NOT

Researchers at the University of Michigan have found that the Apple iPad 2 can interfere with settings of magnetically programmable shunt devices which are often used to treat hydrocephalus. The iPad 2 contains magnets that can change valve settings in the shunt if the tablet computer is held within two inches of the valve, which then causes a shunt malfunction. The researchers thought to do the study because a tablet computer seemed to affect a programmable shunt in one of their patients, a 4-month-old girl with hydrocephalus. Three weeks after the baby had received the shunt, she was examined for shunt malfunction due to a changed setting in the magnetically programmable valve that regulates the flow of cerebrospinal fluid. The baby's mother stated that she had held an iPad 2 while holding the infant. Programmable shunt valve settings can be altered by exposure to magnetic fields. In fact, specialized magnets are used by physicians to adjust the settings on these valves. Since in this case no other environmental factor could be identified that would have led to a shift in the valve settings, the authors decided to test whether the iPad 2 might be implicated

because it contains several magnets and is often used with an Apple Smart Cover, which contains additional magnets. The researchers tested 10 programmable shunt valves with a variety of settings and exposed them to the iPad2 at various distances and lengths of exposure. After exposure of the programmable valves to the iPad 2 and Smart Cover at distances between 0 and 1 cm, the researchers found that the settings had changed in 58% of the valves. After exposure at distances between 1 and 2.5 cm the settings had changed in 5% percent, and 1% at between 2.5 and 5 cm.

## NANN NEWS

NANN'S aggregator web news service, Smartbrief (smartbrief.com) reports the following: **Blood transfusions** were associated with a reduced likelihood and severity of apnea in very low birth weight babies, University of Virginia researchers reported. The data add to the evidence that oxygen-carrying capacity is an important factor in apnea among premature infants [Medscape/Reuters]. **Early-onset sepsis** remains a common diagnosis in the NICU and presents challenges for clinicians, according to a report in *Pediatrics* that said major issues are identifying high-risk neonates and starting treatment, determining which infants do not require treatment, and ending antimicrobial therapy after sepsis is found to be unlikely [Medscape/Reuters]. Fetal growth is not affected when pregnant women use the **HIV drug** tenofovir disoproxil fumarate, according to a study in the journal *AIDS*. NIH researchers said the drug could lead to delayed infant growth in the first year of life [PhysiciansBriefing.com/HealthDay News]. The NICU at Staten Island University Hospital in New York won honors for developing **journals for premature infants** that document their stay and make parents feel more involved in their care [Nurse.com]. An analysis of 223 **home births** in Oregon from 2004 to 2008 suggests perinatal mortality rates are higher for deliveries outside hospitals. Of the eight babies who died, seven were tied to breech presentation, preeclampsia and post-term birth, researchers reported at the ACOG meeting [DoctorsLounge.com/HealthDay News]. Registration for **NANN's 28th Annual Educational Conference**, Oct. 17 to 19, in Palm Springs, CA is open. New at this year's conference are interprofessional sessions and up to 28.5 continuing nursing education contact hours. The **Neonatal Nursing Transport Standards**, 3rd Edition, offers a template for establishing consistency in practice that ensures the safety of both patients and transport team members. This text covers a variety of topics related to care for critically ill newborns through the implementation of endorsed practice standards developed by nursing experts involved in neonatal transport. Contact NANN. Only 3% of ELBW babies in a single NICU who were treated with routine **fluconazole prophylaxis** for seven days or more had **neonatal candidiasis**, according to a study presented at PAS. For babies weighing less than 750 grams, treating 13 infants would prevent one fungal infection, according to the study. A University of Edinburgh study found the risk of perinatal mortality was reduced using **elective labor induction** at term but led to a higher risk of admission to a neonatal unit, compared with expectant management. The study said 1,040 women would need to have induction to prevent one perinatal death but this would result in seven extra admissions to a neonatal unit [MedPage Today]. The Physicians Practice 2012 Staff Salary Survey found that **nurses earn** \$50,964.64 on average with three to five years of experience and \$65,046.15 after 20 or more years. Nurse practitioners with three to five years of experience earn an average of \$80,903.30 annually, and with 20 or more years that



rises to \$90,794.77 [Medscape]. The Valley Hospital in Ridgewood, NJ has trademarked its "Peek-A-Boo ICU," designed as a way to reduce the anxiety of parents who are separated from critically ill newborns. Nurses roll a mobile computer cart equipped with a video camera to the baby's bedside to allow parents to watch the child via a secure, live Internet feed [Nurse.com]. Thirty-six percent of infants who had been treated in a neonatal ICU and failed a standardized developmental test did not receive **referrals for early intervention**, a study in California found. Researchers wrote in the journal *Pediatrics* that lower budgets for the state's early-intervention services as well as tighter eligibility criteria might explain the low referral rate [Reuters]. **Mortality patterns** for infants in an NICU have not changed much in the past decade, but death is now coming at a later age, according to a study from the University of Montreal. Data on infants who died showed that from 2000 to 2002, 71% of babies died before one week and only 14% survived past three weeks, compared with 2007 to 2010 when statistics show 53% of infants died before one week and 24% survived past three weeks [Medscape]. Pregnant women who received **flu shots** were at less risk of stillbirth, delivery before 32 weeks or having LBW babies than women who weren't vaccinated, according to a study in the *American Journal of Public Health*. Researchers assessed 55,570 single births from November 2009 to April 2010 and found no side effects resulting from the vaccination [MyHealthNewsDaily.com]. The United Arab Emirates gave **\$5 million to Mercy Hospital** in Joplin, MO for a pediatric section in its new hospital, scheduled to open in 2015 to replace the one destroyed by a tornado. The money also will be used to develop a neonatal intensive care unit, the first for the city [St Louis Post-Dispatch/AP]. The **High-Frequency Jet and**

**Oscillatory Ventilation** Resource Guide from NANN offers different strategies to use when managing infants on either high-frequency jet ventilation or high-frequency oscillatory ventilation. This laminated ring-bound desk reference also comes with a pocket card with quick guides to both high-frequency jet ventilation and high-frequency oscillatory ventilation. Contact [nann.org](http://nann.org) ... Babies born to mothers who took **antidepressants** during the second trimester were more likely to be born earlier than other babies, according to a study published in *AJOG*. The risk of seizures was also higher [Reuters]... The FCC has agreed to allocate 40 MHz of **broadband spectrum for medical devices**. The move is expected to eliminate transmission interference from consumers' devices [Healthcare IT News]... Researchers found that 190 children who survived **neonatal encephalopathy** and had whole-body hypothermia had a lower risk of dying by ages 6 to 7. The hypothermia group had a higher IQ, as well [Family Practice News]... Precepting the Advanced Practice Nurse: From Expert RN to **Novice NNP**, a new NANNP product (eligible for 4.0 CNE contact hours), discusses current theories and published evidence on the teaching and learning experience and offers practical examples and tools that will enhance the quality of preceptorships for both the preceptor and preceptee... A NANN webinar helps nurses become aware of the implications of **excessive shift length**, discussing the five consequences of fatigue on health care providers and reviewing NANNP's recommendations for shift length. Contact NANN to download the webinar: *The Impact of Advanced Practice Nurses' Shift Length and Fatigue on Patient Safety*... VLBW babies who were exposed to **cycled lighting** during neonatal care showed less fussing and crying behavior at 5 and 11 weeks corrected age than those exposed to dim lighting, according to Swiss



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researchers, who also found that CL-exposed babies had higher motor activity during daytime and improved weight gain [HealthDay News]... Maternal **cigarette smoking** is a risk factor for NEC, according to researchers who also found that maternal gestational diabetes, formula feeding, maternal hypertension and pathologic chorioamnionitis or uteroplacental insufficiency had no correlation with NEC [DoctorsLounge.com]... Healthcare experts urged NICUs and pediatric hospitals to do **disaster planning** during the California Neonatal/Pediatric Disaster Coalition Conference [UC Berkeley]... Babies born by **C-section** were three times more likely to fail an initial **hearing test** in the first two days of life than those born vaginally, according to an Israeli study. The difference narrowed when babies were tested at two days [Reuters]... NANN, the American Academy of Pediatrics, and the March of Dimes were awarded a grant from MedImmune to create a discharge module for professionals to assist parents in **taking high-risk newborns home**. The Premie Discharge Module will be a DVD with videos, illustrations, forms, and other teaching tools. Contact NANN to identify content for the module. Also, register for **NANN's 28th Annual Educational Conference**, Oct 17 to 19, in Palm Springs, CA. New this year is increased time with poster presenters, interprofessional sessions, a Skills Lab with manikins and more CNE than ever before: up to 28.5 CNE contact hour... Milking the umbilical cord before clamping led to better oxygenation for very low birth weight infants in a neonatal ICU, Japanese researchers reported, because **cord milking** helps to stabilize blood pressure and urine output, and reduces the need for transfusions and circulatory and respiratory support [Medscape]... **Antiretroviral treatment** consisting of two or three drugs reduced HIV transmission for babies whose HIV-positive mothers did not receive prenatal ART, according to a study in the New England Journal of Medicine. Another trial showed that HIV-positive babies treated with nevirapine together with zidovudine and lamivudine had higher virologic failure compared with those given lopinavir in combination [PhysiciansBriefing.com/HealthDay News]... A four-week Neonatal Intensive Care Unit Summer Clerkship at Cabell Huntington Hospital in West Virginia gives college students **real-time experience** before they commit to a medical career. The program began 20 years ago and 90% of participants end up at Marshall University's School of Medicine and in the medical field. [New England Cable News/AP]... NANN is offering a **free CNE** for members on the Effects of Multiple Gestations. This module reinforces a neonatal nurse's knowledge on the effects of multiple pregnancies and assesses knowledge in a fun crossword puzzle format.

## NOT SCREENED

Many women are not screened for chlamydia and gonorrhea infection during their pregnancy, and follow-up testing is not always performed as medically recommended for those who test positive, according to a study published online in the American Journal of Obstetrics and Gynecology (AJOG). The findings, based on an analysis of laboratory tests of 1.3 million pregnant women, highlight gaps between medical guidelines and clinical practice in screening for two sexually transmitted infections that pose health risks for pregnant women and their newborn babies. Conducted by scientists at Quest Diagnostics and Rutgers University, the study examined de-identified results of 1,293,423 pregnant women between 16 to 40 years of age in the US who were tested by Quest between 2005 and 2008. The study found that only 59% and 57% of pregnant women were tested at least once for chlamydia and gonorrhea, respectively. Among

women in the high-risk 16 to 24 year age group, only 69% were tested for gonorrhea. Only 33% of women who tested positive for chlamydia on an initial screen were re-tested within six weeks of being diagnosed, and 22% had no follow-up testing. Among women 25 years of age or younger, only one in five (19%) were re-tested after a negative chlamydia screen. The study also found that among women who tested positive on an initial screen, 6.0% and 3.8% were positive on their last prenatal test for chlamydia and gonorrhea infection, respectively. In addition, some women had a positive result after a negative result when tested at different times during their pregnancy, a pattern suggesting they were re-infected by their partners. In addition, the study found that age was strongly associated with infection risk. Sixteen percent of 16 year olds tested positive for chlamydia, the highest of any age group. The risk of infection steadily declined with age, reaching 3% of 26 year olds and less than 1% of 40 year olds. The study, "Chlamydial and gonococcal testing during pregnancy in the United States," is available online. Contact [ajog.org](http://ajog.org) or [questdiagnostics.com](http://questdiagnostics.com).

## HANDS ON

Dads have only recently started to change "nappies," according to research from the University of Warwick, who said statistics show that in 1982, 43% of dads had never changed a diaper. A 2010 study said 65% helped "a great deal" with nappy changing. The lead researcher, Laura King, said, "We must reject suggestions that close father-child relationships have only developed since the 1970s or even 1990s. The stereotype of the distant and tyrannical Victorian patriarch conceals substantial evidence of fathers who cared greatly for their children and played with them, educated them, and even nursed them." The study suggests that in the post Second World War era, fathers were more determined to cultivate much closer relationships with their children than they had experienced with their own fathers. This was reinforced by important social trends. The reduction in average family size meant that many parents could devote more time to each of their children. A decrease in working hours and increased holiday time also meant that men had more time available to spend with their families.

## POOR PADS

Alcohol prep pads were to blame for a small spate of bacteria contamination at a Colorado children's hospital. Three patients fell seriously ill and had positive cultures associated with *Bacillus cereus*, which is typically known to cause food poisoning. It's capable of surviving in alcohol solutions. Lab tests showed that *B. cereus* and other *Bacillus* species were growing from the pads, and the product was recalled throughout the pediatric healthcare system. An investigator noted that many healthcare facilities use these pads but aren't aware they're non-sterile because they're not always labeled as such.

## CAN'T DO IT

A recent survey reports that two-thirds of moms can't breastfeed for as long as they intended, according to a report by Rupert Shepherd in Medical News Today. A CDC survey found that 85% of mothers planned to breastfeed for at least three months. When hospitals doled out infant formula and pacifiers, this also contributed to reduced breastfeeding. Reasons for quitting breastfeeding were that mothers were tired after giving birth, the difficulty of knowing when the baby is getting fed enough, awkwardness about nursing in public, and having to go back to work. Information is from Medical News Today, copyright Medical News Today.



## CARE LESS

Save the Children reported that while newborns now account for 40% of child deaths, only 1% of developmental assistance for maternal and child health targets newborns – this despite that 3.1 million newborns die each year. The report shows that political will to reach the poorest families with the most effective interventions for newborn health has had dramatic results in low-income countries such as Bangladesh, Malawi and Nepal. Other findings: African families have the highest risk of newborn deaths. Maternal mortality is declining faster than before, but newborn mortality is declining at half that rate. Declines in newborn mortality rates are also 30% slower than those of children under 5. Ten countries, including India and Ethiopia, account for two-thirds of neonatal deaths. The report said 75% of newborn deaths could be prevented through use of Kangaroo Care, antibiotics, exclusive breastfeeding, and basic care.

## POOR YET RICH

Economically impoverished Amerindian women have beneficially high levels of omega-3 fatty acids in their breastmilk, much more than women in the US. Researchers at the University of Pittsburgh and Cincinnati Children's Hospital and anthropologists at UC Santa Barbara compared the breast milk fatty acid composition in US and Tsiname women, who live in Amazonian Bolivia. The Tsiname eat locally grown staple crops, wild game, and freshwater fish. Researchers also found that the percentages of DHA in Tsiname breastmilk didn't decrease for the first two years postpartum. According to UCSB researcher Melanie Martin, "Tsiname mothers' omega-6 to omega-3 ratios were four to one, much closer to the ancestral estimates than observed in US women." The ratio of omega-6 to omega-3 in industrialized diets varies from 10 to 1 to as high as 20 to 1. This is most likely due to the absence of fresh fish and regular consumption of processed foods and vegetable oils rich in linoleic acid (an omega-6), as well as trans fats. Martin noted, "The Tsiname mothers' average milk DHA percentage was 400% higher than that of the Cincinnati mothers, while their average percentages of linoleic and trans fatty acids were 84% and 260% lower."

## NO DELIVERANCE

Infant death rates in Appalachia remain significantly higher than much of the rest of the country, and are especially high in the central Appalachian region, according to Penn State health policy researchers. There continue to be more white infant deaths in Appalachia than throughout much of the rest of the nation. The researchers analyzed data from 1976 to 1980 and 1996 to 2000. During both time periods the Appalachian region had significantly fewer physicians throughout the region than in the non-Appalachian area. In the 1970s, the central Appalachian region had approximately one doctor for every 2,000 residents, compared to the non-Appalachian region, which had almost one doctor for every 500 people. Numbers improved in the 1990s, but in central Appalachia there was one doctor for every 1,000 people, while in the non-Appalachian region jumped to having nearly one doctor for every 350 residents. Central Appalachia suffers from poverty and isolation.

## BLOWING SMOKE

Researchers in the Neuroscience and Reproductive Biology section at the Cummings School of Veterinary Medicine conducted a study to determine the transgenerational effects of cannabinoid exposure in adolescent female rats. For three days, adolescent rats were administered a drug that has similar effects in the brain as the active ingredient in marijuana. After

this brief exposure, they remained untreated until being mated in adulthood. The male offspring of the female rats were then measured against a control group for a preference between chambers that were paired with either saline or morphine. The rats with mothers who had adolescent exposure to the pot-like drug were significantly more likely to go for the morphine-paired chamber than those with mothers who abstained. The results suggest that these animals had an increased preference for opiate drugs.

## DNA

Andrew Pollack wrote in the New York Times that for the first time, researchers have determined virtually the entire genome of a fetus using only a blood sample from the pregnant woman and a saliva specimen from the father. "The accomplishment heralds an era in which parents might find it easier to know the complete DNA blueprint of a child months before it is born. That would allow thousands of genetic diseases to be detected prenatally. But the ability to know so much about an unborn child is likely to raise serious ethical considerations as well. It could increase abortions for reasons that have little to do with medical issues and more to do with parental preferences for traits in children." Researchers at the University of Washington used high-speed DNA sequencing and "computational acrobatics." Not that everyone is likely to start making use of the technology, since the cost to do one fetal genome is currently between \$20,000 and \$50,000, but the article notes, "the cost of DNA sequencing is falling at a blistering pace, and accuracy is improving as well. The researchers estimated that the procedure could be widely available in three to five years... The technique described in the paper would not require complete cells from the fetus and would make such DNA testing easier and less risky... The genome was determined from blood samples taken 18.5 weeks into the pregnancy, although the researchers said the technique could probably be applied in the first trimester... The researchers were able to detect 39 of 44 spontaneous gene mutations, though with a huge number of false-positive."

## DNA REDUX

Scientists at Stanford University announced that a simple blood test, rather than amniocentesis, can determine a fetus's genetic make-up. Sharon Begley, reporting for Reuters, wrote that the procedure can be done without knowing who the father is. "Paternity is unknown or incorrect in an estimated 3 to 10% of births in the United States; the father-free method promises to make fetal DNA sequencing possible in every pregnancy, if hurdles including cost and accuracy are overcome." She noted that while determining a fetus's genome might provide a reason for terminating a pregnancy, "it would also let physicians identify conditions that can be treated before birth or immediately after... With prenatal genetic testing, parents would know by the end of the first trimester if the fetus has a genetic or chromosomal defect... Because the new fetal genome test requires only a blood sample, it poses no risk of miscarriage. Sequencing the medically relevant regions of the fetal genome would cost about \$2,000, but that will drop as sequencing costs plummet." Begley writes that the new procedure will be a boon, "But only if the tests become more accurate. The version unveiled by scientists at the University of Washington, [see previous news item] as well as the Stanford procedure, miss some mutations and mistakenly identified some healthy genes as abnormal." She quotes a researcher about another dilemma: "Deluging parents-to-be with information about 20,000 or so fetal genes brings its own challenges. 'Do we tell the pregnant woman

about serious, moderate or mild diseases? About hair color, eye color? About Alzheimer's risks for 70 years later? About the hundreds of variants of unknown significance found in every genome?"

### **SMALL AND LARGE**

The smallest and largest fetuses are at much higher risk of being stillborn than those of average weight, according to researchers at St Michael's Hospital in Ontario, Canada. Very small fetuses account for about six per cent of all stillbirths, while those that weigh above the 99th percentile, account for nearly one per cent. Researchers examined records of all 767,016 live births and all 4,697 stillbirths in Ontario between 2002 and 2007. They found that 19% of stillbirths occur in fetuses under the tenth percentile of weight, but being below the first percentile of weight meant the fetus faced a 9.5 times higher risk of being stillborn than babies who are within the average weight range. The authors conclude that since more than 95% of women in the industrialized world receive an ultrasound before 22 weeks gestation, fetal weight should be estimated and reported at this time of the ultrasound, as a standard practice. In doing so, the early presence of a small or large fetus may help guide ongoing ultrasound surveillance for growth and well-being.

### **THYROID**

Thyroid dysfunction during early pregnancy significantly increases the risk of serious complications, according to researchers at Christian Medical College and Hospital in Punjab, India. Investigators found that even mild thyroid dysfunction that did not meet the criteria for hypothyroidism greatly increased the risk of serious problems. Compared to pregnant women with normal thyroid function, the risk was doubled for miscarriage ( $\leq 20$  weeks of pregnancy), premature labor, and low birth weight, and seven times greater for still birth. Investigators recruited 1,000 pregnant women in their first trimester of pregnancy for the study, as part of a larger project of routine thyroid screening during early pregnancy. They then measured the level of thyroid functioning using the TSA test. Normal thyroid function was identified in 533 patients, and 263 had mild dysfunction. Researchers compared rates of miscarriage, stillbirth, premature labor, and low birth weight.

### **VWD and VWF**

Findings of a first-of-its-kind study of women with von Willebrand disease (VWD) show that current postpartum treatment strategies do not increase levels of von Willebrand factor (VWF) to normal range or even to the levels of women with milder, untreated VWD. VWF is a blood protein important for preventing postpartum hemorrhage. Results of this nationwide study were presented at the World Federation of Hemophilia 2012 World Congress in Paris. In healthy women, VWF levels fell rapidly after childbirth, approached baseline one week postpartum and reached baseline three weeks postpartum. The pattern of decrease in these levels was consistent among all patient groups, but levels were significantly lower in women with VWD. VWF levels were lowest among treated VWD patients. This prospective, observational cohort study compared changes in blood levels of VWF proteins postpartum between 31 women with and 40 women without VWD. Fourteen of the women with VWD were treated during the postpartum period, 12 with VWF concentrate, one with desmopressin plus VWF concentrate and one with desmopressin. At periodic intervals in the immediate postpartum period, von Willebrand factor: Ristocetin cofactor activity (VWF:RCO), factor VIII (FVIII) and von Willebrand factor

antigen (VWF:Ag) levels were measured. Von Willebrand disease affects 1 to 2 percent of Americans, more than half of whom are women. Men and women are equally likely to be affected by VWD. Women, though, may suffer severe health consequences, such as life-threatening bleeding following childbirth, if their condition is not correctly diagnosed and managed. Other common symptoms of VWD include easy bruising; frequent or prolonged nosebleeds; heavy, prolonged menstruation; prolonged bleeding following injury or surgery; and prolonged bleeding during dental procedures.

### **NO GROW**

Researchers from the Ottawa Hospital Research Institute and the University of Ottawa have found a protein in the blood of pregnant women that can predict if they are likely to have a fetus that doesn't grow properly, and thus has a high risk of stillbirth and long-term health complications. The research focuses on Insulin Growth Factor Binding Protein 4 (IGFBP-4). While this protein has been linked to pregnancy before, this study is the first to demonstrate its important role in human pregnancy complications. A key part of the study involved examining IGFBP-4 levels in first trimester blood samples from women who participated in a large study of pregnancies and newborns. Women with high levels of IGFBP-4 were 22 times more likely to give birth to tiny babies (defined as the smallest five per cent by weight for their gestational age), than women with normal levels. The study involved a total of 72 women - half with tiny babies and half with normal weight babies.

### **AT RISK**

Women who experience an initial ectopic pregnancy are less likely to conceive in the future and if they do, are at increased risk of having another ectopic pregnancy, but are no more likely than first time mothers to suffer complications in an ongoing pregnancy according to researchers at the University of Aberdeen. The authors found that women with an initial ectopic pregnancy had a lower chance of conception than those who miscarry and also an increased risk of a repeat ectopic pregnancy compared to women who experienced miscarriage, termination, or a live birth in their first pregnancy.

### **FOLIC ACID AND AUTISM**

Researchers at UC Davis suggests that women who consume the recommended daily dosage of folic acid, the synthetic form of folate or vitamin B-9, during the first month of pregnancy may have a reduced risk of having a child with autism. The study sought to determine whether the folic acid consumed in supplements was the source of the protective effect. The finding suggests that, in addition to women who already have conceived, those who are attempting to become pregnant should consider consuming such supplements. The study found that women who each day consumed the recommended amount of folic acid (600 micrograms, or .6 milligrams) during the first month of pregnancy experienced a reduced risk of having a child with autism spectrum disorder, specifically when the mother and/or her child had a specific genetic variant (MTHFR 677 C>T) associated with less efficient folate metabolism. The authors said that folic acid might offer protection against problems in embryonic brain development by facilitating DNA methylation reactions that can lead to changes in the way that the genetic code is read. The researchers collected data from 835 Northern California mothers of 2- to 5-year-old children who had autism, developmental delay or typical development. Mothers of typically developing children reported greater-than-



average intake of folic acid, and were more likely to meet intake recommendations during the first month of pregnancy than were mothers of children with autism spectrum disorder. As the amount of folic acid consumed increased, the associated risk for autism spectrum disorder decreased. Mothers of children with developmental delay tended to have lower estimated folic acid intake when compared with mothers of typically developing children during the three months before pregnancy. The mothers of infants who were developing normally said they consumed an estimated average of 779 micrograms of folic acid daily and 69% of them at least met the daily guidelines. The mothers of children with autism consumed an estimated average of 655 micrograms of folic acid. Fifty-four percent of them consumed the recommended 600 micrograms or more per day.

### NOT JUST MOM'S CELLS

A pregnant woman's blood stream contains not only her own cells, but a small number of her child's, and some of them remain in her internal organs long after the baby is born, according to researchers at Tufts Medical Center. Researchers revealed a mixed population of trophoblasts (placental cells that provide nutrients to the fetus), mesenchymal stem cells (cells that later develop into fat, cartilage, or bone cells), and immune system cells, and surmised that fetal cells in a mother's blood stream help her immune system tolerate and not attack the fetus. The detection of trophoblasts and immune cells in the maternal lung should aid future studies on this subject, as well as research into pregnancy-related complications like preeclampsia. The presence of fetal mesenchymal stem cells corresponds with previous studies that reported fetal and placental cells differentiating to repair injured maternal organs in both mice and humans.

### DEATH = DEATH

In the first two years following the death of a child, there is a 133% increase in the risk of the mother dying, according to a study from the University of Notre Dame. Researchers studied 69,224 mothers aged 20 to 50 for nine years, tracking the mortality of children even after they had left the household. According to the study, this heightened mortality is concentrated within the first two years following the death of a child, regardless of the age of the child at the time of death. There also appeared to be no difference in results based on household income, mother's education, family size, the child's sex or the child's cause of death. The sample was composed of women who are married (84%), white (87%) and non-Hispanic (91%). Slightly more than half the mothers were between the ages of 20 and 34. Earlier studies found that parents who experienced the death of a child had a higher risk of first-time hospitalization for a psychiatric disorder, and that mothers had a higher relative risk than fathers.

### INDUCED

In "Early Term Birth: Understanding the Health Risks to Infants," an article in the April/May issue of *Nursing for Women's Health*, the clinical practice journal published by the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN), Debra Vela Craighead, MSN, RN, discusses these health risks and the important role women's health care professionals play in potentially improving outcomes. The health risks for infants associated with an elective early term birth include: greater chance of dying early, more likely to need care in the neonatal intensive care unit, problems breathing, including needing a ventilator, problems feeding, including coordinating sucking and swallowing, and increased need for special educational

interventions later in life. The article says nurses can improve health outcomes for moms and babies through education and intervention by asking hospital-based and other childbirth educators to include fetal development and early term birth health risk information in childbirth classes, providing information about the risks of early term birth to the pregnant women for whom they provide care, and educating women and healthcare providers alike about the health benefits of normal spontaneous birth and the prevention of unnecessary elective induction delivery. Contact AWHONN or [health4mom.org](http://health4mom.org).

## PRODUCTS

### STANDARD OF CARE

The Life Pulse High-Frequency Jet ventilator is now a standard of care in over 200 NICUs and PICUs. After 25 years of use in the critical care setting, it has passed the test of time. Jet pulse technology, passive exhalation, and adjustable I:E ratios make the Life Pulse uniquely effective. These features are critical for helping patients recover from non-homogenous lung disease. Bunnell is supportive, committed, and experienced. Their toll free hotline and customer service are consistently ranked tops in the industry. For more information or to arrange a free trial call (800) 800-4358 or visit [www.bunl.com](http://www.bunl.com).

### PACIFICATION

Florida State University announced the availability of a new medical device that uses musical lullabies to help premature babies. The Pacifier Activated Lullaby (PAL), is now being sold to hospitals around the world through a partnership with Powers Device Technologies, Inc. PAL uses music reinforcement to help infants quickly learn the muscle movements needed to suck, and ultimately feed. PAL uses a specially wired pacifier and speaker to provide musical reinforcement every time a baby sucks on it correctly. The musical lullabies are gentle and pleasant to the babies, making them want to continue the sucking motion so they can hear more of the lullaby. Clinical studies conducted by Standley at Tallahassee Memorial Hospital (TMH), University of Georgia Hospital in Athens, University of North Carolina Medical Center in Chapel Hill and Women's and Children's Hospital in Baton Rouge, LA have shown that infants will increase their sucking rates up to 2.5 times more than infants not exposed to the musical reinforcement. To see PAL in action go to [research.fsu.edu/PAL](http://research.fsu.edu/PAL). Contact [powersdt.com](http://powersdt.com).

### EFFECTIVE

Discovery Laboratories, Inc announced it presented neonatal AFECTAIR data at the 11th European Congress on Pediatric and Neonatal Ventilation being held June 6-9, 2012 in Montreux, Switzerland. Though initially presented in the US, these data presentations marked the first introduction of the AFECTAIR neonatal device through scientific exchange to a European pediatric critical care audience. The AFECTAIR neonatal device has been developed by Discovery Labs to simplify the delivery of inhaled medications for critical care patients requiring ventilatory support and was cleared for marketing in the US in early 2012. The AFECTAIR neonatal device will be commercially available in the US and EU in late 2012. Highlights from the two data presentations include: *Utilization of iNO Using a Novel Ventilator Circuit Connector versus Standard of Care Under Simulated Neonatal Mechanical Ventilation Conditions – An In Vitro Study*, Mazela, et al. The Standard of Care (SoC) for ventilator delivery of inhaled nitric oxide (iNO) in pulmonary

hypertension allows for potential iNO dilution, gas loss and environmental contamination. According to this study, which simulated neonatal mechanical ventilation conditions using an in vitro model, use of the AFFECTAIR neonatal device resulted in the achievement of target nitric oxide concentrations using less nitric oxide when compared to the SoC delivery apparatus. *In Vitro Assessment of a Novel Aerosol Delivery System under Simulated Conditions*, Mazela, et al. According to this study conducted in an in vitro model of neonatal mechanical ventilation conditions, when compared with a conventional wye connector, use of the AFFECTAIR neonatal device resulted in improved delivery of aerosolized albuterol sulfate, including: a nine-fold increase in delivered dose under simulated CPAP conditions, a 14-fold increase in delivered dose under simulated mechanical ventilation conditions, and a smaller difference in particle size distribution between aerosol output from the nebulizer and aerosol output from the patient interface. Contact [discoverylabs.com](http://discoverylabs.com).

## TEAMWORK

Covidien announced the launch of its Nellcor SpO2 single parameter module for use with the Philips IntelliVue patient monitoring platform. The Nellcor SpO2 module incorporates Nellcor OxiMax pulse oximetry technology, providing a cost-effective means for clinicians to detect and treat potentially life-threatening events by creating a more complete picture of a patient's respiratory function status. The single parameter module is available in North America, the European Economic Area (EEA) and other select international markets. Use of the Covidien Nellcor OxiMax pulse oximetry technology with Philips monitoring platforms can lead to enhanced patient care by providing clinicians with cardiac-based readings of SpO2 and pulse rate. The Nellcor SpO2 single parameter module is also compatible with the full line of Covidien Nellcor sensors, including: the Nellcor forehead sensor, which gives readings when conventional finger sensors fail, detects changes in oxygen saturation earlier than conventional sensors and is approved for use with ventilated patients; Nellcor non-adhesive sensors, which protect sensitive skin, a particular benefit to patients in the NICU; and single-patient-use oximetry sensors, which protect against hospital-acquired infections. The Nellcor SpO2 single parameter module is compatible with the Philips IntelliVue MP40 through MP90 monitors and the Philips IntelliVue MX 600, MX 700 and MX 800 monitors. Contact [www.covidien.com](http://www.covidien.com).

## NEW PRODUCTS

Neotech Products has been very busy developing new products. The Neotech NeoSeal is a soft, closed-cell foam that is placed on a cannula to provide a seal for traditional nasal or Bubble CPAP and provides soft, effective protection for the fragile septum. The Neotech ChinStrap was developed to help keep the chin stable during CPAP, preventing excessive air loss. It's made of a soft, flexible material, NeoFoam, and is adjustable for various sizes. The split chin design allows the baby to aspirate when necessary. The company added a new member to its electrode family. The Mini NeoLead Electrode is about the size of a dime, provides excellent tracings, and is perfect for micro preemies. Neotech's electrodes are extremely gentle to fragile skin and really stay on. Neotech is also happy to introduce the NeoSpoon, a biodegradable measuring spoon that can be used to quickly and efficiently measure fortifications and formula in the NICU. Last but not least, the company launched its new RAM Cannula as an interface for NIPPV and NCPAP and in just six months it has been successfully used in more than 150 hospitals and in

10 countries. More new products are coming this year. Contact [neotechproducts.com](http://neotechproducts.com).

## TEST PANELS

Quest Diagnostics has extended its endocrine diagnostics menu with the introduction of four new tests panels for congenital adrenal hyperplasia (CAH), an endocrine disorder found in newborns, children and women. The panels are designed to overcome limitations in conventional testing to provide faster, high quality diagnosis of CAH in a single analysis. The new offerings feature a comprehensive panel for newborn screening for CAH. The panel enables analysis of all 13 steroids associated with CAH using the highly sensitive and specific liquid-chromatography tandem mass spectrometry (LC/MS/MS) measurement technique. In addition, the test can be performed on a sample volume of 0.1 milliliter, making it well suited to newborn heel-prick sample collection. The Endocrine Society recommends testing by LC/MS/MS to evaluate CAH and other hyper-androgenic disorders. The company also has introduced three additional CAH panels by LC/MS/MS. One panel aids in diagnosing acute stress conditions in newborns that can be misdiagnosed for CAH. Another panel aids in diagnosing and managing children and adults with the most common forms of CAH, which are caused by 21-hydroxylase or 11-hydroxylase enzyme deficiency. A fourth panel aids in differentiating non-classic CAH from polycystic ovary syndrome (PCOS), a highly common androgen disorder in women that shares similar symptoms with CAH. Contact [questdiagnostics.com](http://questdiagnostics.com).

## MAKING SENSE

Nonin Medical, Inc announced the US market release of its EQUANOX Advance Model 8004CB Series neonatal/pediatric sensor. The EQUANOX Advance 8004CB Series Sensor with Nonin's patent-pending Dynamic Compensation algorithm is the first and only cerebral/somatic sensor to automatically account for pediatric brain-tissue-development variation when measuring oxygen saturation levels. The sensors are designed for use with Nonin's EQUANOX Advance Model 7600 Oximetry System in cerebral or somatic positions on patients weighing less than 40 kg. EQUANOX is a near infra-red spectroscopy (NIRS)-based monitoring device that noninvasively and continuously detects oxygen saturation status in brain and other tissue. The device allows clinicians to quickly react to reverse harmful tissue ischemia events before they become critical. The EQUANOX Advance 8004CB and 8004CB-NA (non-adhesive) Neonatal/Pediatric Sensors, along with the Model 7600 Oximetry System, provide additional advantages including: cerebral and somatic monitoring – up to four channels displayed on one screen for monitoring oxygen saturation in the brain and somatic sites on the body, including kidney and liver sites. Patented dual-light emitters and detectors with four wavelength accuracy – the first and only device that utilizes a dual-light emitting and detecting sensor architecture, which has been shown to more effectively target the cerebral cortex, eliminating surface artifacts that interfere with measurement accuracy. Absolute accuracy – assures accurate measure of tissue saturation at a point in time, not just relative or trending accuracy of changes. Consistency and reliability – rapid, reliable response to change without signal instability and interruptions from ambient electrical and light interferences. Portability and connectivity – lightweight, durable monitor with long battery life and pole-mounting capability for continually monitoring patients during intra-hospital transport. Data output available via Bluetooth wireless technology or RS232 connection. Interfaces with Philips VueLink (through



Philips IntelliVue Monitor), Philips CompuRecord Anesthesia Information System, Spectrum Medical VIPER Independent Data Management System and Sorin Perfusion Data Management System. Contact (800) 356-8874, [www.noninequanox.com](http://www.noninequanox.com).

## NON-COMPLIANCE

MedImmune, the global biologics arm of AstraZeneca, announced results from a new retrospective database cohort study of 8,443 high-risk infants receiving palivizumab in Medicaid programs across 12 states. Approximately 67% of infants were non-compliant with palivizumab. Non-compliance with the FDA-approved dosing of Synagis (palivizumab), defined as not receiving at least 5 doses or having dosing gaps, significantly increased likelihood of hospitalization from respiratory syncytial virus (RSV) among high-risk infants in a Medicaid population. The percentage of RSV-related hospitalization (RSV-H) was significantly higher among non-compliant vs compliant infants (12.0% vs 7.4%,  $P < 0.001$ ) respectively. These data were presented at the 2012 Pediatric Academic Societies (PAS) Annual Meeting in Boston. The FDA-approved labeling for Synagis, Section 2.1 – Dosing Information, states, “The efficacy of Synagis at doses less than 15 mg/kg, or of dosing less frequently than monthly throughout the RSV season, has not been established.” In these analyses, the population under study was infants born with prematurity (34 weeks gestational age or less), congenital heart disease (CHD) or chronic lung disease of prematurity. Also presented at PAS, were two additional sub-analyses of the data: Non-Compliance with Palivizumab Among Racial Minorities in a Medicaid Population, and Factors Associated with Non-Compliance with Palivizumab Among Medicaid Infants. Compliance with Synagis dosing was evaluated across six RSV seasons (2003-2009), with RSV season typically running from November through March. Babies were required to have been discharged between May 1 and September 30 and to have received one or more doses of Synagis during their first RSV season (October through April) with no gaps of > 35 days between any dose. Inclusion criteria were defined as infants born with prematurity (34 weeks gestational age or less), congenital heart disease (CHD), or chronic lung disease of prematurity (CLDP). Contact [medimmune.com](http://medimmune.com).

## UPDATED

K-V Pharmaceutical Company announced that the FDA and the Centers for Medicare & Medicaid Services (CMS) both issued updated statements on Makena that affirm the importance of the only FDA-approved drug for treatment of women with a history of preterm birth. Prior statements by both agencies had been cited by some payers as the basis for denying patients' access to FDA-approved Makena in favor of unapproved compounded hydroxyprogesterone caproate (17P) formulations. In a reversal of its previous statement, the “FDA emphasizes that it is applying its normal enforcement policies for compounded drugs to compounded hydroxyprogesterone caproate.” Once again, the FDA reiterated that “...approved drug products, such as Makena, provide a greater assurance of safety and effectiveness than do compounded products.” The FDA added that 100% of the API samples procured and tested by FDA failed Makena's standards for unidentified impurities. In a related statement, CMS also issued an update, which reiterated FDA's comments that approved drug products, such as Makena, provide a greater assurance of safety and effectiveness compared to compounded products. K-V stated that it has made substantial efforts to work with payers to facilitate insurance coverage of Makena, which is a progestin indicated to reduce the risk of preterm

birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. Contact [kvpharmaceutical.com](http://kvpharmaceutical.com).

## KEEP CALM

PeriGen, Inc, a national provider of fetal surveillance systems, introduced its newest and most advanced electronic fetal monitoring system, PeriCALM Plus, at the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) 2012 Annual Convention. The PeriCALM Plus suite is the only fetal surveillance system that provides automated visual cues that enable clinicians to easily and quickly spot clinically significant trends. This feature, known as PeriGen Visual Cueing, provides an instant view of mothers' and babies' current status and trends over time, helping clinicians to avoid errors, increase patient safety and reduce risk. Importantly, Visual Cueing in PeriCALM Plus is supplemented by real-time, advanced decision-making support based on expert analysis and established labor and delivery protocols. All of PeriGen's fetal monitoring systems include patented, pattern-recognition software, which offers an objective interpretation of fetal heart rate tracings that is comparable to the analyses of recognized clinical experts. PeriCALM Plus couples PeriGen's traditional fetal monitoring suite (PeriCALM) with comprehensive nursing and physician documentation, as well as protocol-driven decision support. PeriCALM Plus 3.16.0 is ONC-ATCB Certified as a modular EHR under the Hospital domain. The system is currently being evaluated by several hospitals across the US, and was recently selected by Wheeling Hospital in Wheeling, WV, an institution that manages more than 1,000 births annually. Contact [perigen.com](http://perigen.com).

## NANN PREVIEW

### Acacia Neonatal

Booth 326

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

- NuTrio Enteral Feeding System including: NuTrio Syringes, NuTrio GraviFeed, NuTrio Extension Sets, NuTrio Feeding Tubes, NuTrio SimpleFeed Infusor
- MedSafe and Multi Access Sets
- ClosedCare I.V. System
- NICU Specialty Tubing
- SafeSample Blood Gas Sampling Set

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

- NuTrio SimpleFeed Infusor
- NuTrio Enteral Combo Syringes

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

All product literature will be available at our booth.

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

Please visit our booth for detailed information about a special drawing we will have on the last day of the show.

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

Acacia Neonatal prides itself on being an innovation leader. Keeping with this principle we are introducing two new

breakthrough products at the 2012 NANN Conference. On display in our booth will be the NuTrio SimpleFeed Infusor, the first and only non-electrical enteral only infusor on the market. Also at this year's show we will be unveiling the NuTrio Combo Syringe, the most flexible syringe available today with the ability to meet a number of needs all with a single syringe including pump feeding, gravity feeding and venting. Contact [acacianeonatal.com](http://acacianeonatal.com).

## Cincinnati Sub-Zero

Booth 523

### What products do you plan to exhibit?

We plan on having our Hyper-Hypothermia system, the Blanketrol III and Kool-Kit Neonate on display, as well as our warming only devices; the Micro-Temp Lt and Norm-O-Temp with the reusable Gelli-Roll blanket.

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

Our Kool-Kit Neonate continues to be a leader in whole body cooling for neonates. We are always looking at ways to improve upon our currently products and how to grow our product lines. We hope to be able to provide you with our beneficial products for neonates in the future.

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

We have a team of clinical educators that are available to assist with creating protocols and provide on site training to your staff at your facility.

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

We will have a clinical nurse specialist in our booth to discuss the many applications and clinical benefits of our product line.

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

Cincinnati Sub-Zero is a leader in Patient Temperature Management and at the NANN conference this year we will have several of our products on display for attendees to have a hands on experience. The Kool-Kit Neonate and Blanketrol III (which will be on display) were designed with the understanding that precision and accuracy are particularly important during cooling, maintaining and re-warming stages of infants.

## Cornerstone Therapeutics

Booth 327

### What products do you plan to exhibit?

Cornerstone Therapeutics will be featuring CUROSURF (poractant alfa) Intratracheal Suspension.

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

New for 2012 are recently published clinical literature focused on outcomes and less invasive ventilation techniques.

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

Our booth will offer visitors the most recent clinical literature on CUROSURF, as well as a User's Guide Video, dosing cards, wall charts and other educational tools.

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

Readers can stop by to learn more about recent CUROSURF

clinical literature, as well as programs Cornerstone has put in place to support units and staff nationwide. For more information on CUROSURF (poractant alfa) Intratracheal Suspension and Cornerstone Therapeutics, please visit booth 327.

## Corpak MedSystems

Booth 108

### What products do you plan to exhibit?

At Booth # 108, Corpak MedSystems will be exhibiting a broad offering of CORFLO Anti-IV Nasogastric Feeding Tubes. They are available in multiple configurations (weighted, non-weighted, styleted, non-styleted) with our famous Anti-clog outlet port. Corpak MedSystems also will be exhibiting our CORFLO Neonatal Anti-IV Enteral Feeding System, the Farrel I Valve Gastric Pressure Relief System for pump-fed patients who are at risk of pulmonary aspiration of gastric contents.

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

Corpak MedSystems now offers a full line of Anti-IV Nasogastric Feeding Tubes which includes multiple configurations for your neonatal and pediatric patient needs.

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

We will be conducting a drawing for a certificate to NANN's 29th Annual Educational Conference on October 2-5, 2013 in Nashville, TN. This certificate allows for attendance at the conference and is valued at over \$400.

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

We offer several products that pertain to patient safety. Our line of Anti-IV Nasogastric Feeding Tubes and Sets minimize the risk of misconnection to intravenous connections. Our Farrell Valve Gastric Pressure Relief System reduces the risk of aspiration pneumonia. The Navigator BioNavigation System confirms PICC/UVC catheter tip location at the bedside, reducing patient exposure to multiple X-rays.

## Crib Notes

Booth 527

### What products do you plan to exhibit?

Crib Notes RN, Crib Notes, Crib Notes MD and Software as a Service.

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

Many new product features as well as new ways to acquire Crib Notes – including Software as a Service.

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

Web site has User Site with many training materials as well as videos.

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

See the best EMR for NICU use.



## DeRoyal

Booth 112

### What products do you plan to exhibit?

NICU Temperature Monitoring Probes, New Enteral Safe Syringes, extension sets and feeding tubes, NICU Safe IV Anti-microbial Patch, NICU BP Cuffs and IV Arm Boards.

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

New affordable latex-free DEHP-free enteral safe feeding system. Plans to allow every NICU to be able to afford to be safe.

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

Literature on product and copies of Joint Commission's 2006 sentinel event alert.

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

Free samples of all products will be provided as well as a desktop note pad gift called The Simplicity Shops Stop.

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

They will leave knowing that a safer NICU will be the result.

## Fisher & Paykel Healthcare

Booth 426

### What products do you plan to exhibit?

Fisher & Paykel Healthcare is launching its first complete Bubble CPAP System including the new FlexiTrunk CPAP Interface and new CPAP Nasal Masks. Also, see the first humidified infant resuscitation system using the MR850 respiratory humidifier. The Neopuff Infant T-Piece Resuscitator facilitates the delivery of warm humidified gas to help protect the pulmonary epithelium and reduce heat and moisture loss especially during prolonged resuscitation. Conditioning cold, dry gas to body temperature and saturated with water vapor can help reduce the risk of an inflammatory response occurring in the infant's airway.

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

Fisher & Paykel Healthcare is introducing two exciting products. First, Fisher & Paykel is launching the first complete Bubble CPAP System including the new FlexiTrunk CPAP Interface and new CPAP Nasal Masks. And we are showcasing the first humidified infant resuscitation system using the heated T-Piece Circuit and MR850 respiratory humidifier.

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

Come and experience hands-on training with the Neopuff Infant T-Piece Resuscitator simulator using the new Ergonomic T-Piece Resuscitation Circuit and our Resuscitation Masks. This is highly recommended for NRP Instructors. Also, ask us about our Optimal Resuscitation workshop for your hospital staff.

### What in-booth promotions will be available?

Fisher & Paykel Healthcare will be giving out samples of the complete FlexiTrunk Interface including accessories – prongs, mask, bonnet, head gear and chin strap. This is ideal for bubble CPAP or ventilator CPAP therapies.

### Why should our readers visit our display?

Come by the F&P booth to see the first all-in-one Bubble CPAP

System including the new FlexiTrunk CPAP Interface and new CPAP Nasal Masks. Also, come and see the first T-Piece Resuscitator and Family of T-Piece Circuits. Please join us at the NANN Conference at booth 426 for a complete review and demonstration of all Fisher & Paykel Healthcare products.

## GN Otometrics

Booth 233

### What products do you plan to exhibit?

GN Otometrics will be showcasing the new and improved MADSEN AccuScreen Newborn Hearing Screener.

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

GN Otometrics reintroduces the MADSEN AccuScreen this year, a new version of the legendary two-step (OAE/ABR) screener featuring touch screen technology. This was developed by the same team who introduced the original AccuScreen and is designed to be fast, accurate and intuitive, and it builds on our reputation of having one of the most trusted newborn hearing screeners. It offers the same precision and workflow integration that's made AccuScreen a first choice for NHS programs around the world.

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

We will have brochures and whitepapers at the GN Otometrics Booth, as well as a team of experts to answer questions about Newborn Hearing Screening.

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

The GN Otometrics team will be available for a hands-on demonstration of the MADSEN AccuScreen. They will explain how this Newborn Hearing Screener can significantly improve workflow by utilizing more efficient OAE &/or ABR.

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

Attendees can take advantage of this opportunity to learn more about Newborn Hearing Screening and how they can significantly improve workflow through efficient device management, test management and automatically exporting patient data to the instrument so they have more time to interact with the baby and parents, or prepare for the next patient. For questions about the new MADSEN AccuScreen and newborn hearing screening, please visit [www.otometrics.com/accuscreen-us](http://www.otometrics.com/accuscreen-us).

## Ivera Medical

Booth 609

### What products do you plan to exhibit?

Ivera Medical's Curo Disinfecting Port Protector is a simple, innovative, disposable medical device that effectively disinfects luer-activated needleless valves, killing the organisms associated with patient bloodstream infection.

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

The new Curo Strip provides caregivers with a perfectly accessible dispenser for Curo Disinfecting Port Protectors anywhere the disinfection caps are needed. The ten-cap, foil-backed dispenser can be hung on an IV pole or other convenient bedside location so that nurses have easy access to consistent

and reliable passive disinfection during every IV access. With two dispenser options – the Curot Strip or individual Curot – nurses can conveniently comply with disinfection protocols by simply peeling the foil seal off the distinctive green cap and twisting Curot over the top of any luer-activated IV access port or needleless valve. Inside Curot a 70% IPA (isopropyl alcohol) saturated sponge-like foam automatically provides effective, consistent and reliable passive disinfection of the port.

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

View the Curot Educational video and instructions for use at [www.curot.com](http://www.curot.com).

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

Attendees who come to learn about Curot will receive a “Go Ahead, Strip!” Curot zippered tote bag.

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

Curot disinfecting port protectors created by Ivera Medical are used on swab-able luer-activated valves to disinfect IV access ports within 3 minutes and act as a physical barrier to contamination for up to 7 days if not removed. In a six-month controlled study by a university hospital on a 32-bed unit, Curot contributed to an 86.2% decline in CLABSIs, a 92% reduction in contaminated blood cultures and projected annual cost avoidance of \$500,000 for the unit.

## **Maico Diagnostics**

Booth 111

#### **What products do you plan to exhibit?**

MB 11 Beraphone ABR hearing screener.

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

Enhanced ABR Technology – CE Chirp stimulus produces a larger ABR response which can mean faster test times.

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

Our MB 11 training video.

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

The MB 11 is the only screening device without costly disposables, stop by so we can show you how to save thousands of dollars each year in disposables. The Maico MB11 newborn hearing screening system uses ABR technology with a unique, CE chirp acoustic stimulus. MB11’s “green technology” features an integrated, reusable earphone and electrodes, avoiding the high costs and medical waste associated with use of disposable electrodes and ear couplers. Visit [maico-diagnostics.com](http://maico-diagnostics.com) for an online educational video or call (888) 941-4201. Please visit booth #111 for demonstrations of the MB11.

## **Medela**

Booth 310

In the Neonatal Intensive Care Unit the need for the protective benefits of human milk is perhaps more evident than anywhere else. Human milk is considered to be a crucial medication to help premature infants grow and protect them from serious complications. Medela’s system of innovative, evidence-based products, services and education helps you deliver

more milk to your vulnerable patients every step of the way. From breastfeeding, to human milk storage, transport and preparation to diagnostics and feeding our comprehensive system will help you • improve outcomes, • reduce costs, • improve patient satisfaction.

#### **What products do you plan to exhibit?**

• **Symphony Preemie+** – Understanding the research led to new products that make feeding human milk even easier with innovations such as Symphony Preemie+, the first pumping program clinically shown to produce more milk for NICU moms.

• **Baby Weigh II Scale** – Check out our Baby Weigh II scale which helps accurately measure infant milk intake. Knowledge of milk intake may improve the clinical diagnosis of feeding problems while providing essential information for precise supplementation of infants who may be at risk for under- or over-consumption.

• **Waterless Milk Warmer** – Medela’s Waterless Milk Warmer is the safer, easier way to warm human milk. The Waterless Milk Warmer: Eliminates risk associated with warming in water; Consistently warms milk to temperatures of that of expressed human milk; Safely thaws human milk.

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

Medela Education provides the latest breastfeeding research through its extensive education programs. Our evidence-based programs detail best practices and are designed to impact and improve practice in hospitals nationwide. Visit [www.MedelaEducation.com](http://www.MedelaEducation.com) to learn more about our evidence-based education programs geared toward the NICU clinician.

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

As a clinician, you understand how important human milk is to improving outcomes for babies in the NICU. Establishing an adequate milk supply can be a challenge for mothers of premature babies who are dependent on a breastpump for initiation and maintenance of lactation. Medela supports your efforts every step of the way and helps you deliver more milk to your NICU patients. And when your patients go home, Medela is there to support them with a full line of breastfeeding and breastpumping products available at retailers nationwide. Mothers can benefit from of a continuum of care with the same technology and benefits they enjoyed in the hospital. Medela’s Breastfeeding Division exists to enhance mother and baby health through the life-giving benefits of breastmilk. This is more than a vision, this is Medela’s destiny.

## **NeoMed, Inc**

Booth 220

NeoMed, Inc is a leading provider of Neonatal and Pediatric Enteral Delivery Systems. During the NANN Conference, we will exhibit our Enteral Safety System, NeoBottle Generation 2, Closed System NeoBottle, SafeBaby Breast Milk Tracking System, and Specialty Kits and Catheters.

At the core of NeoMed’s product line is our Enteral Safety System, which includes a comprehensive line of Oral/Enteral Syringes, Extension Sets, Indwelling Silicone and Polyurethane Feeding Tubes, and Short-Term PVC Feeding Tubes. Features of our Enteral Safety System include Oral/Enteral Only connections, bold graduation and centimeter markings, self-righting plugged tip caps, and easy to clean hubs and tethered plugs.



NeoMed is proud to introduce four new products. The NeoBottle Generation 2 is the next evolution of our NeoBottle, the first collection, storage, and delivery system for HBM and formula that maintains a closed system and aseptic barrier from breast to baby. Use the innovative 100 mL Oral/Enteral Dispenser as a gravity-feeding device with a fenestrated plunger for pole placement and “vent zone” for flow or for pump-assisted feeds in an Atlanta Biomedical Corporation Pump Model 4100.

Our Short-Term PVC Feeding Tube is a cost-effective option for use up to 3 days, engineered with the same safety features as our Polyurethane and Silicone Feeding Tubes, including orange hubs, an encapsulated orange radiopaque stripe, and bold insertion markings at each centimeter to help confirm placement. Finally, medications are created in a myriad of colors. From 0.5 mL to 60 mL, our Clear Pharmacy Dispensers with Blue Gradient Markings, in addition to our Clear Pharmacy Dispensers with Orange Gradient Markings and our Amber Pharmacy Dispensers with White Gradient Markings, gives the pharmacist a choice for medication visualization.

NeoMed is committed to the safe collection, storage, and delivery of human breast milk and formula to neonatal and pediatric patients. NeoMed is proud to collaborate with SafeBabyBMT who recently obtained a US Patent (No. 8,172,129) for their unique Breast Milk Tracking System, which enables the clinician to track, manage, and record the feeding of neonatal and pediatric patients. The combination of NeoMed’s Enteral Safety System and SafeBaby’s Breast Milk Tracking System provides the most comprehensive solution for safe and secure feeding in the critical care environment.

To learn more about NeoMed and SafeBaby, visit us at the NANN Conference in booth 220 or visit our website at [neomedinc.com](http://neomedinc.com). Be sure to stop by booth 220 and enter our raffle for the chance to win an iPad1. (Eligibility to Enter: The NeoMed raffle is only open to legal residents of the United States. The raffle excludes employees and immediate family members [spouses, parents, siblings, and children] of NeoMed, Inc, Specialty Medical Products, NeoMed Fulfillment, and each of their respective dealers, sales representatives, employees, agents, and owners.)

## Nurtured by Design

Booth 319

### What products do you plan to exhibit?

We will exhibit our own two products, The Zaky and the Kangaroo Zak ([www.nbyd.co/NICU](http://www.nbyd.co/NICU)). **The Zakys** are the only evidence-based ergonomic developmental care devices in the market. They virtually replace all positioners, transitional/soothing devices, and bonding aids on all beds/incubators. They mimic parental intervention: the shape, feel, weight, warmth, scent, and touch of the caregiver’s hands that stay with the baby. They keep the scent of the parents (place on the chest or behind the neck). One universal size works with all infants. **The Kangaroo Zak** – It facilitates prolonged, effective, safe, and hands-free Kangaroo Care sessions. The Kangaroo Zak wraps around the torso of the parent, is adjustable, unisex, and holds the weight, positioning, containment, temperature, and boundaries of the baby. The Kangaroo Zak eliminates all risk of accidental falls during Kangaroo Care. These two products are virtually all an NICU needs to provide evidence-based family centered developmental care, individualized for every baby, from

birth, around the clock, regardless of size, medical condition, or developmental stage. All without expensive equipment, invasive procedures or medication. They transform performance, advance results, and optimize supply chain, logistics, storage, ordering procedures, training, and quality control. Our products are used in over 300 hospitals in over 32 countries. Recommended as the standard of family-centered/individualized developmental care and Kangaroo Care by international NIDCAP trainers and many hospitals.

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

New independent clinical research about the effectiveness of simulating maternal intervention in NICUs will be presented in the poster presentation #1096 during NANN’12. (October 18th, 4:45-5:50 pm and October 19th, 7:00-7:45 am). Come see our products, new literature and brochures to educate parents and staff about family centered developmental care and Kangaroo Care. In addition, Nurtured by Design develops tailored solutions for NICUs so talk to us about your challenges about family-centered care, developmentally supportive care, or Kangaroo Care. We are engineers working to develop tailored ergonomic and comprehensive solutions for NICUs. Nurtured by Design is part of an educational collaborative that provides consulting, speakers and workshops with CEU credits.

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

Our core business is evidence-based Kangaroo Care and developmentally supportive care centered in the family. We will have products demonstrations, brochures about Kangaroo Care, posters, videos, etc. You will leave our booth knowing how to use the Zaky and Kangaroo Zaks in your NICU. Yes, they are that easy to use.

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

Come to booth 319 to see the list of fabulous prizes for each day and register to win! The inventor of our products, Yamile Jackson, PhD, PE, will be at the booth during the entire conference. She is the global leader in neonatal ergonomics as it applies to developmental care, she is certified in Kangaroo Care and was the Kangaroo Mother of Zachary (ask her to show you a picture of Zachary, her son and loving inspiration.) She will share proven tips on how to improve developmental care, family centered care, and Kangaroo Care in your NICU. If you prefer, schedule a phone meeting with Yamile anytime at to talk about your individual needs.

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

Developmental Care and Kangaroo Care are evidence-based practices and should not be left to the personal preference of the caregiver. We offer comprehensive neonatal developmental care solutions that are based on ergonomics, individualized care, and clinical evidence. The Zakys are virtually all you need as positioners, transitional/soothing items, and bonding aids for all babies in the NICU. Kangaroo Zak facilitates prolonged, effective, safe, and hands-free Kangaroo Care sessions. Only with us, you provide the highest standard of individualized developmental care that is simple, effective, and most importantly, based on clinical evidence from birth, around the clock, and without expensive equipment, invasive procedures, or medication.

# Philips

Booth 203

## What products do you plan to exhibit?

• AVENT Breastfeeding system • AVENT Breast Care • SmartMonitor 2 and 2PS • Calming and Soothing • Infant Warming • Jaundice Management – BiliChek & BiliTx • OB TraceVue • Avalon FM50 and CTS • Medical Consumables • NeoPAP • Educational offerings • Sleep and Positioning • Feeding and Safety • IntelliSpace Critical Care.

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

Introducing Avalon fetal and maternal monitors with Smart Pulse. Smart Pulse incorporates the maternal pulse measurement into the Toco MP transducer, automatically detecting situations where maternal pulse may be confused with the fetal heart rate without additional sensors or cables. Philips collaborated with healthcare professionals to develop a line of oral/enteral products for use with confidence for neonates and infants throughout the hospital. These syringes, extension sets, and feeding tubes provide 1. Exceptional nutritional support while considering the developmental aspects of feeding premature infants. 2. One source for a complete enteral feeding solution to simplify clinician workflow. 3. Designed incompatibility with luer connectors to reduce the potential for inadvertent delivery through the IV route.

## What educational or training materials will be available?

Opportunity to sign-up for Philips Mother and Child Care free monthly webinars offering CEU credits.

## Why should our readers stop by your display?

• Groundbreaking technology, only from Philips: Avalon Smart Pulse! • The complete enteral feeding solution, feeding tubes are now available! • To sign-up for Philips Mother and Child Care free monthly Webinars offering CEU credits.

# Respiralogics

Booth 611

Respiralogics is a provider of innovative products for NICU, PICU and special care units. We are dedicated to providing patients and health care providers exceptional products. Respiralogics will present the Babi.Plus Bubble CPAP System, the Danny Ties trach ties and the Sil.Flex Stoma Pads and TC Pads.

**Babi.Plus Bubble CPAP System:** Bubble CPAP, a breathing assistance system, is showing promising results in decreasing the incidence of chronic lung disease among premature infants. CPAP is a breathing system commonly used in the NICU to deliver heated and humidified airflow and pressure to an infant's lungs via short nasal prongs in the nose that assists in keeping the infant's lungs open at end exhalation while allowing them to spontaneously breathe. Adding bubbles to the CPAP is proving to be of benefit in effectively treating these infants and allowing them to breathe on their own. The Babi.Plus Bubble nCPAP System was designed to provide a simple method for delivery of Bubble CPAP that will allow for focus on the infant and not the devices. The patent pending design delivers accuracy and stability throughout the course of therapy.

**Danny Ties:** Danny Ties are unique tracheostomy tube holders

with a softer and more comfortable fit around the neck for patients of all ages. The patient with a tracheostomy needs to have a tube holder that securely holds the artificial airway in place to prevent accidental decannulation. As important, the tube holder needs to provide a soft, comfortable fit about the neck while minimizing skin irritation under the collar. Danny Ties are made of soft, absorbent cotton that lays smooth at the edges of the collar, minimize skin irritation and reduce skin breakdown under the collar. The patent pending design of the Danny Ties evenly distributes the quilted collar around the neck to minimize pressure points on the skin.

**Education & Training Materials:** The strong clinical background of our staff and strategic partners serve you well in presentation of new concepts for delivery of patient care, exploration of your requirements to meet clinical needs and assistance with justification through the value analysis process. Most important, we are there to provide ongoing support for your team. Stop by the Respiralogics booth, Booth 611, for a demonstration of Bubble CPAP and see how easy it is to implement a Bubble CPAP program in your NICU.

# SafeBabyBMT

Booth 220

## What products do you plan to exhibit?

The SafeBaby Breast Milk Tracking System, Donor Milk Tracking System and Safe Nutrition.

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

SafeBaby is proud to announce SafeBaby Donor Milk Tracking (DMT). SafeBabyDMT allows a donor bank to completely and electronically track donor milk from "collection" to pasteurization to confirmation of delivery at hospital's NICU. SafeBaby is also pleased to unveil SafeNutrition. SafeNutrition is a comprehensive solution for managing each NICU patient's individual nutritional needs.

## What educational or training materials will be available?

SafeBaby is proud to provide white papers and informational packets that detail the necessity of electronically verifying that the right milk goes to the right child.

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

Working with our sister company, NeoMed, SafeBabyBMT will be raffling off prizes for the visitors at our booth.

## Why should our readers stop by your display?

SafeBabyBMT is dedicated to being the complete NICU feed management solution, and has videos, product demonstrations and other informational materials regarding NICU feeds and the importance of proper electronic validation.



# Misoprostol Use and the Mobius Syndrome

Rita Shah, MD; Uzma Cheema, MD; Ivan Hand, MD

## Abstract

We report case of a male infant born with Mobius syndrome after a failed attempt at a self-induced first trimester abortion. Mobius syndrome is a rare neurological disorder that has been associated with the use of misoprostol. We report on the difficulties in obtaining an adequate history and the complications of misoprostol use obtained outside the traditional medical environment.

## Introduction

For centuries, various abortifacients have been used including ancient rituals, herbs, mechanical evacuation and medicinals. Today, the most commonly used methods are mechanical evacuation and medications. There are greater than 800,000 abortions per year performed in the United States, out of which 62.8% occur prior to the 9th week of gestation with medical abortions accounting for 14.6% of all abortions.<sup>1</sup> Misoprostol is a prostaglandin E1 synthetic analogue initially used to treat NSAID induced gastric ulcers which was subsequently found to have strong vasodilative and uterotonic properties making it suited for use as an abortifacient.<sup>2</sup> One common protocol is to administer methotrexate 50 mg/m<sup>2</sup> followed by treatment with vaginal misoprostol 800 mcg five to seven days later. When taken under medical supervision, a full abortion is achieved in up to 98% of pregnancies less than 49 days of gestation.<sup>3,4,5</sup> Misoprostol is also available on the “black market” where it is used alone and often without medical supervision. Misoprostol when taken as a single agent has a high rate of failed abortions and a reported absolute risk of congenital malformations of up to 1%.<sup>3,6</sup>

## Case Report

A male infant was born at 39 weeks gestational age to a 26 y/o G5P4004 mother of Haitian descent with gestational diabetes who received adequate prenatal care. She denied the use of undisclosed medications or illicit drugs during pregnancy when

questioned upon admission. Upon delivery, the infant presented with grunting, retractions and inspiratory stridor. The Apgar scores were 8 and 8, at 1 and 5 minutes respectively, with a birth weight of 3795 grams. The infant required ventilatory support and was treated with nasal continuous positive airway pressure. Physical examination demonstrated downslanted hypertelorism, decreased grimace, micrognathia, small mouth with downturned corners, poor suck, low set ears, and bilateral clinodactyly (Figure 1). The most striking of all the features was lack of facial movement during crying. Cranial nerve assessment revealed bilateral sixth and seventh nerve palsies. Flexible fiberoptic laryngoscopy performed due to the inspiratory stridor revealed right sided vocal cord paralysis. Other significant findings included right sided hearing loss demonstrated via automated auditory brainstem evoked responses. These findings were all consistent with Mobius syndrome although the etiology of the syndrome remained unknown at the time.

Upon further questioning, the mother admitted having gone to a local herbalist seeking medications to terminate pregnancy at the 4th to 5th week post-conception. She was unable to recall the name or dosage of the pill she took orally, but stated that she had abdominal cramping within 24 hours of ingesting the pill, followed by vaginal bleeding within 3 days. The mother assumed her pregnancy was terminated but after missing her period the following month, sought medical attention where her gynecologist confirmed an intrauterine pregnancy. After the failed abortion, the mother decided to carry the fetus to term.

## Discussion

Mobius syndrome is a sporadically occurring syndrome which is believed to be related to an ischemic intrauterine brain injury. This brain injury is the result of a vascular event causing ischemia to watershed areas in the brain where cranial nerves VI and VII originate.<sup>7</sup> Ischemia then leads to vertebral artery hypoperfusion and brainstem atrophy. Genetic mechanisms have also been cited as a cause and there is an association of the syndrome with the HOXA1 gene with loci at 1p22 and 13q12.2.<sup>8</sup>

In this case report, we believe that misoprostol, used to induce abortion, was the cause of the Mobius syndrome. Based on multiple studies, misoprostol is not recommended as a lone abortifacient because of its relatively low efficacy.<sup>2,3,4,9</sup> It is however routinely used because of its widespread availability, low cost, and minimal maternal side effects. Although its exact mechanism of action is unknown, misoprostol is believed to induce uterine contractions and cervical ripening, thereby,

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expelling the fetus. When used as a single agent, uterine contractions may occur without a complete abortion resulting in adverse outcomes. It is hypothesized that these partial uterine contractions cause hypoperfusion and thus lead to localized hypoxia and ischemia. Resulting flexion of the fetus following these uterine contractions leads to mechanical compression of vital organs such as the brain and the developing nervous system. When this occurs during a critical time in neuronal development it will result in hemorrhage and cellular death. Cranial nerves VI and VII are the most vulnerable because they are located in a thin, dilated portion of the brain with minimal protection.<sup>6,8,10-12</sup> Up to 15% of misoprostol induced abortions are unsuccessful and often lead to congenital anomalies, the most frequent of which is the Mobius syndrome.

Common features of the Mobius syndrome include orofacial and craniofacial anomalies. The frequently seen “mask-like facies” is due to partial or complete impairment of cranial nerve VII. In up to 1/3 of cases, the face is completely immobile.<sup>7</sup> Cranial nerve VI, the abducens nerve, is the next most commonly involved nerve, followed by the hypoglossal nerve.<sup>11</sup> Depending on the extent of cranial nerve involvement, patients may have swallowing, respiratory, and speech difficulties. While the majority of children have normal IQs, up to 10% can have mild to moderate mental retardation.<sup>11</sup>

As physicians, it is important to obtain a thorough history and have a good rapport with patients, ensuring their honesty and open communication. The use of complementary and alternative medicine (CAM) has grown significantly in the United States with data from the 2007 National Health Interview Survey demonstrating that 31.8% of women cared for by an obstetrician/gynecologist used some form of CAM. Even more striking is the fact that only about half (51.8%) reported the use to a physician.<sup>13</sup> There are several reasons for non-disclosure including concern over a negative physician response, believing the information is not relevant and feeling that the physician does not care about CAM therapies.<sup>14</sup> Physicians must be aware of the availability and use of these alternative therapies when treating mothers and their infants. Questions specifically focusing on the use of alternative therapies and abortifacients must be asked of all women. Physicians must be aware of the availability of therapies in our communities and must include these discussions in our patient interactions. In addition, understanding and respecting patient's decisions can help eliminate bias, and decrease the number of patients seeking alternative methods.

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Figure 1. Infant with Mobius syndrome. Note mask-like facies with sixth and seventh nerve palsy, hypertelorism, micrognathia, and high nasal bridge. Feeding tube placed for feeding difficulties. Maternal consent on file for publishing this picture.

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# Decreasing Ventilator Associated Pneumonia in the Neonatal Intensive Care Unit

Powered by evidence and fueled by love: one unit's road to success in increasing milk volumes in pump dependent mothers

Lori Wood

## Introduction

Breast milk is the undisputed gold standard for the provision of not only infant nutrition, but also immunological protection. The policy statement from the American Academy of Pediatrics refers to the provision of breast milk as a matter of public health (American Academy of Pediatrics, 2011). Health benefits such as reduced rates of infections including otitis media, upper and lower respiratory infections, gastroenteritis, as well as sepsis and necrotizing enterocolitis have long been reported. As research continues with regards to the immunological properties of breast milk, and especially colostrum, the inclusion of cytokines, secretory immunoglobulin A, and pancreatic secretory trypsin inhibitor (PSTI) have been found to exhibit protective measures on both gastric and oral mucosa (Spatz, & Edwards, 2009). In light of the foregoing, our facility was very committed to providing fresh, never frozen, breast milk to the infants in our Neonatal Intensive Care Unit (NICU) for their first feedings and for the provision of oral care to our babies to aid in the prevention of Ventilator Associated Pneumonia. Our NICU did not have enough breast milk from our pumping moms to provide both so the quest to solve our problem began.

## Protecting the Vulnerable

The provision of passive immunity and immunological protection via expressed mother's colostrum is a comprehensive approach to tackling the issue of nosocomial infections in the neonatal population. Extremely low birth weight infants as well as critically ill, ventilated babies, are at risk for developing a multitude of illnesses during their stay in the neonatal intensive care unit.

## The Protective Qualities of Colostrum

Colostrum, mother's first milk, provides many beneficial immunological protectors. Secretory IgA, along with other immunoglobulins and cytokines, protect the infant against infectious organisms. PSTI has been shown to have protective qualities on the gastric mucosa. These immune components have been shown to be protective during the first week of life, an especially vulnerable period of time (Araujo, Goncalves, Cornetta, Cunha, Cardoso, Morais, & Giraldo, 2005) (Rodriguez, Meier, Groer, & Zeller, 2009). Furthermore, studies have shown that the concentration of these protective factors, including Secretory IgA, is higher in expressed colostrum during the first week following premature delivery (Araujo et al, 2005) (Dvorak, Fituch, Williams, Hurst, & Schanler, 2003) (Koenig, de Albuquerque

Diniz, Barbosa, & Vaz, 2005). The composition of colostrum changes after the sixth day of lactation. Concentrations of immunological components are reduced, while the milk begins to take on a more nutritional focus with its increase in fats and lactose. Once mature milk is established, a blend of nutrients and immunological factors will be noted (Araujo et al, 2005). These changes coupled with the knowledge of the effects of the constituents of early colostrum, point to the need for the provision of colostrum to the smallest and sickest babies.

## Oropharyngeal Administration of Colostrum

Extremely low birth weight and critically ill infants are most often unable to tolerate oral feedings. Through the collective work of many authors, the administration of colostrum via the oropharyngeal route has been suggested as an effective method of providing this life saving milk (Rodriguez, Meier, Groer, & Zeller, 2009) (Rodriguez, Meier, Groer, Zeller, Engstrom, & Fogg, 2010). Cytokines in colostrum stimulate the oropharyngeal-associated lymphoid tissue (OFALT) and gut-associated lymphoid tissue (GALT) which protect the respiratory and gastrointestinal tracts from infectious pathogens (Rodriguez, et al, 2009). This process potentially activates an immunostimulatory cascade protecting against hospital acquired infections including necrotizing enterocolitis and pneumonia.

## The Importance of First Feedings of Colostrum and Expressed Breast Milk

Recent research points to the importance of feeding expressed breast milk and especially colostrum as the first feeding to ill babies, especially premature infants. The World Health Organization stresses the importance of colostrum as the first feeding (World Health Organization, 2009). Critical periods in neonatal development have been identified. These times are short, but the provision of human milk is essential in ensuring quality outcomes while reducing catastrophic problems such as necrotizing enterocolitis and other inflammatory-based disease processes such as Chronic Lung Disease (CLD) and retinopathy of prematurity (ROP) (Meier, Engstrom, Patel, Jegier & Bruns, 2010). These health issues can be devastating to the future health of the infant as well as the bottom line of the hospital budget. The provision of early breast milk to the sick and premature infant becomes not only a health benefit and moral obligation, but also a cost saving measure for the present and future care of such infants.

## Critical Periods of Exposure to Breast Milk for Premature Infants

Critical periods of exclusive breast milk feedings or as close to

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exclusive as possible are thought to potentially result in better overall health outcomes for at risk babies than for those babies who received partial feedings throughout their NICU stay. Critical periods of human milk exposure include (Meier, et al, 2010):

Colostrum provision during the transition from intrauterine to extrauterine life

- Stimulates rapid growth of the intestinal mucosa
- Induces digestive enzyme production
- “Replaces” the absence of amniotic fluid swallowing that would have occurred in the intrauterine environment but is absent in premature infants

Early enteral feedings/first feeding exposure

- Exposure to the changing early milk to mature milk causes gastrointestinal changes
- Increased feeding tolerance is noted in premature infants
- Reduces morbidities such as NEC, CLD, and ROP
- Even small amounts of formula during this important stage can alter the colonization process and leave a baby vulnerable

Human milk during the NICU stay

- Earlier discharge was noted among infants who received exclusive own mother's milk
- Lower rates of NEC, CLD, ROP

### The Needs of a Unit

Considering all of the research and best practice information available, the need to obtain and provide a mother's own colostrum and breast milk was not only our desire, but a necessity for all of the premature and sick babies in our NICU. We were providing expressed breast milk, but the infants did not have enough available to provide for oral care as well as first feedings and exclusive provision of breast milk to our babies. Pumping education and support were available as well as NICU Lactation Consultants, but babies were still acquiring VAP. The amount of milk necessary to provide needed care and administration was not being met. We needed a solution.

### New Pump Technology

We looked to the research conducted by Dr Paula Meier et al at the Rush University Medical Center in Chicago, IL. There is much knowledge surrounding the issue of increasing breast feeding rates and the provision of breast milk through staff education and evidence-based competency and policy development. Our unit had begun a breast feeding/breast milk awareness education campaign in 2008. This campaign, coupled with VAP education and oral care bundles, allowed us to make strides in decreasing our VAP rates. Our unit had not collected VAP rates prior to 2009 but we had two cases in 2009 and two cases in 2010. Our staff and neonatologists were struggling with simultaneously providing breast milk for feedings and oral care. There simply was not enough milk available for the majority of our patients. Education and understanding was evident but we just didn't have the supply we needed.

Dr Meier published work in 2010 surrounding new breast pump suction patterns used in the Medela Symphony pump. Through blinded randomized clinical trials, Dr Meier's research demonstrated that a new pump with breast pump suction patterns that mimic the patterns of newborns during the initiation of lactation were effective in obtaining more milk output (Meier, Engstrom, Janes, Jegier & Loera, 2010).

The Symphony Pump trials sought to discover whether a

different pattern of sucking, one mimicking the rapid suck rate followed by an irregular rhythm caused by the small amounts of milk available after delivery, would yield more milk in mothers who were separated from their babies and were reliant upon a pump for the initiation of lactogenesis II (Meier, et al, 2010).

Daily milk output was measured for volume. Daily outputs of over 350 ml were counted as sufficient to attain full and exclusive breastfeeding for premature infants and 500 ml per day for term babies. One hundred and two mothers from a sample group of 105 were able to achieve the minimum 350 ml/day volume needed to produce enough milk throughout the breastfeeding needs of an infant. This new pump was proven to have success at extracting the amount of milk needed by a growing preemie and provide a sustained output of milk that would grow with the needs of the baby. Mothers were comfortable and the pump was felt to be convenient (Meier, et al, 2010). This research was suggestive of increased success and milk availability as well as sustained milk output, so our neonatal team decided to implement the pump.

### Implementation of a New Strategy, Changing the Culture

It took the concentrated efforts of our Lactation Consultants and NICU Leadership team to provide the evidence supporting the purchase of new pumps. The potential increased milk volumes, reduction in infections and complications, as well as cost savings associated with these benefits proved enough to suggest a return on investment worthy of action.

We implemented an education plan to establish competencies on pump use and maternal education, utilizing our Lactation Consultants, NICU Leadership, Baby Friendly Committee Members, and NICU staff within our Advanced Clinical Ladder. Previously, our truly engaged and competent nurses and NICU staff who assisted with pump instruction and guidance included a handful of educated and interested staff. Now that we had our Symphony pumps and a dedication to increasing the efficiency of our mother's efforts, we wanted to improve the quality of support offered to our families. By using a team approach to changing the culture of our unit, we were able to build an arsenal of staff that started the education and support but also started the change process by becoming champions for the cause.

Our current policies and procedures were reviewed and changes made to include use of the Symphony pumps and ensure consistency throughout our mother/baby units. VAP bundles including oral care with fresh breast milk were created and staff educated. Education was a key element in the success of our program; the new changes, policies, and bundles needed to be conveyed and buy in secured. Nurses, therapists, and staff needed to understand the science behind the pump, the diligence needed to encourage mothers and support pumping. NICU staff needed to understand why the provision of breast milk was so very important and key to improving the outcomes of our vulnerable infants.

Our conversion to the Medela Symphony Premie+ pumps occurred in August of 2010. The conversion was easy once the commitment had been made. With a variety of educational venues and methods including individual initial education and hands on practice, attendance at group education in a competency fair setting, hands on demonstration by each staff member on setting up the pump, and rounding by our champions, our message, that oral care with breast milk was the gold standard in preventing VAP and a necessary component

in quality care, reached the staff and the new pumping was successful. Nurses and NICU staff saw increased milk volumes which now allowed for enteral feedings and oral care.

### Outcomes Improved!

Maternal and staff satisfaction followed the conversion to our new pumps. Our Lactation Consultants and bedside staff were motivated to continue assisting mothers with their pumping success. VAP bundles including oral care with fresh colostrum and breast milk were adopted by the majority of the staff. Prior to the use of these pumps, staff were inconsistent in their approach to oral care. Our respiratory staff reported that each nurse had his or her own way of suctioning, providing oral care, and caring for the infants. We know had a policy and the necessary education regarding the importance to provide rationale and reasoning. Many of our nurses reported needing the rationale to inspire them to provide the cares. The respiratory therapists were especially helpful and diligent with providing this oral care and assisting parents to help with cares. Mothers were busy pumping with great success while fathers were bringing valuable bottles of colostrum and milk to the bedside. While our data collection on the actual percentage of increased milk volume is not completed at this time, the change was visibly evident. Numerous bottles of fresh milk were now present necessitating the purchase of a new breast milk refrigerator! A new policy was created to guide staff in labeling and storing fresh milk for the use in oral care. Many bottles of fresh, never frozen milk lined our refrigerator shelves and bottles of milk were frozen in the freezer, ensuring that our tiny babies would have all of the immunity providing milk they needed.

Our unit reported zero VAP cases from the start of our program; previously we had sporadic VAP cases over the year. Staff noted that the oral care with fresh milk was having a positive and visible effect. While we did not have a formal tracking instrument, our breast milk champions and leadership were approached on a daily basis with satisfactory reports of decreased oral secretions, film, and deposits. Babies were tolerating the procedure, families were assisting with cares, and staff members were happy with the instant, noted change. Our previous success with initial pumping was high but we had many mothers who needed supplementation with galactagogues such as Metaclopramide. Following our intense education and Symphony pump implementation, our mothers requiring such help fell from approximately 12% of new mothers to only 4%! We noted this change two months after the implementation of our new strategies! There was now enough breast milk for all of the needs of our precious babies.

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# Report on the Application of Continuous and Biphasic Noninvasive Ventilation in 11,330 Neonates: Indications and Outcomes

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## Background

The application of noninvasive ventilation in the NICU has grown significantly over the last 20 years. Evidence has long supported its use in transitioning from mechanical ventilation, and its elective application to avoid intubation is also common.<sup>1,2</sup> A recent mega trial confirmed the notion garnered from anecdotal reports and smaller trials that it is effective as a first intention treatment for RDS, with administration of surfactant and intubation reserved for those failing NCPAP.<sup>3</sup> More recently small studies have suggested that biphasic or noninvasive ventilation might be more effective than continuous positive pressure ventilation<sup>4,5</sup> but a large recently completed trial found no difference.<sup>6</sup>

Widespread use of noninvasive ventilation has been the standard of care in some regions. A decade ago the Polish Neonatal Society successfully undertook such a transformation to a bias towards noninvasive respiratory support.<sup>7</sup> As part of that transition, the Infant Flow Advance (CareFusion Corporation, Yorba Linda, CA, USA) was selected as the standard of care because of its low work of breathing, ease of use and biphasic support mode.

There is little in the literature about the application of noninvasive ventilation for uses other than weaning and RDS or about the general experience with its use outside of well-defined trials in extremely premature infants. The aim of our report is to share our experience with the use of Infant Flow across all neonatal sizes and indications.

## Methods

As a part of the adoption of the noninvasive respiratory support program a registry and database were established to collect baseline, treatment and outcome data on every infant treated with Infant Flow in Poland.<sup>7</sup> Compliance with the data collection was ensured, as the availability of the Infant Flow devices was tied to grant funding for the entire project. In addition, the database management including site monitors was also grant funded. The Great Orchestra of Christmas Charity provided these most generous grants, which have helped transform neonatal care in Poland. The board of the Noninvasive Respiratory

Support Group of the Polish Neonatal Society oversaw the overall process.

The data for this report comes from the experience between 2005 and 2009. Ten percent of the centers are tertiary referral centers, with and without obstetric services; the balance are split equally between the two lower levels of centers.

The database categorizes infants based on their first use of Infant Flow into 8 diagnostic categories. Repeat uses of Infant Flow for the initial indication are captured, uses of Infant Flow later in the course of treatment are also included.

All data from the analysis period was extracted and cross-tabulated in prospectively defined tables. Backward stepwise multivariate logistic regression was used to identify factors associated with treatment failure and selection of NCPAP or SiPAP (PASW version 18, IBM). Differences were considered statistically significant if  $p < 0.05$ .

## Results

Over the 5-year study period 11,330 neonates were treated with Infant Flow in the 110 NICUs. Infants under 1,000 grams represented 13% of the total. Infants between 1,000-2,000 grams made up 42% of the population and those larger than 2,000 grams made up the balance (45%). As would be expected the most prevalent indication was treatment of RDS (69%). Weaning from invasive ventilation accounted for 16%. The next most prevalent indication was for treatment of apnea of prematurity (7%). The balance, 8%, were labeled as "other," which includes 5 diverse categories. Overall 81% of the Infant Flow treatments we deemed successful (ie, no need for intubation or reintubation within 3 days of completion of Infant Flow use). Less than 3% of these infants died before discharge. Of course these two outcomes varied widely according to weight category and indication.

The initial characteristics of the infants for each of the three weight categories and 4 indications are provided in Table 1 a-c. The time that Infant Flow treatment was initiated is also included. As would be expected, the use for RDS was lowest in the smallest category of infants, who were more likely to be intubated. It was however, still prevalent. There were no clinically relevant differences among the gas exchange or Apgar scores. For all but the weaning indication Infant Flow was generally started early in the first day of life. Because weaning, by definition, followed a course of invasive ventilation these infants tended to be a week or older when Infant Flow was initiated.

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1a. <1000 grams				
	RDS	Weaning	Apnea	other
n	487	730	178	122
% wt group	32%	48%	12%	8%
EGA	27 (26-29)	26 (25-28)	27 (26-28)	26 (25-28)
BW	850 (750-940)	800 (700-900)	850 (760-933)	800 (698-873)
Apgar 5	6 (5-7)	6 (4-7)	6 (5-7)	6 (3-7)
hr IF Start	3 (1-5)	19 (5-35) day	21 (9-37)	26 (0-47)
pH	7.28 (7.22-7.34)	7.28 (7.22-7.33)	7.29 (7.23-7.35)	7.29 (7.22-7.33)
PaCO <sub>2</sub>	46 (38-55)	47 (40-54)	48 (40-59)	53 (46-59)
FiO <sub>2</sub> %	30 (25-40)	30 (26-40)	30 (25-40)	30 (25-40)
PF O <sub>2</sub>	147 (113-196)	147 (113-196)	153 (104-193)	136 (105-202)
1b. 1000-2000 grams				
	RDS	Weaning	Apnea	other
n	3265	853	424	265
% wt group	68%	18%	9%	6%
EGA	31 (30-33)	29 (28-31)	30 (29-32)	31 (29-32)
BW	1566 (1320-1800)	1300 (1130-1530)	1380 (1170-1638)	1450 (1215-1740)
Apgar 5	7 (6-8)	6 (5-7)	7 (6-8)	7 (6-8)
hr IF Start	1 (1-3)	7 (3-15) day	8 (2-16)	1 (0-30)
pH	7.29 (7.24-7.34)	7.28 (7.22-7.33)	7.29 (7.24-7.34)	7.29 (7.22-7.33)
PCO <sub>2</sub>	51 (42-58)	45 (38-53)	49 (41-58)	50 (41-59)
FiO <sub>2</sub> %	35 (30-40)	30 (25-40)	30 (25-40)	30 (27-40)
PF O <sub>2</sub>	136 (102-183)	144 (109-191)	147 (106-200)	156 (108-213)
1c. >2000 grams				
	RDS	Weaning	Apnea	other
n	4129	287	142	594
% wt group	80%	6%	3%	12%
EGA	36 (34-38)	37 (34-39)	35 (34-37)	38 (36-40)
BW (kg)	2.7 (2.4-3.2)	2.9 (2.4-3.3)	2.5 (2.2-3.0)	3.1 (2.6-3.6)
Apgar 5	8 (6-9)	7 (5-9)	8 (7-9)	8 (7-9)
hr IF Start	2 (1-6)	7 (4-18) day	2 (1-4)	1 (1-1)
pH	7.29 (7.24-7.35)	7.28 (7.22-7.33)	7.28 (7.22-7.33)	7.30 (7.24-7.35)
PCO <sub>2</sub>	52 (44-60)	48 (41-57)	46 (39-55)	49 (41-59)
FiO <sub>2</sub> %	35 (30-40)	35 (27-50)	32 (27-40)	40 (30-50)
PF O <sub>2</sub>	133 (99-176)	136 (93-173)	137 (105-180)	129 (94-176)

Table 1 Baseline Characteristics

Discrete variables displayed as percent and continuous variables as median (IQR).

The course of treatment, survival and major morbidity for the three weight categories and indications are shown in Table 2 a-c. The use of bilevel support (SiPAP) was quite prevalent, most common in the smaller infants and for weaning. It is also of note that when used, SiPAP was primarily used from the initiation of noninvasive support.

As is apparent in Table 2, the multivariate analysis confirmed that treatment failure was independently associated with EGA ( $p<0.001$ ). The baseline oxygenation (PF O<sub>2</sub> ratio  $<150$ ) was also independently associated ( $p<0.001$ ) with treatment failure in the RDS infants. We also explored factors associated with the selection of SiPAP as the initial mode of noninvasive support. The diagnostic indication, maturity and clinical status all were independently associated with selection of SiPAP. Specifically these included: weight category ( $p<0.001$ ), diagnostic category ( $<0.001$ ), Apgar 5 ( $<0.001$ ) and gas exchange ( $pH<7.25$   $0=0.016$

and  $PF<150$   $p=0.001$ ). Finally, the selection of triggered versus time-cycled SiPAP seemed to be associate with individual clinicians preference and not clinical indicators, the time cycled being the most prevalent.

## Discussion

This is, to our knowledge, the first report of the general use of noninvasive respiratory support stratified by weight and diagnostic categories in a very large population. Our previous report, while general, was much smaller and reflected the adoption period.<sup>7</sup> This descriptive experience, by itself, should prove useful for those exploring the expansion of the use of noninvasive ventilation in their practice. With regard to indications and larger infants, where there is little evidence of relative effectiveness to guide adoption, our outcomes and experience should be comforting.

2a. <1000 grams				
	RDS	Weaning	Apnea	other
n	487	730	178	122
Initial mode SiPAP	37%	50%	39%	48%
SiPAP mode during	44%	60%	47%	58%
days InfantFlow	6 (2-14)	9 (4-17)	7 (3-14)	7 (4-15)
days vent support	14 (3-30)	30 (20-53)	22 (10-35)	30 (7-54)
wks PCA of vent sup	30 (28-32)	31 (30-34)	30 (29-32)	31 (29-33)
Surfactant any	43%	71%	41%	56%
1 dose only	76%	77%	86%	74%
Treatment Failure	46%	45%	34%	43%
Survival	89%	94%	94%	97%
CLD	19%	41%	28%	39%
severe ROP	14%	3.3%	22%	33%
severe neurological	5%	14%	8%	12%

2b. 1000-2000 grams				
	RDS	Weaning	Apnea	other
n	3265	853	424	265
Initial mode SiPAP	30%	47%	28%	35%
SiPAP mode during	35%	51%	37%	39%
days InfantFlow	2 (1-4)	5 (2-7)	4 (2-7)	3 (2-7)
days vent support	3 (1-6)	14 (7-25)	6 (3-13)	4 (2-11)
wks PCA of vent sup	32 (31-33)	32 (31-34)	32 (30-33)	32 (31-33)
Surfactant any	13%	65%	24%	25%
1 dose only	84%	78%	85%	75%
Treatment Failure	18%	26%	18%	25%
Survival	97%	97%	98%	97%
CLD	2%	15%	7%	9%
severe ROP	2%	1%	5%	13%
severe neurological	2%	10%	4%	4%

2c. >2000 grams				
	RDS	Weaning	Apnea	other
n	4129	287	142	594
Initial mode SiPAP	19%	40%	30%	15%
SiPAP mode during	24%	46%	36%	28%
days InfantFlow	2 (1-3)	3 (2-4)	2 (1-4)	2 (1-3)
days vent support	2 (1-3)	8 (5-15)	8 (5-15)	2 (1-4)
wks PCA of vent sup	36 (34-38)	38 (36-41)	35 (34-37)	39 (36-40)
Surfactant any	3%	21%	4%	4%
1 dose only	83%	75%	0%	0%
Treatment Failure	10%	28%	9%	12%
Survival	98%	96%	98%	99%
CLD	0.4%	5.4%	1.7%	1%
severe ROP	0.3%	1.5%	1.4%	0.5%
severe neurological	0.5%	3.4%	1%	0.7%

Table 2 Course of Treatment and Outcomes

Discrete variables displayed as percent and continuous variables as median (IQR). Length of "vent support" included Infant Flow, other noninvasive ventilation and invasive ventilation. Treatment failure was defined as no need for 72 hours for intubation or reintubation after weaning from Infant Flow. Survival was defined as discharge from the hospital. The morbidity rates are among survivors. They were defined as follows: CLD (need for oxygen or ventilation at 36 weeks PCA), severe ROP (need for laser treatment) and severe neurological (grade 3 or 4 IVH or PVL).



It is not surprising that SiPAP tended to be used slightly less in infants with RDS than for the other indications. Most likely those with severe RDS and higher ventilatory demands were intubated. Likewise it is predictable that SiPAP would be used more frequently for weaning, where inadequate ventilation is often a common mode of weaning failure. Large studies or performance improvement projects need to be conducted to explore practice guidelines for the addition of noninvasive biphasic support, much as there are evolving guidelines for the criteria for intubation.

Many of the important parameters of care are not addressed in this report. The selection of the initial CPAP pressure and, if applied, the rate and size of biphasic pressures and all their adjustments based on clinical response are for the most part left to the attending physician, and not recorded in the database. However for the purposes of the database, treatment failure was defined.

Finally, care must be used in evaluating the data with regard to indication, because of the structure of the database. One example is that weaning includes only those infants first intubated and not those who were intubated after failing elective Infant Flow. Apnea of prematurity primarily includes those infants without RDS treated in the first days of life and not infants with problems associated with chronic lung disease. Likewise the database does not include infants treated with ventilator based CPAP. However, use of Infant Flow represents, in our estimation, about two-thirds of the non-invasive respiratory support.

To date we have treated over 25,600 infants with the noninvasive Infant Flow system in Poland. We have published results of several research projects<sup>8,9,10</sup> focused on some of the questions identified above and hope to continue our work.

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# High Flow Therapy and Specialty Gases: Heliox Ventilation and the Development of Precision Flow Heliox

Thomas L. Miller, PhD

## Summary

The purpose of this white paper is to discuss the application of specialty medical gases using high flow nasal cannula therapy (HFT), with specific emphasis on helium-oxygen gas mixtures (heliox). Basic principles of HFT are introduced to explain how breathing gases can be delivered to the lung and airways in precise mixtures through an open system, and done more efficiently compared to closed circuitry models for ventilator assistance. Furthermore, a discussion of heliox with HFT expands on how these concepts work in concert to noninvasively reduce a patient's work of breathing.

Vapotherm pioneered the concept of HFT with the introduction of technologies that were able to surmount prior obstacles to complete respiratory gas conditioning. By delivering adequately conditioned breathing gases to a patient with a nasal cannula interface, flow rates can now be used which surpass conventional limitations of a nasal cannula (typically 6 L/min in an adult) to reach flow rates that meet or exceed a patient's inspiratory flow rate. The achievement of HFT unlocked a number of mechanisms of action for nasal gas insufflation that results in a multifactorial therapeutic effect.

Over the last decade, HFT has been used extensively and has been well studied. A large number of clinical studies have demonstrated the ability of HFT to enhance oxygenation, ventilation and reduce dyspnea in both neonatal and adult patients with various pulmonary pathologies. HFT has been shown to aid patients with acute respiratory failure, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), and asthma among others.

An extensive body of literature on ventilation with heliox shows that there is a marked reduction in respiratory resistance when gas is undiluted by room air and the helium balance gas represents at least 50-60% of the mixture. In this regard, the delivery of heliox with Vapotherm HFT devices has a distinct advantage over other methods of noninvasive specialty gas delivery. By providing a nasal cannula gas flow that exceeds a patient's spontaneous inspiratory flow rate, the patient inhales the precise gas mixture provided by the cannula without any entrainment of room air needed to meet a balance of an

inspiratory demand. Also with this approach, the nasopharyngeal region of the patient's upper airway becomes an internal reservoir of the intended gas mixture. This makes gas delivery more efficient in that it is not diluted by a bolus of trapped expiratory gas and more precise in that it is not affected by variable flow from a delivery system that reacts to spontaneous patient flow. Therefore, when providing heliox via HFT, the intended effect of the specialty gas mixture is not hampered by dilution of the metered gas, and the desired therapeutic affect can be achieved using a minimally invasive patient interface.

## Introduction to the Precision Flow Heliox and Vapotherm's Specialty Gas Program

Vapotherm's technology and device platforms are well suited for the precise delivery of specialty medical gases. In some instances, such as with inhaled nitric oxide, a modified patient disposable cartridge set allows injection and monitoring of a medical gas that requires a unique delivery system. In other circumstances such as heliox ventilation, the blending capabilities of the specialty gas have been integrated into the existing device platform. The Precision Flow Heliox device represents an advancement in heliox delivery by extending breathing gas conditioning in addition to precise blending and flow control. The Vapotherm platform allows for the delivery of breathing gases at or near body temperature and saturated with water vapor. This approach allows breathing gases to be delivered via nasal cannula, as opposed to a conventional face mask, at flow rates that meet or exceed a patient's inspiratory demand.

High flow respiratory gas delivery with nasal cannula results in an advantageous physiologic impact. This impact is based on fundamental mechanisms associated with purging nasopharyngeal dead space and exposing the lung and airways to ideally warmed and humidified respiratory gases. This paper focuses on the impact of HFT delivery of heliox, however the concepts pertaining to precise and efficient delivery of specialty gases apply to other gases that are currently in use or being explored for mechanical and/or anti-inflammatory effects.<sup>1</sup> Heliox use as a respiratory gas is based on the premise that the lower density of helium compared to nitrogen results in a significant reduction of flow resistance in the patient's airway resulting in reduced work of breathing. Together, a high-flow nasal cannula with heliox makes heliox delivery possible without a face-occluding mask and also makes heliox gas delivery more efficient by means described in the following section.

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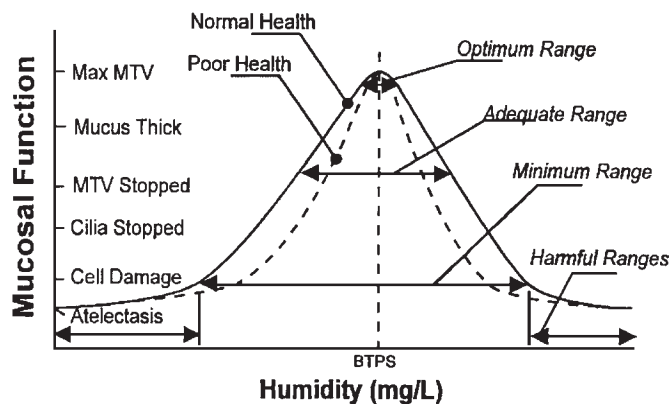


Figure 1 (above). This figure from Williams et al<sup>3</sup> shows that mucosal function is dramatically impacted by absolute humidity, which is a function of both relative humidity and temperature. Here BTPS represents body conditions where gas contains 44 mg/L of water vapor. MTV = mucus transport velocity.

### Fundamentals of High Flow Therapy (HFT)

The Vapotherm platform utilizes innovative membrane humidification technology to efficiently condition gas to body temperature and saturated with water vapor, as well as an innovative water-jacketed delivery tube design to maintain energy state of the conditioned gas as it is conducted to the patient. These technologies allow for an array of mechanisms by which nasal cannula gas flow that is in excess of a patient's inspiratory flow rate can improve respiratory efficiency and work of breathing. These next two sections represent a synopsis of the literature on this experience, which provides the background for understanding the role of HFT in the noninvasive delivery of specialty medical gases.

### Humidification or Breathing Gases

The nasal mucosa is designed to warm and humidify breathing gas prior to entering the conducting airways and the lungs.<sup>2</sup> This is accomplished by a large surface area to interact with inspiratory gas. Exposing the nasopharyngeal tissues to a continuous flow of gas that is greater than a normal minute ventilation rate and which is also unsaturated with water vapor and below body temperature can overload these tissues. This operational overload results in significant dysfunction, drying and damage of the nasal mucosa<sup>3,6</sup> that furthermore contributes to compounding conditions such as staphylococcal sepsis<sup>7</sup> and perhaps contributing to lung inflammation.<sup>8</sup> Additionally, even at low flows, conventional nasal cannula therapy is uncomfortable and raises numerous patient complaints, particularly related to dry nose and mouth.<sup>9</sup>

To support respiratory therapies, efforts have been made to create systems that saturate and adequately warm respiratory gases. Ideally, inspiratory gas should be warmed to body temperature (37°C) and humidified to 100% relative humidity (Figure 1).<sup>10,11</sup> Typically, low flow nasal cannula therapy less than 4 L/min is not thought to require humidification.<sup>12</sup> However, for flows greater than 6 L/min the American Society for Testing and Materials requires humidification systems to produce inspiratory gas with at least 60% relative humidity at ambient temperatures.<sup>13</sup> However, in our modern definition of HFT, whereby cannula gas is constantly bathing the nasal mucosal tissues, it is recommended that gases are conditioned to mimic body conditions more precisely. The Vapotherm family of devices that use vapor transfer membranes with a water jacketed

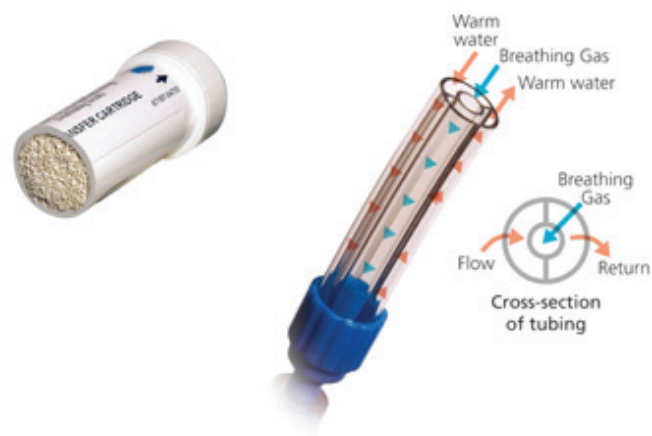


Figure 2. Technologies such as the Vapotherm Vapor Transfer Cartridge (A) have improved the task of gas conditioning. The large surface area of the hollow tube filled with vapor-permeable fibers allows the respiratory gas passing through to be instantly warmed to a precise temperature and humidified to saturation. Vapotherm's water-jacketed patient delivery tube (B) maintains the conditioning state of the patient gas in the center lumen with a dynamic insulation system. In this tube design, water circulated out and back into the outer jacket is at the temperature the gas is intended to be.

delivery tube system have been shown to produce 99.9% relative humidity, with the passage of water into the breathing gas in a vapor phase (Figure 2).<sup>13</sup> Humidification with vapor versus aerosolized water is the least likely to cause airway and lung injury by latent heat loss and deposition of water droplets.<sup>11</sup>

In a bench study, Drs Waugh and Granger evaluated the capability of two HFT gas conditioning systems to meet American Association of Respiratory Care (AARC) standards and manufacturers' claims.<sup>13</sup> This data showed that the Salter Labs high-flow cannula system (Salter Labs, Arvin, CA) produced inspiratory gas that was at ambient temperature and between 72% and 79% relative humidity at up to 15 L/min of flow. The Vapotherm system, however, produced inspiratory gas at body temperature (37°C) and 99.9 ± 0.0% relative humidity. Compared to manufacturer's claims, these test results were significantly less for the Salter Labs device at 5 and 10 L/min of flow ( $p < 0.01$ ) but significantly more for the Vapotherm device at all flow rates ( $p < 0.001$ ).

In a randomized crossover study, Woodhead and colleagues evaluated the impact of Vapotherm compared to conventional nasal cannula therapy on the nasal mucosa of preterm infants post extubation.<sup>14</sup> Thirty infants received either Vapotherm or HFT by way of a conventional cannula setup for 24 hours and then were switched to the opposite modality (conventional or Vapotherm) for an additional 24 hours. Using a blinded scoring system accounting for nasal erythema, edema, thick mucus and hemorrhage where a subjective value was assigned ranging from 2 to 10 in arbitrary units, Vapotherm infants had much better tolerance compared to conventional humidification ( $2.7 \pm 1.2$  vs  $7.8 \pm 1.7$ ;  $p < 0.001$ ).

In summary, the Vapotherm devices have demonstrated superior gas conditioning and delivery capabilities that have been shown to be protective of the nasal tissues with constant high gas flows. This is arguably even more important with certain specialty gases such as helium, where the thermal conductance is much greater than air and can therefore strip energy from the nasal tissues faster, leading to greater deterioration. Thus, the Vapotherm platform is ideally suited for the administration of these gases.



## Mechanisms of Action for Vapotherm HFT

With Vapotherm technology, the conditioning of respiratory gases is therefore adequate for delivering flow rates that would otherwise result in significant drying and damage to the nasal mucosa.<sup>4,5,14</sup> As described below, it is the relatively precise use of these higher gas flows that is defined by Vapotherm as HFT. In the acute care setting, HFT has been used to treat respiratory distress or failure, and in these applications has been shown to improve respiratory gas exchange<sup>15</sup> and mechanics.<sup>16</sup> The mechanisms of action for HFT are summarized here, however, a more complete description of these mechanisms can be found in a review paper by Dysart, Miller and colleagues.<sup>17</sup>

HFT is the delivery of respiratory gas by nasal cannula in an open system at a flow rate that exceeds a patient's spontaneous inspiratory flow. In simplest terms, this means that the cannula provides enough flow to meet a patient's inspiratory flow requirement so they will not have to breathe room air, and will only inhale cannula gas to the lung. For the typical adult in the hospital setting, this would be between 25 and 35 L/min based on normative values for adult pulmonology. Infants are more complex because of their proportionally greater extrathoracic dead space<sup>18</sup> and they typically require flow between 4 and 8 L/min. With these nasal flows, and without the aid of non-rebreather masks, intubation or some other form of elaborate airway control, a patient will inhale the intended gas mixture despite the perceived openness of the interface. Moreover, during exhalation cannula flow continues to purge the anatomical dead space of the upper airway, creating an internal reservoir of cannula gas ready for the next inhalation. This aspect of HFT actually improves respiratory efficiency and results in a ventilation effect. HFT has a number of other influences that result in more favorable gas equilibrium values in the lungs and reduced respiratory effort. The key factors considered to be mechanisms of action for HFT are as follows:

- 1) HFT provides for washout of nasopharyngeal dead space which contributes to establishing improved fractions of alveolar gases with respect to carbon dioxide as well as oxygen.<sup>19, 20</sup>
- 2) The distensibility of the nasopharynx provides significant resistance on inspiratory efforts relative to expiratory efforts.<sup>21</sup> HFT provides adequate flow rates to match inspiratory flow and thus eliminates the inspiratory resistance associated with the nasopharynx and the related work of breathing.
- 3) The provision of adequately warmed and humidified gas to the conducting airways is associated with improved conductance and pulmonary compliance compared to dry, cooler gas.<sup>22</sup>
- 4) The provision of adequately warmed and humidified gas through the nasal and pharyngeal regions reduces the metabolic work associated with gas conditioning.
- 5) When manipulated correctly, the flow that flushes the nasopharynx can be restricted to provide positive distending pressure for lung recruitment.<sup>23</sup>
- 6) The ideal humidification of the inspired gas has been shown to restore mucociliary function and reduce symptoms of airway exacerbations.<sup>24, 25</sup>

Based on these factors, HFT has been shown to be effective in adults<sup>26,27</sup> as well as children.<sup>28</sup> Certainly, the provision of high gas flows through the nasopharynx will tend to develop mild distending pressure<sup>29-31</sup> which often intuitively seems to be



Figure 3. The Precision Flow Heliox Device. This device is designed to blend, heat, humidify, and deliver heliox gas mixtures through a nasal cannula. The device is calibrated for use with an 80/20 heliox mixture as a balance gas (actually, 79% helium and 21% oxygen), and can be blended with oxygen to increase the fraction of oxygen up to 100%. Note that whatever the fraction of oxygen is set to, helium makes up the balance of the mixture; e.g. if oxygen is set to 40%, then helium is 60%.

the cause for the level of clinical efficacy observed. However, mechanistic research suggests that the most impactful of these factors is the nasopharyngeal flush, which results in the purging of CO<sub>2</sub> from the dead space gas volume that would otherwise be re-breathed during a subsequent inhalation.<sup>19</sup> As such, Vapotherm has focused research on the dynamics of flow through the nasopharynx and the dependency on cannula design. Using computational fluid dynamics modeling, we have learned that cannula design related to nasal prong size and orientation can create a tradeoff between purge efficiency and pressure development in the nasopharynx. Moreover, pressure in the nasopharynx is variable based on the flow patterns and the development of vortices. Therefore, cannula design can affect the points at which pressure is generated throughout the geometry of the nasopharyngeal space. This information has been used to refine the patient interface for the multiple applications to which HFT can be applied.

Some of the most recent clinical data in HFT pertains to the long term use of humidification therapy. A study by Hasani and colleagues described how conditioned cannula gas flow used for humidification therapy over a one-week period in bronchiectasis patients resulted in improved clearance of labeled markers from the airway.<sup>24</sup> Another study by Rea and colleagues demonstrated reduced exacerbation days and increased time to exacerbations of COPD patients who used conditioned cannula gas flow for humidification treatment over a longer term.<sup>25</sup> These lessons could have an important carryover to understanding the efficacy of a flow therapy when gas is soothing the airway, versus delivery of a cool dry gas that appears to be promoting airway reactivity and potentially, inflammation.

## Key References: Vapotherm High Flow Therapy

This section summarizes the major research that pertains to the use of HFT. This table presents relevant reports and key findings published in peer-reviewed journals.

STUDY	MAJOR CONCLUSIONS
Dysart et al. <sup>17</sup>	<ul style="list-style-type: none"> <li>Comprehensive literature review describing the mechanisms of action for HFT:</li> <li>Washout of the nasopharynx</li> <li>Attenuates the inspiratory resistance associated with the nasopharynx</li> <li>Improves conductance and pulmonary compliance compared to dry, cooler gas</li> <li>Reduces the metabolic work associated with gas conditioning</li> <li>Provide positive distending pressure for lung recruitment</li> </ul>
Frizzola et al. <sup>19</sup>	<ul style="list-style-type: none"> <li>Mechanistic preclinical research demonstrating that the core mechanism of action is dead space flush</li> <li>Demonstrated ventilation effect</li> <li>More pronounced effect with less occlusive prongs</li> </ul>
Chatila et al. <sup>15</sup>	<ul style="list-style-type: none"> <li>Crossover prospective trial in 10 COPD patients</li> <li>High flows of humidified oxygen improved exercise performance and oxygen dependency in part by enhancing oxygenation</li> <li>Patients were able to exercise longer on higher flows with less dyspnea, better breathing pattern and lower arterial pressure compared to low flow oxygen delivery</li> </ul>
Roca et al. <sup>43</sup>	<ul style="list-style-type: none"> <li>Crossover trial in acute respiratory failure: high flow cannula compared to face mask oxygen therapy</li> <li>High flow cannula resulted in higher blood oxygenation and lower respiratory rate without changing blood pCO<sub>2</sub></li> <li>Patients found the cannula interface to be more tolerable and more comfortable</li> </ul>
Price et al. <sup>44</sup>	<ul style="list-style-type: none"> <li>Retrospective analysis of 72 patients with Type 1 hypoxemic respiratory failure using HFT</li> <li>HFT reduced respiratory rate and improvement in oxygenation for treated patients</li> </ul>
Calvano et al. <sup>45</sup>	<ul style="list-style-type: none"> <li>Case study of an end-stage respiratory failure patient with multilobar pneumonia</li> <li>Patient had a DNR order and could not tolerate a NIV mask</li> <li>HFT reduced her agitation and improved her dyspnea, oxygenation, tolerance of oxygen therapy, and comfort at the end of life</li> </ul>
Dewan & Bell. <sup>20</sup>	<ul style="list-style-type: none"> <li>Prospective trial of 10 COPD patients who were receiving transtracheal oxygen (TTO) through a stoma</li> <li>TTO compared to both high and low flow nasal cannula oxygen</li> <li>HFT, but not low flow nasal cannula, resulted in the same exercise tolerance and dyspnea score as TTO</li> </ul>
Parke et al. <sup>31</sup>	<ul style="list-style-type: none"> <li>Prospective trial in postoperative cardiac patients</li> <li>Aim was to demonstrate the level of airway pressure generated by high flow cannula in adults</li> <li>High flow cannula generates a low level of distending pressure in adults: 2.7 +/- 1.04 cmH<sub>2</sub>O</li> </ul>
Hasani et al. <sup>24</sup>	<ul style="list-style-type: none"> <li>Prospective trial in bronchiectasis patients</li> <li>Aim to investigate the impact of HFT on airway clearance</li> <li>High flow cannula with humidified breathing gas improves airway function via enhanced mucociliary clearance</li> </ul>

## Key References: Heliox Ventilation

This section summarizes significant research that pertains to the use of heliox as a respiratory gas mixture. This table presents relevant reports and key findings published in peer-reviewed journals.

STUDY	MAJOR CONCLUSIONS
Myers. <sup>33</sup>	<ul style="list-style-type: none"> <li>Comprehensive review of the concepts behind heliox ventilation</li> <li>Lesser density gas reduces airway resistance and therefore work of breathing</li> <li>Reynolds Number: Lower density support laminar flow</li> <li>Graham's law: Helium diffuses faster than nitrogen</li> </ul>
Jolliet et al. <sup>37</sup>	<ul style="list-style-type: none"> <li>Discussion of heliox use in ventilation of adults</li> <li>Resulted in decreased airway resistance</li> <li>Reduced dynamic hyperinflation and intrinsic positive end-expiratory pressure, which reduces needed lung inflation pressures, respiratory acidosis and work of breathing</li> </ul>
Migliori et al. <sup>38</sup>	<ul style="list-style-type: none"> <li>Study of heliox gas delivery in infants</li> <li>Improved gas exchange and work of breathing</li> <li>Reduced the need for mechanical ventilation</li> </ul>
Wolfson et al. <sup>40</sup>	<ul style="list-style-type: none"> <li>Studied respiratory mechanics in spontaneously breathing infants with bronchopulmonary dysplasia receiving heliox</li> <li>Decrease pulmonary resistance and work of breathing</li> <li>Reduced risk of respiratory muscle fatigue</li> </ul>
Singhaus et al. <sup>41</sup>	<ul style="list-style-type: none"> <li>Safety study: rabbits pups raised in heliox environment compared to controls</li> <li>No difference in growth parameters or developmental milestones</li> </ul>
Nawab et al. <sup>42</sup>	<ul style="list-style-type: none"> <li>Piglet model to assess markers of inflammation with heliox ventilation versus control</li> <li>Lung morphology showed improved distribution of heliox gas through the lung</li> <li>Proinflammatory mediators and matrix remodeling proteins levels were significantly lower with heliox versus nitrogen-oxygen mix</li> </ul>

## Heliox Ventilation

Heliox has been used as a breathing medium since the 1930's.<sup>32</sup> A body of literature exists which evaluates heliox ventilation as an alternative to nitrogen-oxygen mixtures for use as a respiratory therapy that reduces airway resistance. Heliox ventilation results in a marked reduction in respiratory resistance when the gas is undiluted by room air and the helium balance gas represents at least 50-60% of the mixture. This section is a redacted report of the key research pertaining to heliox ventilation, which has been well-studied over the past few decades.

A detailed paper by Myers on the theory of various therapeutic gases describes how helium reduces airway resistance and therefore work of breathing.<sup>33</sup> Helium has a lower density than nitrogen and thus contributes to a lower Reynolds number. Reynolds number predicts the pattern of flow for a liquid through a passage. A higher Reynolds number predicts more turbulent flow and vice versa. With a less turbulent flow pattern, the resistance to flow is reduced, as is the pressure gradient needed to drive the gas through the airway (ie work of breathing). Meyers also discusses Graham's law which states that the rate of diffusion for a gas is inversely proportional to the square root of its density. Based on this principle, a less dense gas moves faster with less driving force.

In an invited review on aerosol drug delivery using heliox, Corcoran and Gamard further explain that the effects of heliox are more pronounced in the upper airway.<sup>34</sup> Within the respiratory system, the upper airways normally provide the greatest resistance to flow. Also, gas flow in the upper airways is likely always turbulent, even with heliox, whereas in the most distal airways flow is likely always laminar. Corcoran and Gamard propose that the impact of heliox is not truly a matter of making flow more often laminar, but rather reducing resistance to flow where it is turbulent. Unlike laminar flow, when flow is turbulent the pressure gradient needed to drive flow is directly related to gas density.<sup>35</sup> As such, when flow is turbulent in the upper airways, heliox gas mixtures require less driving force to generate flow or will have greater flow with any given driving force, compared to respiratory gas mixtures where the balance gas is nitrogen.

In addition to the impact of helium density on airway resistance, another property of helium may contribute to better ventilation. In a paper by Mildner and colleagues evaluating the use of heliox with high-frequency oscillatory ventilation, the authors describe how gases such as carbon dioxide diffuse faster in helium than in nitrogen.<sup>36</sup> In this study, CO<sub>2</sub> transit time through heliox was substantially less than through a nitrogen-oxygen mixture. These results indicate that heliox may be a more effective medium for diffusive mixing at the alveolar level, and therefore more effective at removal of CO<sub>2</sub>.

Putting theory into practice, Joliet and Colleagues discuss the use of heliox gas mixture in patients receiving mechanical ventilation.<sup>37</sup> These authors describe how the lesser density of heliox resulting in decreased airway resistance may also facilitate exhalation time and end-expiratory lung volumes. Using heliox, they saw a reduction in dynamic hyperinflation and intrinsic positive end-expiratory pressure. This effect in turn decreases necessary lung inflation pressures, respiratory acidosis, and work of breathing. These authors also discuss how the use of heliox could be a valuable approach to decrease post-extubation respiratory distress.

Heliox ventilation has been demonstrated effective in pediatric/ infant populations as well. Migliori and colleagues showed that heliox ventilation improved gas exchange and work of breathing to reduce the need for mechanical ventilation in infants.<sup>38</sup> Grosz and colleagues shows that heliox ventilation was safe and effective at relieving upper airway obstruction in pediatric patients.<sup>39</sup> In infants with bronchopulmonary dysplasia, a study by Wolfson and colleagues, demonstrated decreased pulmonary resistance and work of breathing while spontaneously breathing heliox.<sup>40</sup> These later authors also showed a reduced risk of respiratory muscle fatigue and discussed the possibility that the reduced energy expenditure may allow more calories to be used for growth and development.

In terms of safety, the most comprehensive evaluation of the effects of helium exposure was done by Singhaus and colleagues.<sup>41</sup> These authors assessed the safety of a chronic heliox incubator environment on developing rabbit pups. They showed that there were no differences in growth parameters or a developmental milestone between the pups grown in a heliox environment compared to controls. Furthermore, in a piglet model of respiratory distress, Nawab and colleagues showed that breathing heliox attenuated lung inflammation, presumably by reducing mechanical and oxidative stress.<sup>42</sup>

Because of the high safety record and known tolerance, as well as the indications for efficacy in reducing the resistive work of breathing, heliox is an existing mode of therapy used in many hospitals throughout the world. As such, there are numerous medical devices such as respiratory gas blenders and mechanical ventilators already cleared to deliver heliox mixtures. The combination of HFT with heliox offers no increased risk and there are distinct advantages of this combination.

## Summary: Combination of HFT with Heliox

The delivery of heliox with the Vapotherm Precision Flow Heliox device (Figure 3) has a distinct advantage over other methods of noninvasive heliox delivery. By providing a nasal cannula gas flow that exceeds a patient's spontaneous inspiratory flow rate, the patient inhales the precise gas mixture provided by the cannula without the entrainment of room air. Also with this approach, the nasopharyngeal region of the patient's upper airway becomes an internal reservoir of the intended gas mixture, making blended medical gas delivery more precise and efficient. Therefore, when providing heliox via HFT the effects of helium balance gas on respiratory resistance is not hampered by the dilution of the helium gas by entrainment of room air, and the desired therapeutic affect can be achieved using the minimally invasive cannula patient interface.

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# Time Required for Effective FiO2-Titration in Preterm Infants: a Comparison

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## Introduction

Proper targeting of SpO2 in preterm infants has become a topic of increasing interest over the last decade. Prior to that time, the pulse oximeter was used primarily to alert nurses to episodes of severe desaturations, or slow deterioration of oxygenation. Subsequently, reports confirmed the physiological rationale that lowering SpO2 target levels would result in significant reductions in pulmonary and retinal morbidity without apparent increases in developmental and neurological outcomes or mortality.<sup>1-3</sup>

As part of a massive research effort to determine the optimum SpO2 target range, two recently concluded mega RCTs found that dropping the target range too low (85%-89%), while further improving retinal and pulmonary morbidity, resulted in increased mortality.<sup>4</sup> Recommendations for SpO2 targeting are expected in 2014 after integration of the results of three large studies and evaluation of long term outcomes.<sup>5</sup>

Evaluation of these studies and selection of the best SpO2 target range is, however, complicated by several factors. Disordered breathing and changes in extrapulmonary shunt result in episodes of significant desaturation, in addition to continual wandering of the SpO2 outside of the desired target range. Staff training<sup>6,7</sup> and workload<sup>8,9</sup> have both been shown to be barriers to effective SpO2 management of preterm infants. The oxygen saturation of many preterm infants is quite unstable. As a result, studies have shown that preterm infants receiving respiratory support spend only about half of the time within the intended target range.<sup>3,10</sup>

There is very little in the literature describing or testing the relative effectiveness of specific FiO2-titration strategies for infants during respiratory support. FiO2-titration strategies should consider not only the timing and magnitude of an increase in FiO2 needed to address SpO2 levels below the target range, but also the timing and magnitude of response to SpO2 levels above the target range, the latter being either a result of either improving oxygenation or a need to wean a previous FiO2 increase. Some have suggested that many desaturations resolve quickly and unless prolonged are best not addressed. This thinking is intended to avoid the frequent need to wean FiO2 to mitigate hyperoxemia.<sup>1,11</sup> This delayed approach also has the advantage of reducing the amount of time required by nursing staff to address SpO2 alarms. Regardless of approach, it is generally accepted that an effective clinical strategy includes nursing observation of the infant with a persistent alarm or following an FiO2 adjustment.

Automated FiO2 control systems for neonates have been tested and show promise of improved SpO2 control.<sup>12,13,14</sup> Moreover, the potential for labor savings associated with automation is of great interest. One system is commercially available outside the US (CLiO2 option for the Avea ventilator, CareFusion, Yorba Linda, CA).<sup>15</sup> We recently compared CLiO2 with two different, strictly applied, manual FiO2-titration strategies.<sup>16</sup> We found CLiO2 generally more effective and safer than either of the manual strategies.

The aim of this analysis is to determine the nursing time needed for adjustment and monitoring to implement each of the three FiO2-titration approaches.

## Methods

Nursing time associated with FiO2-titration includes the time to adjust the FiO2 and observe the infants response, as well as time to observe persistent alarms, even when adjustment of FiO2 is not deemed necessary. This need is applicable not only to the manual methods, but also to CLiO2. We defined, what was to our thinking, optimal practice guidelines. We made the following baseline assumptions: 1) alarms were set for silence for 20 seconds; 2) when the FiO2 was changed the nurse would stay with the patient and observe its response for 3 minutes if the SpO2 was at extremes (<80% >98%), and 2 minutes if just outside the target range; 3) for alarms that persisted for 1 minute or more but did not result in an FiO2 adjustment, 1 minute of time was allocated for observation; and, 4) for less persistent alarms, 30 seconds was allocated for observation.

Our previous study identified two distinct groups of infants. The first group experienced frequent severe desaturations (average 4 per hour). They spent about half of the time in the intended target range and during manual control more than 10% of the time at extreme saturations (either above 98% or below 80% SpO2). The second group with less frequent severe desaturations (average 1 per hour) spent about three-quarters of the time in the intended target range. During manual control they spent less than 5% of the time at extreme saturations. In all cases we found CLiO2 tended to result in better control. Our database includes FiO2 and SpO2 readings for every 5 seconds for 113 hours of monitoring of 8 infants. We analyzed this database to determine the frequency, duration and magnitude of episodes outside the SpO2 target range and tabulated it for the two categories of infants.

In our previous study a dedicated operator implemented the two manual titration strategies. They were labeled Attentive and Observative. In both, response to episodes of SpO2<80% or >98% was faster than to small SpO2 excursions (Attentive within 30 sec and 1 min, Observative within 2 min and 3 min, respectively).

We built an Excel (Microsoft, Redmond, WA) model based on the frequency, magnitude and duration of the episodes for each of

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Authors Wilinska and Swietlinski are with The Medical Centre of Postgraduate Education, Warsaw, Poland; Bachman is with Economedrx, Lake Arrowhead, CA. Economedrx is a clinical research consultancy which provides services to CareFusion, the manufacturer of the automated system.

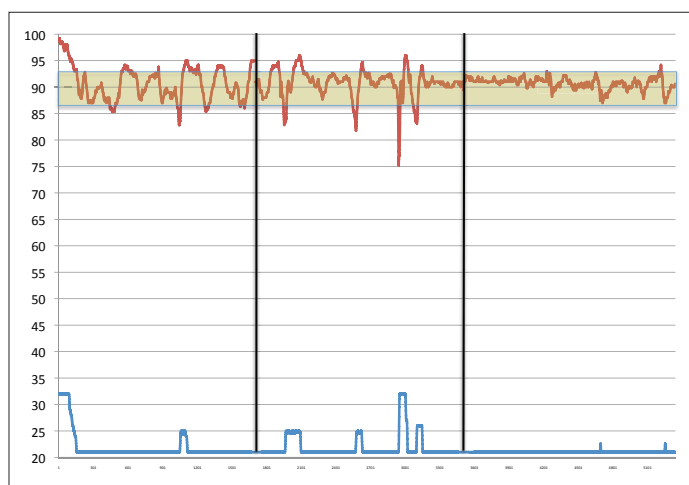


Figure 1a. Typical SpO<sub>2</sub> and FiO<sub>2</sub> in Stable Infant: 7.5 hours  
This 690-gram female was born at 27 weeks EGA. She was intubated on day one and studied on day 5. The upper line is the SpO<sub>2</sub>% and the lower line the FiO<sub>2</sub>%. The shaded area is the intended SpO<sub>2</sub> Target Range. The order of control strategies was Observative, Attentive and CLiO<sub>2</sub>. Oxygenation stability is apparent as she spent most of the day on room air, with only a few SpO<sub>2</sub> desaturations below the intended target range. These spells were generally followed by high saturations during the periods of manual control (first two panels). During CLiO<sub>2</sub> control there were only two very small short adjustments that appear to have headed off desaturations below the target range, and did not result in an overshoot.

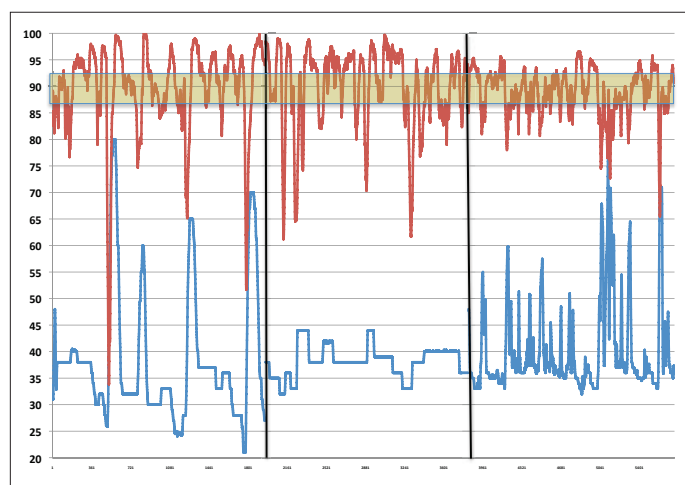


Figure 1b. Typical SpO<sub>2</sub> and FiO<sub>2</sub> in Unstable Infants: 7.5 hours  
This 740-gram male was born at 27 weeks EGA. He was intubated on day one and studied on day 7. The upper line is the SpO<sub>2</sub>% and the lower line the FiO<sub>2</sub>%. The shaded area is the intended SpO<sub>2</sub> Target Range. The order of control strategies was Attentive, Observative and CLiO<sub>2</sub>. He is still on moderate levels of oxygen and also highly unstable. This infant is typical of those in the unstable category with 2.7 desaturations below 80% SpO<sub>2</sub> per hour, some being much more profound. Increases in FiO<sub>2</sub> in response to these episodes were typically followed with overshoot above the target range. This overshoot is much more marked during the two periods of manual control with their more prolonged increases in FiO<sub>2</sub>. As is typical in the study, more time was spent in the target range during CLiO<sub>2</sub> control.

the categories of infants. It calculated the nursing time required to implement, with the defined oversight, for the three control methods.

## Results

Infants with infrequent severe desaturations spend about three-quarters of the time within the target range, experiencing episodes outside the target range an average of every 4.4 minutes. About half of these did not trigger an audible alarm, and an adjustment was only required once or twice per hour (Observative, Attentive respectively). In contrast the infants with frequent severe desaturations spent about half the time in the target range, with episodes outside the target range every 1.2 minutes. About half of these did not trigger an audible alarm, but an adjustment was only required every 13 (Observative) or 9 minutes (Attentive). Our previous study showed that during CLiO<sub>2</sub> control no FiO<sub>2</sub> adjustments were required and that persistent episodes were less frequent.

The charts of FiO<sub>2</sub> and SpO<sub>2</sub> shown in Figure 1a, b illustrate a typical test run of 7.5 hours for the three control methods for each of the two infant stability categories. The contrast between the stable and unstable oxygenation groups is apparent in these two infants. In the more stable infant group we found the percent time below and above the Target range (87%-93% SpO<sub>2</sub>) were similar, though favoring CLiO<sub>2</sub> slightly. (12%/11% CLiO<sub>2</sub>, 19%/9% Observative, and 15%/11% Attentive). In the less stable group the difference >93% SpO<sub>2</sub> is more marked (15%/22% CLiO<sub>2</sub>, 30%/21% Observative, 21%/23% Attentive).<sup>16</sup>

The amount of estimated nursing time needed per hour to implement the three strategies is shown in Figure 2. For the more stable group of infants it is modest (4.3 minutes per hour for CLiO<sub>2</sub> and 6.8 minutes per hour for Observative and 8.3 minutes per hour for Attentive). For the unstable group the time requirements become excessive for the two manual approaches

(33 minutes per hour for Observative and 45.5 minutes per hour for Attentive), but not for CLiO<sub>2</sub> (9.5 minutes per hour).

Nearly three quarters of the time projected for the two manual strategies in managing the unstable infants was associated with observation following adjustments. That was also the case during the Attentive strategy in stable patients, while it reflected only about one third of the time during the Observational strategy.

## Discussion

Our model of the time requirement to implement an ideal practice of FiO<sub>2</sub>-titration suggests that use of an automated system would require 10 minutes of nursing time per hour in the most unstable group of infants. This, in itself, is an important finding, as automated FiO<sub>2</sub> control is not an autopilot, but rather requires oversight.

In contrast to CLiO<sub>2</sub>, the two manual approaches would require 30 and 45 minutes per hour, respectively, to ideally manage the unstable patient. This amount of time is clearly not practical, even with a 1:1 nursing patient ratio.

Our previous study suggests better control with CLiO<sub>2</sub> than either of these strategies in stable and unstable infants.<sup>16</sup> Claire et al also reported, in a group of 32 relatively unstable infants, better control with CLiO<sub>2</sub> than with routine care over a 24-hour period.<sup>15</sup> In that study, routine care required an adjustment every 13 minutes and CLiO<sub>2</sub> only every 150 minutes. This is consistent with our model for unstable infants (every 9-13 minutes). However, Claire's report did not address the time associated with observing the infant with a persistent alarm or following an FiO<sub>2</sub> adjustment.

This factor of how quickly one responds to an unacceptably persistent SpO<sub>2</sub> can be characterized as attentiveness. Included in attentiveness is the necessary time to observe the infant's



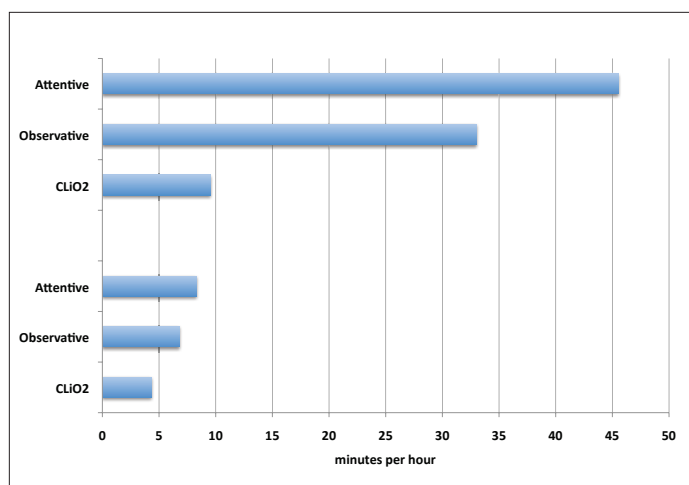


Figure 2. Nursing Time Requirements  
The horizontal denotes the projected time in minutes per hour. The vertical axis is categorical split into two groups. The upper group is the unstable infants, and the lower group the stable infants. Within each infant group are the three FiO<sub>2</sub>-titration strategies.

response. In contrast to attentiveness is vigilance. Our model assumes constant vigilance; 60 minutes per hour, 24 hours a day. This is a significant benefit of an effective automated approach. Claure et al reported significantly more prolonged episodes of low saturations during routine care.<sup>15</sup> Our report of the two manual strategies, implemented with a dedicated operator and excellent vigilance, suggested better maintenance of a target range and less time in extreme saturations than generally reported in routine care.<sup>16</sup> These two observations tend to confirm the benefit of attentiveness and vigilance with an automated system. Some have reported more frequent desaturations with lower target ranges.<sup>17</sup> Others have reported an important difference in the time in extreme saturations with relatively small shifts in target range.<sup>18</sup> We speculate that these three issues might also be associated with or exacerbated by a lack of vigilance.

Our analysis, while provocative, clearly has limitations. Other manual FiO<sub>2</sub>-titrations strategies would have different results. Certainly a more permissive approach to observing the persistent alarm conditions or timing of FiO<sub>2</sub> adjustments would require less time. Nevertheless, we previously reported that more attentive response led to better SpO<sub>2</sub> control, albeit with an impractical time requirement.<sup>16</sup> Thus it is reasonable to expect a significantly more permissive approach, while reducing time requirements, would likely result in poorer SpO<sub>2</sub> control. It is not clear, however, what level of actual SpO<sub>2</sub> control is necessary for optimal outcomes.

We conclude that, in infants with frequent severe desaturations, the time demands of optimal saturation management, without automatic control, are impractical in the NICU. In contrast, in those more stable infants the time savings of automatic control are not significant, and its only advantage would be improved SpO<sub>2</sub> control as a result of vigilance. Finally we suggest the need for further evaluation of the limitations of effectiveness of manual SpO<sub>2</sub> control approaches. This should address both attentiveness and vigilance. Attentiveness relates to staffing and practical guidelines suited for manual FiO<sub>2</sub> adjustments and SpO<sub>2</sub> targeting. It is also important to understand what degree a lack of vigilance plays in shortfalls in achieving desired SpO<sub>2</sub> control in the routine environment.

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# Advancing Brain Oriented Care in the NICU: Challenges and Opportunities

Yamile Jackson, PhD, PE, PMP

Parents often describe the NICU as a roller coaster, and it was in fact our own experience. The Institute for Family-Centered Care (IFCC) lists the core concepts that help parents as: Dignity and Respect, Information Sharing, Participation, and Collaboration.<sup>1</sup>

“Family Participation” in NICUs has as many interpretations as the number of hospitals in the US; however, in all NICUs, newborns and their families need each other from birth.

Since there are no standards, procedures, or scorecards that help a family or the staff determine the level of “participation of families” in an NICU, it is easy to understand why virtually all professionals give a positive response when asked if they practice “family centered care.” Some even say they do because they are open 24/7. The 5 months in the NICU when my son Zachary was born in 2001 at 28 weeks and weighing 906 grams changed my personal and professional life and I made a promise to him that his pain and struggle to survive were not going to be in vain. My story is a painful one but with a happy ending, and I truly believe that in 2001 I experienced an environment that was more centered in the family than what many families experience now in many NICUs.

I truly believe that Zachary beat all the odds and is alive and healthy in large part because the staff empowered me and taught me how to be *effectively involved*. I kangarooed Zachary for 5-7 hours of the 10-12 hours I spent in the NICU. I had to leave because there was no place for me to stay longer than that. The staff taught me how to become his “developmental specialist” so I could continue his care at home after discharge. My appreciation goes to each and every staff member in all NICUs around the world and my mission is to help you offer developmental care that is centered in the Family Centered Care (FCC) is imperative in the NICU more so than in any other unit of the hospital because everything we do (or don’t do) affects the lifetime of the baby, the family, and society at large. Working together with families will improve the babies’ odds of a life as normal as possible.

I classify Parental Participation in NICUs in three general categories, independent of the excellence in medical care:

## 1. Staff Centered Care: These NICUs say (or think) they

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can provide developmental care without the parents. They do not have a process or standards for implementation of developmental care or a plan for parents to participate in the care of their child. They think that Kangaroo Care (KC) is just to place the baby on a parent’s chest but often restrict the time of holding. Staff has had no training on the method and KC is left to chance or to the personal preference of the staff.

Some reasons given by these NICUs are that they may not want to change the status quo, they silently still have a culture that parents “get in the way of my work” so they don’t encourage parents to be involved or ask questions. Usually in these NICUs, not all the staff feels responsible for providing FCC (ie, “it is the responsibility of the nurse, not the neonatologist or the therapist,” etc).

In these NICUs, parents may feel like “visitors” and do not understand the importance of being involved, and this deters them from being in the NICU. Parents in these NICUs usually feel powerless and have to “wait for permission” to visit, touch, hold, or interact with their baby (if they are “allowed or invited”). Many of the NICUs that fall into this category may have a 24/7 open schedule for parents but the staff may invite parents to “go take care of yourself, rest, and call us, because your baby is in good hands here.” Very few parents are there at any given time. Parents feel overwhelmed, impotent, and helpless in an NICU that does not empower them to help their babies, independently of how many hours the NICU is open. I feel that babies in these NICUs are sentenced to solitary confinement and a life in solitude.

**2. Parent Centered Care:** These NICUs’ main programs and activities are developed to support the families go through the experience of prematurity, and while they are important, most of these activities keep them away from their baby (ie, scrapbooking, massage, parties, support meetings for parents, etc). Parents ask questions and are able to feel like parents in the NICU but do not fully understand the impact of their involvement, their rights, or the evidence behind Kangaroo Care. Kangaroo Care is practiced but not in a systematic or standardized way and mostly depends in the personal preference and knowledge of the nurse in each shift.

**3. Baby and Parent Centered Care:** These NICUs educate and help parents to be the “missing link” in the multi-disciplinary team that support comprehensive development and maturation of the baby. These NICUs provide evidence-based developmental

care as their standard and understand that they are only able to provide the best medical and developmental care to the baby when parents are actively and effectively involved. Most of the support activities for parents are facilitated when the parent is doing Kangaroo Care (ie, counseling, support, scrapbooking, education, write in journals, etc).

Parents feel empowered to suggest and ask questions. They know the importance of sleep for brain development and they guard the sleep/awake cycles. Parents know how important they are for the baby so they make the time to be present and to kangaroo as long as possible. These NICUs have a systematic approach for developmental care and Kangaroo Care (planning, process standards that include eligibility criteria/readiness assessment, documentation, tools, training, implementing, measuring, and constantly improving them).

It is not difficult to infer the level of family participation in a NICU: simply look around the Unit. At any given time, what percentage of parents is present? For the time parents are present, what percentage of time they spend holding the baby in skin-to-skin, or if they don't qualify for Kangaroo Care, they are by the bedside bonding, touching, talking, and reassuring the baby that h/she is not alone or abandoned? Are parents confident about their ability to provide the best possible developmental care for their baby at the NICU and after discharge? Are fathers involved and encouraged to kangaroo their babies? Do parents feel hopeless and impotent or do they know how much they can help their babies and what Kangaroo Care can do so they need to be present? How those numbers have changed from last year/month?

"Family centered care is a philosophy of care that embraces a partnership between staff and families. Unrestricted parental presence in the NICU, parental involvement in infant caregiving, and open communication with parents are basic tenets of family centered care. By virtue of their continual presence and role in the NICU, nurses are in a unique position to support family centered care."<sup>2</sup>

## **Here are 10 things that you can do today to improve FCC:**

### **1 – Include the fathers**

Don't restrict family-centered-care to the mother alone. Mothers are the most effective source of comfort for the baby at birth because the baby knows them; however, fathers are just as important to the baby's life and must become a source of comfort as soon as possible. If fathers know they are important, they will be present.

Some fathers feel that the name "kangaroo" is too "maternal," so I started calling it "kangaroos and penguins."\* Female kangaroos protect and feed the baby, and it is the male penguins that guard the eggs and keep them warm – like fathers in the NICU. It includes fathers and encourages them to hold skin-to-skin as much as possible.

### **2 – Participation with a purpose**

If parents come to the NICU and sit next to the incubator for hours, without being engaged in any way, they can start questioning the value of being there and start thinking about all the things they need to be doing at home, with their kids, at work, so they leave, or come to the NICU less often. *If they don't see the value of being there, or they don't understand how they*

*can interact, don't blame the parents.*

For instance, the nurses that took care of Zachary taught me (not only told me) what I could do for my baby, how to use my hands to comfort him, how to hold him in Kangaroo Care, how to know when he and I qualified for it, and I felt empowered – I was there as long as they would allow me, and I kangarooed 5-7 hours every day. I truly believe that our heavy involvement as parents was part of the reason that Zachary could beat incredible the odds not only for survival but also for minimizing or even eliminating many life-long deficiencies.

There is a new study that shows that parents report more behavioral and emotional problems in VLBW children at age 3 if they themselves have had symptoms of depression, parenting stress, or weak sense of coherence 1 year earlier. The new finding of this study was to show the significance of the father's psychological well-being on the behavioral development of a preterm child.<sup>3</sup>

Parents in a Family Centered NICU are a very important part of the multi-disciplinary team that cares for the baby and they provide INDIVIDUALIZED, UNDIVIDED ATTENTION, and CONSTANT level of care especially through Kangaroo Care. Parents are responsible for continuing the care after discharge; hence the importance of encouraging, training, and supporting parents in the NICU.

Susan Ludington teaches that premies should be in Kangaroo for 6 months or until the baby gives signs of not tolerating skin-to-skin contact, so all NICU babies can be kangarooed at some time during hospitalization. Many NICUs do not allow Kangaroo Care for patients on ventilators, for example so they need to know the evidence and expand skin-to-skin contact to critically ill neonates.<sup>4</sup>

### **3 – It is not only the best thing to do but it is also good business.**

Parents are your customers, and every day we want them satisfied with the level of care. I meet thousands of moms in person or virtually through chats, blogs, email, websites, and they talk about their experiences. Some say they are not being "allowed" to hold her baby and their experiences (good or bad) are all over the internet. Do you know how long the day is for a mother who cannot hold her baby? What are moms saying about your NICU in social media? Are they the ones that post pictures smiling holding their child and feeling empowered, or they are the ones who feel hopeless, swearing not to go back to your hospital if they have another child?

### **4 – Every parent wants to hold his/her sick baby but will refrain if they feel it will be detrimental for the baby.**

Don't ask "Would you like to hold your baby?" The question for the parent should be, "There is evidence that you and your baby will benefit from Kangaroo Care. How many hours do you plan to be here in the NICU this week? We would like to reach x% doing skin-to-skin from the time you are here."

If there is not a formal procedure for Kangaroo Care, then the baby receives a level of care that depends on the nurse of that shift. At least teach the parents the eligibility criteria for Kangaroo Care and empower them to be the drivers of Kangaroo Care and keep a log of how many hours they kangaroo.



## 5 – There is evidence that Kangaroo Care is beneficial for the parents.

The NICU staff needs to be taught that the benefits of holding a baby extend far beyond the baby's health. In my opinion, holding Zachary made us realize that we continued to be the most important persons in his life, made us be better parents, and helped us be a tighter family. That, in my opinion, was a very important legacy that the NICU provided us.

Benefits of Kangaroo Care for the parents include:

- Kangaroo Care is beneficial for parents because it promotes attachment and bonding, improves parental confidence, and helps to promote increased milk production and breastfeeding success<sup>5,6,7,8,9</sup>
- Resilience and feelings of confidence, competence, and satisfaction regarding baby care<sup>10,11,12</sup>
- KC helped mother with history of stillbirth who had anxiety and breast feeding difficulties with term newborn<sup>13</sup>
- KC helps mother develop caregiving skill<sup>14,15</sup>
- Increased milk volume, doubled rates of successful breastfeeding and increased duration of breastfeeding<sup>16</sup>
- Doing KC made fathers feel like important contributors to babies' care. Paternal relationship changed from an impersonal one to one characterized by "belonging" and "protecting the child."<sup>17</sup>
- Physiologically, the mother's breasts respond to her infant's thermal needs<sup>18,19</sup>
- KC is profoundly beneficial for adoptive parents with critically ill preterm infant<sup>20</sup>
- Dr Charpak states that "placing the infant in KC shows faith in parents' current and future ability to care for their infant, and the intimacy and respect in the NICU environment may explain the greater sense of competence, improved breast milk production, and breastfeeding success seen in mothers who kangaroo their infants."<sup>21,22</sup> "Parents will do anything for their babies" – it is no different for parents of preemies. It is not easy for a nurse or doctor to perform painful procedures in front of parents just as parents don't like to see their babies in pain. Tell the parent that there is evidence that Kangaroo Care is effective in decreasing pain during and after invasive procedure in preterm infants.<sup>23,24</sup> If they know the evidence, parents will not likely say, "Put him back and let him hurt."

## 6 – Parents who know how important they are for the baby's outcome will do anything possible to be present.

One of the major roadblocks to FCC is that parents are not present. There are some things that we can control (ie, education, compassion, environment) and some that we can't (ie, the laws, the parents' commute, other responsibilities, etc) and the time parents are in the NICU is GOLD!

It is not enough to "invite" parents to the NICU and tell them "you are welcome to be here anytime." Parents have a responsibility and want to help their baby but they need to have a clear picture about what they can do to improve the outcome of the baby and what happens if they don't do it. Parents really want to be involved but don't know how, when, or the impact that would have.

Unfortunately the law in the US is not on the side of parents of newborns, especially preemies. The US is one of the only four countries *in the world* that have no national law mandating paid time off for new parents (together with Liberia, Papua New

Guinea, Swaziland).<sup>3</sup> In the US, parental leave can be provided on a voluntary basis by individual employers, and a handful of states have enacted policies that provide partially paid leave under certain circumstances.<sup>25</sup>

The Family and Medical Leave Act of 1993 (FMLA) mandates up to 12 weeks of job-protected leave, including parental leave, but it has two significant weaknesses: it does not cover all workers, and the leave offered is unpaid. Moreover, less than half (46%) of all women workers are estimated to be covered, and some estimates show that only 20% of new mothers are covered and eligible for FMLA.<sup>26</sup>

It is not difficult to understand why parents need to make the decision of taking any parental leave from work when the babies are discharged from the NICU instead of when they are hospitalized. We must not wait until the laws change to provide effective FCC, nor wait until the baby is ready for discharge to help the mother learn to take care of her preemie. Our job is to educate the parents that they are the only source of comfort of the baby so they are present as much as possible, and with Kangaroo Care we can optimize *every minute* that parents are in the NICU.

## 7 – Do not judge parents who don't want to participate in parent-support meetings, or other activities.

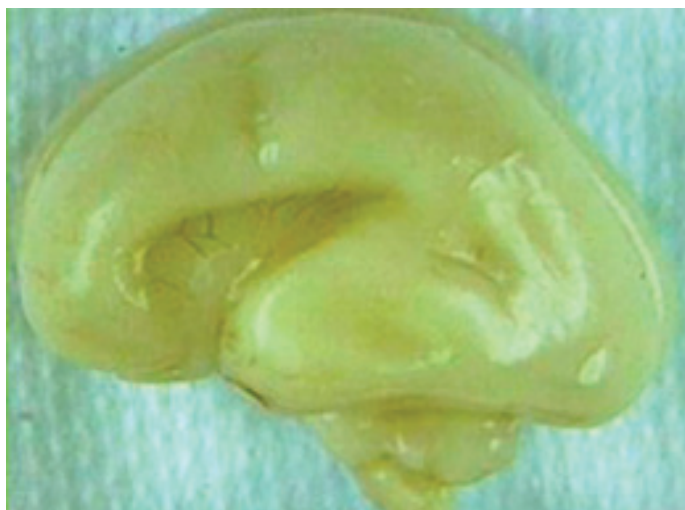
Not every parent copes with prematurity the same way and my support system was at home with my family and friends. I only participated in one of the parent-support meetings and it was definitely not for me. First, it kept me away from my baby, and second, the only common denominator of all the parents in the meeting was that we all had a sick baby (which is the whole point about having these meetings). The conversation was mostly about "how your baby is doing." I didn't like hearing about babies *doing worse than Zachary* because I felt the pain of the parent talking about it, and I felt guilty for feeling relieved that my baby was not that sick. On the other hand, I didn't like hearing about those that were *doing better than Zachary* and going home because I was the one feeling the pain and I felt bad for not wanting to hear about how great another baby was doing while mine had so many complications.

## 8 – Tell them the bad news but follow with the good news.

Parents need and want to know how prematurity can affect their baby's life and what they can do to mitigate deficiencies and disabilities. Contrary to what I heard in the NICU in 2001, there is evidence that babies do not "catch up" at 2.5 to 3 years old and that many disabilities or deficiencies will not be known for years. Premature babies are not just tiny; they are at risk for a number of health concerns, including breathing difficulties, brain injury, eye disorders, infection, bowel problems and heart dysfunction. Some of these are short term and others long term.<sup>27</sup>

One study found that at age 6, 22% of low birth weight children had at least one psychiatric disorder, with attention deficit disorder and anxious disorders being the most common. One study found that at age 6, 22% of low birth weight children had at least one psychiatric disorder, with attention deficit disorder and anxious disorders being the most common.<sup>28</sup> More than half of babies who are born 10 weeks or more before their due date suffer brain damage;<sup>29</sup> and almost half of children who survive extremely preterm birth have neurologic

and developmental disabilities.<sup>30</sup> A study from the United Kingdom suggests that extremely preterm babies who survive to leave the hospital have about a 50-50 chance of being free of disability at age 2 ½ years.<sup>31</sup>



Brain of a 24 weeker: 2 Inches wide.



40 weeker: ¼ size of an adult's brain.  
Photos provided by the Foundation for Premature Infants.

However, the good news is that the evidence is bright when it comes to brain development and parental intervention. The baby's sleep is a basic physiological need. Sleep is very important for recovery, growth, *brain development, learning, and memory*. Moreover, disturbances in sleep can cause exhaustion, damage to the developing body, dysfunction of the immune system resulting in susceptibility to infection, and it can cause serious stress and agitation.<sup>32,33</sup> There is evidence that babies sleep better in Kangaroo Care,<sup>34</sup> cerebral oxygenation is improved during Kangaroo Care,<sup>35</sup> and all the numerous benefits of Kangaroo Care for the baby.

There is still the perception that Kangaroo Care is reserved for improving breast milk production or for under-developed countries that don't have access to equipment. Fortunately, it is recommended for babies in high-tech environment in NICUs in developed countries<sup>36</sup> as it supports an infant's optimal adaptation to extra-uterine life, provides optimal neurosensory environment for brain development, facilitates maternal-

infant bonding and attachment, empowers mother as primary caregiver, facilitates initiation of lactation and breastfeeding, and prepares for a successful discharge.<sup>37</sup>

Because preterm infants are susceptible to cerebral lesions due to immaturity, the effects of KC on cerebral hemodynamics ("blood movement") should be known. Cerebral oxygenation is an important parameter in cerebral hemodynamics.<sup>38</sup>

### **9 – Parental participation and Kangaroo Care may contribute to the prevention of deficiencies in development, and prevention is your legal responsibility.**

"The field of neonatology has expanded beyond the primary aim of saving infants' lives to minimizing survivors' long-term complications, and thus extending clinicians' responsibilities beyond the baby to the broader family."<sup>39</sup>

Survival rate is no longer enough measurement of the quality of a NICU. Prevention of deficiencies or disabilities is the responsibility of the NICU's physicians and medical health professionals. You owe patients a duty to provide professional health care for the premature infant during hospitalization and provide the best possible results that last a lifetime. Individuals may face liability if they fail to do so based upon errors, bad choices, recklessness, carelessness or negligence. Such a situation amounts to medical malpractice upon which a lawsuit may be filed. New evidence is changing the practice in NICUs and the medical-legal climate in which nurses find themselves today has changed in recent years.<sup>40</sup>

It is the professional's responsibility to keep current by reading up-to-date literature and attending continuing education or in-service activities to maintain knowledge and competency. Ignorance is not a satisfactory defense.<sup>41</sup> Now nurses are considered both independent professionals and employees of hospitals or institutions. Nurses are increasingly named as individual defendants in lawsuits, a change from previous decades.<sup>42</sup>

Kangaroo Care is a basic right of every baby and parent in the NICU and no longer can be denied unless the baby or parents are ineligible (and the reason is kept in the record).

### **10 – Kangaroo Care is an evidence-based method plus it is arguably one of the most cost effective interventions.**

If you are not ready (or have budget, resources, time, etc) to implement a systematic approach to Kangaroo Care practice, at least start by learning about Kangaroo Care and teaching it to the parents, purchase a good chair and stool (or recliner), a hand-held mirror, a good wrap for the safety/comfort of the baby and so that parents can sleep, and provide bottled water and protein bars (or snacks that don't smell or make crumbs) by the bedside.

If you cannot or are not willing to provide them, please give the information and the opportunity for parents to purchase and bring them to the unit. They will be happy to do it if they know that Kangaroo Care reduces neonatal mortality and morbidity<sup>[43]</sup> and all the hundreds of results from research that is compiled by Susan Ludington and available at the United States Institute for Kangaroo Care's website.<sup>44</sup>

Let me give you my perspective: Kangaroo Care saved my baby's life during a natural disaster that shut down the power to the hospital and we kept him alive "by hand" for 9 hours until he

Yamile C. Jackson (PhD in ergonomics and human factors engineering, a licensed Professional Engineer, and a certified Kangaroo Care Professional) founded Nurtured by Design, Inc, the global leader in neonatal ergonomics, developmental care, and Kangaroo Care. More than products, Yamile designs ergonomic devices that effectively facilitate comprehensive evidence-based developmental care from birth and around the clock while engaging the parents' natural instincts to nurture and heal. She is also one of the facilitators of the Kangaroo Care Certification Course offered by the United States Institute for Kangaroo Care (USIKC) since 2010. For her work and inventions, Yamile has won 17 awards including "Outstanding Woman-Owned Small Business of the Year" by the SCORE Foundation, "Ultimate Latina Award - Health Category" by the US Hispanic Chamber of Commerce, and was a finalist for the Institute of Industrial Engineers' "Creativeness in Ergonomics Practitioner of the Year Award." Zachary's story of survival and/or the products have been featured in national and international media and even served as inspiration for the made-for-TV movie called "14:Hours" aired on TNT in 2005. Yamile's email is [yamile@nurturedbydesign.com](mailto:yamile@nurturedbydesign.com).

was evacuated. The cost of his care reached \$1,000,000 for the 5 months we spent in the two NICUs. After he went home each 30-minute therapy session for Zachary was \$200-300. Investing in training and tools for Kangaroo Care is negligible compared to the benefits of prevention of deficiencies and the humanized care you will be providing each and every baby in your NICU.

The NICU for us was a roller coaster and Kangaroo/Penguin Care was our seatbelt.

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*Editorial...continued from page 4*

affected have large public health and resource impacts.

The authors concluded: The persistence of elevated morbidity into early term gestation has practical implications for practitioners and policy makers with the first step being recognition. The gradient in morbidity underlines the importance of risk versus benefit considerations when semi-elective delivery is planned before 39 weeks; this must include not only consideration of respiratory but other morbidities as well as their impact on the healthcare system, particularly bed and personnel availability. Hospital policy should clearly discriminate between elective and semi- elective deliveries, and lung maturity should not be the only factor in determining readiness for induction. Educational and research initiatives such as those of AWHONN and The National Institute of Child Health and Human Development aimed at late preterm infants should be extended to include early term infants to improve our knowledge and care of these infants. Families should be educated about the gradient in maturity, especially when involved in discussions about timing of delivery. Absence of traditional risk factors for morbidity such as maternal diabetes, induction and caesarean delivery is not synonymous with absence of risk. Recognition of SES as an independent risk factor is important and an income based measure as used in this study is but one facet of the social determinants of health. Pregnancy is often a window of opportunity for health care providers to address lifestyle factors such as smoking, substance use and control of diabetes and to build ongoing relationships with families to improve continuity of care and maternal health. Physicians and health care providers should ensure that their patients are aware of programs available to them to provide financial, educational and social support and ultimately improve health outcomes.

\*From BMC Pregnancy and Childbirth 2012, 12:62, Chelsea A. Ruth, Noralou Roos, Elske Hildes-Ripstein, Marni Brownell. The authors are with the University of Manitoba, Winnipeg, © 2012 Ruth et al; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License.



Les Plesko  
Editor

# Capacity Building of Nurses Providing Neonatal Care in Rio de Janeiro

Brian A. Darlow, Andrea A. Zin, Gina Beecroft, Maria E.L. Moreira, Clare E. Gilbert

## Abstract

**Background:** Increased survival of preterm infants in developing countries has often been accompanied by increased morbidity. A previous study found rates of severe retinopathy of prematurity varied widely between different neonatal units in Rio de Janeiro. Nurses have a key role in the care of high-risk infants but often do not have access to ongoing education programs. We set out to design a quality improvement project that would provide nurses with the training and tools to decrease neonatal mortality and morbidity. The purpose of this report is to describe the methods and make the teaching package (POINTS of care—six modules addressing Pain control; optimal Oxygenation; Infection control; Nutrition interventions; Temperature control; Supportive care) available to others.

**Methods/Design:** Six neonatal units, caring for 40% of preterm infants in Rio de Janeiro were invited to participate. In Phase 1 of the study multidisciplinary workshops were held in each neonatal unit to identify the neonatal morbidities of interest and to plan for data collection. In Phase 2 the teaching package was developed and tested. Phase 3 consisted of 12 months data collection utilizing a simple tick-sheet for recording. In Phase 4 (the Intervention) all nurses were asked to complete all six modules of the POINTS of care package, which was supplemented by practical demonstrations. Phase 5 consisted of a further 12 months data collection. In Phase 1 it was agreed to include inborn infants with birthweight  $\leq 1500$  g or gestational age of  $\leq 34$  weeks. The primary outcome was death before discharge and secondary outcomes included retinopathy of prematurity and bronchopulmonary dysplasia. Assuming 400–450 infants in both pre- and post-intervention periods the study had 80% power at  $p = < 0.05$  to detect an increase in survival from 68% to 80%; a reduction in need for supplementary oxygen at 36 weeks post menstrual age from 11% to 5.5% and a reduction in retinopathy of prematurity requiring treatment from 7% to 2.5%.

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## Background

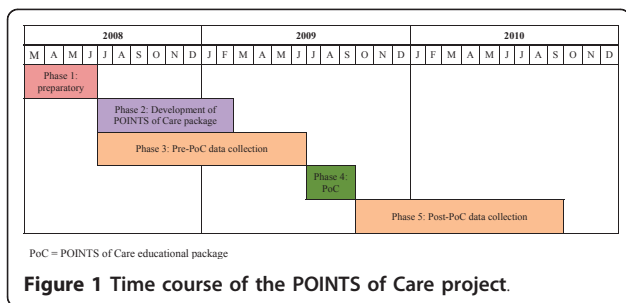
As neonatal care develops in countries with emerging economies it has been common to observe increasing survival but also increased morbidity among survivors. Retinopathy of prematurity (ROP), one of the major morbidities following preterm birth, has become a significant cause of blindness in children in middle income countries in Latin America, Asia and Eastern Europe. Gilbert and colleagues have called this the “third epidemic” of blindness due to ROP<sup>1,2</sup> being a mixture of first epidemic risk factors (uncontrolled use of 100% oxygen) and second epidemic risk factors (increased survival of extremely low birth weight babies). In these countries, unlike in the established market economies, some babies affected by severe ROP have relatively high gestational age and birthweights (that is  $> 30$  weeks and/or  $> 1250$  g respectively) and it is clear that many cases are preventable with more optimal neonatal care.

Despite improvements in many health indicators, the proportion of preterm deliveries in Brazil has increased from just 4% in the early 1980s to more than 10% after 2000.<sup>3</sup> Although many of these preterm births are 34 week's gestation or more and birthweight over 2000 g, the number of infants at risk of ROP have considerably increased over this period.<sup>3</sup>

Nurses have a key role to play in the care of high-risk and preterm infants. However, many countries have a severe shortage of qualified nurses and a great deal of care is administered by nurse assistants or auxiliary nurses (NAs), who may have only minimal training. There is often a lack of ongoing education programs for nurses and NAs and, in addition, many neonatal intensive care units (NICUs) lack protocols for common care practices. Zin has previously reported that the incidence of severe ROP (ROP needing treatment according to the Early Treatment for Retinopathy of Prematurity trial recommendations) in 7 NICUs in Rio de Janeiro varied from 2.1% to 7.8% and that NICUs with the lowest rates had more optimal nurse to patient ratios.<sup>4</sup>

In a national study involving all New Zealand infants with birthweight  $< 1500$  g admitted to a neonatal unit in 1986, the two largest hospitals had both the lowest mortality and lowest morbidity, including rates of ROP, after adjustment for birthweight and gestation.<sup>5</sup> Although there are a number of possible explanations for this finding, one possibility is that these hospitals were able to deliver overall better care. The authors proposed that ROP might be a good index of overall quality of care.

We therefore hypothesized that providing nurses/NAs with a focused education package and strengthening the capacity of nurse supervisors, as well as supplying minimum essential



equipment, in neonatal units in Rio de Janeiro, Brazil, would improve survival and decrease morbidity, particularly ROP. Further, we considered that the training package would improve current nurse/NA practices and empower them to undertake additional responsibilities for babies in their care where these were supported by their medical colleagues.

The aim of this report is to describe the methods used in this quality improvement project, and to make available the interactive training package called POINTS of Care.

Ethical approval was obtained from the London School of Hygiene & Tropical Medicine and, in Rio de Janeiro, the Ethical Review Board from Secretaria Municipal de Saúde, the Regional Health Authority, and the Brazilian Ministry of Health's Ethics Committee (CONEP). Informed consent was obtained from all health personnel involved in the study. Informed consent was not required from mothers of preterm babies, as only routine audit data were collected and used in the analyses.

## Methods/Design

Six government funded NICUs, caring for 40% of preterm infants with BWs of  $\leq 1500$  g born in Rio de Janeiro in 2008, were invited to take part. Five of these NICUs had been included in Zin's previous prospective study of ROP.<sup>4,6</sup> They all had existing ROP screening and treatment programs and they were willing to participate.

Our original plan was to adopt an interrupted time series (ITS) methodology; that is, to introduce the intervention in NICUs A and B for three months with NICUs C-F as controls, then add the intervention in NICUs C and D for three months and finally E and F for three months. However, during our initial NICU visits we learned that many nurses/NAs worked in more than one NICU in our study, which would have led to contamination. We therefore altered the design to a controlled before-and-after (CBA) study with data collection for 12 months, an educational intervention package over three months, followed by a further 12 months data collection (Figure 1).

**Phase 1: Preparatory phase (4 months):** During this initial phase of the study multidisciplinary workshops were held in each of the six NICUs to identify outcomes of interest, to decide upon methods of data collection and to undertake a situation analysis with respect to staffing levels and availability of protocols for care and essential equipment. Head nurses, registered nurses, NAs, and some ancillary health professionals and neonatologists/residents attended these workshops.

During the workshops the major findings from Zin's previous study of ROP were presented by way of introduction. Following this process it was agreed to focus assessment on outcomes

among very low birthweight infants only (VLBW: birthweight  $\leq 1500$  g and/or gestation  $\leq 34$  weeks). In addition to mortality and ROP, unit staff identified outcomes as being important to them. Infection, necrotizing enterocolitis and neonatal chronic lung disease were morbidities that were of particular concern. Staff also wished to evaluate breast feeding, nutritional support and achievement of adequate growth.

As there was no systematic way of collecting daily information prior to the start of this study, a daily "tick sheet" was introduced, based on that used in Christchurch, New Zealand, after modification by neonatologists and nurses in Rio. NICUs agreed that data would be collected by one to two senior staff in each NICU daily during the study.

A standard reporting form was used to collect information on staffing levels, and on the availability of functioning equipment, for example air-oxygen blenders, vital sign monitors and pulse oximeters. Structured sheets were designed to record observation of nurse's practices before and after training, and this was piloted to test suitability.

A data collection form for the outcomes of interest was developed and pilot tested. Data were extracted by a trained Research Assistant from the tick sheet summaries, discharge summaries, medical records and ophthalmologists' records.

**Phase 2: Development of intervention:** During the interactive workshops in each NICU in Phase 1, care teams were asked to identify major concerns and education gaps so that an intervention strategy could be tailored to the overall needs of the NICUs. At the end of this process it was agreed that the intervention package would be as follows: self-guided use of educational materials, a DVD with practical demonstrations and provision of minimum essential equipment. Design, development and pilot testing of the educational component of the intervention took place at the same time as the 12 month pre-intervention period of data collection (Phase 3—see below). The topics addressed comprised Pain control; optimal Oxygenation; Infection control; Nutrition interventions; Temperature control; and Supportive care, which we called "POINTS of Care." These topics were all approved by local senior neonatologists and management.

Six mini-courses were developed, one for each of the POINTS of Care educational package. As far as possible the main elements of each education package were strongly evidence based and reflected material based on Cochrane reviews (when available)<sup>7</sup> and the in-house protocol handbook of the Neonatal Intensive Care Unit, Christchurch Women's Hospital, Christchurch, which is reviewed annually. Each mini-course comprised precourse questions, guiding principles, facts about the topic, and then repeated questions so that nurses could assess what they had learned. After going through the educational materials, nurses were asked to make suggestions to improve care in their NICU.

Each NICU had a verbal presentation of one of the POINTS of Care mini-course to assess the content, comprehension and local relevance before the final versions were produced. Practical demonstrations were also undertaken jointly by a nurse educator from New Zealand (GB) and two experienced local nurses to refine the DVD content.

Alongside the written material a DVD was developed that gave a practical demonstration of one aspect of each of the POINTS of



Care mini-courses. This DVD came with an instructors booklet giving a clear learning objective for each video clip. The nurse educator from New Zealand used this material to train the local nurse educators. The clinical scenarios covered were as follows: Pain – a baby having a heel prick blood test demonstrating the beneficial effects of oral sucrose; Oxygen – illustrating the importance of setting and responding to saturation alarms; Infection – illustrating how work surfaces can become contaminated; Nutrition – skin to skin contact whilst having a nasogastric tube feed; Temperature – a preterm baby having a bath; Supportive care—a baby receiving nasal CPAP having routine care and positioning. A small, pocket sized booklet with a summary of the main principles and facts of each mini-course on one double-sided, laminated page was also designed so that each nurse and NA could have a personal copy at all times. All educational material was developed in English and translated into Portuguese. A questionnaire was developed to assess nurse's knowledge before and after the training package and this was pilot tested.

**Phase 3: Pre-intervention period (12 months):** Data were collected using the tick sheets, discharge summaries and other data sources for the period July 2008 to June 2009 inclusive. In addition, all NICUs were visited monthly during this period by one of two senior local nurses who made unannounced visits at different times of the day. They supervised data collection and were available to assist with any difficulties with the process. During these visits standardized observations were made on medical and staffing levels; whether the unit was overcrowded; the availability of essential consumables and the proportion of babies on supplemental oxygen who were being monitored. They observed and recorded hygiene behavior of nurses and checked the proportion of monitors which had alarms that were correctly set. They also observed and recorded how nurses responded to alarms going off for up to five babies receiving supplemental oxygen, and recorded the temperature on arrival in the NICU of the last five babies admitted.

**Phase 4: Delivery of the intervention (3 months):** After discussion it was agreed that formal teaching of all qualified nurses and NAs on all six NICUs in all six POINTS of Care was not practical or feasible. All nurses and NAs were, therefore, asked to work through each mini-course in their own time, or working in groups, to earn a certificate. Written course material was supplemented by the DVD, with these practical demonstrations being undertaken by one of the two local nurses who helped develop the content. In all cases this process was supported by the Head Nurse of the NICU. Neonatologists were requested to read the mini-courses so that they were familiar with the material and could answer any questions from the nurses.

Further interactive workshops were held in each NICU after completion of the POINTS of Care module so that nurses/NAs could identify potentially better practices to introduce to their unit. Key items of equipment (eg saturation monitors and probes, blenders etc) identified as priority needs, were itemized at this time and ordered (within budget constraints) by the end of 2008.

#### **POINTS of Care Summary:**

1. POINTS of Care training packages. Every nurse and NA was asked to work through each of the six mini-courses, answer a series of question pre-course, read the educational material, answer the same questions post-course and make suggestions

on any practice changes that might be appropriate for their NICU. On completion of all six mini-courses participants were issued with a certificate of achievement.

2. Interactive workshops in each NICU to identify potentially better practices that could be integrated into everyday care of that unit and identification of essential items of equipment.
3. Questionnaires to all nurse/NAs to assess their attitudes to the course.
4. Nurse educator “champions” visited each NICU monthly to reinforce concepts taught in the mini- courses and hold practical sessions using the DVD.

**Phase 5: Post intervention data collection period (12 months):** Data collection continued after the intervention exactly as in Phase 3 for a further 12 months from October 2009 to September 2010 inclusive. Visits by one of the two experienced local nurses continued at about monthly intervals during this period to reinforce POINTS of Care training and to audit NICU practices.

#### **Outcomes**

The overall aim of this project was to reduce mortality and morbidity, specifically bronchopulmonary dysplasia (BPD), severe ROP, sepsis and necrotizing enterocolitis (NEC), and to improve the nutritional status of premature babies being cared for in NICUs in the government sector in Rio. Outcomes were limited to babies who were inborn on the study units and who had birthweights of  $\leq 1500$  gs or gestational age of  $\leq 34$  weeks.

The primary outcome was death before discharge.

Secondary outcomes were:

- Death before discharge, by BW categories
- Retinopathy of prematurity: a) Type 1 ROP or treatment of ROP (Type I ROP defined as: Zone I, ROP stage 1-2 with Plus; Zone I, ROP stage 3 with or without Plus; Zone II, ROP stage 2-3 with Plus)<sup>8</sup> and b) ROP of any stage
- Bronchopulmonary dysplasia a) oxygen required at 36 weeks post-menstrual age (PMA), for babies  $< 32$  week's gestation b) oxygen required at 28 days of age and c) oxygen required at 28 days of age, by birthweight
- Necrotizing enterocolitis (clinical diagnosis with radiological evidence of pneumatosis or pneumoperitoneum)
- Sepsis: a) early-onset sepsis: blood culture positive sepsis within 48 h of birth; b) late-onset sepsis (suspected): clinical sepsis after 48 h of age and treated with antibiotics for seven days and c) late-onset sepsis (culture positive): as above but with a positive blood culture. Both suspected and culture proven late-onset sepsis will be reported as a) percentage of admissions with one or more episodes, and b) number of sepsis episodes per 1,000 baby days.
- Days to regain BW
- Change in nurses' knowledge of key elements of neonatal care, as measured by questionnaire before and after undergoing the training package
- Change in nursing practices, assessed by observation during unannounced visits
- Nurses' satisfaction with educational package, assessed by a structured questionnaire

**Power calculations:** From existing data, it was anticipated that approximately 400-450 babies with BWs  $< 1,500$  g would be admitted to the study units each year. A study with a one

year pre-intervention period and a one year post intervention period would be adequately powered to detect the following differences, at 80% power and at  $p = < 0.05$ : an increase in survival from 68% to 80%; a reduction in BPD (oxygen at 36 weeks post menstrual age) from 11%<sup>9</sup> to 5.5% and a reduction in ROP requiring treatment from 7% to 2.5%.

**Data management:** Data on the clinical outcomes were entered into a database created in Access by an experienced, trained research assistant. The quality of data entry was checked by the Principal Investigator, who cross-checked data from randomly selected data forms against that entered into the database. Standard procedures were used to clean the data; for example, frequency distributions and cross tabulations with review of the data collection form for outliers. Data were transferred into STATA for analysis. Data from the other data sources (such as questionnaires administered to nurses; observation of nurses practices) were entered into further databases created in Access, or into Excel spreadsheets. These data sources were analysed in Excel (nurse observation) or in STATA (comparison of nurses knowledge and practices before and after undergoing POINTS of Care training).

## Discussion

There is a great deal of evidence from high quality randomized clinical trials and systematic reviews on the efficacy of a wide range of interventions in relation to the care of preterm babies.<sup>7,10</sup> However, as in all areas of public health, there is often a gap between this evidence base and the delivery of interventions in the real world.<sup>11,12</sup> This has led to considerable discussion and debate concerning how complex interventions, which may entail improving the knowledge, skills and attitudes of staff, and interventions to improve the functioning of other aspects of the health system (for example, health management information systems; leadership and governance) can best be evaluated.<sup>11,13,14</sup>

As with new drugs or medications, randomized clinical trials provide the highest level of evidence and this is also true of the evaluation of complex interventions. However, evaluation of complex interventions is complicated by the need to attribute the inputs to the outputs, outcomes and ultimate impact of the intervention on health. Evaluation of changes to the health system, such as training staff and providing additional equipment, also needs to take account of, and measure if possible, unintended positive or negative consequences, as well as the impact of extraneous factors, such as a policy change, or change in the environment external to the health system, such as extremes of climate. In relation to nursing interventions for the prevention of morbidity in preterm infants being cared for in intensive neonatal care units, the evidence of impact is limited.<sup>15-18</sup>

When the results of this study are published we will discuss the findings in relation to the challenges and constraints of delivering and evaluating complex interventions, highlighting the difficulties of attributing inputs to outcomes and measures of impact.

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# Respiratory Syncytial Virus Outbreak in Neonatal Intensive Care Unit: Impact of Infection Control Measures plus Palivizumab Use

Camila de A. Silva, Livio Dias, Sandra R. Baltieri, Tatiane T. Rodrigues, Neusa Brandolise Takagi, Rosana Richtmann

## Abstract

**Background:** The occurrence of a respiratory syncytial virus (RSV) outbreak in a Neonatal Intensive Care Unit (NICU) is related to unfavorable outcomes, as this infection can lead to respiratory distress and death in premature infants. We report the successful control of an outbreak that occurred in April 2010 in a NICU.

**Methods:** After the index case, of 18 premature infants placed in the same room 10 infants were infected. Of those 10, 6 developed mild to moderate respiratory symptoms, 4 persisted asymptomatic and no death occurred. Contact and respiratory precautions were rapidly initiated, the infants were cohorted in 3 different rooms and palivizumab was administered to all contacts

**Results:** The outbreak was controlled and no new cases were subsequently identified.

**Conclusion:** Standard infection control measures plus palivizumab prophylaxis were efficient in rapid control of the outbreak.

## Introduction

Respiratory syncytial Virus (RSV) is a single stranded RNA virus of the Paramyxoviridae family. A and B sub-types are involved in the majority of outbreaks; the A subtype is responsible for most of them.<sup>1</sup>

RSV can cause respiratory symptoms in patients of all ages, but most cases occur in children under one year.<sup>2</sup> Special populations as premature infants born before 35 weeks of gestational age (GA), patients with underlying lung disease and patients with congenital heart disease are at risk of more morbidity and mortality from RSV infection.<sup>3</sup>

Transmission is most commonly by direct contact, as the virus can remain for hours on surfaces and the hands of health care workers.<sup>4</sup> When the virus circulates in the general population, health care workers and visitors can bring RSV to neonatal units.

Infected infants are important sources of infection of others and they can continue excreting virus for longer periods.<sup>5</sup>

RSV outbreaks in NICU are expensive, besides the increased morbidity and mortality.<sup>6</sup> Conventional infection control methods such as hand hygiene and patient isolation in cohorts are recommended, but those procedures should be supplemented by the use of palivizumab, a monoclonal antibody directed to glycoprotein F, as an effective adjuvant to standard infection control measures.<sup>7-9</sup> The aim of this manuscript is to report that the combination of infection control measures with passive immunotherapy in a country where new antiviral agents is not easily available, succeeded in the rapid control of an outbreak in NICU.

## Methods

Our NICU is located at a private maternity hospital in São Paulo, a city with 1,000 births per month, which has two NICUs situated in different floors of the building and does not receive patients from other institutions. Each unit has an overall capacity of 25 beds distributed in a large hall with 21 beds and three in the isolation room. In addition, our hospital has one semi intensive care unit with 21 beds, distributed in 5 different rooms. The outbreak started in the NICU situated on the second floor.

Due to the seasonal characteristic of RSV in São Paulo (April to August), the palivizumab prophylaxis is indicated (intramuscular 15 mg/kg/day, each 30 days) to infants less than 32 weeks of GA, or congenital heart disease or chronic lung disease. The palivizumab antibody use depends on each patient health insurance authorization policy.

Routinely, the infant that presents respiratory symptoms suggesting viral infection is tested for RSV using an immunoassay test (QuickVue RSV test – bio Mérieux). Contact and droplet precautions with gowns, gloves and masks are promptly initiated in all suspect cases. The nasopharyngeal RSV test is repeated after 14 days of the diagnosis and then weekly to check the precautions measures necessity.

It is considered as RSV infection if all neonates who present clinical evidence of lower respiratory tract infection and RSV immunoassay test positive. Neonate asymptomatic carriage was defined as a positive RSV immunoassay test and no clinical respiratory symptoms suggesting viral infection.

Protection rate of palivizumab was calculated by the number

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	GA (weeks)	Birth weight (grams)	Age (days) at RSV diagnose	Time of viral excretion	Underlying condition	Respiratory symptoms	Symptoms
Index case	27	965 g	79	2 weeks	PDA/BPD	Yes – MV due to RSV infection	Yes
1	27	830 g	65	Negative control*	Hydrocele/GI Malformation	YES – MV due to RSV infection	Yes
2	27	585 g	46	3 weeks	RDS/PDA/inguinal hernia	MV – Worsening of parameters	Yes
3	26	560 g	80	5 weeks	RDS/PDA/BPD	MV – worsening of parameters	Yes
4	33	1720 g	97	Negative control*	Onphalocele/PDA/PH/BPD	n-CPAP due to RSV	Yes
5	25	795 g	51	3 weeks	RDS/PDA/ARF	MV – worsening of parameter s	Yes
6	34	2575 g	38	3 weeks	RDS	Previous in MV	No
7	25	715 g	26	2 weeks	RDS/PDA	Previous in MV	No
8	25	650 g	26	2 weeks	RDS/PDA/BPD	MV – worsening of parameter s	Yes
9	27	1230 g	32	Negative control*	RDS/PDA	No – No O2 Support	No
10	32	2150 g	37	2 weeks	RDS	No – No O2 support	No

Table 1 Characteristics of the patients in NICU with RSV positive test

GA = Gestational Age PDA = patent ductus arteriosus; BD = Bronchopulmonary dysplasia  
RDS = Respiratory distress syndrome; GI = Gastrointestinal; PH = Pulmonary hypertension  
ARF = acute renal failure; MV = Mechanical ventilation; n-CPAP: nasal continuous positive airway pressure  
\*Negative Control – negative test on the 14th day after diagnostic

of contacts neonates free of RSV symptomatic disease who received palivizumab prophylaxis.

The suspicion of the present RSV outbreak began on 02 May 2010 as the first contact neonate of the index case presented clinical respiratory symptoms of viral disease.

## Results

The index case occurred in a 27-week GA, 965 g of birth weight preterm infant presenting on April 19th tachypnoea, increase of respiratory secretions and respiratory failure requiring mechanical ventilation. The patient was 79 days old with bronchopulmonary dysplasia. The infant received palivizumab in the same day his rapid test became positive for RSV that means April 19th. At that moment, contact and droplet precautions were initiated. Two weeks after the onset of RSV infection, the RSV test was still positive.

On 02 May/10 and 03 May/10 two patients in the same NICU of the index case developed respiratory symptoms and tested positive for RSV. Prevention control measures were then implemented and all infants in the same room were tested for RSV, even in the absence of respiratory symptoms. The cases and contacts babies were moved to a semi intensive unit to better cohort them into separate rooms. Hand hygiene and environmental cleaning measures were reinforced.

All babies (18 infants) occupying the NICU at the moment of the outbreak were placed in 3 cohorts. Eight of them with negative RSV test were maintained for 7 days in a room under contact precaution, considering RSV incubation period. None of these patients developed symptoms during this period and specific precautions were suspended. The remaining 10 infants were positive for RSV and they were placed into two different rooms according to the presence or absence of symptoms. Six presented symptoms and four were asymptomatic. All positive tested patients were isolated in incubators and the use of gloves and mask was oriented to visitors and staff personnel.

Symptomatic infants presented mild to moderate symptoms, with cough, fever and coryza. Two patients (cases 1, 4) and

the index case, however, required ventilation support due to RSV infection. Cases 3, 5 and 8 were already under mechanical ventilation and required an increase on ventilatory parameters after the infection. Cases 6, 7, 9 and 10 did not present symptoms. No specific antiviral treatment for RSV infection was given, except palivizumab.

In Brazil we do not have inhalatory ribavirin available. No death occurred due to RSV infection.

All contacts and the index case received palivizumab. Cases 1, 2, 3 and 9, received palivizumab previously to the onset of outbreak according to institutional policy although cases 1, 2 and 3 presented respiratory symptoms of RSV infection. Palivizumab was prescribed to all other 14 patients occupying the same NICU within the beginning of the outbreak. Palivizumab protection rate for symptomatic infection was 67% (12/18 cases).

RSV positive cases were tested weekly after 14 days of the first detection and, in most cases, still tested positive at subsequent tests. The longest viral shedding time was 5 weeks. Symptomatic patients were isolated until hospital discharge and the asymptomatic ones were removed from the semi intensive unit when the viral test becomes negative. There were no new cases detected and the outbreak was successfully controlled in 5 days (onset 2 May/10 and last case 6 May/10).

## Discussion

Besides the index case, ten RSV cases were diagnosed in our NICU, most of them under 28 weeks GA. Premature infants are highly susceptible to RSV infection due to the immaturity of their immunological system and the low levels of maternal antibodies.<sup>10</sup> The occurrence of RSV outbreak in the NICU may be related to unfavorable outcomes, including death.<sup>11,12</sup> Fortunately, among patients included in this study no deaths occurred and only 30% of the infected patients needed ventilation support attributed to the infection.

Viral infection diagnosis is usually based on symptoms, but in an NICU outbreak the investigation of all contacts is fundamental because of the possibility of asymptomatic infection. Therefore

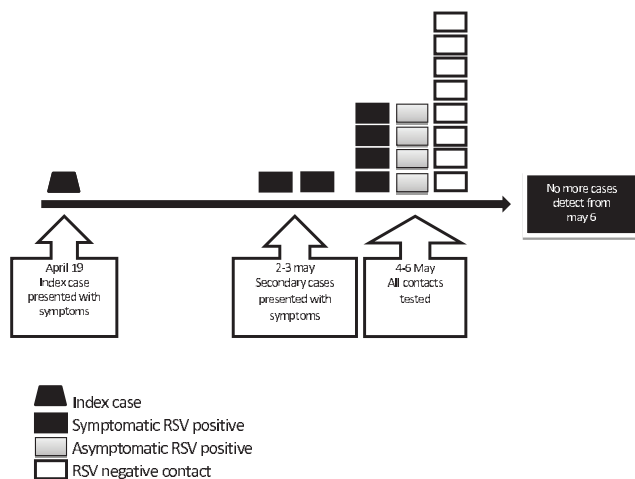


Figure 1. All RSV positive infants were premature, average GA was 28-weeks (range: 25-34w), birth weight of 1,181 grams (range: 560-2,575 g) and 50 days old (range: 26-97) at RSV infection diagnosis.

asymptomatic and symptomatic infants must be quickly identified and isolated to avoid viral dissemination. Contact precautions are well established as a control measure for RSV outbreaks and the use of masks might be added when the risk of respiratory particles dispersion is expected.<sup>13</sup> We incorporated the use of masks by visitors and staff in order to prevent contamination and avoid carriers into the NICU. It is recommended that infected patients should be kept in cohorts away from the other healthy prematures. Our strategy to transfer patients to other unit prevented the interdiction of the NICU and allowed the admission of other patients.

## Conclusion

Usually, RSV shedding time last for 2 weeks; however, under specific conditions such as immunosuppressed hosts and preterm infants this period might be much longer.<sup>5</sup> In the present study RSV excretion was documented for five weeks, showing that viral testing, despite the role of detecting new cases, is crucial to determine the duration of precautions. The “quick test” to diagnose RSV was chosen due for the simplicity of the method, low cost and fast results. Dizdar et al demonstrated the use of a quick test as an efficient method in order to identify and control a RSV NICU outbreak.<sup>9</sup>

Presently, palivizumab use is not formally indicated to control outbreaks. However, it may attenuate the gravity of clinical manifestations and help to control viral dissemination, according to some authors.<sup>7,9,11,14</sup> Despite the use of palivizumab, ten patients included in this study presented with infection, six of them symptomatic and four asymptomatic. We believe that palivizumab did not prevent infection, probably because the infants were already in the incubation period of RSV. The presented symptoms however were mild and no death occurred.

The control of RSV nosocomial outbreaks remain a challenge to medical staff and infection control practitioners mainly because many institutions do not have adequate isolation facilities. Early detection of cases, reinforcement of hand hygiene and contact precaution remains the most important measures to control outbreaks. Although no independent analyses of each measure could be done, we believe that the use of palivizumab, contact and droplet precautions and the periodic viral testing to determinate the suspension of precautions were crucial for the successful control of the outbreak.

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# Failure of a Repeat Course of Cyclooxygenase Inhibitor to Close a PDA is a Risk Factor for Developing Chronic Lung Disease in ELBW Infants

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## Abstract

**Background:** The optimal treatment regimen or protocol for managing a persistent patent ductus arteriosus (PDA) in extremely low birth weight (ELBW) infants has not been well established. This study was aimed at evaluating the failure rate of a cyclooxygenase (COX) inhibitor (COI) for PDA closure and to determine the incidence of a PDA requiring ligation in ELBW infants. We examined the clinical characteristics and risk factors that may predict the clinical consequences of failure of PDA closure by COI.

**Methods:** Medical information on 138 infants with birth weight (BW) <1000 gm who survived for >48 hours was retrieved. Clinical characteristics and outcomes of patients whose PDAs closed with COI were compared with those who did not close. **Results:** Of the 138 patients, 112 survived to discharge. Eighty (71.4%) of those who survived received 1-3 courses of COI treatment for a symptomatic PDA. A total of 32 (40%) failed COI treatment and underwent PDA ligation. Multivariable logistic regression analysis suggests that the observed differences in the outcomes in infants with or without symptomatic PDA can be explained by the babies with symptomatic PDA being more immature and sicker. No significant difference was seen in the incidence of chronic lung disease (CLD) in infants whose PDA was treated medically versus those who failed medical treatment and then underwent ligation. However, after adjusting for disease severity and other known risk factors, the odds ratio of developing CLD for surviving babies with a persistent PDA compared to those whose PDA was successfully closed with 1-2 courses of COI is 3.24 (1.07-9.81;  $p=0.038$ ).

**Conclusions:** When successfully treated, PDA in ELBW infants did not contribute significantly to the adverse outcomes such as CLD, retinopathy of prematurity (ROP) and age at discharge. This suggests that it is beneficial for a hemodynamically significant PDA to be closed. The failure of a repeat course of COI to close a PDA is a major risk factor for developing CLD in ELBW infants.

## Background

Spontaneous closure of the ductus arteriosus (DA) usually occurs within hours to days after birth in term infants. However, the incidence of failure of DA closure in premature infants ranges from 10% to 60% depending on the gestational age, birth weight and diagnostic criteria used.<sup>1,2</sup> In extremely low birth weight (ELBW) infants (birth weight less than 1000 grams), only 34% have a spontaneous permanent closure of the DA.<sup>3</sup> A significant left-to-right shunt through the PDA may increase morbidity and therefore contribute to mortality in premature infants. The increased pulmonary blood flow due to a left to right shunt through a PDA can lead to deterioration of the respiratory status of premature infants and may contribute to the development of bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD).<sup>4</sup> A patent ductus arteriosus (PDA) with a significant left-to-right shunt may also increase the risk for renal insufficiency, reduced brain perfusion<sup>5</sup> and possible necrotizing enterocolitis (NEC).<sup>6</sup> Although indomethacin, a cyclooxygenase inhibitor (COI), is very effective in closing the DA of preterm infants,<sup>7,8</sup> its efficacy is limited in very immature infants.<sup>9</sup> In ELBW infants, the success rate of DA closure after the first course of indomethacin has been reported to be between 20 and 40%.<sup>9,10</sup> When a PDA fails to close after medical management or when treatment with COI is contraindicated, surgical ligation is an alternative. Currently, most neonatologists use repeat courses of indomethacin or ibuprofen in an attempt to close the PDA before committing the patient to surgical ligation.<sup>6,11</sup> Recent studies have suggested an increased risk of CLD, ROP and/or neurosensory impairment may be associated with PDA ligation.<sup>12,13</sup> However, it is unclear whether the clinical condition of the baby requiring surgical ligation or the procedure itself contributes to an adverse outcome.<sup>2</sup> Therefore, the optimal treatment regimen for a persistent PDA in ELBW infants has not been established. The aim of the current study was to evaluate the clinical course of ELBW infants with a PDA treated with COI, the rate of failure of COI for PDA closure and the incidence of PDA requiring surgical ligation. We compared the clinical characteristics and outcomes of babies whose PDA were successfully closed by COI with those whose DA remained patent after COI treatment and determined if any of these factors contributed to the clinical outcomes of the ELBW infants.

## Methods

We performed a retrospective data analysis. Medical information of infants with a birth weight (BW) <1000 gm born at the Mount Sinai Medical Center in New York between August 1, 2004 and July 31, 2009 was retrieved from our perinatal data base and

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The authors are with the Mount Sinai Kravis Children's Hospital and Department of Pediatrics, Mount Sinai School of Medicine, New York. The authors wish to thank Dr Ian Holzman for critical review of the manuscript and Ms Larissa Gontar for help with data collection. Reprinted from BioMed Central, BMC Pediatrics, © 2012 Adrouche-Amrani et al; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License.



medical records. The study was approved by the Program for the Protection of Human Subjects of the Mount Sinai Medical Center. It was our practice during that period to: 1) perform echocardiography only when a PDA was suspected due to the presence of a murmur, wide pulse pressure, or deterioration of pulmonary status possibly secondary to left to right shunting; 2) treat a PDA with COI in infants who were diagnosed with a hemodynamically significant PDA as judged by our attending neonatologists and/or confirmed by echocardiography; 3) use indomethacin as the preferred choice, but use ibuprofen for some babies with decreased urine output; 4) not use indomethacin for prophylactic ductal closure in infants less than 48 hours of age; 5) give indomethacin 0.2 mg/kg every 12 hours for 3 doses or ibuprofen 10 mg/kg followed by 5 mg/kg daily for 2 more doses as one course; 6) obtain echocardiography confirmation of a moderate to large PDA with significant left to right shunt before surgical ligation; 7) give a third course of COI when PDA ligation could not be done expeditiously due to scheduling issues. We collected clinical data and determined the incidence of spontaneous closure of the DA, the failure rate of 1-3 courses of COI for PDA, the incidence of PDA treated with surgical ligation, and the clinical outcomes of these infants. Successful PDA closure was defined as disappearance of the PDA murmur and/or echocardiogram evidence of PDA closure. Echocardiographic evidence of trivial flow through DA and no further treatment needed was considered to have closed PDA.

The clinical data collected included gestational age, birth weight, gender, Apgar scores, admission temperature, first arterial blood gas, surfactant treatment, duration of intubation for mechanical ventilation, total fluid administered during the first three days of life, and the age when an infant received the first course of COI. The urine output, serum sodium concentration, body weight and total fluid status before, during and after the first course of COI were also recorded. The disease severity was quantified by the oxygenation index (OI) and the five-item clinical risk index for babies (CRIB) II score as described.<sup>14,15</sup> The clinical outcome measurements include the age at extubation, the age at full enteral feeds (defined as baby receiving no intravenous fluid and >120 ml/kg/day of enteral feeds), the incidence of severe (grade 3 or grade 4) intraventricular hemorrhage (IVH), CLD (defined as supplemental oxygen requirement at 36 weeks postmenstrual

age), ROP, necrotizing enterocolitis (NEC) with Bell stage II or higher, blood culture proven bacteremia, and the age at discharge.

Data analysis was conducted with PASW Statistics 18.0 (SPSS Inc.). Continuous variables between groups were compared using the T-test for independent samples for normally distributed data and the Mann-Whitney test for non-normally distributed data. Proportions between groups were compared using the Chi-square test. For dichotomous outcomes, odds ratios adjusted for confounding and effect modifiers were determined using logistic regression as indicated in the text. For continuous outcome variables, multivariable regression analysis was used to determine the effect of a PDA and its treatment as indicated in the text. The data are presented as mean (standard error of the mean) and  $P < 0.05$  is considered significant.

## Results

A total of 189 infants with a BW <1000 gm were born at the Mount Sinai Hospital between August 1, 2004 and July 31, 2009. Of those patients, 14 patients with major congenital anomalies and 37 who died at age <48 hours of life were excluded from the analysis.

Data from the remaining 138 patients were reviewed. Among those 138 patients, 26 died before discharge. Seven of those 26 died at age  $\leq 7$  days of life. The causes of death for those 26 patients were mainly respiratory failure due to extremely immature lungs (13/26). Other causes of death include NEC or sepsis (9/26), severe IVH (2/26), and twin to twin transfusion (2/26). Of the 112 babies who survived to discharge, 32 (28.6%) did not develop a hemodynamically significant PDA (the DA closed spontaneously). The remaining 80 patients (71.4%) were diagnosed with a hemodynamically significant PDA and received at least one course of COI. Among the 80 patients who received COI treatment for a PDA, 26 (32.5%) infants closed their PDA after one course of COI. One infant had her PDA ligated after the failure of one course of COI to achieve ductal closure due to significant side effects of COI usage. The remaining 53 patients received a second course of COI and 16 of these patients (30.2%) closed their PDA after the second course of COI. Therefore, there were a total of 37 of 80 patients (46.2%) whose DA remained clinically significant after 2 courses of COI treatment. PDAs were ligated in 22 out of these 37 patients after the second course and the other 15 babies received a third course of COI. Among the 15 infants who received a third course, 6 (40%) closed their PDA and the remaining 9 infants underwent PDA ligation. Therefore, a total of 32/80 (40%) underwent surgical ligation of the PDA. Most of the ligations were performed in the second or third week of life.

Detailed analysis was done on those 112 patients who survived to discharge. The demographics of infants with vs those without hemodynamically significant PDAs are shown in Table 1. The babies with hemodynamically significant PDAs were less mature, had lower birth weights, higher CRIB II scores, higher OI, and received more fluid during the first 3 days of life. The overall outcomes for babies with hemodynamically significant PDAs were worse, as evidenced by an older age at extubation, reaching full enteral feeds later, and having a longer duration of hospitalization. Furthermore, the babies with hemodynamically significant PDAs had a higher incidence of CLD and ROP.

In order to ascertain whether these adverse outcomes in the babies with hemodynamically significant PDA might be

**Table 1 Demographics of the ELBW infants who survived to discharge**

	No PDA (n = 32)	PDA (n = 80)	P
BW, gm	815 (20)	753 (14)	0.015
GA, wks	27.3 (0.4)	25.2 (0.1)	< 0.001
Male Gender (%)	14 (44%)	38 (48%)	ns
CRIB II score	9.9 (0.4)	12.4 (0.2)	< 0.001
OI	3.1 (0.5)	4.2 (0.3)	0.033
Surfactant use	23 (71.9%)	77 (96.3%)	0.001
Intubated > 2 days	18 (56.3%)	71 (88.8%)	< 0.001
Fluid 1 <sup>st</sup> 3 days, ml/kg/d	102 (3)	113 (2)	0.045
CLD	10 (31.3%)	42 (52.5%)	0.042
NEC	3 (9.4%)	8 (10.0%)	ns
IVH III-IV	0 (0.0%)	6 (7.5%)	ns
ROP	6 (18.8%)	51 (63.8%)	< 0.001
Age at extubation, days	8 (3)	29 (4)	< 0.001
Age at full feeds, days	21 (1)	33 (2)	< 0.001
Age at discharge, days	83 (5)	105 (6)	0.041

**Table 2 Comparisons of the ELBW infants whose DA closed with 1<sup>st</sup> course of COI vs. who did not close with 1<sup>st</sup> course**

	Closed (n = 26)	Not Closed (n = 54)	P
BW, gm	764 (23)	749 (17)	ns
GA, wks	25.6 (0.2)	25.0 (0.1)	0.014
Male Gender (%)	14 (54%)	24 (44%)	ns
CRIB II score	12.0 (0.4)	12.6 (0.3)	ns
OI	3.4 (0.3)	4.5 (0.3)	ns
Age 1 <sup>st</sup> Dose, days	5.5 (0.8)	6.8 (1.4)	ns
Fluid 1 <sup>st</sup> 3 days, ml/k/d	114 (5)	113 (2)	ns
UOP before Rx, ml/k/h	3.7 (0.2)	3.9 (0.2)	ns
UOP during Rx, ml/k/h	3.3 (0.3)	3.2 (0.2)	ns
UOP after Rx, ml/k/h	3.3 (0.3)	3.2 (0.2)	ns

attributable to the pre-existing risk factors of lower birth weight, lower gestational age, higher CRIB II scores, and higher OIs in these infants, we performed a multivariable logistic regression analysis. Since both birth weight and gestational age are included in the CRIB II score, logistic regression with CLD as the clinical outcome adjusted for CRIB II and OI was performed. This analysis reveals an adjusted odds ratio for CLD in those with vs those without PDA of 1.10 (95% confidence interval [CI]: 0.37 – 3.30, P=0.867). Similarly, the adjusted odds ratio for ROP in those with vs those without symptomatic PDA is 3.20 (95% CI: 0.93 – 11.10, P=0.065). These data suggest that the observed difference in CLD and ROP in babies with hemodynamically significant PDA vs those without can be explained by the babies with hemodynamically significant PDA being less mature, having a lower birth weight, and being sicker as indicated by higher CRIB II scores and OI. Furthermore, multivariable regression analysis shows that a hemodynamically significant PDA did not add significantly to either CRIB II score or gestational age alone as a predictor of age at extubation or age at discharge. However, a multivariable regression analysis shows that the addition of a hemodynamically significant PDA to either CRIB II (R<sup>2</sup> increases from 0.176 to 0.234 by addition of PDA to the model, p=0.006) or gestational age (R<sup>2</sup> increases from 0.195 to 0.232 by addition of PDA to the model, p=0.025) improves a regression model for predicting age at full feeds. Presence of a hemodynamically significant PDA prolongs the time to full feeds by 8.0 ± 2.8 days in the multivariable model with CRIB II score and by 6.8 ± 3.0 days in the model with gestational age.

Among the 80 patients who received COI treatment for PDA, 26 (32.5%) infants closed their PDA after one course of COI. The comparisons of the infants whose DA closed with 1st course vs who did not close with 1st course are presented in Table 2.

**Table 3 Baseline characteristic of the ELBW infants whose DA was closed after 2nd course COI vs. those whose DA remained patent after 2nd course**

	Closed (n = 42)	Not Closed (n = 37)	P
BW, gm	777 (17)	724 (21)	ns
GA, wks	25.5 (0.2)	24.9 (0.2)	0.007
Male Gender (%)	23 (55%)	15 (41%)	ns
CRIB II score	12.0 (0.3)	12.9 (0.4)	ns
OI	3.7 (0.3)	4.7 (0.5)	ns
Intubated > 2 days	36 (85.7%)	34 (91.9%)	ns
Age 1 <sup>st</sup> Dose, days	5.6 (0.6)	7.3 (2.0)	ns

As shown in the Table 2, other than the babies whose PDA was closed with the first course of COI being slightly more mature than those whose PDA did not close, none of the factors that we examined distinguished infants who responded to one course COI vs those who did not.

The baseline characteristics of infants whose PDA closed with either one course or two courses of COI vs those whose DA remained patent after 2nd course of COI are presented in Table 3. The babies whose PDA closed with either one or two courses of COI were slightly more mature than those who had persistent hemodynamically significant PDA but were otherwise not different (we excluded the baby whose PDA was ligated after the first course of COI). As is shown in Table 4, the incidence of CLD in infants whose DA remained patent after two courses of COI was almost twice that of babies whose DA closed with either one or two courses of COI. Furthermore, logistic regression analysis shows that, when compared to those whose PDA was successfully closed with the first or second course of COI, after adjusting for CRIB II score, OI, intubation for more than 2 days, and culture proven later onset bacteremia, the odds ratio of having CLD for surviving babies with persistent hemodynamically significant PDA is 3.24 (95% CI: 1.07 – 9.81, p=0.038). Adding PDA ligation as a potential confounder did not improve the logistic model. These data demonstrate that failure of closure of PDA after 2 courses of COI is a significant risk factor for development of CLD in ELBW infants.

Table 5 shows a comparison of infants with PDA which closed with one (n=26), two (n=16), or three (n=6) courses of COI vs those who underwent surgical ligation after failure of one (n=1), two (n=22), or three (n=9) courses of COI. Other than the fact that babies whose DAs were ligated received more courses of COI, neither the risk factors nor the outcomes we examined distinguished the babies who underwent ligation from those who did not.

## Discussion

In this retrospective data analysis study, we found that less than one third of the ELBW infants who survived to discharge closed their DA spontaneously. The babies who had spontaneous closure of their DA were more mature, had a higher birth weight, and were less ill as indicated by lower CRIB II scores and lower OI. As compared to those who had a symptomatic PDA requiring treatment, the overall outcomes for the babies who closed their DA spontaneously were better, as demonstrated by a younger age at extubation, reaching full enteral feeds earlier, and having a shorter duration of hospitalization, and with lower incidences of CLD and ROP. These data are well known and consistent with numerous reports in the literature.<sup>3,16-18</sup> However, our analysis using multivariable logistic regression suggests that the observed difference in outcomes such as CLD and ROP in ELBW infants with a symptomatic PDA vs those without can be explained by the babies with a symptomatic PDA being less mature and sicker (by CRIB II and OI). Furthermore, regression analysis shows that a hemodynamically significant PDA as managed in our NICU does not add significantly to either CRIB II score or gestational age alone as predictors of age at extubation or age at discharge.

Recent papers have suggested that there is little evidence of benefit of closing a PDA in extremely preterm infant and that potential side effects and complications related to COI and surgery are significant.<sup>6,19</sup> However, in a recent study from Western Australia, where surgical ligation was not practical,

**Table 4 Outcomes of the ELBW infants whose DA was closed after 2nd course COI vs. those whose DA remained patent after 2nd course**

	Closed (n = 42)	Not Closed (n = 37)	P
CLD	16 (38.1%)	25 (67.6%)	0.013
NEC	5 (11.9%)	3 (8.1%)	ns
IVH III-IV	3 (7.1%)	3 (8.1%)	ns
ROP	27 (64.3%)	24 (64.9%)	ns
Age at extubation, days	27 (6)	33 (5)	ns
Age at full feeds, days	33 (2)	34 (2)	ns
Age at discharge, days	101 (4)	109 (13)	ns

persistent PDA when left untreated was associated with much higher mortality, even after adjustment was made for initial disease severity, gestational age and other perinatal factors.<sup>20</sup> In addition to their being a well accepted association between CLD and PDA, our data also suggest that it is beneficial for a hemodynamically significant PDA in ELBW infants to be closed. This evidence supports the current practice of closing all hemodynamically significant PDAs in ELBW infants.

The presence of a hemodynamically significant PDA prolongs the time to full feedings by approximately one week in the multivariable model with either CRIB II score or gestational age. This is not surprising since it was our practice to routinely withhold feedings in babies whom we treated for PDA. The practice of withholding feedings or not initiating enteral feeds in babies who are receiving COI was based mainly on the concern that use of indomethacin may increase the risk for spontaneous intestinal perforation.<sup>21</sup> Indeed, by using multivariate regression analysis and two different derivations with a national dataset, Attridge et al found significant associations between early use of indomethacin and spontaneous intestinal perforation.<sup>22</sup> However, they did not find an association with indomethacin when it was given after day of life four.<sup>22</sup> Therefore, withholding enteral feedings may not be necessary in extremely premature infants who are receiving COI treatment for PDA after day of life four.

**Table 5 Comparisons of ELBW infants with PDA closed by COI treatment vs. those with PDA who failed medical treatment and underwent surgical ligation**

	COI Only (n = 48)	COI & Ligation (n = 32)	P
BW, gm	772 (16)	726 (24)	ns
GA, wks	25.4 (0.2)	24.9 (0.2)	ns
Male Gender (%)	26 (54%)	12 (38%)	ns
CRIB II score	12.1 (0.3)	12.9 (0.4)	ns
OI	3.9 (0.3)	4.5 (0.5)	ns
COI courses	1.6 (0.1)	2.3 (0.1)	< 0.001
Age 1 <sup>st</sup> Dose, days	5.6 (0.6)	7.5 (2.3)	ns
CLD	21 (43.8%)	21 (65.6%)	ns
NEC	6 (12.5%)	2 (6.3%)	ns
IVH III-IV	4 (8.3%)	2 (6.3%)	ns
ROP	29 (60.4%)	22 (68.8%)	ns
Age at extubation, days	27 (5)	33 (5)	ns
Age at full feeds, days	33 (2)	34 (2)	ns
Age at discharge, days	102 (4)	110 (14)	ns

In our NICU, COI treatment was initiated relatively late as compared to other published studies, and this may explain our relatively higher failure rate of COI treatment for PDA. We do not routinely perform screening echocardiograms in all ELBW infants in our NICU. It has been shown that a conservative approach for PDA management was associated with decreased rates of surgical ligation without significantly increased morbidity in extremely premature infants.<sup>23</sup> In the current study, surgical ligation was reserved for PDA closure when treatment with COI failed or was contraindicated. No indomethacin was given within 48 hours of age as prophylaxis and most surgical ligation happened between 2-3 weeks of life. Complications of surgical ligation were not observed in our series. Recently, a few studies have reported that surgical ligation is a risk factor associated with CLD.<sup>13,24</sup> Whether this association is related to surgical ligation, the PDA itself, or just extreme prematurity has been a matter of debate among neonatologists. Although in our study no statistically significant difference was seen in the incidence of CLD in infants whose PDA responded to COI treatment versus those who failed and then underwent surgical ligation, our numbers are quite small. Interestingly, the incidence of CLD in infants whose DA remained patent after 2 courses of COI was almost twice that of babies whose DA closed with either the first or second course of COI. After adjusting for CRIB II score, OI, intubation for more than 2 days, and culture proven bacteremia, the odds ratio of having CLD in surviving babies with persistently hemodynamically significant PDA is still significantly higher when compared to those whose PDA was successfully closed with one or two courses of COI. This may suggest that the failure of closure of a PDA with a second course of COI rather than surgical ligation is a significant risk factor for developing CLD in ELBW infants.

Adding PDA ligation as a factor did not improve the logistic model for an adjusted odd ratio of having CLD in ELBW infants who did not respond to a 2nd course of COI. This may suggest that some intrinsic factors which cause the DA to fail to respond COI treatment may contribute to the pathogenesis of CLD. However, our study is limited due to its retrospective nature. Furthermore, due to the small number of patients in our study and the arbitrary nature of the decisions to pursue surgical ligation vs a third course of COI after failure of a 2nd course of COI, we cannot comment on the potential role of the third course of COI for closure of PDA and the role of surgical ligation in the development of CLD. Nevertheless, it may be beneficial to identify potential clinical factors that predict the failure of COI treatment for PDA to guide the clinical management of PDA in ELBW infants. Unfortunately, we, as well as others,<sup>25,26</sup> are unable to identify any clinical factors which can be reliably used to predict which specific infant will fail to close a hemodynamically significant PDA with COI treatment. More recently, it was demonstrated that using echocardiography to direct the use of COI may lead to fewer doses of COI for PDA closure in premature infants.<sup>27</sup> This approach requires the availability of frequent echocardiographic evaluation, which may be problematic in many neonatal intensive care units.

## Conclusions

In conclusion, 71.4% of ELBW infants who survived to discharge were diagnosed with hemodynamically significant PDA and received treatment. When treated, PDA in ELBW infants did not contribute significantly to adverse outcomes such as CLD, ROP and age at discharge, suggesting that it is beneficial for a hemodynamically significant PDA to be closed. The incidence



of CLD in infants whose DA remained patent after a 2nd course of COI was almost twice that of those whose DA closed with either one or two courses of COI. The adjusted odds of having CLD for surviving babies with persistent hemodynamically significant PDA is greater than three times that of babies whose PDA was successfully closed with either one or 2 courses of COI. Adding PDA ligation as a factor did not improve the logistic model for adjusted odd ratio of having CLD in those infants. This may suggest that persistent patency of the DA after two courses of COI rather than PDA ligation is a significant risk factor for developing CLD in ELBW infants. Due to small numbers of infants who responded to a third course of COI and the lack of obvious benefit, we can not draw any conclusions regarding to the use of third course COI in ELBW infants with hemodynamically significant PDA who failed the 2nd course of COI. The identification of reliable factors or biomarkers to guide the use of COI<sup>28</sup> or surgery may ultimately improve the outcomes of ELBW infants with hemodynamically significant PDA and should be the direction of future studies.

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# Wharton's Jelly Obtained by Umbilical Cord Biopsy — Preliminary Results

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## Introduction

The practical definition of a stem cell is the functional definition, the ability to regenerate tissue over a lifetime. For example, the gold standard test for a bone marrow or hematopoietic stem cell (HSC) is the ability to transplant one cell and save an individual without HSCs. In this case, a stem cell must be able to produce new blood cells and immune cells over a long term, demonstrating potency. It should also be possible to isolate stem cells from the transplanted individual, which can themselves be transplanted into another individual without HSCs, demonstrating that the stem cell was able to self-renew.

Recent reports on trans-differentiation of mononuclear cells derived from human umbilical cord into neural cells aroused great interest among investigators. Lian et al<sup>1</sup> reported their experience with human umbilical cord Wharton's jelly derived mesenchymal stem cells differentiation into nerve-like cells. They found that mesenchymal stem cells from Wharton's jelly could proliferate 4 to 5 times in 3 to 5 days. These proliferated cells were mainly elongated fibroblast-like cells with or without branching, very similar to the stem cells from the bone marrow. These results were consistent with a previous report showing Wharton's jelly derived stem cells could self-replicate, and differentiate into multiple cell types under appropriate induction conditions.<sup>2</sup>

Given this potential growth, Wharton's jelly could be more feasible for cell transplantation, and also could represent a less invasive more economical source of stem cells compared with bone marrow.<sup>3,4</sup>

## Materials and Methods

Prior to entering into the study, mothers gave written consent. To exclude effect of stress of labor, patients were consented in the prenatal clinic, before hospital admission for labor.

Patients having a full term birth either by a vaginal delivery or a cesarean section were enrolled in the study. Exclusion criteria consisted of cord blood donors, patients in active labor or preterm labor, placental malformation, umbilical cord malformation, choreoamnionitis, documented viral infections (HIV, Hepatitis B, Hepatitis C).

After delivery of the newborn and delivery of placenta the umbilical cord was assessed. Immediately after clamping the umbilical cords of 6 full term babies the intervacular gelatinous substance (Wharton's Jelly) was identified and sampling performed at the placental end of the cord with a baby biopsy punch (Cooper Surgical, Trumbull, CT). Collected material was diluted with RBC lysis buffer and transferred to a 50 ml conical tube. Cells were pelleted by centrifugation at 1500 rpm for 10 min. The interphase layer containing stem cells was collected and washed twice with PBS/1% BSA. Cells were counted using a Coulter Counter and cell viability was assessed by Trypan blue exclusion. Sample sizes and the amount of biopsy site bleeding was assessed.

## Results

Successful sampling was performed in all 6 umbilical cord samples. The size of tissue removed varied from 1.5 to 3mm<sup>3</sup> depending on the size of punch biopsy forceps. Bleeding was minimal in 5 cases and excessive in only one due to the involvement of umbilical cord vessels.

## Discussion

Wharton's Jelly is a gelatinous substance found within the umbilical cord as a mixture of water, gelatin, lipids, proteins, and enzymes. Wharton's jelly is a rich source of stem cells, fetal specific proteins, fatty acids, and phospholipids, among other components. It provides protection to the blood vessels in the umbilical cord. It is named for an English physician and anatomist Thomas Wharton (1614-1673) who first described it in his publication *Adenographia* or "The Description of the Glands of the Entire Body," first published in 1656. In general, dry Wharton's jelly is a composition of acid mucopolysaccharides (35%), gelatin (25%), hyaluronan (15%), fetal-specific proteins and enzymes (gelatinase A-metalloproteinase (MMP)—2,72 KD and gelatinase B (MMP)—9,92 KD. It also contains a small amount of lipids (phospholipids and glycolipids).

Wharton's jelly stem cells should be distinguished from umbilical cord stem cells. The concept of using umbilical cord blood as a source of stem cells has been proposed for many years.<sup>5-8</sup>

Though stem cells obtained from the umbilical cord blood is easy it does have some disadvantages. Morseix summarized these disadvantages of cord blood for stem cell retrieval with the following:

- Unable to obtain additional "donor" cells, after the initial samples, for leukocyte infusion or second transplants

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- Small volume
- Fewer total HSCs available due small volume
- Slower engraftment
- High up-front cost due to need for large inventory
- Short shelf life because units may become “outdated” due to changes in blood banking standards.

Mitchel et al and Wang et al were one of the first to show the potential of Wharton's jelly as a source of stem cells.<sup>10,11</sup> Bakhshi et al isolated and cultured mesenchymal stem cells from umbilical cord segments dissected after birth. These stem cells were grown in cell culture and allowed to divide and replicate. Morphology was documented and cell surface markers were determined by flow cytometry.<sup>12</sup> While Wu et al used Wharton's jelly derived stem cells to repair damaged rat hearts.<sup>13</sup> However, all of these studies used the whole umbilical cord to obtain the stem cells. Our study shows it is feasible to obtain stem cells from Wharton's jelly in a more economical manner using a biopsy punch.

We had previously explored the Wharton's jelly potential as a source of stem cells (unpublished data). Of particular significance is the preliminary data shows Wharton's jelly components may be used not only to affect apoptosis, but more importantly metoptosis.

Resulting from this feasibility study we are now using our experience with Wharton's jelly sampling to obtain tissue for potential stem cell and protein, retrieval in vivo. With encouraging preliminary results we are in the process of developing a working protocol for using Wharton's jelly biopsy derived tissue as a source of mesenchymal stem cells.

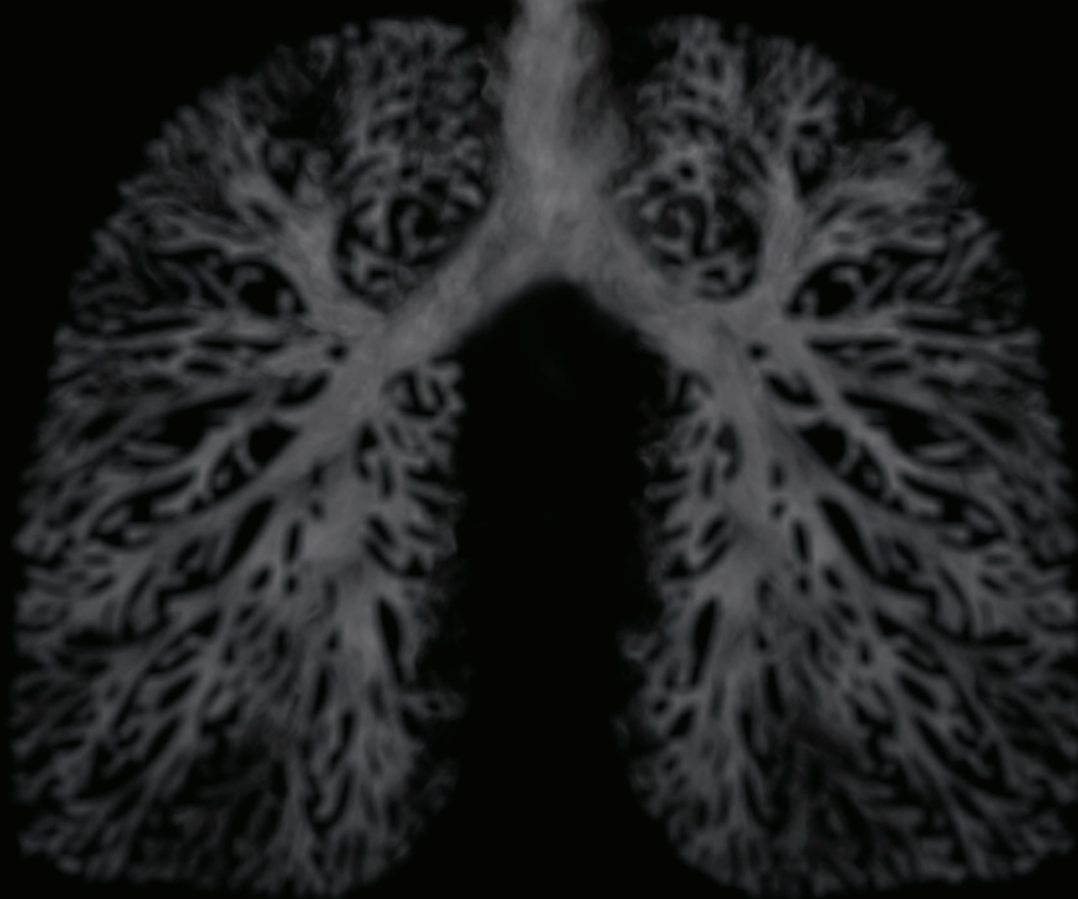
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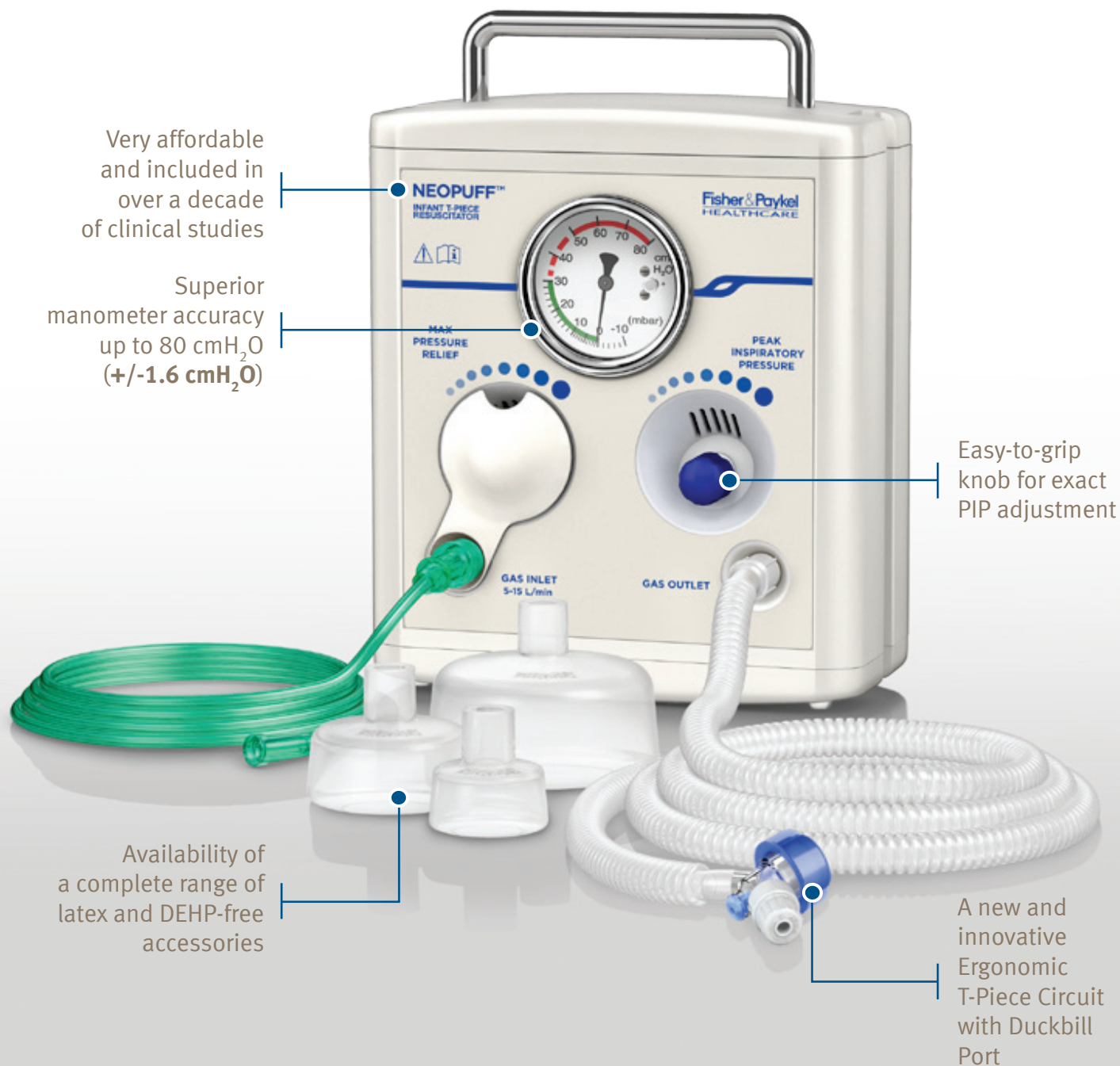
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