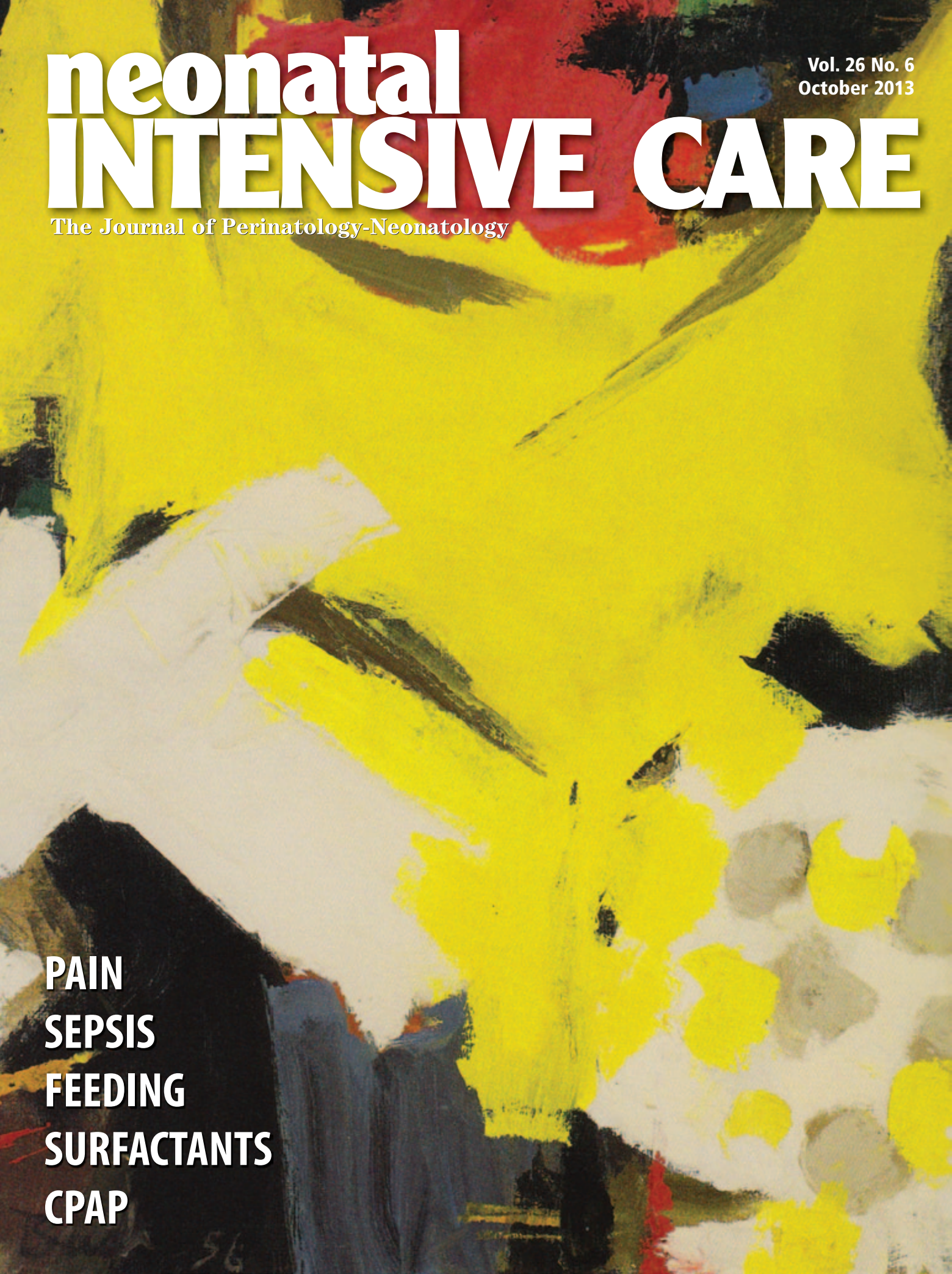
Vol. 26 No. 6
October 2013

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology



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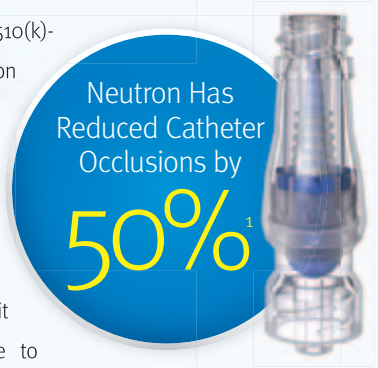

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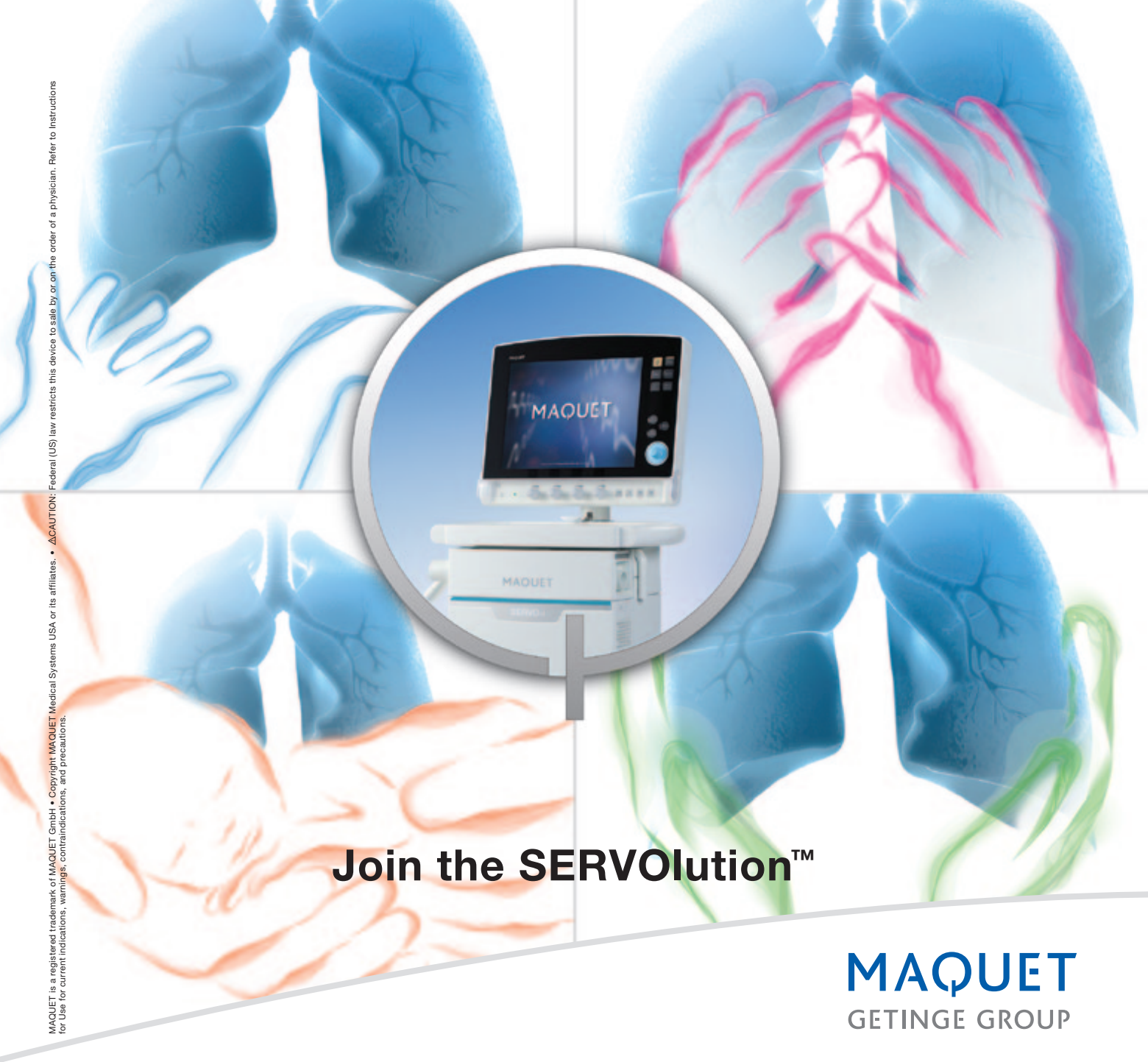

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Editorial Advisory Board

Effects of the ACA

While we've discussed some onerous aspects of Obamacare as it may affect companies, especially smaller ones, that make products for the neonatal/perinatal marketplace, there's also ample evidence that implementation of the act is likely to be a boon for babies and moms.

With the Affordable Care Act launching this month, we looked at its ramifications for neonatology and perinatology.

A good place to begin is to see what the American Pediatric Society has to say about it. The APS website states: "'Neonatologists Must Sign Up for Medicaid Payment Increase' — The Affordable Care Act includes a historic investment to expand access to health care for children, and we want to make sure you know about it. The ACA requires states to increase Medicaid payment for certain 'primary care' Evaluation and Management codes (CPT 99201-99499) and vaccine codes to Medicare rates for services rendered in CYs 2013 and 2014. An American Academy of Pediatrics (AAP) analysis of billing data estimates that pediatric neonatologists stand to receive an average 42.5 percent increase in Medicaid revenue as a result of the increase." For more see: http://www.aap.org/en-us/advocacy-and-policy/state-advocacy/Pages/Medicaid-Payment-Increase.aspx.

Here are some of Obamacare's features as it applies to pregnancy and related infant and family services. (It should be noted that some of these features apply, for the time being, only to new plans created since March 23, 2010. Others will follow.) The information below is from babycenter.com.

Health insurance companies must provide an easy-to-understand summary of benefits and coverage, using a standard form for comparison. States must provide consumer assistance. Coverage can't be dropped for paperwork mistakes; children can't be denied coverage because of a preexisting condition. New plans allow beneficiaries to choose a pediatrician from a given health plan's provider network. New plans allow moms to see an oby-gyn without a referral and have to allow for seeking emergency care at a hospital outside the plan's network without prior approval.

The ACA offers various preventive care services that the new plans have to fully cover, including contraception, folic acid supplements, HPV DNA testing for women over 30, STI screening, preconception and prenatal care, alcohol and tobacco counseling, Rh compatibility screening, iron deficiency anemia screening, gestational diabetes screening, screening for infections that can affect babies, and breastfeeding support, supplies, and counseling.

For newborns the ACA offers gonorrhea preventive care for the eyes, screening for congenital hypothyroidism, hearing problems, PKU, and sickle cell anemia. For all kids the act provides for immunizations, fluoride supplements, iron supplements, lead screening, autism screening, TB testing and dyslipidemia screening.

Looks good — if it delivers.

Les Plesko, Managing Editor

News

☐ October 2013

PAY RAISE

Neonatologists registered the biggest increase in pay among the 23 specialties tracked in the 20th annual Modern Healthcare Physician Compensation Survey. Crain's Detroit Business reported: "This year's survey saw more ups than downs and, according to the 13 recruiting firms and professional associations providing data, neonatologists' pay ranged from $246,003 to $328,819 and increased an average of 11.9% to $295,416 from $264,015 the previous year." However, Crain's quoted a professor of pediatrics as noting, "For physicians in academic practice, more and more compensation is being siphoned off to support other aspects of [a] university's mission… Billings may be up, collections may be up, but academic physicians are not seeing these large increases." Crain's also noted that an aging workforce, a declining birth rate and a consolidation of healthcare organizations will lead to a "re-regionalization of the neonatology field, with fewer small departments in community hospitals."

CAN'T BE TRUSTED

Jordan Robertson reports for Bloomberg News that electronic health records have created problems, and cited a case where a medication dropped out of an elderly patient's record, and its absence caused her death. Robertson writes that the FDA has found that that dangerous doses of drugs have been given because of confusing drop-down menus; patients have undergone unnecessary surgeries because of incorrect info, and computer network delays in sending medical images have resulted in serious injury or death. According to a study by the Pennsylvania Patient Safety Authority, the number of medical error reports doubled between 2010 and 2011, to 1,142, with 3,099 registered over an eight-year period. Yet converting to such records is now mandatory. The market generated $24.2 billion last year. On the plus side, Robertson notes, more than 17 million medication mistakes are now avoided in the US each year because of prescription-ordering systems. On the downside, by way of anecdotal example, nurses at a California hospital complained that an EMR system was causing medications to be ordered for the wrong patients. In one month, 129 complaints were filed by nurses at county detention facilities, where the problems were most acute. Software companies don't have to report malfunctions to the FDA, even if they result in serious injuries or death. According to the Office of the National Coordination for Health Information Technology, part of the HHS, there's no evidence of safety problems associated with electronic records. The most dangerous time for patients as regards electronic records errors, is when the software is initially installed. In the first five months when a system was installed at Children's Hospital of Pittsburgh, mortality rates increased to 6.6%, up from 2.8% for the previous year. Delays were said to be

a contributing factor, a major issue being the number of clicks required to submit prescriptions, and restrictions imposed by the software about when doctors could order medications for new patients.

WHILE WE'RE ON THE SUBJECT

Dr Douglas Farrago writes on his website, Authentic Medicine: "Ready for the new controversy in healthcare? Before electronic medical records took over there was a criticism of doctors that they didn't put enough information or documentation in the patient's chart for each visit. This was really for billing and coding purposes and in no way reflected reality or the work doctors did with a patient. Doctors were punished for this by not being able to bill as much for each visit. With the advent of the EMR or EHR there came an advantage to the new technology. It made it easier to code each visit and get an optimal reimbursement. Of course, no advantage can ever go to the physicians so that will have to stop as well. In a new American Medical News article, they list how the Centers for Medicare & Medicaid Services are now scrutinizing the accuracy of physician documentation for those who use the features of electronic health record systems to support their billing. 'Auditors and lawmakers have suggested that recent increases in the rates at which doctors bill costlier, higher-level services could be attributable to the enhanced billing capabilities provided by EHRs.' We are damned if we do and damned if we don't! The whole thing is a stupid cat-and-mouse game anyway. Coding and billing and auditing are creations of the insurance companies who want to screw docs out of payment. Any benefits given to the physicians will soon be removed by the all powerful insurers. And the worst part is that none of it means anything to patient care. That is why a 'monthly membership' model without billing a third-party would remove all this. Without the risk of auditing the only thing that would be placed in the chart is the basic SOAP note and those things pertinent to the patient's care."

DISCHARGE TRANSITION

NANN announced the addition of its newest Special Interest Group (SIG), Discharge Transition. Chaired by Arlene Lovejoy, MS RNP CNS RNC-NIC C-NPT, the purpose of this SIG is to examine, assess and educate on the systems, processes and psychosocial impact of transitions from the acute care setting of the neonatal patient/client and his/her family into ambulatory care settings. The SIG will also investigate and establish best practice recommendations for these transitions for health care practitioners and the home caregivers. Contact nann.org.

HACK ATTACK

Dina Fine Merin, writing in Scientific American, said medical device makers need to protect their products from cyber attacks, especially since many medical devices are connected to the internet. The Department of Homeland Security said hard coded passwords that allow techs to gain access to multiple machines leaves these products vulnerable to unauthorized hackers. DHS singled out 300 devices, including drug infusion pumps, ventilators and external defibrillators, and the agency said it knew of hundreds of devices that have been affected by vulnerabilities or "incidents." Devices that run on Windows XP may also be affected by typical viruses common to home and office users. Merin noted that the Department of Veterans Affairs have reported 327 incidents, and though these didn't harm any patients, they created problems for patients and cost hospitals money. For instance, Merin wrote, "One such incident occurred in 2010 when the Conficker computer worm infected an entire sleep lab at a VA hospital. All the patients had to be rescheduled… and the manufacturer had to reformat all the devices, at a cost to the hospital of about $40,000." Conficker can also expose patient data and passwords. Malware can slow down devices or disable them. The FDA has issued guidelines that urge device makers to address potential problems before they occur. However, Merin pointed out that installing patches to fix software security creates potential problems as well, and companies who have secured their equipment are loathe to admit it, lest hackers take these claims as a challenge.

PERINATAL SAFETY

Joint Commission Resources announced the release of the August 2013 issue of The Joint Commission Journal on Quality and Patient Safety, which features an article on how the Minnesota-based Fairview Health Services hospital system reduced its rate of adverse outcomes related to births by a mean of 11% over three years, resulting in substantial reductions in costs. In "A Perinatal Care Quality and Safety Initiative: Are There Financial Rewards for Improved Quality?" Katy B. Kozhimannil, PhD, MPA, and her co-authors describe Fairview

Health Services' establishment and use of a Zero Birth Injury (ZBI) initiative between 2008 and 2011 to increase perinatal safety and quality in all six of its hospitals. The foundation of the ZBI initiative was developed using evidence-based practices recommended by the Institute for Healthcare Improvement (IHI) and was supplemented through participation in the Premier Perinatal Safety Initiative, which provided access to additional quality metrics and lessons learned. As a result of reducing the adverse events, the hospital system saved $284,985 in costs; but it earned $324,333 less revenue, for a net financial decrease of $39,348 (or a $305 net financial loss per adverse event avoided). "Our findings highlight the need for payment systems that align incentives between patients, providers, and payers to improve care and financially reward, rather than penalize, the health care delivery systems that produce quality improvements," said Kozhimanill. "Changes under the Affordable Care Act, such as Accountable Care Organizations and other shared-savings plans, may provide a foundation for transforming perinatal care payments." Contact jrcinc.com.

CRACK

Katie McDonough at the website Salon.com, writes that "after nearly 25 years of research, one of the nation's largest long-term studies on the so-called 'crack baby' epidemic of the 1980s has concluded that there are no statistically significant differences in the long-term health and life outcomes between full-term babies exposed to cocaine in-utero and those who were not… Researchers found poverty to be a key determining factor in how well children performed later in life." The study was undertaken at Albert Einstein Medical Center. McDonough notes: "While the cocaine-exposed children and a group of non-exposed controls performed about the same on tests, both groups lagged on developmental and intellectual measures compared to the norm."

SPIKE

Washington State authorities have noted an unexplained rise in the rate of anencephalic pregnancies over the last three years, according to an article in the Daily Mail. The nationwide rate of anencephaly is 1 to 2 per 10,000, but it's 8 to 10,000 in Washington. The CDC looked at family history, weight, behavior, use of medication, and source of drinking water among pregnant moms, but found no differences between moms who had anencephalic babies and other moms.

GENTLER IVF

The website Raw Story's David Ferguson reported that a team of doctors at the Imperial College in London announced the birth of a baby boy born through the use of a new in-vitro fertilization technique that they hope will prove to be gentler and safer for women hoping to become pregnant. According to NewScientist.com, researchers are experimenting with the hormone kisspeptin, which helps women ovulate without the side effects and risks associated with current methods. The current practice is to give a woman the hormone hCG, which causes ovulation, and the eggs are gathered surgically, fertilized in the lab, and implanted in the woman's uterine wall. This process can cause ovarian hyperstimulation syndrome in a third of women undergoing IVF. Kisspeptin is said to reduce the risk of OHSS.

TAKE IT TO HEART

Pediatric surgeons are using the body's regenerative powers to treat babies born with hypoplastic left heart syndrome.

Ron Winslow, writing in the Wall Street Journal, reported that doctors at Boston Children's Hospital have fixed the hearts of 13 kids so far. Meanwhile, at the Mayo Clinic, doctors are looking at ways to boost the functioning of the right ventricle, in the absence of the left one. Doctors surmised that if they could unblock valves affected by the defect, they could restore blood flow and cause the ventricle to grow. In the surgeries, doctors cut away fibrous tissue that builds in the left ventricle due to lack of sufficient blood flow. This clearing of tissue unleashed the ventricle's growth potential. This approach has rehabilitated the left ventricle in about one-third of cases. At the Mayo Clinic, the focus is on making the right ventricle stronger. Umbilical-cord blood cells are harvested at birth and processed to separate out stem cells, which are then frozen. The infant undergoes the first surgery shortly after birth. If all goes well, the stem cells are injected directly into the heart during the second operation four to six months later. The process could be applied to growing left ventricles as well. Seeding a rehabilitated left ventricle with stem cells could ultimately enhance the chances of success for that approach.

OUTGOING BREASTFEEDERS

Mothers who are more extroverted and less anxious are more likely to breastfeed and to continue breastfeeding than those who are introverted and nervous. Researchers at Swansea University in the UK surveyed 602 mothers with infants aged six to 12 months. The questionnaire examined the mothers' personalities, how long they breastfed, and their attitudes and experiences of breastfeeding. The stable extroverts were significantly more likely to initiate and keep on breastfeeding, while introverts felt more self-conscious about breastfeeding in front of others and believed people wanted them to formula-feed.

BBB-BREASTFEEDING

Among kids who stutter, breastfed kids recovered earlier. Researchers at the University of Illinois and Illinois State studied 47 children. Boys, who stutter more, benefited the most. If they breastfed for more than a year, they had one-sixth of the odds of developing persistent stuttering. Earlier studies have already found an association between breastfeeding and language development. Researchers said the connection may be that long-chain fatty acids in human milk play a role in the development of neural tissue, and differecnes in neurodevelopment could cause subsequent difficulties in speech fluency.

THE PREBIRTH OF STRESS

Harvard researchers found that epigenetic disruptions are already common at birth and that these aberrations result from stressors in the intrauterine environment, such as maternal smoking, diet, or the presence of endocrine-disrupting chemicals. As such, they posited that epigenetic mechanisms contribute to chronic disease susceptibility before birth. The researchers examined the expression pattern of imprinted genes important for growth and development and analyzed the parental expression pattern in the cord blood and placenta of more than 100 infants.

KEEP PARENTS INFORMED

April Dworetz, an assistant professor of pediatrics specializing in neonatology at Emory University wrote in the New York Times: "I am a neonatologist. I save babies. Most of them, especially those born after 28 weeks, will at most suffer mild or moderate disabilities. But of those born before 28 weeks — 30,000 of the half million babies born prematurely each year in this country — many will have serious physical, social or cognitive problems. Consider that a one-pound, one-ounce girl born unexpectedly at 23 weeks' gestation has a 92 percent chance of dying early or having moderate to severe neurodevelopmental impairment… A few months ago I cared for just such a child. Let's call her Miracle. She was born at 23 weeks' gestation and weighed a little over a pound. Despite the bleak prognosis, her parents asked that we resuscitate her in the delivery room. So we did. But over the next eight weeks, to keep her alive, we had to prick Miracle's heel so many times she developed scarring. We suctioned her trachea hundreds of times. We put tubes through her mouth and into her stomach, we stabbed her again and again to insert IVs, and we took blood from her and then transfused blood back. We gave her antibiotics for two severe infections. Each of these events created suffering, for Miracle and her parents. Her mother visited daily and developed an anxiety disorder. Her father came in only once a week, the pain and sadness was so great. After eight weeks, Miracle came off the ventilator we had put her on. But three days later we had to turn it back on, and it was possible she would die or remain on the ventilator permanently if we didn't give her steroids, which can

have side effects as serious as cerebral palsy. Her mother opted for the steroids. But Miracle's father was angry. He muttered to me: "Why do you do this? Why do you keep these babies alive?" I've been thinking about that question for decades and haven't found a simple answer… Ultimately, parents have the right to decide, but we physicians must help them make informed decisions. I asked Miracle's father whether anyone had talked to him about resuscitating Miracle before she was born. He vaguely remembered a conversation, but hadn't understood what treating such a tiny premature baby meant. And nobody talked to him after Miracle was born about continuing life-sustaining treatment. In fact, he had gotten to her two-month birthday without realizing that her suffering might end in death. We had updated his wife, but she didn't like to hear bad news, and didn't tell him… We need to make sure both parents are always kept part of the discussion, to ensure we have their informed consent throughout treatment. It can't be just one conversation… Sometimes, I think we doctors need to do more than inform. On occasion, I've offered to make a life-or-death decision for parents. If they agree, they are essentially making the decision, but are shifting the burden to me. It's harder for parents to say, 'I unplugged my baby,' than to let the doctor do it… In my world, though, the 'surrogate' decision makers are young parents of infants like Miracle. And they are still completely unprepared. It's time we broaden the discussion to include them." [The baby lived, though it has chronic lung disease. This item has been edited.]

ABORTION LINK

The website Science Daily reported via Daily Kos that the link between abortion and preterm delivery in a subsequent pregnancy has disappeared over the last three decades. According to a study at the University of Cambridge, abortion was a strong risk factor for subsequent preterm birth in the 1980s but over the link progressively weakened and was no longer present. The likely reason is a change in methods of abortion. The authors found that the procedure thought most likely to be lead to an increased risk of preterm birth was surgical abortion without the use of drugs, and that this method dropped to being used in 0.4% of abortions by 2008. Also, abortions that did not involve any surgery rose to 68%.

TOP-RANKED

California Hospital Medical Center (CHMC) has exceeded all expectations in achieving outstanding outcomes for neonatal morbidity and mortality. The downtown Los Angeles hospital ranks among the top three in the state of California according to a recent report from the Community Perinatal Network (CPN), a nonprofit organization dedicated to promoting optimal perinatal care for patients and families statewide. CHMC is the 13th largest center for births in the state. The accomplishment is all the more impressive considering the risk factors of the hospital's patient population. "Our patient population risk factors for perinatal morbidity and mortality are three times higher than the general childbearing population, yet we have a 50 percent lower neonatal morbidity and mortality rate when compared to the state," explained Pat Stone, Chief Nursing Executive at CHMC. CPN reports that 77% of all patients who delivered at CHMC in 2009 were Hispanic. However, nearly 20% were African American — an increase that is noted because the chance of death or severe illness is three times higher in the African American population than that of the general child-bearing population.

PERILS OF YOUR PEERS

BioMed Central's new online journal Biome recently published an editorial about peer review by Gregory Petsko. Here are the highlights: "Increasing frustration with a peer review process that sometimes seems to reflect all the civility of being thrown to the lions in the Coliseum has led to a flood of commentaries with suggestions for reform. These range from a restrained comment from Raff et al in Science, in which they point out that getting experimental work published can take as long as or longer than doing the work in the first place, and that the extra experiments demanded by referees frequently only strengthen the conclusions marginally, to an invective against the tyranny of reviewer experiments (sic) in which Hidde Ploegh makes similar points in Nature. Current in many labs is a spoof carol with the first line 'Wreck their scrawls with caustic volleys,' sung to the tune of to the tune of 'Deck the Halls'. Suggestions for reform include Virginia Walbot's comment on how to train postdocs not to be pit-bull reviewers and, among many others, the publication policy of eLife, whose stated raison d'etre is to change the peer-review process, as well as the policy operated by BMC Biology, whereby authors may opt out of re-review after revision of their papers. It could reasonably be argued that none of this would ever have become necessary had the scientific community not lost sight of the fact that the responsibility of a reviewer is to review the paper as written, not to redesign the science the way he or she believes it should have been done. As Bob Horvitz has neatly put it: '…what is in the paper is fundamentally the responsibility of the authors, not of the reviewers.' Furthermore, journal editors should be willing to disregard unreasonable requests from reviewers, and not act as though the role of the journal was to set the direction of science and micromanage its conduct. Editors need to be more responsible, and journal policies could use improvement, but arguably the problem with peer review can only be fixed by an attitude adjustment on the part of reviewers: a recognition that follow-up and confirming experiments belong in future papers, combined with a humility that eschews showing off in favor of actually doing one's job. As Walt Kelly's philosophical possum Pogo so eloquently put it, 'We have met the enemy, and he is us.'"

CARDIAC OUTPUT MEASUREMENT

A paper by Noori, Drabu, Soleymani and Seri reported that cardiac output can be continuously and non-invasively estimated in neonates by electronic velocimetry (ICON and AESCULON, Cardiotronic, Osypka Medical), and found that EV is comparable with echocardiography for estimating cardiac output.* Published in Archives of Diseases in Childhood, the paper is titled "Continuous non-invasive cardiac output measurements in the neonate by electrical velocimetry: a comparison with echocardiography." According to the abstract: Electrical velocimetry (EV) is a non-invasive method of continuous left cardiac output monitoring based on measurement of thoracic-electrical bioimpedance. The objective was to validate EV by investigating the agreement in cardiac output measurements performed by EV and echocardiography. In the prospective observational study, left ventricular output (LVO) was simultaneously measured by EV (LVO_{ev}) using AESCULON (Cardiotronic, Osypka Medical) and by echocardiography (LVO_{echo}) in healthy term neonates during the first two postnatal days. To determine the agreement between the two methods, the researchers calculated the bias (mean difference) and precision (1.96×SD of the difference). As LVO_{echo} has its own limitations, the authors also calculated the "true precision" of EV adjusted for echocardiography as the reference method. The authors performed 115 paired measurements in 20 neonates. LVO_{ev} and LVO_{echo} were similar (534±105 vs 538±105 ml/min, p=0.7). The bias and precision of EV were -4 and 234 ml/min, respectively. The authors found the true precision of EV to be similar to the precision of echocardiography (31.6% vs 30%, respectively). There was no difference in bias and precision between the measurements obtained in patients with or without a hemodynamically significant patent ductus arteriosus. The authors concluded that EV is as accurate in measuring LVO as echocardiography and the variation in the agreement between EV and echocardiography among the individual subjects reflects the limitations of both techniques. * Noori S, Drabu B, Soleymani S, et al. Arch Dis Child Fetal Neonatal Ed (2012). doi:10.1136/archdischild-2011-301090, Produced by BMJ Publishing Group Ltd (&RCPCH under license), © BMJ Publishing Group Ltd.]

PRODUCTS

A MAJOR LEAP

Respiralogics' new **baby** line represents a major leap forward in the delivery and maintenance of nCPAP and noninvasive ventilation for infants in the NICU and PICU by providing comfortable, secure and skin-friendly fixation. Clinicians' experiences and critical eye were integral in the design and development of the **baby** products, which were developed after listening to many a clinician's frustration with current products. The new Respiralogics line includes: Baby Nose Bumper and Circuit Bumpers for the baby who Just Wants To Have A Pretty Nose after therapy is complete. The skin-friendly Baby Nose Bumper "mustache" is made of RespiraGel, Respiralogics' new

hydrocolloid-based adhesive. Baby Nose Bumper gently holds the nasal interface to the mustache-area, providing a secure grip and gentle cushion for the nares. Circuit Bumpers provide a cushion for the breathing circuit by gently attaching the inspiratory and expiratory limbs to the Baby Cap. Baby Nose Bumper and Circuit Bumpers allow ideal fixation and comfort of the patient interface. Baby Cap is for the baby who Just Wants A Soft, Comfortable Cap. Baby Cap holds the nasal prongs and circuit in place, providing optimal fixation for infant nCPAP and NIV. The inspiratory and expiratory limbs are secured to the Baby Cap with Circuit Bumpers. Baby Chin Strap is for the babies who Just Can't Keep Their Mouth Closed. Baby Chin Strap is a single patient use device intended to help keep small patients' mouths closed during delivery of nasal CPAP and NIV. Baby Chin Strap provides support with a soft, skin-friendly strap placed under the chin and secured to the Baby Cap with hook and loop tabs. Baby Chin Strap is a comfortable solution for mouth leaks. It adjusts to provide the support needed to easily close the mouth. [RespiraGel, Baby Cap, Baby Nose Bumper and Baby Circuit Bumpers and Baby Chin Strip are trademarks of Respiralogics.] Contact respiralogics.com.

BIRTH CENTER

Austin's OBGYN North announced that its new birth center, Natural Beginning, will operate alongside OBGYN North's 31 year old practice. Natural Beginning will operate in conjunction with OBGYN North. The birth center will have three rooms available for laboring women, each with a SaniJet birthing tub and queen-sized bed. It will be staffed by certified nurse midwives and registered nurses on-call 24 hours a day, 365 days a year. All of Natural Beginning's midwives will be certified nurse midwives (CNM), meaning they have completed a masters degree in nursing with a specialty in midwifery. This allows Natural Beginning's midwives to be credentialed at the hospital as well, and to continue their patients' clinical care if transfer to the hospital should become necessary. Another feature unique to Natural Beginning will be the use of nitrous oxide for laboring women who request it. Natural Beginning will be the only birth center in Texas to use nitrous oxide. As of 2010, it was only used in two hospitals in the United States. Patients of OBGYN North and Natural Beginning will have the opportunity, at the beginning of their pregnancy, to decide whether they would like to birth at St David's North Austin Medical Center within the Women's Center of Texas or at the birthing center. Contact obgynnorth.com or natural-beginning.com.

MEDAL WINNER

Fisher & Paykel Healthcare was recognized recently for Optiflow Junior, its new nasal cannula designed specifically for infant and pediatric patients, with a silver award at the prestigious Medical Design Excellence Awards. The award is further recognition of the company's customer-led design processes. The Medical Design Excellence Awards (MDEA) are the medical technology industry's premier global awards and are judged by a multidisciplinary panel of independent jurors comprised of a balance of clinicians, engineers, and designers. Optiflow Junior was first released to market in March 2012 following years of engineering and development which included significant in-hospital customer research. Optiflow Junior is a revolutionary system for

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* Mireles-Cabodevila, E., Hatipoğlu, U., & Chatburn, R. L. (2013). A rational framework for selecting modes of ventilation. Respiratory Care, 58(2), 348-366.

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providing simple and effective delivery of oxygen therapy to infants in respiratory distress, and combines an anatomically contoured nasal cannula with optimally humidified flow. It is a high performance product that responds to requirements from parents, nurses and doctors — flow delivered through soft anatomical prongs, ease of use with a patented Wigglepad system which enables easy re-application, adjustment and maintenance, and longer circuits and a clothing clip that enables improved mother child bonding and feeding. The result is a cannula that is loved by clinicians, parents and babies. Contact www.fphcare.com.

ADVANCED SUPPORT

Dräger demonstrated its new AutoBreath technology at the 2013 AWHONN Conference. AutoBreath automates the neonatal resuscitation process, allowing clinicians to set and deliver consistent BPM, PIP, FIO2, PEEP, and LPM — which can contribute to a decrease or elimination of potential hazards such as air trapping, hemodynamic insult, and inadequate ventilation. Dräger offers AutoBreath as an advanced respiratory support option of the Resuscitaire Radiant Warmer. AutoBreath allows for matching ventilation rates with the recommended clinical protocols and guidelines for neonatal resuscitation. Because it eliminates inconsistencies in care caused by fatigue and different levels of clinician experience, AutoBreath supports more consistency in care across shifts. When using the AutoBreath feature, clinicians can use two hands to provide a better seal, which may reduce air leakage from the face mask. Contact draeger.com.

NOW AVAILABLE

GN Otometrics announced that the MADSEN Capella^2 is now available for sale in the United States. Designed for otoacoustic emission (OAE) testing, the Capella^2 is a result of a technology partnership between Intelligent Hearing Systems, a recognized leader in clinical OAE, and Otometrics, the leader in clinical usability. Capella^2 allows clinicians to conduct an objective and accurate analysis of cochlear function for all age groups. The user interface of the Capella^2 is integrated into the OTOsuite software and incorporates a functionality that exceeds other OAE systems available in the market today. As with other clinical tools within OTOsuite, clinicians can continue to provide their patients with the best possible care without compromising workflow efficiency. Contact otometrics.com.

INSTALLED IN ALL

University Children's Hospital Basel in Basel, Switzerland, and Masimo announced that the hospital has become the first multi-department pediatric facility in Central Europe to install on all general ward beds Masimo Patient SafetyNet, a remote monitoring and clinician notification system shown to keep patients safer, enabling a 65% reduction in rapid response team activations and 48% reduction in ICU transfers. The installation at the University Children's Hospital Basel — Universitats-Kinderspital Beider Basel (UKBB) — took place after an extensive evaluation process resulting in the organization's standardization to Masimo SET pulse oximetry. UKBB joins a growing list of prominent health systems around the world using Patient SafetyNet, which combines the performance of Masimo SET pulse oximetry, the enabler of reliable monitoring in the general ward, with ventilation monitoring and wireless clinician notification. Patient SafetyNet can help ensure patients' safety by noninvasively and continuously measuring and tracking their underlying physiological conditions and changes that signal declining health status in real time. When changes occur in the measured values, which may indicate deterioration in the patient's condition, the system automatically sends wireless alerts directly to clinicians. Patient SafetyNet has been clinically shown to reduce preventable and costly rescue events, transfers to intensive care units, and deaths related to opioid-induced respiratory depression. Contact masimo.com.

CCHD SCREENING

Covidien's Nellcor pulse oximetry portfolio facilitates quick, noninvasive screenings for CCHD. The products are FDA-510(k) cleared for use on neonates, so physicians can rely on them for accurate CCHD screenings. Now, as part of a broad effort to educate clinicians on the importance of CCHD screenings and encourage hospitals to implement routine CCHD screening for all newborns, Covidien has begun labeling and promoting the use of Nellcor pulse oximetry as a tool to aid healthcare practitioners in CCHD screening. Covidien's CCHD awareness activities ensure clinicians understand how to use pulse oximeters and best generate reliable readings. Covidien offers free CCHD educational resources through its new Professional Affairs and Clinical Education (PACE) Online Platform. Covidien's new CCHD labeling was introduced as part of the FDA 510(k)-cleared labeling for motion tolerant Nellcor pulse oximeters. In 2011, the US Department of Health and Human Services added CCHD screening to the Federal Recommended Uniform Screening Panel Guidelines. As a follow up to those guidelines, the Consensus Work Group's recommendation specified the use of pulse oximeter devices that are motion-tolerant, report functional oxygen saturation, have been validated in low perfusion conditions, and have been cleared by the FDA for use in newborns. The performance of Nellcor pulse oximeters demonstrates that the criteria are fully met and the devices provide accurate readings even during patient movement. This can be particularly important for CCHD screenings in newborns because their tendency to move can prevent accurate readings. With the FDA's recent clearance of the expanded performance claims, Nellcor pulse oximeters are now the only oximeters on the market certified to be in compliance with ISO 80601-2-61 International Organization for Standardization. Nellcor pulse oximetry technology provides the industry's most accurate readings in neonates (±2% accuracy), largely because it relies on cardiac-based signals to generate readings closely tied to the patient's physiology. The result is consistent performance during a number of challenging conditions, including patient motion, noise and low perfusion, all of which can impede the assessment of patient respiratory status. Contact covidien.com.

TOUGH

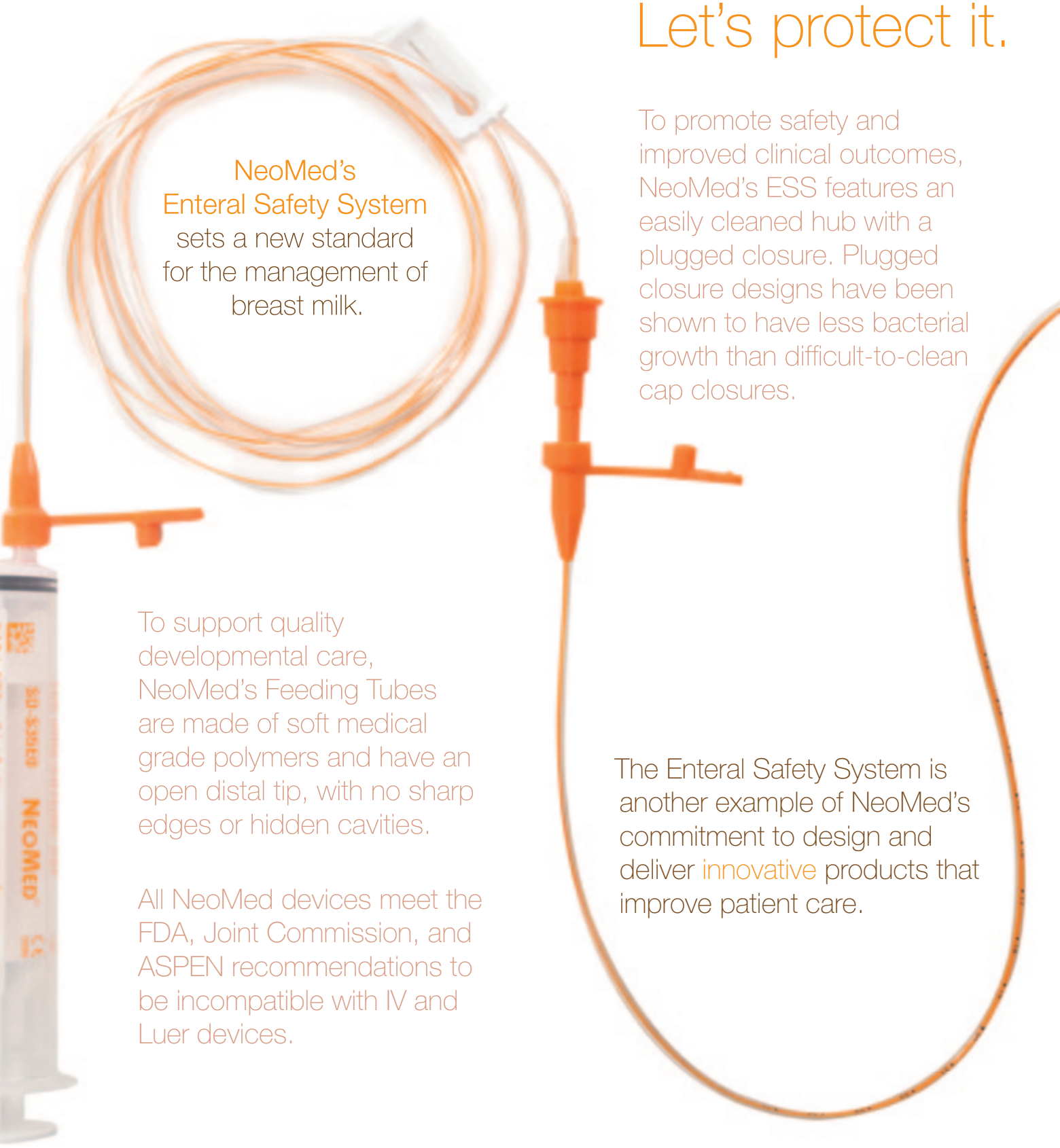
Panasonic announced upgrades to the Panasonic Toughbook H2 handheld tablet PC. The certified device includes a faster processor, expanded storage and other improvements, while retaining critical features to enhance usability and durability, including the ability to survive a 6-foot drop. With these upgrades, the Toughbook H2 delivers greater performance for clinicians and other mobile professionals. Key improvements are: an upgraded processor, expanded storage, improved battery life, and enhanced connectivity. The 3.5 lb Toughbook H2 handheld tablet PC runs the Microsoft Windows 7 Professional (32-bit or 64-bit) operating system and includes optional integrated technology such as barcode, fingerprint, insertable or contactless SmartCard/RFID readers. Its 10.1-inch XGA LED transflective touchscreen with Panasonic CircuLumin technology allows for full circle viewability from the brightest sunlight to

Breast milk is precious.

Let's protect it.

NeoMed's
Enteral Safety System
sets a new standard
for the management of
breast milk.

To promote safety and improved clinical outcomes, NeoMed's ESS features an easily cleaned hub with a plugged closure. Plugged closure designs have been shown to have less bacterial growth than difficult-to-clean cap closures.



To support quality developmental care, NeoMed's Feeding Tubes are made of soft medical grade polymers and have an open distal tip, with no sharp edges or hidden cavities.

All NeoMed devices meet the FDA, Joint Commission, and ASPEN recommendations to be incompatible with IV and Luer devices.

The Enteral Safety System is another example of NeoMed's commitment to design and deliver innovative products that improve patient care.

NEOMED®

100 Londonderry Ct, Suite 112 Woodstock, Georgia 1.888.876.2225 www.neomedinc.com

pitch darkness. For healthcare environments, the Toughbook H2 has a fully-sealed design, with no fan vents or exposed ports, for easy disinfection, reducing the risk of potentially pathogenic microorganisms being spread from patient to patient. The device is a secure and intuitive platform for barcode medication administration (BCMA), vitals capture and electronic medical records (EMR) capture and review. Contact panasonic.com/toughbook/h2.

QUALITY MEASURES

PeriGen announced pledging its support for the first published draft of nursing care quality measures specifically addressing the priorities of women's health and perinatal populations. The measures were developed and released last April for public review, comment and further refinement by the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). AWHONN is firmly established as the standard-bearer for women's health, obstetric, and neonatal nurses. The National Quality Forum (NQF) is responsible for reviewing and endorsing quality measures. To achieve NQF endorsement, a measure must meet stringent criteria and undergo a multi-step endorsement process. NQF has endorsed 14 perinatal and reproductive health measures and one newborn measure. PeriGen offers the only perinatal solutions already enabling L&D nurses, physicians and other caregivers throughout the spectrum of OB care to automatically extract over 60 data points and quality measures. PeriGen's documentation modules are reinforced by a robust Decision Support mechanism intended to encourage compliance with quality measures and practice-based standards for improved reporting and patient care. AWHONN has implemented a well thought-out, phased development process designed to encourage participation by all stakeholders and to help create consensus and buy-in for the final version. Contact perigen.com.

IMPLEMENTED

PeriGen announced that Mary Greeley Medical Center in Ames, IA has implemented PeriGen's PeriCALM fetal surveillance solution and has simultaneously interfaced PeriCALM with Epic Stork, the OB/GYN module for Epic, the medical center's enterprise-wide electronic health record (EHR). The PeriCALM solution suite includes PeriCALM Patterns, the only fetal surveillance solution that is both cleared by the FDA and validated by the NIH based on the findings of an extensive, independent study that determined that an analysis of fetal strip tracings performed manually by top NIH experts matched the findings from PeriCALM Patterns automated, real-time analysis more than 97% of the time. PeriCALM modules provides comprehensive, patented, FDA-cleared clinical decision support and fetal monitoring tools, including: PeriCALM Patterns that uses patented algorithms to help clinicians interpret fetal strips and provides a consistent, objective and standardized assessment of the data as a basis for collaborative care at the bedside. The tool has been cited as invaluable in facilitating communication among nurses, residents and physicians. PeriCALM Curve, a dynamic labor progression software that compares a laboring mother's progress in real-time to a reference population to aid in the diagnosis of abnormal or difficult childbirth. The solution accommodates a diverse population by adjusting for changing conditions including contraction frequency, epidural use and cervical effacement for each mother. Contact perigen.com.

MOST WIRED

PeriGen congratulates its nine provider clients named among the "Most Wired Hospitals and Health Systems." Published in the 15th annual "Most Wired" survey in July's Hospitals & Health Networks magazine, the survey's list recognizes US medical facilities that have made significant inroads advancing clinical information technologies to improve patient care and operational efficiencies. The clients are Atlantic Health Systems, NJ; Banner Health, AZ; Baystate Health, MA; Continuum Health Partners, NY; Maimonides Medical Center, NY; MedStar Health, MD; St Joseph's Hospital Health Center, NY; and Winthrop-University Hospital, NY. In the most-improved category was Mary Greeley Medical Center, IA. Contact perigen.com.

HELPING OUT

Winthrop-University Hospital in Mineola, NY, is fulfilling its vision of broadening perinatal technology from Labor & Delivery to the Post-Partum and Well Baby Nursery units, encompassing the full range of comprehensive obstetric (OB) needs from labor, birth to early infant care. The OB multi-department technology expansion was made possible with the PeriGen'sPeriCALM Plus complete perinatal charting and fetal monitoring system designed to bring obstetrical services to the highest level of patient care excellence. PeriGen's PeriCALM Plus solution includes PeriCALM Patterns, the only fetal surveillance solution that is both cleared by the FDA and validated by the NIH. Winthrop's OB leaders recognized the advantages of PeriGen's PeriCALM Plus' real-time fetal heart rate pattern recognition and clinical decision support analysis capabilities, in addition to its easy interoperable interfacing with different application platforms including Siemens' Soarian enterprise electronic health record (EHR) system. Contact perigen.com.

NANN ONLINE STORE

NANN's online store has a new look. The NANN store went through an upgrade to make your online experience enjoyable and successful. You are now able to search for products by type, name and topic with ease. Tailor your shopping experience and filter NANN products by topics you're interested in like clinical practice, developmental care, downloadable products and more. You can even review purchased products and share NANN products with your colleagues through your social media networks. Contact nann.org.

INVITATION

NANN's Program Planning Committee invites submissions of abstracts to present at NANN 30th Annual Educational Conference, September 10 to 13, 2014, in Phoenix. The committee has recognized the need of topics that should appeal to both the novice and expert neonatal nurse. The committee highly encourages personal findings and research. The following are suggested areas of interest: pharmacology, medication safety, developmental care, advances in research, implementation of evidence-based practice and other topics will be considered. The deadline to submit is Monday, November 4. Contact nann.org.

UNIQUE

CODAN will introduce to market a unique burette set that creates a closed system for safe IV administration to neonate and pediatric patients. The device features multiple swabable, needlefree ports that reduce blood stream infections (BSI) while also ensuring easy access for solution delivery/flush and sampling. The set offers fluid control through precise priming volumes and in-line air prevention. CODAN features non-DEHP, latex-free tubing, ETO sterilization and is assembled into one package to reduce prep time. Additionally, this set features a

universal spike adapter that works with any pump sets and the exclusive CODAN FlowStop Cap for multiple-day self-priming and further improved infection control. For more information about the company or the full neonate/pediatric product line, please visit codanuscorp.com.

GOING SOLO

The new SOLO single prong cannula (affectionately nicknamed "Unicorn" by users) is Vapotherm's latest product. The SOLO cannula provides a whole new way to assure an open system while delivering High Flow Therapy to neonatal and infant patients. With its single prong design, SOLO eliminates concerns about over occlusion of tiny nares, simplifies NG tube placement, and may facilitate the delivery of High Flow Therapy in patients with anatomical defects. SOLO works with the Vapotherm Precision Flow to provide the same gentle and effective ventilatory support of a dual prong cannula, and only Vapotherm can deliver High Flow Therapy through a single prong. The SOLO cannula delivers up to 8 lpm, and standardizing on the SOLO simplifies fitting the right cannula for the patient. In general, Vapotherm High Flow Therapy offers an approach to avoid the skin breakdown from tight fitting masks and nasal prongs and the costly adverse events associated with intubation, while simplifying access to care for, feed, and hold the patient. Dr Jorge Rojas, an early adopter of the SOLO cannula tells us, "The single prong cannula has worked very well for us particularly to support neonates under 1000 grams. With the single prong cannula we do not worry about occluding too much of the nares." Contact vtherm.com, (866) 827-6843.

EXTENDED CARE

VSee, a new HIPAA-compliant telemedicine tool, extends care and access from the NICU at one-tenth the cost of traditional tele-NICU systems. With 3 webcams, VSee's simple one-click solution sends all 3 camera video streams from a Mac Mini to a laptop or mobile device for easy, secure consultations. Seasoned specialists can provide immediate intervention via VSee and avoid costly, time-consuming transfers between hospitals. Anxious parents can have anytime access to their baby, calling in even from an iPad. VSee is the winner of the American Telemedicine Association video contest. It requires no server or infrastructure, crosses all firewalls, and uses half the bandwidth of traditional video conference tools. VSee is HIPAA-compliant and FDA-registered. Contact vsee.com.

EASY TO FIND

PDC Healthcare announced the extension of its DuraSoft Laser Patient ID System to encompass the entire patient population including infants, pediatrics, and adults. DuraSoft is now offered in ten different formats to serve as an easy drop-in replacement of an existing laser patient ID system, eliminating the need for IT involvement or re-formatting. One of the new formats, DuraSoft TenderCare, helps ensure that every infant is positively identified with their parents. The 4-part set includes one wristband for mom, one for dad, and two for baby's wrist and ankle. DuraSoft TenderCare is ideal for labor & delivery departments using laser printers for print-on-demand automated patient identification, helping to improve patient safety by reducing manual errors. Another new format includes an infant-sized, pediatric-sized, and adult-sized wristbands on a single sheet, so the size-appropriate wristband can be selected on the spot and there is no need to dedicate two separate printers in the pediatrics unit or children's hospital. DuraSoft also features an antimicrobial additive that protects the wristband surface against tested non-pathogenic bacteria. It's lightweight, ultra-soft, and requires no assembly prior to application. It is moisture-resistant and protects information from fading or smearing from water, alcohol or hand-sanitizer. It's also market-compatible with PDC Healthcare's Ident-Alert Color Coded Snaps. Contact pdcorp.com.

NANN PREVIEW

Abbott Nutrition

Booth 220

Abbott Nutrition invites you to Booth 220 to learn more about customizing nutrition for babies in your NICU. We are featuring our two newest products — Similac Human Milk Fortifier Concentrated Liquid and Liquid Protein Fortifier. These new additions to our comprehensive product line work together to give you even more flexibility to provide the right nutrition for babies in the NICU.

New Similac Human Milk Fortifier Concentrated Liquid is the only non-acidified concentrated liquid fortifier available. Liquid Protein Fortifier has extensively hydrolyzed casein protein for easy digestion and absorption. By using them together, you can customize feeding solutions to fit baby's individual needs in the NICU, adjust protein as baby grows, and eliminate the risk of contamination from powders by using commercially sterile liquid products. These options can be mixed with human milk or infant formula.

In addition, Similac preterm infant formulas are designed to support the nutrient needs of preterm infants from the start. Our preterm infant formulas now have lutein for developing eyes.

Abbott Nutrition is committed to advancing scientific innovation to provide more solutions for infant nutrition and human milk. Visit Booth 220 to find out more about how you can customize nutrition from the start with the most comprehensive NICU offerings available. We can help give you the flexibility to deliver individual feeding solutions like no other with multiple options for human milk fortification, preterm formulas with lutein, and much more.

Acacia Neonatal

Booth 219

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 IV System, NICU Specialty Tubing SafeSample Blood Gas Sampling Set.

What's new this year? Tell us about your latest products or future plans.
Grip-Lok Securement Device MediPop Pacifier Delivery System.

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 exhibit 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 2013 NANN Conference. We will be unveiling the versatile MediPop pacifier delivery system, which is perfect for transitional feeding or medication delivery use. We will also display Grip-Lok hydrocolloid securement devices for nasal gastric, picc lines and umbilical catheters. These hydrocolloid securement devices follow the NANN skincare guidelines and are very gentle on fragile neonatal skin. View these products and more at our booth, all of which further our goal of advancing health care in the NICU. You can also visit us at acacianeonatal.com or contact us at info@acacianeonatal.com for more information on these and other Acacia Neonatal products.

Beevers Medical Solutions

Booth 700

What products do you plan to exhibit?
• Luma Wrap — Our newest product. Luma Wrap is a see-through infant swaddler. • Cannulaide — Cannulaide works with leading prongs to provide a reliable, observable air seal. Cannulaide is translucent to aid in inspecting the condition of the patient's nares, which should be done frequently. • Sticky Whiskers — Secure nasal cannulas gently with Sticky Whiskers. Our Sticky Whiskers Velcro interface allows a cannula to be secure yet still repositionable. • Mini Whiskers — Mini Whiskers is the industry's first cannula securement product tailored specifically for babies less than 2000g. The product is designed for the best care in prevention of skin irritations and breakdowns.

Tell us about your latest products and future plans.
Our latest product, Luma Wrap, was designed in response to repeated requests from nurses for a see-through swaddle blanket to be used on hyper-reactive babies receiving phototherapy in the Neonatal Intensive Care Unit. Luma Wrap is a translucent, highly breathable, phototherapy-compatible, infant swaddler made of a non-woven material that is about 90% light-permeable. Luma Wrap provides centered and comfortable boundaries to benefit restive babies who exhaust themselves with frantic movements while on phototherapy.

Discuss educational or training materials that will be available.
We will have all of our product brochures available to look at and/or send with our booth visitors. Information about the white paper, "How Does System Pressure Correlate with Nasopharyngeal Pressure in an Infant NCPAP In-Vitro Model" by Kate Beevers will also be available.

Tell us about any speakers or in-booth promotions.
We are always seeking evaluations from clinicians. For all competed surveys, we give out mugs on which our motto, "It's all about the babies," is written.

Why should our readers stop by your display?
First and foremost, we would love to meet you and talk with you! We love meeting new people and hearing about experiences in the NICU. Relationships with people are very important to us. Because at BMS "It's all about the babies," it is vital that we stay in conversation with the nurses at the bedside. We want to know what would make the care given at the bedside more efficient and more productive for the patient and the caregiver. Our motto for the past 18 years has been, "Sophisticated protection doesn't have to be complicated." Come visit us!

Cincinnati Sub-Zero

Booth 720

What products do you plan to exhibit?
Blanketrol III Hypo-Hyperthermia Device, Micro-Temp LT LocalizedTherapy Unit, Kool-Kit Neonate and Gelli-Roll

What's new this year? Tell us about your latest products or future plans.
CSZ is a leader in patient temperature management products. We offer a variety of products to help manage your patient's temperature with water and air based products. Our Blanketrol III and Kool-Kit Neonate are widely used for Targeted Temperature Management. CSZ is always looking at the future and working on new products.

What educational or training material will be available?
We have a training video on our equipment and a clinical team that can help your facility develop your protocol for neonatal whole body cooling or any other help that you may need.

Why should our readers visit your display?
Cincinnati Sub-Zero has been developing temperature management products since 1963. We are one of the leaders in neonatal cooling and have had great success with our products and cooling for HIE. One of our clinical team members will be at the booth to help answer any questions about our products or potential treatment options.

CODAN

Booth 308

What products do you plan to exhibit?
IV Tubing including: a. Administration Sets, b. Extension Sets, c. Closed system administration and extension sets, d. Swabable Componentry.

Tell us about your latest products and future plans.
Closed systems to assist in the prevention of infections and multiple systems with very low priming volume for precise solution administration.

Discuss educational or training materials that will be available.
Information detailing: a. Swabable ports (infection control), b. LightSafe tubing (photo degradation reduction).

Why should our readers stop by your display?
CODAN manufactures IV Tubing and only IV Tubing. CODAN is a thought-leader and specialist in the industry of IV Tubing and are highly regarded for their componentry, precision and innovation. CODAN's manufacturing facility is based in Santa Ana, CA and uses only the best in all practices and methods.

Fisher & Paykel Healthcare

Booth 418

What products do you plan to exhibit?

Fisher & Paykel Healthcare will be featuring 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 minimize heat loss at birth, and preserve patient energy. It also drops the risk of an inflammatory response occurring in the infant's airway reducing the work of breathing,

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

Fisher & Paykel is showing the first complete Bubble CPAP System including the new FlexiTrunk CPAP Interface and new CPAP Nasal Masks. We are also 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 your 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 418 for a complete review and demonstration of all Fisher & Paykel Healthcare products. For further information, please contact: David Hendrickson, Neonatal Product Manager, Fisher & Paykel Healthcare, Inc, (800) 792-3912 x 1331, david.hendrickson@fphcare.com.

Ivera Medical

Booth 615

What products do you plan to exhibit?

Ivera Medical will exhibit our full suite of disinfecting port protectors including: Curos caps and Curos Strips for cleaning and protecting needleless IV connectors, Curos Tips for the effective disinfection of male-luer devices, and Curos for Tego caps for dialysis catheters. The Curos product line includes simple, innovative, disposable infection prevention products intended for use on swabbable luer access valves and male luer connectors. Curos products disinfect IV access ports and connectors, killing the organisms associated with catheter-related bloodstream infections, and act as a physical barrier to contamination. Simply peel off a foil seal and twist Curos products over the top of a luer-activated IV access port or male luer connector. Inside the device is a 70% IPA (isopropyl alcohol) which, once secured, automatically provides effective, consistent and reliable passive disinfection. The Curos Strip provides caregivers with a perfectly accessible dispenser for Curos port protectors at the point of care. The ten-cap, foil-backed dispenser can be hung on an IV pole so that nurses have easy access to consistent and reliable passive disinfection during every IV access. This deployment option, in conjunction with the bright green color of Curos Caps and Tips, provide a highly visual reminder for nurses and auditable visual cue for infection control rounding.

Tell us about your latest products and future plans.

Curos Tips are the latest innovation from Ivera Medical designed to improve the effective disinfection and maintenance of IV tubing sets. The new patent-pending Curos Tips use 70% isopropyl alcohol (IPA) to passively disinfect and protect male luer connections on intravenous access devices including IV tubing and syringes. Curos Tips come in a convenient strip dispenser which places five disinfecting Tips in easy reach of clinician at the point of care. When placed on male luer connectors, Tips passively bathe the connector's surface with alcohol. In three (3) minutes Tips disinfect the device, killing the organisms often associated with bloodstream infection. Once attached, Curos Tips act to cover and protect the male luer. The highly visible bright green caps allow auditors to monitor caregiver disinfection practice compliance.

Discuss educational or training materials that will be available.

Ivera will provide visitors with product information and information related to peer-reviewed clinical evidence studies.

Tell us about any speakers or in-booth promotions.

Stop by to learn about our passive disinfection products and take home Curos samples in our 2013 Curos Tips "Practice Safe Sets" zippered tote bag.

Why should our readers stop by your display?

See how Curos Disinfecting Port Protectors can keep you covered and learn about the clinical evidence supporting the role of Curos in efforts to address catheter-related bloodstream infection. *Rady Children's Hospital San Diego, CA*: • CLABSI rate decreased 68%. • The number of blood isolates meeting criteria as contaminants decreased 25%. *California Children's Services (CCS) Neonatal Infection Prevention Project*: • CLABSIs fell 70% during the study period. • CLABSI Rates Continue To Fall Significantly For The "All Birth Weights." *West Virginia University Health System, Morgantown, WV*: • 87% reduction in CLABSI. • 92% reduction in contaminated blood cultures from central lines. *Banner Estrella Medical Center, Phoenix, AZ*: • CLABSI rate reduced from 1.9 in 2010 to 0.5 during the 1-year trial period. *Grady Health System, Atlanta, GA*: • The average rate of CLABSI decreased 45% in the SICU and 59% in the MICU in the 10 months following Curos implementation as compared to the baseline 10 months prior to the Curos intervention. *Barnes Jewish Hospital & Washington University in St Louis Medical School, St Louis, MO*: • On the intervention ward using Curos, monthly median CLABSI rate declined 32% while the control ward saw only 3.6% reduction. *Intermountain Medical Center & BYU College of Nursing*: •

PICC line and overall CLABSI rates were significantly decreased.
• Net cost savings using alcohol cap was $683,030. Read more about Curos use in clinical practice at www.curos.com.

Maico Diagnostics

Booth 724

What products do you plan to exhibit?
The MB 11 BERAphone and MB 11 Classic ABR hearing screening devices.

Tell us about your latest products and future plans.
The MB 11 BERAphone and MB 11 Classic ABR hearing screening devices offer alternatives for your hearing screening program.

Why should our readers stop by your display?
Stop by to learn how the MB 11 can reduce operating costs associated with newborn hearing screening.

Otometrics

Booth 439

What products do you plan to exhibit?
The MADSEN AccuScreen newborn hearing screener will be featured at the Otometrics booth at the NANN 2013 Exhibit.

Tell us about your latest products and future plans.
With the MADSEN AccuScreen, there is no cart required! The new AccuScreen is a hand-held newborn hearing screener with all the capabilities of a cart-based system. Its breakthrough touch-screen display, with vibrant icons and intuitive navigation, allows nurses to focus on the infant instead of the technology. It features a fast and easy 2-step OAE and/or ABR testing combined in a single device that significantly improves workflow and test time.

Tell us about any in-booth promotions.
The Try-before-you-buy program is exclusively available during the conference to the NANN attendees who are interested in newborn hearing screening. The Try-before-you-buy program gives first-time users a chance to experience the capabilities of the AccuScreen for a limited time before committing to purchase. Interested customers may simply: 1. Stop by at the Otometrics booth; 2. Listen to a 3-minute overview of the Try-before-you-buy program; 3. Register for the Try-before-you-buy program during the conference.

Why should our readers stop by your display?
Product demonstrations will be available upon request. Everyone is invited to stop by the Otometrics booth to witness firsthand the capabilities of the AccuScreen hand-held newborn hearing screener and learn the ways on how to simplify workflow and shorten test time. They can also learn about our new low-cost disposables program. Our team will be available at all times to answer any questions about AccuScreen and other hearing care solutions. In the meantime, NIC readers may read about AccuScreen at www.otometrics.com/accuscreen-us or call our customer service hotline at (855) 289-2150.

Vapotherm

Booth 524

What products do you plan to exhibit?
Vapotherm's Precision Flow High Flow Therapy System with its family of comfortable patient interfaces, featuring the new SOLO Single Prong Cannula.

Tell us about your latest products and future plans.
The new SOLO single prong cannula (affectionately nicknamed "Unicorn" by users) is Vapotherm's latest product. The SOLO cannula provides a whole new way to assure an open system while delivering High Flow Therapy to neonatal and infant patients. With its single prong design, SOLO eliminates concerns about over occlusion of tiny nares, simplifies NG tube placement, and may facilitate the delivery of High Flow Therapy in patients with anatomical defects. SOLO works with the Vapotherm Precision Flow to provide the same gentle and effective ventilatory support of a dual prong cannula, and only Vapotherm can deliver High Flow Therapy through a single prong. The SOLO cannula delivers up to 8 lpm, and standardizing on the SOLO simplifies fitting the right cannula for the patient. In general, Vapotherm High Flow Therapy offers an approach to avoid the skin breakdown from tight fitting masks & nasal prongs and the costly adverse events associated with intubation, while simplifying access to care for, feed, and hold the patient. Dr Jorge Rojas, an early adopter of the SOLO cannula tells us, "The single prong cannula has worked very well for us particularly to support neonates under 1000 grams. With the single prong cannula we do not worry about occluding too much of the nares."

Discuss educational or training materials that will be available.
Vapotherm provides extensive training and support on high flow therapy and the Precision Flow in particular. At the booth there will be presentations on mechanisms and clinical use of thigh flow therapy, a clinical reference list and the new NICU pocket guide which provides tips on clinical use of high flow therapy in the NICU.

Tell us about any speakers or in-booth promotions.
We will have samples of the new SOLO cannula for attendees to see the new technology.

Why should our readers stop by your display?
An opportunity to experience Vapotherm High Flow Therapy first hand will also be available for those who stop by the booth! We will have samples of the SOLO cannula, and presentations that describe the mechanisms of action and clinical experience with high flow therapy.

More on Fetal Pain: Experiences from In-Utero Invasive Procedures

Boris M. Petrikovsky MD, PhD, Paulina Fein, Barry I. Dynkin

Introduction

The Medilexicon medical dictionary defines pain as "A variably unpleasant sensation associated with actual or potential tissue damage and mediated by specific nerve fibers to the brain where its conscious appreciation may be modified by various factors." "If a patient is unable to report his pain, such as an infant, or a person with dementia, there are a number of observational measures a doctor can use." When the patient in pain is cognitively impaired, "the patient's subjective report is the most effective and accurate way of evaluating pain. If the cognitively impaired patient is observed carefully it is possible to pick out clues as to the presence of pain, eg restlessness, moaning, groaning, grimacing, etc." The question as to when, or if, fetuses feel pain is a widely debated topic. Various researchers defend positions ranging from the notion that a fetus cannot feel pain under any circumstances to the conviction that a fetus might be able to experience pain within a few weeks of conception. These vast variances in viewpoints occur because "the hypothesis that human fetuses are capable of perceiving pain in the early stages of a pregnancy has not received sufficient evidence to be proven or disproven; the development stage of a research and instrumentation is so far insufficient to this task. The issue is considerably complicated by the usual difficulties in perceptual research of unresponsive subjects."

Fetal awareness of noxious stimuli requires functional thalamocortical connections. "Evidence regarding the capacity for fetal pain is limited. Little or no evidence addresses the effectiveness of direct fetal anesthetic or analgesic techniques. Similarly, limited or no data exist on the safety of such techniques for pregnant women."

In a search through "research from 1995, matching the following key words: 'pain' and 'fetus' with the following: 'subplate,' 'thalamocortical,' 'myelination,' 'analgesia,' 'anesthesia,' 'brain,' 'behavioral states,' 'substance p' focused on: (a) fetal development of neural pathways; (b) fetal electrophysiological, endocrinological and behavioral reactions to stimuli and pain," 217 papers were retrieved. 157 of them "were highly informative; some reported similar data or were only case-reports, and were not quoted."

Most endocrinological, behavioral and electrophysiological studies of fetal pain are performed in the third trimester, and they seem to agree that the fetus in the third trimester can experience pain. But the presence of fetal pain in the second trimester is less evident. In favor of a second trimester perception of pain is the early development of spino-thalamic pathways (approximately from the 20th week), and the connections of the thalamus with the sub-plate.

Research at Imperial College in London showed that fetuses as young as 18 weeks react to an invasive procedure with a spike in stress hormones and a shunting of blood toward the brain — a strategy, also seen in infants and adults, to protect a vital organ from threat. The test subjects were 45 fetuses that required a painful blood transfusion, giving one-third of them an injection of the potent painkiller fentanyl. The results were striking: in fetuses that received the analgesic, the production of stress hormones was halved, and the pattern of blood flow remained normal.

The goal of this study is to report fetal responses to invasive procedures breaking through fetal skin performed for accepted clinical indications.

Materials and Methods

31 fetuses between 19 and 28 weeks of gestation underwent invasive procedures: skin biopsy in 6, liver biopsy in 3, placement of uroamniotic shunt in 17, placement of thoracoamniotic shunt in 3 and cardiocentesis in 2. Fetal response to invasive procedures was assessed with the help of an additional ultrasound machine. A modified neonatal infant pain scale (NIPS) was used to assess and grade fetal pain: a second ultrasound machine was used to record fetal responses to invasive procedures.

Facial expression	
0- Relaxed muscles	Restful face
1- Grimace	Tight facial muscles, furrowed brow, chin, jaw
Breathing pattern	
0- Relaxed	Usual pattern for individual fetus
1- Change in breathing	Irregular respirations, tachypnea
Arms	
0- Relaxed	No muscle rigidity, occasional random movements
1- Flexed/Extended	Tense straight arms, rigid and/or rapid extension/ flexion
Legs	
0- Relaxed	No muscular rigidity, occasional random movements
1- Flexed/extended	Tense straight legs, rigid and/or rapid extension/ flexion

NIPS Interpretation

0 No pain
1-3 Moderate pain
4 Severe pain

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Results

Behavioral changes likely reflecting fetal pain during penetrating procedures were detected in 29 out of 31 fetuses. Pain was moderate in 24 fetuses according to the NIP scale and severe in 5 fetuses. Pain correlates with the degree of invasiveness and length of the procedure. Liver biopsies and thoracoamniotic shunts cause the most pain. Pain appears to correlate directly with gestational age.

Legal, Policy, and Societal Implications

Despite the fact that the research at hand does not provide a conclusive determination as to the point at which a fetus might first be capable of experiencing pain, it brings up important questions regarding the prudence of fetal anesthetic procedures. As long as there is an ambiguity as to the possibility of a fetus experiencing pain, it might be prudent to implement fetal anesthetic procedures as a prophylactic measure. Some contend that even if the fetus is capable of experiencing pain in some sense, the distinct nature of this sensation from the analogous sensation of pain in a mature human combined with the fetus' inability to recall the experience make it irrelevant. However, anesthesia is implemented in other cases of potentially diminished cortical function and conscious experience, such as patients in a coma or with diminished cognitive function, and with other patients who may lack the ability to recall the pain such as patients suffering from severe Alzheimer's disease and newborns receiving circumcision. It is undeniable that the conscious sensation of pain in a comatose or newborn patient is either entirely lacking or fundamentally distinct from that of a fully developed, conscious patient. Nonetheless, anesthesia is almost ubiquitously implemented in procedures on these patients. So long as there is any ambiguity as to the ability of fetuses to experience pain, it seems it would be eminently appropriate to develop anesthesia protocols for fetuses undergoing any medical procedures, from a minor reparative surgery to the termination of a pregnancy.

The possibility that a fetus might be capable of experiencing pain, even pre-viability, might be relevant to the legal determination and the societal debate of the appropriate extent of a woman's right to choose to terminate her pregnancy. One of the central elements of the jurisprudence of abortion is the complex balancing of the state's recognized interest in protecting the potential life of the fetus and the mother's important interests in her reproductive freedom and the preservation of her bodily autonomy and integrity. This balancing has shifted over time from the minimal regulations permitted in the early days following Roe v. Wade 410 U.S. 113 (1973) to the increased restrictiveness permitted after Planned Parenthood v. Casey 505 U.S. 883 (1992). Much of the balancing of interests performed in both cases depends heavily on various scientific determinations that have evolved over time. Foremost among these considerations is the point at which a fetus becomes viable. However, it seems clear that the point at which a fetus begins to experience conscious sensation, or even a diminished cognitive experience of pain, is germane to the complex and nuanced balancing process as well. Furthermore, this determination has substantial value in the process of determining which regulations and restrictions (among those found to be constitutionally permissible) are prudent and ethical.

The lack of a conclusive answer to the central question precludes the possibility of drawing any legal, legislative, or social prescriptions from the work at hand. Rather, the results reveal a question in desperate need of an answer and demand extensive further research into the fundamental, underlying question. Regardless of one's political proclivities, ignorance as to such an essential question that has such an important relation to one of the most complex, nuanced political and social questions of the day ought to be deemed unacceptable and further research must be pursued, both with regards to the underlying question and the development of appropriate fetal anesthetic procedures.

Conclusion

The hypothesis that human fetuses are capable of perceiving pain in the early stages of a pregnancy has not received sufficient evidence to be proven or disproven. The issue is considerably complicated by the usual difficulties in perceptual research of unresponsive subjects. However, our experience suggests that fetuses undergoing invasive procedures are experiencing pain as judged by the NIP scale. This suggests that fetal anesthetic protocols ought to be implemented as a prophylactic measure so long as there is ambiguity as to the point at which a fetus might be able to experience pain and that more research as to the underlying question is required.

References

- Bellieni, C. V., and G. Buonocore. "Is Fetal Pain a Real Evidence?" National Center for Biotechnology Information. U.S. National Library of Medicine, 25 Aug. 2012. Web. 29 Mar. 2013.
- "Circumcision Study Halted Due to Trauma." CNN. Cable News Network, 23 Dec. 1997. Web. 30 Mar, 2013.
- "Definition: 'Pain'" pain N.p., n.d. Web. 29 Mar. 2013
- "Infant Circumcision with Anesthesia: Does it really help the pain? — The WHOLE Network: Accurate Circumcision & Foreskin Information." The WHOLE Network: Accurate Circumcision & Foreskin Information. N.p., 20 Aug. 2011. Web. 30 Mar. 2013.
- "KidsHealth." Circumcision. N.p., n.d. Web. 30 Mar. 2013.
- Lee, S.J., H.J. Ralston, E. A. Drey, J.C. Partridge, and M.A. Rosen. "Fetal Pain: A Systematic Multidisciplinary Review of the Evidence." National Center for Biotechnology Information. U.S. National Library of Medicine, 24 Aug. 2005. Web. 29 Mar. 2013.
- Marty, Robin. "Fetuses Cannot Feel Pain Until 35 Weeks." RH Reality Check. N.p., 9 Sept. 2011. Web. 29 Mar. 2013.
- Narvaez, Darcia, Ph.D. "Myths about Circumcision You Likely Believe." Pyschologytoday.com, N.p., 11 Sept. 2011. Web. 28 Mar. 2013.
- "Neonatal Perception." Wikipedia.com. N.p., n.d. Web. 29 Mar. 2013.
- Nordqvist, Christian. "What is Pain? What Causes Pain?" Medical News Today. MediLexicon International, 09 Apr. 2009. Web. 29 Mar. 2013.
- Paul, Annie Murphy. "The First Ache." The New York Times, 10 Feb. 2008. Web. 29 Mar. 2013 (9)
- Robinson, B. A. "Can a Embryo or Fetus Feel Pain? Various Opinions and Studies." All about Religious Tolerance: The Religious Tolerance.org Web Site. Ontario Consultants on Religious Tolerance, 15 May. 2010. Web. 31 Mar. 2013.
- "What is Uterine Atony?" WiseGEEK.org. N.p., n.d. Web. 31 Mar. 2013.
- Williamson, Paul S., and Nolan D. Evans. "Neonatal Cortisol Response to Circumcision with Anesthesia." Neonatal Cortisol Response to Circumcision with Anesthesia. N.p., n.d. Web. 30 Mar. 2013. (14)

Relationship between Maternal and Infant Plasma Selenium Levels with Sepsis and Various Outcomes Measures

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Abstract

Objective: Selenium (Se) is an essential trace element and has a significant role in the cellular and humoral immune systems. This study was designed to evaluate maternal and cord blood Se in a group of high risk preterm infants who developed late bacterial sepsis.

Study Design: Maternal and cord plasma Se using ICP-MS techniques were prospectively measured in 256 premature infants <34 weeks; 33 infants developed sepsis and were compared to 223 nonseptic infants using Chi Square, t-test and multivariate logistic regression analyses.

Results: A significant biochemical Se deficiency (<60 mcg/L) at birth was found in 58%. The infants' Se levels were about half of their mothers' levels: 108 mcg/L ($p<0.003$) who were 98% Se sufficient (>70 mcg/L). Pre-eclamptic pregnant patients had lower Se levels at delivery (<100 mcg/L) ($p=0.06$). Se deficiency was more common among males and infants of diabetic mothers. Eight infants died (3%), 5 from sepsis. Se deficiency ($p<0.03$), oxygen exposure ($p<0.001$) and mechanical ventilation ($p<0.002$) had a strong association with BPD.

Conclusion: Se did not have an impact on the etiology of sepsis. Traditional risk factors for sepsis, extreme prematurity (<30 weeks), very low birth weight, PPROM, chorioamnionitis and instrumentation significantly contributed to sepsis. However, Se appears to play a role in the development of BPD.

Key words: gestational age, maternal, premature infants, Se, sepsis, BPD

Introduction

Selenium (Se) is an essential trace element and component of a number of seleno proteins, including glutathione peroxidase, which has a role in protecting against oxidative damage. Se is also known to affect the function of all components of the immune system[1] and Se levels can influence the ability to respond to infections.[2,3] The role of Se in innate and acquired immune responses is mediated through its incorporation into glutathione peroxidase.[4] Adequate Se levels are important for cellular (T cytotoxic cells, natural killer cells) and humoral (B cells) immune system development and function.[5]

Darlow et al studied the effect of Se supplementation on morbidity outcomes in very low birth weight infants and found fewer supplemented infants had sepsis after the first week of life.[6] The same author in a meta-analysis of three trials on the benefits of Se supplementation found it was indeed associated to fewer episodes of sepsis, but it was not associated with improved survival or a reduction in other morbidities such as chronic lung disease and retinopathy of prematurity (ROP).[7] Two out of the three trials in this Cochrane review were from geographical areas with low population Se concentration.

Besides the immune deficiencies there are other risk factors associated with neonatal sepsis[8] to consider including prematurity, low birth weight, preterm premature rupture of fetal membranes (PPROM), prolonged labor, chorioamnionitis (CHORIO), maternal urinary tract infections (UTI), instrumentation such as internal fetal scalp electrodes, catheter utilization [umbilical artery catheter (UAC), umbilical vein catheter (UVC), percutaneous intravenous central catheter (PICC)] and mechanical ventilation. The data published by Darlow et al,[6] dominated by one large trial from a country with low Se concentration (New Zealand), may not readily translate to the United States' (US) population. Therefore, the hypothesis of this study was that premature infants <34 weeks gestation that developed late bacterial sepsis, after three days of life (DOL), had significantly lower cord plasma Se at

Figure 1.

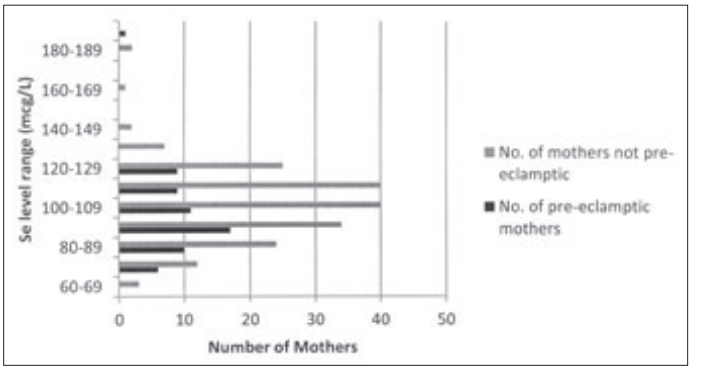

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Table 1. Clinical characteristics and outcomes of the infants with sepsis.

Infant No.	GA (wks)	Birth Weight (grams)	Maternal Complications	Risk Factors for Sepsis	Mechanical Ventilation (days)	Onset of Sepsis (DOL)	Blood culture	CP Se (µg/L)	Outcome
1	24	680	Twin, TTTS, IUFD Twin "B", PPROM	PPROM, IMV, UAC, UVC, PICC	18	10	Escherichia coli	60	Death - severe RDS BPD, PIE, PVL, died DOL 18
2	32	1780	Twin B, monochorionic, monoamniotic	IMV, PICC	17	22	Beta-hemolytic Group B Streptococcus	68	Alive – severe RDS, BPD
3	32	1565	Twin A, monochorionic, monoamniotic	IMV, PICC	4	22	Beta-hemolytic Group B Streptococcus	68	Alive – severe RDS, BPD
4	24	520	Twin B vanishing Twin A	UAC, UVC, PICC	28	7	Klebsiella pneumoniae	50	Alive – severe RDS, BPD, pneumonia, ROP
5	28	1050	Singleton, gestational diabetes, PPROM	PPROM, UVC, PICC	1	7	Coagulase-negative Staphylococcus aureus	80	Alive – RDS, NEC
6	25	690	Twin Di-Di, PROM, UTI	PPROM, UAC, UVC, UTI	21	21	Klebsiella pneumoniae	54	Death – severe RDS, IVH, NEC, BPD, died DOL 22
7	25	700	Twin Di-Di, PPROM, CHORIO, UTI	PPROM, UVC, UAC, UTI	2	7	Beta-hemolytic Group B Streptococcus	57	Alive – RDS, Imperforate anus, surgery
8	24	680	Singleton, CHORIO, GBS	CHORIO, UAC, UVC, PICC	53	30	Methicillin-resistant Staphylococcus aureus	53	Alive - Severe RDS, BPD, NEC, Hydrocephalus, IVH grade 4
9	23	720	Twin A, TTTS, Polyhydramnios, Cerclaje	CHORIO, Cerclaje, Laser ablation	1	4	Candida albicans	54	Death – Pneumonia, IVH, died DOL 4
10	28	890	Twin B, TTTS, AEDBF, preterm labor	PICC, PPROM	12	7	Enterobacter	65	Alive – severe RDS, PDA, BPD
11	27	1070	Singleton, Gastric bypass, IUFD	UAC, UVC, PICC	1	81	Klebsiella pneumoniae	59	Alive – severe RDS, PDA, BPD, NEC
12	26	860	Singleton, CHORIO, Abruptio, Compound presen.	PROM, CHORIO, UVC, UAC, PICC	2	18	E. fergusonii	58	Alive – severe RDS, BPD, HTN, NEC
13	24	870	Singleton, CHORIO, PPROM, GBS	PROM, CHORIO, PICC	8	4	Pseudomonas aeruginosa	52	Death – severe RDS, PIE, died DOL 8
14	25	890	Twin A, Mono Dichorionic, PROM, CHORIO	PPROM, CHORIO, UVC, PICC	6	19	Staphylococcus aureus	51	Alive – severe RDS, BPD, PDA, RDP
15	25	850	Twin B, mono amniotic, DiChorionic, PROM	PROM, Chorio, UAC, UVC, PICC	5	56	Staphylococcus aureus	59	Alive – severe RDS, BPD, ROP
16	29	1430	Singleton, ITP, PPROM, Preterm labor	UVC, PPROM, PICC	9	14	Escherichia coli	37	Alive – Pneumonia, E. coli, ROP, Suprarenal hemorrhage
17	29	1230	Singleton, IDM Class B, PIH	CHORIO, UVC, UAC	38	7	Staphylococcus aureus	47	Alive – severe RDS, BPD, HTN
18	29	1300	Singleton, PPROM, CHORIO, Foul Smelling AF	CHORIO, PICC, PPROM	4	7	Morganella morganii	45	Alive – Severe RDS, BPD
19	24	720	Singleton, PPROM, CHORIO	CHORIO, PICC, UAC, UVC	54	7	E. fergusonii	46	Alive – severe RDS, PDA, PIE, BPD
20	28	420	Singleton, Severe PREECL, PIH, LOW AFI	PPROM, CHORIO	10	18	Methicillin-resistant Staphylococcus aureus	45	Alive – severe RDS, NEC, Chest abcess
21	31	1480	Singleton, PIH, CHORIO	PPROM, CHORIO	0	5	Staphylococcus aureus	64	Alive – wet lung syndrome
22	29	880	Twins, TTTS, Mono, Diamn,	None	1	30	Staphylococcus aureus	70	Alive – RDS, BPD, IVH
23	27	860	Singelton, HIV +, Abruptio	HIV +, UAC, UVC	19	10	Coagulase-negative Staphylococcus aureus	48	Alive – RDS, BPD, Pneumonia
24	26	970	Twins Di-Di	PPROM, PICC	15	21	Coagulase-negative Staphylococcus aureus	61	Alive – severe RDS, BPD, ROP
25	29	1140	CHORIO, Abruptio, Obesity, IDM, Meconium stained, Singleton	CHORIO	2	20	Group B Streptococcus	55	Alive – RDS, PDA
26	30	1429	Singleton, PROM, S. Chorionic bleeding	PPROM	12	7	Staphylococcus aureus	50	Alive – RDS, Pneumothorax
27	28	810	Singleton Preeclampsia (severe), AEDBF	UAC, UVC, PICC	5	7	Citrobacter	45	Alive – RDS, BPD, Pneumonia, Hydronephrosis
28	31	1550	Singleton, GBS	PPROM	0	7	Group B Streptococcus	54	Alive – intestinal obstruction, surgery, intestinal stricture

29	25	870	Singleton, Preterm Labor, CHORIO	Preterm Labor, CHORIO	29	16	Pseudomonas aeruginosa	48	Alive – severe RDS, PDA (large), BPD
30	28	1190	Singleton, CHORIO, Purulent AF	CHORIO	1	19	Klebsiella pneumoniae	49	Alive – NEC, Pneumonia, ROP, Liver, Cholestasis
31	24	500	Twin Di-Di, AEDBF, HELLP, PREECL	UAC, UVC	10	10	Candida albicans	65	Death – severe RDS, PIE, NEC, died DOL 10
32	26	780	Twin Di-Di, Vaginal bleeding	PPROM, UAC, UVC, PICC	15	10	Coagulase-negative Staphylococcus aureus	59	Alive – RDS, BPD, UTI to Enterobacter
33	28	420	Preterm Labor, MEC staining	UAC, UVC	10	18	Staphylococcus aureus	49	Alive – RDS, BPD, ROP

AEDBF: absent end diastolic blood flow; AF: amniotic fluid; AFI: amniotic fluid index; BPD: bronchopulmonary dysplasia; CHORIO: chorioamnionitis; Di-Di: diamniotic dichorionic; DOL: day of life; GBS: Group B Streptococcus; HELLP: a group of symptoms that occur in pregnant women who have: H — hemolysis EL — elevated liver enzymes LP — low platelet count; HIV: human immunodeficiency virus; IDM: insulin dependent diabetes mellitus; IMV: intermittent mandatory ventilation; ITP: immune thrombocytopenia; IVH: intraventricular hemorrhage; IUFD: intrauterine fetal demise; MEC: meconium; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; PICC: percutaneous intravenous catheter; PIE: pulmonary interstitial emphysema; PIH: pregnancy induced hypertension; PPROM: preterm premature rupture of membranes; PREECL: pre-eclampsia; PROM: premature rupture of membranes; PVL: periventricular leukomalacia; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; TTTS: twin to twin transfusion syndrome; UAC: umbilical artery catheter; UTI: urinary tract infection; UVC: umbilical vein catheter.

birth than premature infants without sepsis. In two previous publications we have shown an excellent correlation between cord plasma Se and postnatal Se at 3 and 37 DOL, and found a significant Se deficiency in extremely premature infants under 30 weeks gestation and <1500 g with severe respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD).[9,10] Since our two previous studies found a significant Se deficiency associated with increased RDS and BPD morbidities, we also looked at the relationship between maternal-infant Se and their various neonatal outcomes such as BPD, ROP, intraventricular hemorrhage (IVH), and mortality in this study.

Methods

This study was approved by the TriHealth Institutional Review Board. Participants were admissions to the Neonatal Intensive Care Unit at Good Samaritan Hospital in Cincinnati, OH from September 2007 to March 2011. Infants included in the cohort had a birth weight between 501 g and 1500 g or a gestational age (GA) between 22 weeks 0 days and 33 weeks 6 days. The GA was determined by Ballard scoring.[11] Infants of mothers who were <34 weeks gestation by best obstetric estimate were consented and if they delivered after 34 weeks gestation were not eligible to be in the study.

We estimated the best GA in weeks using the following hierarchy: 1) obstetrical measurements based on last menstrual period, obstetrical parameters, and prenatal ultrasound as recorded in the maternal chart; and 2) neonatologist's estimate based on physical exam, neurological examination, or combined physical and GA exam by Ballard score.[11] We used cord plasma Se because it correlates with GA and is a good predictor of postnatal Se as our previous work showed preterm infants had significantly lower plasma Se until a postnatal age of 37 days.[9,10]

Late neonatal sepsis (bacterial sepsis or meningitis) is diagnosed if a bacterial or fungal pathogen are recovered during sepsis work-up from a blood and/or cerebral spinal fluid culture obtained after DOL 3 and signs and symptoms suggestive of sepsis are present such as apnea, temperature instability, feeding intolerance, worsening respiratory distress or hemodynamic instability and treatment with five or more days of intravenous antibiotics after cultures were obtained.

Based on previous research,[12] we defined maternal Se deficiency as ≤70 mcg/L and infant's biochemical Se deficiency as ≤60 mcg/L.[9,10]

Demographic information such as ethnicity, sex, birth weight, multiple gestations, diabetes, preeclampsia, maternal cesarean section, and APGAR score was prospectively collected. Additional data including well known risk factors for infection (PPROM, CHORIO, UTI, instrumentation such as internal fetal scalp electrodes, catheter utilization [UAC, UVC, PICC] and mechanical ventilation), respiratory outcomes, RDS, oxygen exposure, BPD were collected. Other neonatal outcomes such as

Figure 2.

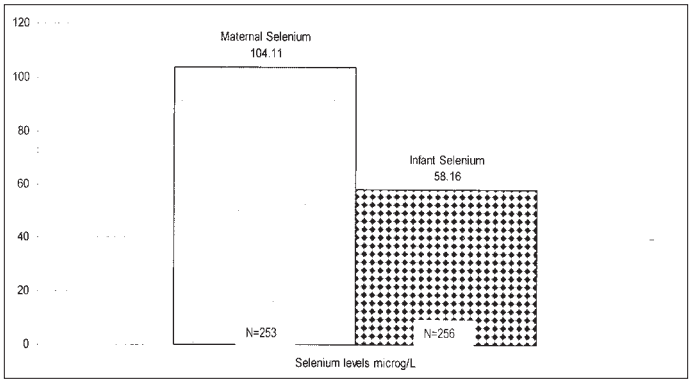


Figure 3.

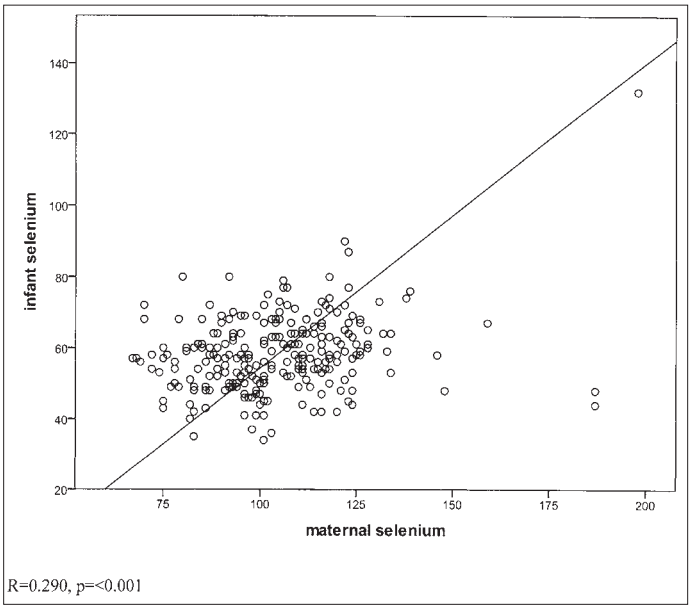


Table 2. Univariate Analysis of Sepsis with Demographic and Risk Factors

Continuous Variables			
Variable	Sepsis, N=33, N ± SD	No Sepsis, N=223, N ± SD	p-value
Gestational age (weeks)	27.2 ± 2.4	30.3 ± 2.1	<0.001
Weight (g)	994.1 ± 320.5	1447.6 ± 411.8	<0.001
Apgar 1 minute	3.6 ± 2.2	6.1 ± 2.5	<0.001
Apgar 5 minutes	6.4 ± 2.0	8.2 ± 1.3	<0.001
Maternal Se	113.9 + 17.2	102.6 ± 18.8	0.001
Infant Se	56.4 ± 9.4	58.4 ± 11.0	0.313
Categorical Variables			
Variable	Sepsis, N=33, N (%)	No Sepsis, N=223, N (%)	p-value
Sex			
Male	19 (58)	115 (52)	0.519
Female	14 (42)	108 (48)	
Race			
Caucasian	22 (67)	172 (77)	0.190
African-American	11 (33)	51 (23)	
Birth			
Single	19 (58)	140 (63)	0.109
Twin	14 (42)	65 (29)	
Triplet	0 (0)	18 (8)	
Delivery			
Vaginal	13 (39)	78 (35)	0.621
C-Section	20 (61)	145 (65)	
Gestational age (less than 30 weeks)	28 (85)	75 (34)	<0.001
Pre-eclampsia	3 (9)	60 (27)	0.027
Diabetes	2 (6)	43 (19)	0.063
AGA/SGA/LGA			
Appropriate	31 (94)	197 (88)	0.442
Small	2 (6)	16 (7)	
Large	0 (0)	10 (5)	
Risk Factors	32 (97)	158 (71)	<0.001
O2 Exposure	32 (97)	156 (70)	<0.001
Mechanical Ventilation	28 (85)	66 (30)	<0.001
Infant Se (deficient)	23 (70)	127 (57)	0.165
BPD 36 weeks	22 (67)	33 (15)	<0.001
PDA	22 (67)	44 (20)	<0.001
CHF	13 (39)	25 (11)	<0.001
RDS/SEV	30 (91)	120 (54)	<0.001
Air Leak	8 (24)	10 (5)	<0.001
IVH	8 (24)	12 (5)	<0.001
Pneumonia	11 (33)	2 (1)	<0.001
NEC	9 (28)	14 (6)	<0.001
ROP	16 (50)	31 (14)	<0.001
Mortality	5 (15)	3 (1)	0.001

Risk Factors: PPROM, CHORIO, UAC, UVC, PICC

patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), ROP, IVH and mortality were also prospectively collected. The clinical diagnosis of BPD was determined by supplemental use of oxygen or mechanical ventilation dependence at a corrected GA of 36 weeks post conception. IVH grade II or higher was diagnosed by cranial ultrasound and/or cranial tomography (CT). RDS, PDA, NEC and IVH were also diagnosed per Vermont Oxford Data Base criterion.[13] Criteria for "severe" RDS included those infants who required positive pressure mechanical ventilation through an endotracheal tube for more than 48 hours and inspired oxygen concentration in excess of 0.6 (FiO2 = 60%). ROP stage II or higher was diagnosed by an eye exam prior to discharge with staging according with the International Classification of ROP.[8]

Laboratory Techniques

Maternal and cord blood plasma Se were measured using IPC-MS techniques. After informed consent was obtained, 3-5 ml of anticoagulated blood was drawn from the umbilical cord at birth using Monoject trace element venous blood collection tubes containing sodium heparin. Just prior to delivery or at the time of delivery blood was collected from the mother to measure maternal plasma Se levels.

All specimen processing was performed in the Hatton Biochemical Laboratory by a single senior chemist who was "blinded" to the clinical data. Pre-analysis processing consisted of centrifugation of whole blood at 1500 x g for 10 minutes 4 °C. After centrifugation, plasma was transferred to an acid washed 2ml micro centrifuge tube and stored at -70 °C. For ICP-MS plasma Se determination, samples stored at -70 °C were brought to room temperature. Plasma samples and control samples were then diluted 1:20 with a diluent of 1% ultrapure nitric acid, 10% ethanol, and 0.5% Triton -X. Calibration standards were prepared with the same matrix and all samples, standards and controls were spiked with a 12 mcg/L gallium internal standard. Diluted plasma samples, controls and calibration standards were then introduced to the ICP-MS spectrophotometer for analysis of Se concentration.

Statistics

Assuming a rate of late sepsis (late bacterial or coagulase negative staph) of 14% (based on our recent statistics from the Vermont-Oxford database)[13] and expecting to see 80% of the infants who have late onset sepsis to also have Se deficiency, the study needed a total of 200 infants (172 without sepsis and 28 with sepsis for a 14% rate of late sepsis) to achieve 80% power to detect a difference between 80% Se deficiency among septic infants and 50% deficiency among non-septic infants (30% reduction). A two-sided significance level of 0.05 was used. SPSS 19.0 statistical software (SPSS, IBM Corporation, NY, USA) was used to calculate all statistical analyses.

Descriptive statistics including mean and range were calculated on all continuous variables. Frequencies and percentages were calculated for all categorical variables. Chi-square analyses were conducted comparing sepsis outcome with all categorical variables and student t-test were conducted comparing sepsis outcome with all continuous variables. Chi-square and student t-test analysis were then conducted comparing infant Se levels with all other variables. Correlations examining the relationship of infant and maternal Se with sepsis and other variables were conducted. Logistic regression was used to examine Se in the

Table 3. Univariate Analysis of Infant Se with Demographic and Risk Factors

Continuous Variables			
Variable	Infant Se Deficient (<60 microg/L) N=150, N ± SD	Infant Not Se Deficient (≥60 microg/L) N=106, N ± SD	p-value
Gestational age (weeks)	29.6 ± 2.5	30.3 ± 2.0	0.210
Weight (grams)	1361.5 ± 451.7	1428.2 ± 392.5	0.012
Apgar 1 minute	5.8 ± 2.4	5.9 ± 2.8	0.643
Apgar 5 minutes	7.9 ± 1.5	8.0 ± 1.6	0.612
Maternal Se	101.1 ± 18.9	108.1 ± 18.2	0.003
Categorical Variables			
Variable	Infant Se Deficient (<60 microg/L) N=150, N (%)	Infant Not Se Deficient (≥60 microg/L) N=106, N (%)	p-value
Sex			
Male	88 (59)	46 (43)	0.016
Female	62 (41)	60 (57)	
Race			
Caucasian	121 (81)	73 (70)	0.030
African-American	29 (19)	33 (31)	
Birth			
Single	88 (59)	71 (67)	0.293
Twin	49 (33)	30 (28)	
Triplet	13 (9)	5 (5)	
Delivery			
Vaginal	56 (37)	35 (33)	0.477
C-Section	94 (63)	71 (67)	
Gestational age (less than 30 weeks)	70 (47)	33 (31)	0.013
Pre-eclampsia	35 (23)	28 (26)	0.573
Diabetes	34 (23)	11 (10)	0.011
AGA/SGA/LGA			
Appropriate	132 (88)	96 (91)	0.421
Small	13 (9)	5 (5)	
Large	5 (3)	5(5)	
Risk Factors	114 (76)	76 (72)	0.438
Sepsis	23 (15)	10 (9)	0.165
Antibiotics	130 (87)	80 (76)	0.022
O2 Exposure	120 (80)	68 (64)	0.005
Mechanical Ventilation	61 (41)	33 (31)	0.110
BPD 36 weeks	41 (27)	14 (13)	0.007
Sepsis	23 (15)	10 (9)	0.165
PDA	48 (32)	18 (17)	0.007
CHF	26 (17)	12 (11)	0.183
RDS/SEV	96 (64)	54 (51)	0.037
Air Leak	10 (7)	8(8)	0.786
IVH	15 (10)	5 (5)	0.122
Pneumonia	11 (7)	2 (2)	0.051
NEC	16 (11)	7 (7)	0.259
ROP	34 (23)	13 (13)	0.038
Mortality	3 (2)	5 (5)	0.218

Risk Factors: PPROM, CHORIO, UAC, UVC, PICC

outcomes of sepsis and BPD at 36 weeks while controlling for other significant risk factors for both outcomes.

Results

Descriptive Statistics

A total of 256 infants met the inclusion criteria and were consented for the study. Only 10% of eligible patients refused to consent to this study. There were 6 patients born in 2007, 89 born in 2008, 62 born in 2009, 81 born in 2010, and 18 born in 2011. Of these infants, 52% (134) were male and 48% (122) were female. Seventy-six percent (194) of the infants were white and 24% (62) were African American. Overall, 63 (25%) mothers developed antepartum preeclampsia and 45 (18%) mothers developed gestational or had preexisting insulin dependent diabetes. The delivery method was vaginal for 36% (91) of the infants and C-section for 64% (165) of the infants. Single birth occurred 61% (159), twin birth occurred 31% (79), and triplet birth occurred 7% (18). Eighty-eight percent (228) of these infants were appropriate for GA (AGA); however, 7% (18) were small for GA (SGA), and 4% (10) were large for GA (LGA). The mean birth weight was 1,389 ± 429 g. The mean GA at birth was 29.9 ± 2.3 weeks with 59% (153) of the infants 30 weeks or older and 40% in this study (103) of the infants less than 30 weeks. The median APGAR at one minute was 6 and at five minutes was 9. There were eight neonatal deaths in this study for a mortality rate of 3%.

Maternal Se level ranged from 67 to 198 mcg/L with a mean of 104 ± 18.9 mcg/L. A majority of the mothers were not Se deficient (98%). Although not deficient, pre-eclamptic mothers had lower Se than non-pre-eclamptic mothers (average of 101.2 mcg/L versus 105.1 mcg/L) (p=0.056) (Figure 1). Infant Se level ranged from 34 to 132 mcg/L with a mean of 58.2 ± 10.7 mcg/L. Infant Se deficiency, defined as a Se level at delivery of less than 60 mcg/L[9,10,12] occurred in 59% (150) of the infants. Forty-seven percent (70/150) of the Se deficient infants were under 30 weeks gestation. Sepsis occurred in 13% (33) of the infants: 28 of the 33 were < 30 weeks GA and 5 were ≥ 30 weeks GA. Table 1 describes the characteristics of the infants who developed sepsis between the ages of 4 and 31 DOL. Five out of 33 septic infants died from neonatal sepsis (15%) due to the following microorganisms: Klebsiella, Staphylococcus aureus, Beta Hemolytic Streptococcus Group B, Escherichia coli, Candida albicans and Pseudomonas aeruginosa (Table 1).

Univariate Analysis

The analysis examining sepsis outcome found several significant demographic and risk factor variables for sepsis (Table 2). Infants with a GA of <30 weeks, a lower birth weight, a lower one minute APGAR, and a lower five minute APGAR were more likely to have sepsis as suspected. PPROM, CHORIO, and catheter utilization (VAC, UVC, PICC) were significant risk factors for developing sepsis. Oxygen exposure and mechanical ventilation in days, maternal preeclampsia, and higher maternal Se level were also all significant risk factors for developing sepsis. The analysis examining the sepsis outcome with other outcomes found that infants with sepsis were also more likely

Table 4. Multivariate logistic regression relating sepsis and risk factors

Variable	Estimated Slope Coefficient	Standard Error	Adjusted OR	95% CI	p-value
Intercept	-1.603	1.940	---	---	---
BirthWeight (grams)	-0.002	0.001	0.998	0.996-1.000	0.039
Maternal Se (mcg/L)	0.019	0.012	1.019	0.996-1.043	0.107
Infant Se (mcg/L)	0.002	0.021	1.002	0.961-1.044	0.934
Mechanical Vent (days)	0.107	0.029	1.113	1.051-1.178	<0.001
Gestational Age (<30 weeks)	-0.327	0.715	0.721	0.177-2.928	0.647
Sepsis risk (VAC, UVC, chorioamnionitis, PICC)	-1.308	1.094	0.270	0.32-2.309	0.232
Infant Sex (Female)	-0.215	0.501	0.807	0.302-2.155	0.668
Race (African American)	-0.488	0.532	0.614	0.216-1.742	0.359
Gestations (Multiple)	-0.193	0.498	0.825	0.311-2.189	0.699
Delivery (C-Section)	0.622	0.516	1.863	0.678-5.118	0.228

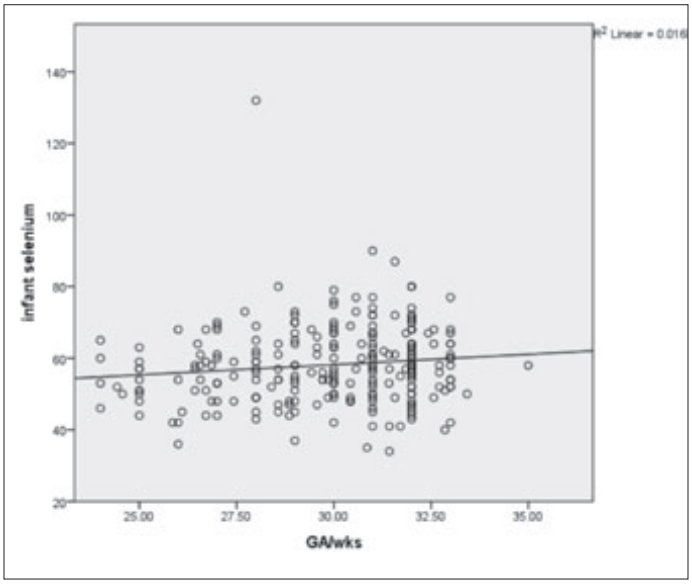
to have severe RDS, PDA, CHF, BPD at 36 weeks, pulmonary air leak, IVH, pneumonia, NEC, ROP, and mortality. Se deficient infants did not have an increase in sepsis.

As expected the infants who developed sepsis were a "sicker" population of infants as judged by their associated morbidities, such as RDS and BPD, and they had significantly more traditional risk factors for infections (PPROM, CHORIO, and catheter utilization) for sepsis (Table 2).

The univariate analysis examining infant Se (deficient or not deficient) found multiple significant demographic and risk factor variables (Table 3). Se deficient infants (<60 mcg/L) were more likely to be Caucasian, male, have lower birth weights, and be <30 weeks gestation. The Se deficient infants were also more likely to be exposed to oxygen, have mothers with diabetes, and have mothers with a lower maternal Se level. The analysis examining the infant Se levels (deficient or not deficient) found several significant outcome variables: Se deficient infants were more likely to have severe RDS, PDA, BPD at 36 weeks and ROP.

A subset analysis compared maternal Se level, infant Se level, sepsis, and mortality in infants 30 weeks GA and older to infants <30 weeks GA (using 30 weeks as a categorical variable rather than a continuous variable). Maternal Se levels significantly differed between infants 30 weeks GA and older (99.8 ± 16.2 mcg/L) to infants less than 30 weeks GA (110.8 ± 21.0 mcg/L) ($p \leq 0.001$). There was no significant difference in infant Se level between infants 30 weeks GA and older (59.1 ± 10.1 mcg/L) to infants less than 30 weeks GA (56.7 ± 11.5 mcg/L) (p=0.073). The sepsis rate significantly differed between infants 30 weeks GA and older (5 infants, 3%) to infants less than 30 weeks GA (28 infants, 27%) (p=<0.001). The mortality rate also significantly differed between infants 30 weeks GA and older (1 infant, 0.7%) to infants <30 weeks GA (7 infants, 7%) (p=0.006).

Figure 4.



R=0.125, p=0.046
Infant Se deficiency defined as less than 60 microg/L.

Several correlations were conducted. First, a Pearson correlation with maternal Se and infant Se levels was computed. Infant Se levels significantly increased as maternal Se levels increased (R=0.290, p=<0.001) (Figure 2 and Figure 3). When maternal Se levels were low, infant Se levels were also low. Next, a correlation between sepsis and maternal Se was conducted and found a significant relationship. The risk of sepsis increased as maternal Se levels increased (R=0.220, p=<0.001). A correlation with sepsis and infant Se level found no significant relationship (R=-0.063, p=0.313). Another correlation that examined the relationship of age in gestational weeks and infant Se level found a significant positive correlation (R=0.125, p=0.046) (Figure 4).

Multivariate Regression

The logistic regression model for risk factors regressed on sepsis, controlling for the variables listed in the first column of Table 4, found infant weight (p=0.039, adjusted OR=0.998, 95% CI=0.996-1.00) and days on mechanical ventilator (p<0.001, adjusted OR=1.113, 95% CI=1.051-1.178) had a significant impact on the risk for developing sepsis (Table 4). This model indicated that sepsis is more likely to occur in infants with a lower birth weight and with infants that had a greater number of days on a mechanical ventilator. The other factors (maternal Se level, infant Se level, GA, sepsis risk based on risk factors, gender, sex, race, GA, and route of delivery) did not impact significantly impact the sepsis outcome. The model adequately fit the data (Hosmer and Lemeshow significance = 0.985).

The logistic regression model for risk factors regressed on BPD at 36 weeks (Table 5) found that days of oxygen exposure (p<0.001, adjusted OR=1.096, 95% CI=1.057-1.138), days on mechanical ventilator (p=0.002, adjusted OR=1.321, 95% CI=1.109-1.573), and infant Se level (p=0.032, adjusted OR=1.070, 95% CI= 1.006-1.139) had a significant impact on the risk for developing BPD at 36 weeks (Table 5). This model indicates that BPD at 36 weeks is more likely to occur in infants that

Table 5. Multivariate logistic regression relating BPD at 36 weeks and risk factors

Variable	Estimated Slope Coefficient	Standard Error	Adjusted OR	95% CI	p-value
Intercept	-8.028	3.091	-----	-----	-----
Gestational Age (<30 weeks)	-0.973	0.850	0.378	0.071-1.999	0.252
Oxygen Exposure (days)	0.092	0.019	1.096	1.057-1.138	<0.001
Mechanical Vent (days)	0.278	0.089	1.321	1.109-1.573	0.002
Sex (Female)	-0.063	0.594	0.939	0.293-3.009	0.915
Race (African American)	1.309	0.828	3.704	1.731-18.775	0.114
Weight (grams)	0.001	0.001	1.001	0.999-1.003	0.463
Delivery (C-Section)	0.503	0.630	1.653	1.481-5.685	0.425
Gestations (Multiple)	-0.654	0.618	0.520	0.155-1.744	0.289
Gestational Size (Large or Small)	-0.910	0.947	0.402	0.063-2.575	0.336
Air Leak	1.042	1.032	2.836	0.375-21.421	0.312
Maternal Se	-0.019	0.018	0.982	0.947-1.017	0.310
Infant Se	0.068	0.032	1.070	1.006-1.139	0.032

experienced a greater number of days with oxygen exposure and a greater number of days on a mechanical ventilator and simultaneously had low cord plasma Se at birth. The other factors in this regression model (GA, sex, race, weight, delivery, singleton or multiple gestation, gestational size, air leak, and maternal Se level) did not have a significant impact on developing BPD at 36 weeks. The model adequately fit the data (Hosmer and Lemeshow significance = 0.533).

Discussion

During the last 10 years the incidence of neonatal sepsis at our institution has been 10.6% among 1,752 infants born with birth weights between 501 g to 1,500 g.[13] The mortality from sepsis varies from 12% to 20% in this extremely high risk group of infants in our institution.

A majority (98%) of the mothers in this study <34 weeks gestation were not Se deficient. Only three of the maternal patients (1.2%) had serum Se levels at delivery <70 mcg/L, considered to be Se deficient.[12] A few studies have investigated Se and preterm labor. Cross sectional studies in India, Holland, Germany and Iran have all reported lower plasma Se concentrations in women delivering preterm as compared with women delivering at term.[14]

A study in Poland reported lower maternal and cord blood Se in 46 women who delivered preterm compared with 42 women delivering at term. In this study their low Se and glutathione peroxidase concentrations may have contributed to their susceptibility to sepsis.[15]

A study from the United States of 13 premature and 15 term infants also reported Se deficiency in premature infants, although maternal Se concentrations were normal.[16] This is in agreement with our study findings. Dietary intake in most parts of Europe is lower than in the United States. For example, the daily Se intake (96-134 mcg) was three times higher in the US population compared to the Polish population.[15]

Dietary intake of Se varies tremendously among different populations. Factors that affect the intake include the geographic origin of the food items and the meat content of the diet. Tap water and vegetarian diets in the US contain very little Se. We reported in a previous study[9] an investigation of the maternal dietary intake of Se and other nutrients and found that the intake of Se, macronutrients and vitamin E were all adequate in our Cincinnati, Ohio population and that there was not a difference in Se intake between full term and preterm pregnancies. Since Se deficiency (<70 mcg/L) occurred in only three mothers (1.3%) we concluded that the Se intake in our population of mothers was adequate.

Infant Se

Cord plasma Se levels ranged from 34 to 132 mcg/L with a mean of 58.2 ± 10.7 mcg/L. Infant Se deficiency (<60 mcg/L)[9,10,14] occurred in 151 (58%) of our infant population. In our two previous studies[9,10] we found similar Se deficiencies at birth. This deficiency is probably due to a "shortened" gestation because of placental transfer and Se storage in the fetal liver occuring between 28 and 40 weeks. The mean GA in the present study was 29.9 ± 2.3 weeks. We previously reported that Se deficiency in premature infants under 30 weeks gestation was significantly associated with increased respiratory morbidities such as RDS and BPD.[9,10]

Se deficient infants (<60 mcg/L) were more likely to be Caucasian male with a lower birth weight and <30 weeks gestation ($p < 0.01$, Table 2). The Se deficient infants were more likely to be exposed to oxygen ($p < 0.005$), have mothers with diabetes ($p < 0.01$) and have mothers with lower Se levels ($p < 0.003$, Figure 3). A review of the literature did not find mention of a causal relationship between male gender and Se deficiency. Several studies from China, Kuwait, Turkey and the USA[17] have shown a decrease in maternal plasma Se levels in women with gestational diabetes. Plasma Se deficiency during pregnancy is associated with glucose intolerance,[17] suggesting that Se deficiency may affect glucose metabolism downstream from insulin.

The analyses examining the infant Se levels (deficient or not deficient) found that Se deficient infants were more likely to have an increased respiratory morbidity (RDS and BPD) as we found in a previous study[9,10] (Table 3). We did not study postnatal Se intake in breast milk formula and total parenteral nutrition (TPN). This Se deficiency in the neonate "persists" for as long as 5 weeks, as we have previously demonstrated.[9,10] The low levels of Se at 3 and 37 days respectively in our previous work was possibly explained by the lack and/or insufficient intravenous Se supplementation after birth rather than poor maternal nutrition and/or maternal Se levels and it supports the validity of using cord blood Se values as a screening alternative to the most difficult blood extractions in the neonate.

Sepsis

In the univariate analysis section of our study (Tables 2 and 3), we found equivalent Se levels in the septic (n=33) and "nonseptic" infants (n=223). One hundred fifty Se deficient premature infants did not have an increased sepsis outcome yet the analysis examining sepsis outcome, when we used GA

30 weeks as a categorical variable, found that sepsis was more likely to occur under 30 weeks gestation with lower birth weight and lower Apgar score. This confirmed previous research that found a higher degree of prematurity and a lower weight at birth resulted in a higher rate of sepsis.[8] Sepsis was also more common in males. As expected, well known traditional risk factors for sepsis such as PPROM, CHORIO, catheter utilization (VAC, UVC, PICC), mechanical ventilation, and oxygen exposure were also significantly associated with sepsis (Tables 2 and 4).

Preeclampsia

Maternal preeclampsia and higher maternal serum Se were also found to increase the risk for developing sepsis (Table 2). Maternal and cord blood Se and glutathione peroxidase has been shown to be lower in pre-eclamptic pregnancies;[18] however our study confirmed lower Se in pre-eclamptic mothers. There was no significant difference in the rate of preeclampsia between Se deficient and non-deficient infants (Table 3). Serum Se concentrations in one study from the USA have been reported higher than in Europe in pre-eclamptic women.[18] In the European studies reduced GPx could be associated with an increased generation of toxic lipid peroxide contributing to the endothelial dysfunction and hypertension of the Se deficient pre-eclamptic women.[18]

The higher maternal Se levels we found in septic infants seems to validate the findings in our premature infants that perinatal Se deficiency is not associated with neonatal sepsis. It is possible that even if they were deficient in their plasma levels, their liver storage of Se were adequate. Infants with sepsis were more likely to have severe RDS, PDA, pulmonary air leak, pneumonia, BPD at 36 weeks gestation, NEC and mortality (Table 2).

The subset analysis that compared maternal Se, infant Se levels and mortality in infants 30 weeks GA and older to infants less than 30 weeks gestation demonstrated that even though the sepsis rate and mortality was significantly greater under 30 weeks gestation there was not a significant difference in Se levels in infants 30 weeks GA and older using GA as a categorical variable.

A Pearson correlation that examined the relationship of GA and infant Se levels found a significant positive correlation (Figure 4). This finding is in agreement with Iranpour who also found cord plasma Se was strongly correlated with GA and birth weight.[19] A Pearson correlation in our study also determined that infant Se levels also increased when maternal Se increased (Figures 1 and 2). When maternal Se levels were low, infant Se levels were also low. We have no explanation as to "why" the risk for sepsis increases as maternal serum Se levels increased. This warrants further research to be conducted in this area. A correlation with sepsis and infant Se levels found no significant relationship. Our interest in the impact of Se on sepsis was motivated by Darlow et al,[6] who published in 2000, on the effect of Se supplementation on outcome in infants with birth weight under 1500 g. Subsequent Cochrane Review by Darlow in 2004 showed supplementation with Se was associated with a reduction in one or more episodes of sepsis. This data was dominated by one large trial from a country with low Se concentrations that may not pertain or be applicable to our US population where Se deficiency is rare.[6]

Multivariate Regression

The logistic regression model for risk factors regressed on sepsis found only infant's weight and days on mechanical ventilation to have a significant impact on sepsis. The other factors including maternal and infant Se levels did not significantly impact the sepsis outcome. Even though our infants were Se deficient, Se did not seem to play a role in the incidence of neonatal sepsis yet well known risk factors for infections, such as PPROM, CHORIO, UAC, UVC and PICC, significantly contributed to sepsis development (Tables 1 and 4). Neither maternal Se levels nor infant Se levels seem to have contributed to the development of sepsis disproving our main hypothesis that Se deficiency leads to sepsis. As we were also interested in the impact of Se levels in other morbidities we found in the logistic regression on BPD at 36 weeks, that oxygen exposure, days on mechanical ventilation, and infant Se level had a significant impact on the risk for developing BPD at 36 weeks (Table 4). These results confirm our previous work.[9,10]

Conclusions

In summary we found a significant biochemical Se deficiency at birth in premature infants <34 weeks GA. Their Se levels were about half of their mother's levels, who were 98% Se sufficient. Se at birth correlated with GA and Se deficiency was associated to a shortened gestation. Se levels at birth did not have any impact on the incidence of late sepsis. Traditional risk factors for sepsis: extreme prematurity(<30 weeks), PPROM, chorioamnionitis and invasive catheterization (UAC,UVC,PICC's), significantly contributed to sepsis. We found Se deficiency had a strong relationship in the development of BPD showing that extremely premature infants with RDS and undergoing therapy with oxygen and mechanical ventilation suffered perhaps the lack of Se-glutathione peroxidase antioxidant activities and developed BPD. BPD remains a multifactorial disease and Se plays a significant role in its development.

References

1 Kiremidjian-Schumacher L, Stotzky G: Se and Immune Responses. Environ Res 1987;22:277-303.
2 Beck MA: Se and Host Defense Towards Viruses. Proc Nutr Soc 1999;58:707-711.
3 Kukreja R, Khan A: Effect of Se Deficiency and its Supplementation on DTH response, Antibody Forming Cells and Antibody Titre. Indian J Exp Biol 1998;36-:203-205.
4 Boyne R, Arthur JR: The Response of Se-Deficient Mice to Candida Albicans Infection. J Nutr 1986;116:816-822.
5 Dylewski ML, Mastro AM, Picciano MF: Maternal Se Nutrition and Neonatal Immune System Development. Biol Neonate 2002;82:122-127.
6 Darlow BA, Winterbourn CC, et al. The Effect of Se Supplementation on Outcome in Very Low Birth Weight Infants: A Randomized Controlled Trial. Journal of Pediatrics 136(4); 2000:473-80.
7 Darlow BA, Austin NC. Se supplementation to prevent short term morbidity in preterm infants. Cochrane Review. The Cochrane Library, Issue 4, 2004, UK John Wiley and Sons.
8 Neonatal Bacterial Sepsis in Avery's Diseases of the Newborn. 9th edition. Elsevier Saunders 2012; 538-550 & 1539-1543.
9 Falciglia HS, Johnson JR, Sulivan J, Hall CF, Miller JD, Riechman GC, et al. Role of Antioxidant Nutrients and Lipid Peroxidase in Premature Infants with Respiratory Distress Syndrome and Bronchopulmonary Dysplasia. Am J Perinat Vol 20(2); 2003:97-107.
10 Falciglia HS, Ginn-Pease ME, Falciglia GA, Lubrin AH,

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Preterm Feeding Competence in the NICU: Research Investigations of Breast and Bottle-feeding

Jean Rhodes, PhD, CNM, IBCLC

For most preterm infants attainment of full oral feeds is one of the final indicators of readiness for discharge. Meeting this goal requires development of both sufficient feeding stamina and coordination of sucking, swallowing and breathing. Since each baby matures at a different pace, attaining feeding proficiency requires daily multidisciplinary evaluation and management of feeding plans as well as coordination with families regarding feeding preferences, interventions and plans.

Incorporating breastfeeding into NICU practice has progressed slowly over the last several decades. During the 1970s as neonatal intensive care units were becoming the standard of care for premature infants, United States breastfeeding rates were at their nadir; therefore, practices, policies and technology to support breastfeeding and human milk feeds were in the early stages of development. Since that time, extensive research describing benefits of human milk for preterm infants has stimulated demand for human milk for preterm infant as well as support for their pump-dependent mothers. However, clinical studies specific to preterm feeding skills at breast are much less common.

Outside of the NICU, breastfeeding is considered the exemplar for human feeding. During breastfeeding, mothers and infants respond physiologically to one another almost instantaneously, regulating milk production, flow, consumption and demand. Inside the NICU, most of our knowledge of preterm infant feeding progression is based on a bottle-feeding paradigm. The purpose of this article is to evaluate breastfeeding research for a new look at preterm feeding practices.

Preterm Infant Responses to Breast and Bottle-feeding in the NICU

In 1985, one of the earliest studies of physiologic responses to different feeding methods was published by Meier and Pugh.[1] Their research of preterm infants feeding suggested these infants responded differently when breastfeeding than when they were bottle-fed. The authors reported the breastfeeding sessions with immature babies lasted longer than bottle-feeding sessions, but infants were better able to self-regulate the pace of feedings and had more coordinated sucking and swallowing.

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Within a few years, Meier[2] reported additional evidence of NICU infant responses to bottle-feeding compared to breastfeeding. In a 1988 study of five preterm infants — with infants serving as their own controls — 71 feeding sessions were monitored for transcutaneous PO2 (tcPO2) and body temperature changes. Results demonstrated transcutaneous oxygen pressures decreased during bottle-feeding but not during breastfeeding. Meier hypothesized these tcPO2 pattern differences might be due to fewer interruptions in breathing, perhaps in part to non-nutritive sucking (NNS) during breastfeeding, which allowed infants to breathe instead of stopping to swallow. Thus infants maintained more stable tcPO2 levels, especially at the end of feedings.

In this study[2] and in the previous study with Pugh,[1] Meier suggested breastfeeding preterm infants are probably at least as stable physiologically as infants who are bottle-feeding. In 1989 Mathew and Bhatia[3] published similar data comparing responses to bottle- and breastfeeding in term infants. Of 15 healthy term newborns fed by both methods, bradycardia was noted in two bottle-feeding sessions but in none of the breastfeeding sessions. Likewise, oxygen saturations less than 90 were identified in 50% of bottle-feedings compared to 20% of breastfeeding sessions. Mathew[4] also published data reporting a high frequency of cardiopulmonary disturbances in 35-36 week preterm infants within their first two weeks of bottle-feeding. These disturbances included short and prolonged apnea, bradycardia and decreased oxygen saturations. However, he did not compare these results to breastfeeding sessions in the same population.

In terms of feeding effectiveness, some studies have suggested preterm infants transfer lower milk volumes during breastfeeding than during bottle-feeding, with breastfeeding transfer rates insufficient for necessary weight gain.[5-7] But more recent research suggests otherwise. In 2009 Berger et al[8] evaluated milk intake, length of feeding, and resting energy expenditure immediately after breast and bottle-feeding in preterm babies. Not surprising, average feeding durations were longer when infants breastfed, however, there was no statistical difference in volume of milk transferred by feeding method (42.2 mL by breast versus 43.5 mL by bottle) or in resting energy expenditure.

Focus of Preterm Feeding Research on Artificial Teats and Bottles

Despite these promising results, research on the mechanics and physiology of breastfeeding in preterm infants is the

exception, while studies of bottle-feeding and development of preterm feeding skills outside the realm of breastfeeding are the norm. Historically, studies of preterm feeding have focused on bottle-feeding skills or equipment. For example, in 1989 Mathew[9] evaluated multiple brands and types of artificial nipples, determining there was wide variability in flow characteristics. Regarding bottle nipples for preterm infants, Mathew concluded, "the high incidence of feeding-related apnea and/or bradycardia in premature infants may be related in part to the use of high flow nipples units" (p.691).[9] In a separate study, Mathew[10] determined milk flow from an artificial nipple is most related to hole size and in a separate study he concluded milk flow — especially from high flow nipples — reduces ventilation during bottle-feeding and that preterm infants have a limited capacity to regulate milk flow.[11]

Human nipples are obviously very different from bottle nipples in terms of numbers of ductal openings, tactile consistency, and responsiveness of nipple tissue to stimulation. Milk flow varies during breastfeeding, regulated by infant sucking patterns and augmented by maternal hormonal responses (milk ejection reflex). Thus, literature related to milk flow from artificial nipples has little relevance for infant feeding at breast.

Breastfeeding Dynamics

Recent ultrasound studies of breastfeeding infants by Geddes, Sakalidis and associates[12-19] demonstrate infants remove milk during breastfeeding by suction. For both term and preterm infants, a suck cycle begins with the mid-tongue up and in close contact with the palate, compressing the nipple from tip to base. The tongue then moves downward, with the anterior portion of the tongue lowering to a lesser degree than the mid-portion. The mid-tongue reaches its lowest point; the nipple evenly expands in size, moving closer to the junction of the hard and soft palates. Milk ducts open and milk flows into the intra-oral cavity. The tongue then rises until it is back in contact with the palate again. Milk remains in the intra-oral space until the mid-tongue returns to the palate. Then the infant swallows.[12,13,18,19] Preterm infants' sucking dynamics have been found to be similar but vacuum levels are not as strong.[14]

This model of milk removal is very different from the mechanics of milk removal during bottle-feeding described above by Mathew.[9-11,14] Breastfeeding intraoral dynamics described by Geddes and Sakalidis have since been applied to the design of an artificial nipple for bottle-feeding that requires vacuum creation for milk removal. Additional study reveals no differences in term infants' oxygen saturation and heart rates during breastfeeding or feeding with this artificial teat.[15,17] These studies are a reversal of the normal trend in infant feeding research, because they exemplify breastfeeding science informing bottle-feeding practices rather than breastfeeding practices guided by bottle-feeding norms.

The Role of Central Pattern Generators and Non-Nutritive Sucking

Steven Barlow is well known in the Speech-Language-Hearing sciences for his work in neurological modeling of human feeding behaviors associated with central pattern generators in the brainstem.[20-23] According to Barlow, the suck central pattern generator (sCPG) is modulated by sensorimotor inputs and connections in the cerebellum that regulate ororhythmic activity.[22] Overall, sensorimotor control of oral feeding involves coordination of several brainstem central pattern generator networks that control suck, swallow and breathing. Each network or CPG can mature at a different rate, complicating coordination of feeding skills in preterm and compromised infants.[20-23]

Human suck behaviors appear in utero with non-nutritive sucking (NNS) observed between 28-32 weeks, stabilizing into predictable patterns in healthy preterm infants generally between 32-34 weeks gestation.[22,24] However, nutritive suck (NS) involving coordination of suck-swallow-breathe is not usually seen in humans until 34 weeks or later. In many studies, enhanced NNS opportunities are correlated with improved feeding and swallowing, reduction of time to oral feeds and reduced length of hospital stay.[25-27]

Complicating development of feeding skills are illnesses that delay ororythmic pattern formation required for effective suck and development of feeding skills.[28] In 2012 Barlow[28] and associates published a study exploring non-nutritive suck (NNS) burst patterns in both healthy preterm infants and those with a history of respiratory distress syndrome (RDS). Coordinated NNS — defined as burst-to-burst patterns that are similar and only minimally variable — indicated healthy neural development of the suck central pattern generator (sCPG). Development and integrity of the sCPG are foundational to coordination of other feeding skills such as swallowing and breathing.

In this study, the authors identified a basic, well-organized NNS burst-pause pattern in healthy preterm infants by 32 weeks postmenstrual age. However, preterm infants with RDS had markedly different NNS burst-pause patterns with shorter NNS burst lengths and a more rapid decline in frequency of sucks. The authors attributed altered and less coordinated NNS burst patterns of RDS infants to impeded sCPG development, speculating developmental delays occur with sensory deprivation and motor restrictions associated with treatments for RDS. These include prolonged nasogastric feeding, the presence of endotracheal tubes, respiratory support devices secured to the face, and restricted movements and sensations of hands and fingers.

Human non-nutritive suck capabilities precede nutritive suck and advancement of oral feeding skills. Thus, many studies have examined interventions to stimulate maturation of patterned NNS. Barlow and others have proposed cross-system interactions between pathways of CPGs can influence development of one another through a process of entrainment.[20-23,29-31] For example, non-nutritive suck trainers — mechanized pacifiers capable of producing patterned oral stimulation — have been shown to facilitate NNS burst-pause pattern development in preterm infants and to increase sucking pattern stability resulting in increased oral feedings.[29,30] Other interventions in preterm infants including various methods of stimulation — oral, bodily tactile (stroking) and kinesthetic (range of motion exercises) have been shown to enhance nutritive sucking and swallow-breathe coordination.[32,33]

Interventions to Enhance Feeding Progression

A recent study by Lau and Smith[34] suggests preterm infants' feeding progression can be enhanced by novel stimuli. In this research the authors evaluated the effects of two interventions on preterm feeding performance and length of time to attain oral feeding proficiency. Seventy healthy preterm infants -- born between 24-33 weeks gestation — were randomized into 3

groups including: 1) a control group receiving NICU standard of care; 2) a group that received a specific non-nutritive sucking exercise; and 3) a group that received very small milk boluses to encourage swallowing. In this study, all infants received pacifiers for NNS as part of NICU standard of care.

Study findings included that the NNS exercise did not accelerate oral feeding performance. The authors hypothesized this was possibly due to the limited oral structures stimulated by the exercise. They noted some aspects of infants' cheeks, gums, lips and tongue were not stimulated, and thus, tactile stimulation necessary for improved feeding was limited.

However, introducing small milk boluses as soon as ventilator support and CPAP were discontinued did improve feeding progress. Consistent with Barlow's theory of CPG development, Lau and Smith's study demonstrates different feeding skills (sucking and swallowing) occur at different time points in development but can be accelerated by sensorimotor experience and stimulation. Study infants in the swallowing exercise group were allowed to practice swallowing and breathing in a very controlled manner while they were also developing stable NNS patterns.

Nutritive and Non-nutritive Suck at Breast: What Do We Really Know?

Consistently, intervention studies of NNS in preterm infants have focused on oral stimulation with pacifiers, motorized teats or the investigator's fingers. Many NICUs also encourage mothers intending to breastfeed to provide NNS at breast but clinical studies are lacking the practice as a feeding intervention. What is happening during NNS at breast? Is the infant tasting mother's milk? Is the infant swallowing milk, albeit small volumes? What are infants' physiologic responses to NNS at breast compared to with NNS on an artificial teat? Does breast NNS accelerate progression to breastfeeding competence?

If, as Barlow and others suggest, the quantity and quality of sensorimotor experience is relevant to oral skill development, studies of breast NNS could augment our understanding of development of both feeding skills and CPG networks. In theory, NNS at breast likely provides the preterm infant with an enriched sensorimotor experience — beyond those with artificial teats — involving smell, taste, maternal skin warmth and texture, and nipple consistency as well as tactile and kinesthetic sensations related to being positioned and held for breastfeeding. If these stimuli are qualitatively and quantitatively different than those provided by artificial devices, are they helpful in CPG development and entrainment with enhanced progression towards nutritive feeds? At this time, there is not enough research data to respond but these are valid questions to explore.

Clinical reports are changing perceptions about what preterm infants can do if they are allowed unrestricted access to the breast. Since 2009 Nyqvist and associates[35,36] have described NICU infants in Uppsala, Sweden beginning to breastfeed (not just NNS) as early as 29 weeks with attainment of full breastfeeding and adequate weight gain by a median of 35 weeks. In this model, kangaroo care is encouraged 24 hours a day, seven days a week with semi-demand breastfeeds augmented occasionally by cup or tube. Data from these reports are promising, suggesting additional exposure to mother's breasts and more opportunities for breastfeeding experiences accelerate infant feeding competence. However, additional research studies are needed to make results generalizable to other populations.

Concluding Remarks

Can breastfeeding research accelerate feeding progress for NICU infants? The evidence suggests feeding skills of preterm infants develop somewhat independently with potential for faster integration if the infant is exposed to specific sensorimotor stimuli. Although breastfeeding is a confluence of sensory experiences, most research has investigated artificial stimuli and interventions removed from the breastfeeding relationship. Perhaps future innovations in NICU feeding practices for breast and bottle-fed infants can emerge from research of the breastfeeding dyad.

References

1 Meier P, Pugh EJ. Breast-feeding behavior of small preterm infants. MCN Am J Matern Child Nurs. Nov-Dec 1985;10(6):396-401.
2 Meier P. Bottle- and breast-feeding: effects on transcutaneous oxygen pressure and temperature in preterm infants. Nurs Res. Jan-Feb 1988;37(1):36-41.
3 Mathew OP, Bhatia J. Sucking and breathing patterns during breast- and bottle-feeding in term neonates. Effects of nutrient delivery and composition. Am J Dis Child. May 1989;143(5):588-592.
4 Mathew OP. Respiratory control during nipple feeding in preterm infants. Pediatr Pulmonol. 1988;5(4):220-224.
5 Meier PP, Brown LP, Hurst NM, et al. Nipple shields for preterm infants: effect on milk transfer and duration of breastfeeding. Journal of human lactation : official journal of International Lactation Consultant Association. May 2000;16(2):106-114; quiz 129-131.
6 Meier PP, Engstrom JL. Test weighing for term and premature infants is an accurate procedure. Archives of disease in childhood. Fetal and neonatal edition. Mar 2007;92(2):F155-156.
7 Meier PP, Engstrom JL, Crichton CL, Clark DR, Williams MM, Mangurten HH. A new scale for in-home test-weighing for mothers of preterm and high risk infants. Journal of human lactation : official journal of International Lactation Consultant Association. Sep 1994;10(3):163-168.
8 Berger I, Weintraub V, Dollberg S, Kopolovitz R, Mandel D. Energy expenditure for breastfeeding and bottle-feeding preterm infants. Pediatrics. Dec 2009;124(6):e1149-1152.
9 Mathew OP. Nipple units for newborn infants: a functional comparison. Pediatrics. May 1988;81(5):688-691.
10 Mathew OP. Determinants of milk flow through nipple units. Role of hole size and nipple thickness. Am J Dis Child. Feb 1990;144(2):222-224.
11 Mathew OP. Breathing patterns of preterm infants during bottle feeding: role of milk flow. J Pediatr. Dec 1991;119(6):960-965.
12 Geddes D. Breast anatomy and milk ejection during breastfeeding: Ultrasound exploration of infant sucking dynamics during breastfeeding: normal versus difficult feeding. ISRHML Conference: Breastfeeding and the use of human milk. Science and practice; 9/30/2012, 2012; Trieste, Italy.
13 Geddes D. Ultrasound exploration of infant sucking dynamics during breastfeeding: normal versus difficult feeding. ISRHML Conference: Breastfeeding and the use of human milk. Science and practice; 2012; Trieste, Italy.
14 Geddes DT, Nancarrow K, Chooi H, Hepworth AR, Simmer

K. Factors affecting milk intake in breastfed preterm infants. Research poster and abstract. ISRHML Conference: Breastfeeding and the use of human milk. Science and practice; 2012; Trieste, Italy.
15 Geddes DT, Sakalidis VS, Hepworth AR, et al. Tongue movement and intra-oral vacuum of term infants during breastfeeding and feeding from an experimental teat that released milk under vacuum only. Early Hum Dev. Jun 2012;88(6):443-449.
16 Sakalidis VS, Kent JC, Garbin CP, Hepworth AR, Hartmann PE, Geddes DT. Longitudinal Changes in Suck-Swallow-Breathe, Oxygen Saturation, and Heart Rate Patterns in Term Breastfeeding Infants. J Hum Lact. Mar 14 2013.
17 Sakalidis VS, McClellan HL, Hepworth AR, et al. Oxygen Saturation and Suck-Swallow-Breathe Coordination of Term Infants during Breastfeeding and Feeding from a Teat Releasing Milk Only with Vacuum. Int J Pediatr. 2012;2012:130769.
18 Sakalidis VS, Williams TM, Garbin CP, et al. Ultrasound Imaging of Infant Sucking Dynamics during the Establishment of Lactation. J Hum Lact. Sep 10 2012.
19 Sakalidis VS, Williams TM, Hepworth AR, et al. A comparison of early sucking dynamics during breastfeeding after cesarean section and vaginal birth. Breastfeed Med. Feb 2013;8(1):79-85.
20 Barlow SM. Central pattern generation involved in oral and respiratory control for feeding in the term infant. Curr Opin Otolaryngol Head Neck Surg. Jun 2009;17(3):187-193.
21 Barlow SM. Oral and respiratory control for preterm feeding. Curr Opin Otolaryngol Head Neck Surg. Jun 2009;17(3):179-186.
22 Barlow SM, Burch M, Venkatesan L, Harold M, Zimmerman E. Frequency Modulation and Spatiotemporal Stability of the sCPG in Preterm Infants with RDS. Int J Pediatr. 2012;2012:581538.
23 Barlow SM, Finan DS, Lee J, Chu S. Synthetic orocutaneous stimulation entrains preterm infants with feeding difficulties to suck. Journal of perinatology : official journal of the California Perinatal Association. Aug 2008;28(8):541-548.
24 Pickler RH, Best AM, Reyna BA, Gutcher G, Wetzel PA. Predictors of nutritive sucking in preterm infants. J Perinatol. Nov 2006;26(11):693-699.
25 Harding C. An evaluation of the benefits of non-nutritive sucking for premature infants as described in the literature. Arch Dis Child. Aug 2009;94(8):636-640.
26 Pinelli J, Symington A. Non-nutritive sucking for promoting physiologic stability and nutrition in preterm infants. Cochrane Database Syst Rev. 2010(6):CD001071.
27 Arvedson J, Clark H, Lazarus C, Schooling T, Frymark T. Evidence-based systematic review: effects of oral motor interventions on feeding and swallowing in preterm infants. American journal of speech-language pathology / American Speech-Language-Hearing Association. Nov 2010;19(4):321-340.
28 Barlow SM, Burch M, Venkatesan L, Harold M, Zimmerman E. Frequency Modulation and Spatiotemporal Stability of the sCPG in Preterm Infants with RDS. Int J Pediatr. 2012;2012:581538.
29 Barlow SM, Finan DS, Lee J, Chu S. Synthetic orocutaneous stimulation entrains preterm infants with feeding difficulties to suck. J Perinatol. Aug 2008;28(8):541-548.
30 Poore M, Zimmerman E, Barlow SM, Wang J, Gu F. Patterned orocutaneous therapy improves sucking and oral feeding in preterm infants. Acta paediatrica. Jul 2008;97(7):920-927.
31 Zimmerman E, Barlow SM. Pacifier Stiffness Alters the Dynamics of the Suck Central Pattern Generator. J Neonatal Nurs. Jun 2008;14(3):79-86.
32 Fucile S, Gisel EG, McFarland DH, Lau C. Oral and non-oral sensorimotor interventions enhance oral feeding performance in preterm infants. Dev Med Child Neurol. Sep 2011;53(9):829-835.
33 Fucile S, McFarland DH, Gisel EG, Lau C. Oral and nonoral sensorimotor interventions facilitate suck-swallow-respiration functions and their coordination in preterm infants. Early human development. Jun 2012;88(6):345-350.
34 Lau C, Smith EO. Interventions to improve the oral feeding performance of preterm infants. Acta Paediatr. Jul 2012;101(7):e269-274.
35 Nyqvist KH. Early attainment of breastfeeding competence in very preterm infants. Acta Paediatr. Jun 2008;97(6):776-781.
36 Nyquist KH. From kangaroo care to feeding at the breast for the competent preterm infant. ISRHML Conference: Breastfeeding and the use of human milk. Science and practice; 9/27/2012 - 10/1//2012, 2012; Trieste, Italy.

Relationship between…continued from page 32
Frank DJ, Chang W. Vitamin E and Se Levels of Premature Infants with Severe Respiratory Distress Syndrome and Bronchopulmonary Dysplasia. J of Pediatric Perinatal Nutrition, vol 2 (1); 1988:35-49.
11 Ballard JL, Khory JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, Expanded to Include Extremely Premature Infants. J Pediatr 1991;119:417-423.
12 Dietary Reference Intake (DRI): Substitute of Medicine. Food and Nutrition Board 2000. 2000: 284-324.
13 Vermont Oxford Data Base: Nightingale Report,Center 14, Burlington Vermont 2006.
14 Mistry HD, Broughton Pipkin F, Redman CW, Poston L. Se in reproductive health. Am J Obstet Gynecol. 2012 Jan;206(1):21-30.
15 Dobrzynski W, Trafikowska U, Trafikowska A, Pilecki A, Szymanski W, Zachara BA. Decreased Se concentration in maternal and cord blood in preterm compared with term delivery. Analyst 1998:Jan;123(1): 93-97.
16 Mask G, Lane HW. Selected measures of Se status in fullterm and preterm neonates, their mothers and non-pregnant women. Nutr Res 1993;13: 901-11.
17 Hawkes WC, Alkan Z, Lang K, King JC. Plasma Se decrease during pregnancy is associated with glucose intolerance. Biol Trace Elem Res 2004;100:19-29.
18 Mahomed K, Williams MA, Woelk GB, Mudzamiri, Madzime S, King IB, et al. Leukocyte Se, zinc and copper concentrations in pre-eclampic and normotensive pregnant women. Biol Trace Elem Res 2000;75:107-18.
19 Iranpour R, Zandian A, Mohammadizadeh M, Mohammadzadeh A, Balali-Mood M, Hajiheydari M. Comparison of maternal and umbilical cord blood Se levels in term and preterm infants. Zhongguo Dang Dai Er Ke Za Zhi 2009;11:513-6.

Safe Administration of Breast Milk in the Neonatal Intensive Care Unit Utilizing an Electronic Medical Record

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Abstract: Breast milk provides optimal nutrition for newborn infants, and promotes maternal infant bonding. In the Neonatal Intensive Care Unit (NICU), many babies cannot directly breastfeed, and mothers are encouraged to express breast milk for later feeding to their baby. The expressed breast milk (EBM) typically is given to NICU infants until the infant is strong enough to breast feed. A typical NICU may give thousands of EBM feedings per year, presenting management challenges in identifying, storing, and administering EBM.

Administration of the wrong mother's EBM to another mother's baby has been recognized as a common NICU error. In 2003, we developed a barcode-based process to match EBM to the patient utilizing the NICU electronic medical record (EMR), Crib Notes, and we have documented over 200,000 breast milk feedings in the system. We have successfully reduced the error rate of EBM misidentification, however during this period of time, an error was recognized.

The error involved a container of another mother's breast milk that was inadvertently sent home with an infant at discharge, and later fed to the infant by the parent. In collaboration with nursing, physicians, parents and the EMR vendor, a safety initiative at Main Line Health Systems in Pennsylvania was developed to address and expand the identification processes surrounding breast milk management and administration. Since the patient safety initiative was initiated in December 2009, no further breast milk errors at discharge have occurred.

Background

Breastfeeding provides the optimal nutritional, immunologic, and developmental benefits for all newborn infants and promotes maternal-infant bonding. In the NICU, many babies cannot directly breastfeed, and mothers are encouraged to express milk for later feeding to their baby. The expressed breast milk (EBM) typically is given to premature or compromised infants via nasogastric gavage tube until the infant is strong enough to nipple or breastfeed.

In a typical NICU, over half of the mothers may be collecting 4-8 aliquots of EBM/day, and hundreds of aliquots may be stored in the NICU at any one time. The large number of aliquots and feedings administered within a NICU presents management challenges in identifying, storing, and administering EBM. A common NICU error is feeding the wrong mother's EBM to another mother's baby (Dougherty & Giles, 2000), (Suresh, Horbar, Plsek, Gray, Edwards, Shiono, et al 2004), (Gray, Gautham, Ursprung, Edwards, Nickerson, Shiono, et al 2006). In our health care system, we were experiencing 1-3 errors/year with approximately 650 admissions a year.

Understanding that barcoding technology improves patient safety practices (Wald, 2001), in 2003, we developed and implemented a unique barcode-based process to match EBM to the patient utilizing the NICU electronic medical record system (EMR), Crib Notes. From May 1, 2003 to January 2009 there were no recognized errors when the expected rate was ~10. In January of 2009, an aliquot of another mother's breast milk was sent home with an infant at the time of discharge and later fed to the infant by the parent.

Problem Statement

The process of managing breast milk identification at the time of infant discharge was found to be outside the scope of the then current EMR verification design.

Significance of the Problem

Breast milk carries the potential of transmitting serious pathogens such as human immunodeficiency virus (HIV), cytomegalovirus (CMV), and bacteria (Drenckpohl, Bowers, & Cooper, 2007). There is often great concern about potential infections when a baby inadvertently receives EBM from the mother of another baby. When such events occur, both mothers and the infant who received the EBM typically are tested for potential pathogens with repeat testing of the infant 6 weeks and 6 months later. In addition to the biologic risks, inconvenience, pain, and cost of blood testing, this error often causes the involved families to lose confidence in the nursing staff and the organization.

Goals of the Safety Initiative

- To expand the current breast milk verification process within the EMR to include relabeling of breast milk feedings when breast milk is transferred from one container to another, and to include verification of breast milk at discharge.
- To reduce the risk of giving a baby breast milk from another baby's mother, and to reduce the number of breast milk misidentification errors to zero in our NICUs.

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Plan of Action

We formed a multidisciplinary safety group including representatives from nursing, parents, and physicians. Sessions included the identification of additional potential error scenarios surrounding the process of transferring and relabeling breast milk and sending unused breast milk home with the parents.

A change to the original system was proposed, and organizational support for the safety initiative was obtained. The Crib Notes EMR vendor was approached to developed additional identification processes involved in the transfer and relabeling process, and scanning of breast milk at the time of discharge.

Methods-Scanning Process

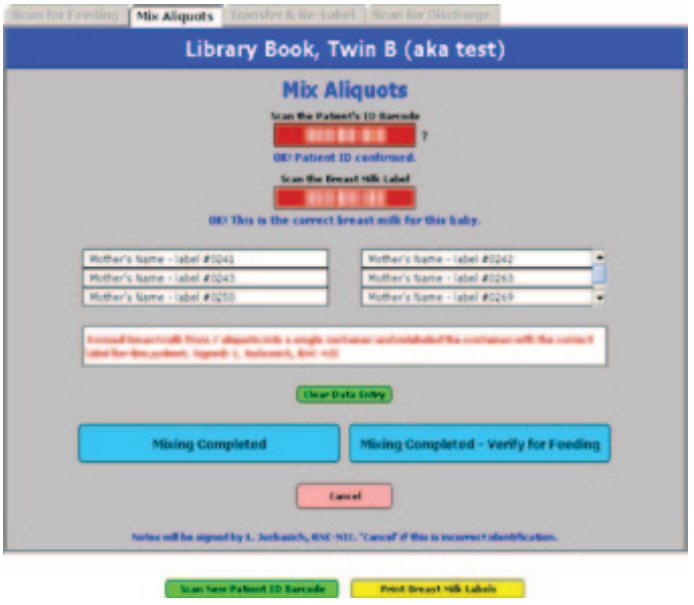
The changes included both visual and audible confirmation when correct infant or breast milk is scanned. A warning screen, and associated audible "wrong" alert if the incorrect infant or breast milk is scanned.

Verifying EBM Before a Feeding

- Patient's ID label and label on the EBM container are scanned for ID verification
- Confirmation messages display on the computer screen if correct
- Feeding is given, then document volume taken

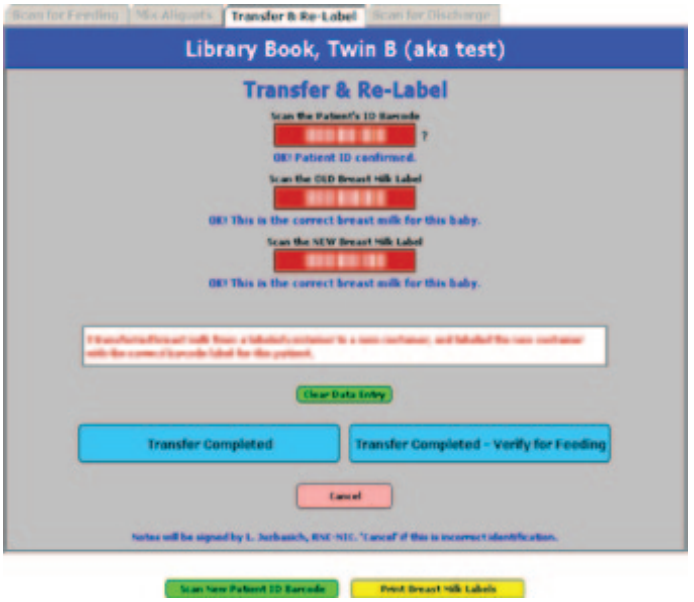
Verifying mixed aliquots

- Patient's ID label is scanned, and all samples of breast milk to be combined are scanned
- Confirmation messages display after each scan
- Mixing completed- administer feeding, then document volume taken



Verifying for Transfer and Relabeling

- Patient's ID barcode is scanned
- Barcode from the original milk container is scanned
- A new barcode label is affixed to the new container and new label is scanned
- EBM is then transferred from the original container to the new container
- Confirmation messages will display on the screen prior to feedings



Verification at Discharge

- Patient's ID barcode is scanned and all EBM aliquots to be sent home with the infant are scanned
- Confirmation messages display after each scan
- Correctly scanned EBM aliquots are then placed in a transport bag with freezer packs for the parents to take home

Process Control & Quality Improvement

Correct Process

- Verify the patient and EBM before a feeding
- Documentation of the amount of the feeding after verification
- Feeding records for which the process was done correctly are displayed in the EMR with a closed circle signifying the process was completed correctly

Incorrect Process

- Feeding before verification cannot prevent errors
- If the nurse documents an EBM feeding before verification the system will prompt the nurse to verify the feeding
- Feeding records for which the process was done incorrectly

are displayed in the EMR with an open circle

A nurse-specific compliance report documents

- Number of EBM feedings recorded by each nurse
- Percentage of times the process was done correctly and incorrectly

Results

December 9, 2009 to April 23, 2010
Total number of feedings = 30,614
Breast milk feedings = 4,770
Number of errors at discharge = 0

Nursing Staff

The nursing staff understands the benefits and supports the expanded breast milk verification processes. We found the new methodology to be simple to use and highly efficient. The staff remains vigilant in preventing breast milk administration errors in the hospital and at discharge.

Summary

Our NICUs instituted an initiative to decrease EBM misidentification by adapting conventional technologies for the highly specialized problems surrounding breast milk administration. Other NICUs may replicate our initiative by obtaining organizational support to promote the adoption of software technology that supports and proactively promotes patient safety for EBM administration. The importance of supporting the unique needs of the NICU patient population cannot be overstated when organizations are considering and selecting an EMR for the NICU environment. Electronic records that are "tweaked" or adapted from an adult perspective do not support functions that are relevant to the safety of these vulnerable premature and full-term infants.

Conclusion

Our organization recognized the importance of our initiative, and supported the implementation and development of a system centered on the NICU population and focused on the providers who work in this environment. Among the many important benefits of this decision has been the near complete resolution of patient identification problems associated with the handling of EBM. Our environment is safer in this respect, and we have essentially eliminated parent distress over EBM identification issues for the four processes of breast milk administration. We recommend that other organizations implement complete solutions for managing EBM to achieve similar advances that enhance patient safety in the NICU.

References

- Dougherty, D., & Giles, V. (October, 2000). From breast to baby: Quality assurance for breast milk management. Neonatal Network, 19(7), 21–25.
- Drenckpohl, D., Bowers, L., & Cooper, H. (May/June, 2007). Use of the six sigma methodology to reduce incidence of breast milk administration errors in the NICU. Neonatal Network, 26(3), 161-166.
- Gray, J. E., Gautham, S., Ursprung, R. Edwards, W. H., Nickerson, J., Shiono, P. H., et. al. (2006). Patient misidentification in the neonatal intensive care unit: Quantification of risk. Pediatrics, 117, 43-47.
- Wald, H., Shamania, K. G., (2001). Prevention of misidentifications. In K. G. Shajania, B. Duncan, W. McDonald, K. M., & R. M. Wachter, (Eds.), Making Health Care Safer: A Critical Analysis of Patient Safety Practices. Rockville, MD: Agency for Healthcare Research and Quality. AHRQ Publication 01-E058.
- Suresh, G., Horbar, J. D., Plsek, P., Gray, J., Edwards, W. H., Shiono, P. H., et al. (2004). Voluntary anonymous reporting of medical errors for neonatal intensive care. Pediatrics, 113(6), 1609-1618.

A Neonatal Nurses' Guide to High Flow Nasal Cannula Therapy

Thomas L. Miller, PhD

This paper provides basic information for neonatal nurses about the use of high flow nasal cannula therapy for neonates, focusing on defining the therapy for neonatal applications, and contrasting it with adult applications. The paper outlines the purposes of high flow therapy (HFT), and its uses for neonates who are sicker than infants requiring a regular cannula. While neonatal nurses do not typically provide hands-on high flow therapy, a familiarity with the system is an aid to providing comprehensive care. The primary takeaway for neonatal nurses is that HFT is not primarily a form of pressure therapy, but uses a nasal cannula to ventilate CO2 from the upper airway, and also provides O2 therapy. HFT is an effective bridge between oxygen therapy and mechanical ventilation.

Introduction

HFT uses a nasal cannula to provide noninvasive ventilation support. The nasal cannula delivers heated and humidified medical gas mixtures at flow rates in excess of a patient's inspiratory flow rate.

Over the past several years, there has been a marked increase in the use of nasal cannulae to deliver high flows of humidified respiratory gas to neonatal patients. During this period, research has been conducted and published examining safety and efficacy as well as exploring means of optimizing the therapeutic impact of high flow nasal cannula. This review provides definitions, an overview of the therapeutic approach and mechanisms of action, as well as a review of published research.

In 2000, Vapotherm introduced the concept of High Flow Therapy with patented humidification membrane technology to efficiently condition gas to within normal physiological range and without rainout. The membrane cartridge system saturates the gas with energetically stable water vapor and uses a water-jacketed delivery tube to maintain the energy state of the conditioned gas as it is delivered to the patient. The system is uniquely designed to function under the high internal device pressure associated with the action of pushing high flow rates through a nasal cannula.

Defining HFT

HFT is the delivery of respiratory gas through a nasal cannula at flow rates that exceed a patient's demand, whereby this definition pertains to both the inhalation and exhalation phases of breathing. The technological advances that allow for HFT are related to precise heating and humidification; however, the resultant efficacy is a function of more efficient oxygen therapy and an impact on ventilation by way of dead space washout. The foundational premises of HFT are that cannula flow rates of respiratory gas exceed a patient's spontaneous inspiratory flow rate as well as be sufficient to purge anatomical dead space during exhalation. In this regard, a patient will not entrain room air while taking in a breath, making each breath composed of ideally conditioned gas with a precise fraction of oxygen. Moreover, when the gas flow is adequate, the nasopharyngeal region is purged during exhalation so as to improve ventilation by the elimination of expiratory CO2. In adults, both objectives are typically accomplished by a similar flow rate making flow a matter of exceeding inspiratory flow rate; however, infants are more complex because of the relative differences in the extrathoracic dead space.

In the current literature, definitions of HFNC are inconsistent, particularly as it pertains to comparisons to other therapies. Some investigators define the application of a HFNC therapy as simply using cannula flows greater than convention, which in neonatal medicine is greater than 2 L/min, or in some cases greater than 1 L/min.[1] However, based on the mechanistic research that has demonstrated how HFT affects respiratory function, HFT is correctly defined as the application of flow rates that accomplish the two aforementioned objectives. Again, these objectives pertain to meeting inspiratory demand as well as purging anatomical dead space in the window of time between breaths.

A widespread assumption is that HFNC provides for a continuous positive airway pressure (CPAP) effect. Whereas pressure will develop in the delivery of HFT, mechanistic studies suggest that pressure is not the primary mechanism of action responsible for observed physiologic outcomes. A more detailed comparison of HFT to CPAP is found in a later section of this paper.

An example of why we need agreement on the definition of HFT is the 2011 Cochrane review on the use of "High flow nasal cannula for respiratory support in preterm infants."[1] These authors reviewed four studies and concluded that high flow nasal cannula may result in a higher rate of reintubation compared to CPAP. However, these reviews defined HFNC as flow rates greater than 1 L/Min, which may not exceed every infant's

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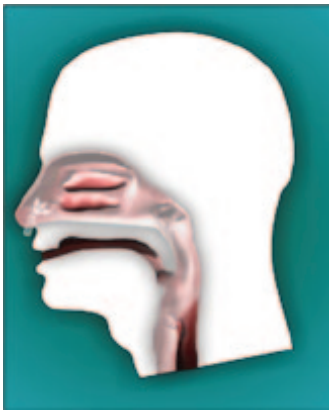
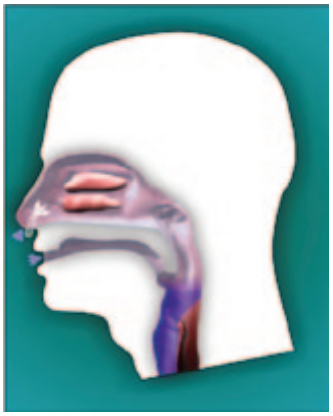


Figure 1. During inhalation the cannula flow needs to be adequate to meet inspiratory flow demand.



During exhalation the cannula flow needs to be adequate to purge the nasopharyngeal dead space volume between breaths.

inspiratory flow demand and certainly would not be sufficient to purge nasopharyngeal dead space during exhalation. The evidence cited to support that CPAP outperforms HFNC comes from the one study by Campbell and colleagues.[2] These authors administered HFNC as if it were a CPAP therapy, and used an equation to assign flow rates. Specifically, this equation was proposed to predict flow needed to achieve a certain airway pressure, and as such, the mean cannula flow rate used in this study was only 1.8 L/min.

It is fair to conclude from these data, as well as years of experience with nasal cannulae, that flow at rates less than 2 L/min may not be as effective as CPAP. However, this finding has little relevance to true high flow nasal cannula therapy (ie HFT) which is defined by the mechanistic literature to facilitate purging of the entire volume of nasal, oral and pharyngeal dead space. In this regard, the findings of Campbell and colleagues should not be unexpected and should not be used to represent the efficacy of HFT per its mechanistic definition.

How it Works

There are a number of mechanisms by which HFT can improve respiratory function in the neonatal population.

Essentially, HFT makes the nasopharyngeal region a reservoir of fresh gas by way of purging the end-expiratory gas from this space during exhalation. Therefore, the patient's subsequent breath is more efficient in that it is composed of more fresh gas and less end-expiratory gas. With this improvement in efficiency, a patient can achieve adequate alveolar ventilation (V_A) with less minute ventilation (V_E), compared to pressure therapies that force greater lung expansion to achieve greater V_E. Vapotherm recommends that HFT should not be used to produce a substantial distending airway pressure, although some pressure inevitably is generated. Rather, HFT should be used so as to minimize resistance to gas exhausting from the nasopharynx around the cannula and through the mouth. In other words, HFT should be used to maximize the purging of the nasopharynx with the least amount of flow and associated pressure. A recent publication validating the dead space washout concept as the principal mechanism of action showed that the least occlusive cannula geometry resulted in an optimal efficacy with less than 75% of the flow and pressure required when snug fitting prongs are used to generate distending pressure.[3] Additional studies have shown how flow dynamics and heated humidification contribute to other mechanisms of action that reduce work of breathing and support airway function. These other mechanisms are summarized below and described in a review paper by Dysart et al.[4]

HFT in the Context of Current Practices in Neonatal Respiratory Care

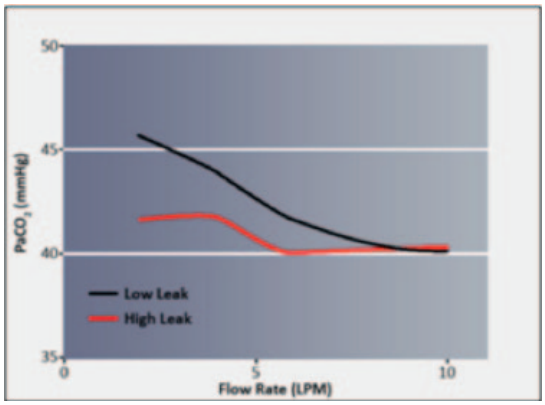
Since the 1980s, there has been a focus on developing strategies for noninvasive ventilation subsequent to the defining of bronchopulmonary dysplasia (BPD), the relationship to lung bio-inflammatory potential and the recognition of the need for lung protective ventilation strategies. Along these lines, there has been a major emphasis on CPAP and other noninvasive forms of ventilation, such as bilevel CPAP, that have reduced the need for mechanical ventilation.[12] Other major developments have surfaced in the last few decades, such as exogenous surfactant replacement therapy and inhaled nitric oxide, which have been widely adopted and used in conjunction with noninvasive respiratory support. For example, the INSURE technique (INtubate, SURfactant, Extubate) has allowed surfactant delivery to be combined with noninvasive ventilation with notable success.[13] Together these combinations of therapies have fostered tremendous improvements in infant mortality, but occurrence of BPD remains high.

In the context of this push for noninvasive ventilation strategies, dead space elimination, and thus HFT, is not a novel concept. Dead space elimination contributes to improved alveolar ventilation without forcing greater tidal volumes. In this regard, we need to reinforce that the term ventilation should not necessarily be synonymous with artificial breathing machines that deliver tidal breaths, but can encompass other, less invasive ways to facilitate exchange of respiratory gases within the lungs. Optimal gas conditioning capabilities have allowed for gas delivery by nasal cannula to exceed the conventional limits without degradation of the nasal tissues.[14] This advancement has opened the door for a noninvasive way to eliminate anatomical dead space, making ventilation more efficient.

HFT, as we term the use of HFNC in a specified way so as to maximize the elimination anatomical dead space, has many peripheral advantages that are associated with the patient

High Flow Therapy Mechanisms of Action

MECHANISM	DESCRIPTION
Dead space washout	Reduce dead space making minute ventilation more efficient.[3,5]
Reduce inspiratory work of breathing	Exceed inspiratory flow thus eliminating nasal resistance.[6]
Improved lung mechanics	Warmed, humidified gas has been shown to improve conductance, compliance and lung elasticity.[7]
Eliminate metabolic work associated with gas conditioning	Attenuates the energy and water loss associated with conditioning inspiratory gas.
Provision of mild distending pressure	Flow can be restricted such as to provide positive distending pressure for lung recruitment.[8-10]
Improve secretion mobilization	Ideal humidification of the inspired gas has been shown to restore mucocilliary function and reduce symptoms of airway exacerbations.[11]



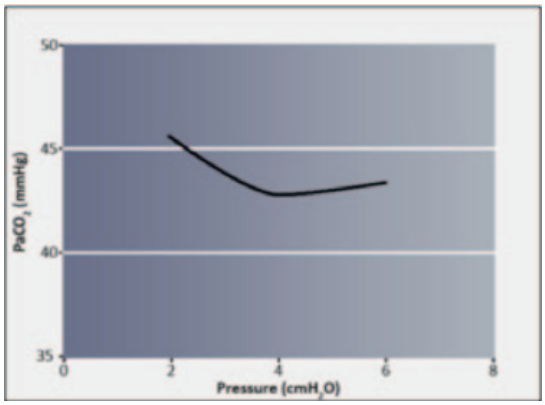


Figure 2. These graphs adapted from Frizzola et al.[3] show that high flow therapy (HFT) provides a ventilation effect (impact on arterial CO2 tension) not seen with continuous positive airway pressure (CPAP). Moreover, the effect is more pronounced and occurs at lower flows when the cannulae are fitted to allow a high degree of leakage around the nasal prongs.

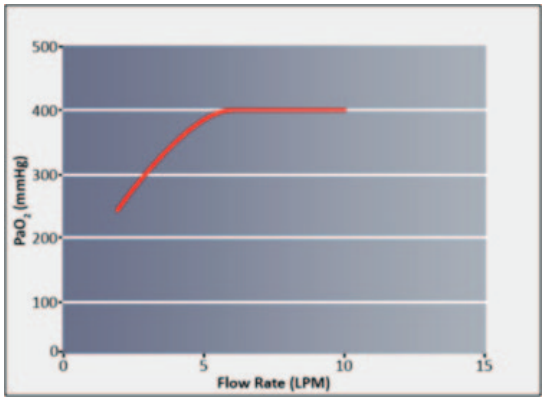


Figure 3. This graph adapted from Frizzola et al.[3] shows the oxygenation relationship with HFT titration. Arterial oxygen tension rises with increased flow to a plateau, after which more flow has no further effect. This inflexion point is explained in the tracheal gas insufflation literature as the point where flow is adequate to purge all available dead space.

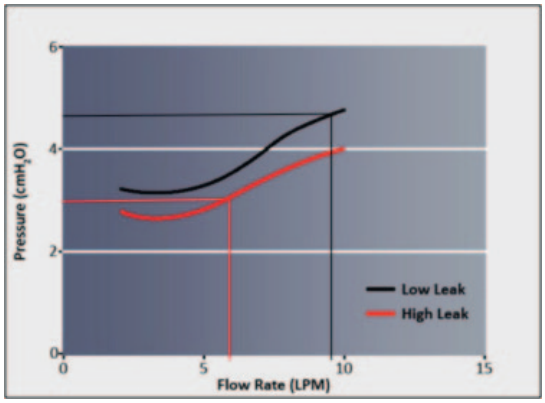


Figure 4. This graph adapted from Frizzola et al.[3] shows the end-distending pressure response to nasal prongs which occlude the nares (low leak) versus prongs that occlude no more than 50% of the nares (high leak). In each case pressure rises with increased flow, dissociating this relationship from the oxygenation curve (Figure 3). Referring back to Figure 2, note that the non-occlusive prongs facilitated better ventilation, accomplishing optimal effect at a lower flow, seen here where the extrapolation bars cross the x-axis. By following these bars to the y-axis, note the non-occlusive prongs accomplish this efficacy with significantly less distending pressure.

interface being easier to manage than a sealed CPAP system. These include patient tolerance, ease in nursing management, and accessibility for kangaroo care, as well as physiologic concerns such as prone positioning to support spontaneous breathing.[15,16] As we better define and optimize HFT as primarily a therapy to eliminate dead space, and understand the coinciding ability to generate mild pressure and hydrate the air passages, HFT holds promise to emerge as a significant advancement in neonatal respiratory support.

HFT: A Unique Noninvasive Respiratory Support Modality

The act of ventilation refers to the circulation of air so as to replace stale or noxious air with fresh air. In mammalian physiology this process involves tidal volumes and lung compliance because of our anatomical dead space. In other words, if we were to remove dead space entirely by putting our alveolar surface on the outside of our body (eg gills on a fish), we would not need to have tidal volume excursions to expose the alveolar surface to adequate V_A in support of respiration. Obviously, this is not practical for numerous reasons, including the need to condition gas before coming into contact with the blood, and our adaptation to use dead space for retaining CO2 as our innate pH buffering mechanism.

Nonetheless, by reducing dead space we can reduce the V_E needed to accomplish adequate V_A and therefore reduce work of breathing. Dead space elimination tactics have been used for years in the form of tracheal gas insufflation[17,18] and transtracheal oxygen delivery.[19] In the last 10 or more years, advancements in heated humidification devices have made it possible to accomplish ventilation by way of dead space elimination with a nasal cannula.

Translational research has shown that the primary mechanism of action for HFT is purging anatomical dead space, thus achieving V_A with lesser V_E. A pivotal mechanistic study was done using neonatal piglets with a severe respiratory distress induced by central venous oleic acid delivery.[3] In this model, three conditions were compared: HFT with a low leak around the prongs (ie snug fit in the nares), HFT where no more than 50% of the nares were occluded (ie non-occlusive prongs) and conventional mask CPAP. The low leak condition was created to mimic the situations where clinicians try to get a CPAP effect, whereas the ≤50% occlusion condition fits our recommendation for the application of HFT. Under these conditions, the model

evaluated titration of flow/CPAP pressure on CO2 removal, oxygenation and pressure development.

As shown in Figure 2, under both HFT conditions, arterial CO2 inversely correlated with flow rate wherein arterial CO2 tension (PaCO2) in these spontaneous breathers could be reduced back to pre-injury levels. Moreover, the PaCO2 in the <50% occlusion condition was significantly reduced at lower flow rates compared to the low leak condition, indicating that a less occlusive prong design facilitates nasopharyngeal purge. CPAP alone was never able to achieve this ventilation effect. With CPAP, PaCO2 was slightly reduced with a mild pressure increase, but then PaCO2 rose as CPAP pressure went above 4 cmH2O, presumably due to overdistension.

As shown in Figure 3, regarding oxygenation, under both HFT conditions a flow dependent increase in arterial oxygen tension (PaO2) was demonstrated until a plateau was reached. This saturation pattern is indicative of dead space washout and fits the hypothesis of the study based on the background modeling of tracheal gas insufflation.[20] The concept behind dead space purge techniques is that there is a finite amount of time (late stage exhalation and end-expiratory pause) to purge the space and a finite amount of dead space volume that can be purged. As flow is increased, more of the volume can be purged until flow is sufficient to purge all of the volume in the allotted time, after which additional flow produces no additional effect. With respect to oxygenation, CPAP was as effective as HFT although not a function of pressure titration.

Pressure in this study was measured by direct perpendicular placement of a pressure catheter in the trachea through an anterior cervical cut-down. As shown in Figure 4, the pressure data from this study shows a direct relationship between flow and baseline pressure shift, which is in agreement with the clinical studies. Here the pressure from the low leak condition is always greater than the ≤50% occlusion condition. Importantly, there was dissociation between oxygenation and the pressure response where pressure continues to rise beyond the flow rate at which oxygenation response reaches a plateau. This dissociation between pressure and physiologic oxygenation response supports dead space flush as the primary mechanism of action. Moreover, because the cannula fit impacted the flow rate needed to accomplish optimal efficacy (ie flow rate where PaO2 plateaued and PaCO2 reached baseline levels), pressure was actually inversely related to physiologic improvement if we consider cannula design as a categorical variable. In other words, the less occlusive prong design accomplished maximal efficacy with approximately 60% of the flow needed to do so with the occlusive prong design, which translates to approximately one-half of the inadvertent distending pressure. Optimized prong fit translates to better outcome with less pressure.

The clinical side to this translational modeling was done in COPD patients (data presented at the 2011 CHEST meeting and in review for publication). Adults were examined because they can be compliant in ways that an infant cannot, but the resulting evidence regarding ventilation is fundamental to the concept of dead space and translates to the infant as well. This study shows that HFT with room air results in at least a 13% reduction in V_E while maintaining the same PaCO2 compared to both no support and supplemental oxygen conditions. This ventilation effect is potentially greater in infants because of the greater relative extrathoracic dead space volume compared to adults.[21]

CPAP versus HFT

CPAP systems are specifically designed to be a closed system in conjunction with the infant's respiratory tract. The proposed mechanisms of action for CPAP are complex and multifactorial, but include the concept that pressure is able to recruit lung alveoli by increasing FRC, thus improving compliance so that a greater V_E can be achieved to account for the necessary V_A.[22] From a mechanical perspective, CPAP supports spontaneous breathing by making it less taxing to stretch the lung and by minimizing atelactrauma during lung stretch. HFT, on the other hand, is aimed at achieving V_A with a lesser V_E so as to reduce the necessary lung stretch. Nonetheless, the accompanying humidification and mild pressure effects with HFT would attenuate atelectrauma as well.[7,23]

HFT is designed to be an open system, wherein the gas is not intended to be contained for the development of a pressurized patient airway. In an HFT system, pressure inside the device circuit is by necessity quite high, in the range of nearly 400 cmH2O.[24] This is the result of pushing high flow through the substantial resistance of the relatively tiny nasal prong orifices. Because of this relatively enormous cannula resistance and the fact that the system circuit is not sealed with the patient's airway, physics dictates that circuit pressure does not transmit to the patient. The development of patient airway pressure is a coinciding effect during HFT and is a function of the resistance to the flow exiting from the patient's nasopharynx through the oral cavity and nose.

To keep the coinciding nasal pressure from reaching levels that would need to be monitored, the literature dictates that a cannulae should not occlude more than 50% of the nares. This recommendation is based on the work of Dr Locke and colleagues who showed that nasal prongs having an outside diameter that is no more than 50% of the internal diameter of the nares does not result in distending pressure during low flow O2 therapy. Conversely, cannula having an outside diameter that was three-quarters of the inside nare diameter resulted in significant pressure at low flows. The message here is that keeping nares open by 50% of the diameter represents adequate anatomic release. Note that this 50% diameter rule ensures that the surface area of the unoccluded region of the nares is greater than the surface area of the occluded area, based on the nonlinear, direct relationship between surface area and distance from the center of a circle. Vapotherm's recommendations and cannulae offerings are consistent with this requirement.

When applied correctly, mild airway pressure does develop during HFT and is considered a mechanism of action based on the rationale for CPAP.[22] This pressure is a function of both the rate of flow through the patient's upper air space and the anatomical resistance to this flow as it passes through the anatomy;[25] however, the pressure is not at the level of closed CPAP system and varies regionally as a function of the gas flow patterns (preliminary data). From a review of the research related to airway pressures in neonates during HFT, data shows that airway pressure with HFT can be expected to be less than or approximately equivalent to airway pressure when a CPAP of 6 cmH2O is applied,[8-10,23,24,26] and equally as variable as airway pressure during CPAP.[24] In interpreting these data it is important recognize that some investigators were trying to create CPAP by minimizing the leak through the nose and mouth. Nonetheless, the data showed only modest pressures.

Application of HFT in the NICU: Flow Rate Titration and Rationale

Despite the inconsistency in the literature defining the flow rates needed for HFT, when used appropriately reports indicate improved extubation success and potentially a reduction in intubation rates.[27,28,29,30] In addition, the simplicity of the cannula interface with loose fitting nasal prongs reduces facial skin and nasal abrasions associated with more intense therapies. HFT is simple to administer and manage compared to positive airway pressure therapies that require intense monitoring to ensure that the patient interface remains properly placed.

The range of flows to be used in infants is between 1-8 L/min. While infants have a very small tidal volume, in the range of 4-6 mL/kg, their respiratory rates are quite high. In sick children, respiratory rates can approach 100 breaths per minute, making peak inspiratory flows very high relative to minute volumes. Another consideration with infants, which pertains to the mechanisms of dead space purge, is the relative size of the anatomical reservoir which consists of the extra-thoracic dead space volume of the nasal, oral and pharyngeal cavities. Infants have a much larger anatomical reservoir compared to older children and adults.[21] Small infants have an extrathoracic dead space volume around 2.3 mL/kg, whereas in children over six years of age and into adulthood this value drops to approximately 0.8 mL/kg. Therefore, as compared to an adult, an infant may need greater relative flow rates to realize the full benefits of purging the anatomical reservoir in the window of opportunity between breaths (flow rates that go beyond simply meeting inspiratory demand). This three-fold greater anatomical reservoir volume in small infants translates to dead space making up a much greater fraction of their tidal volume as compared to larger children and adults.

As a result of these factors, small infants have a greater propensity to benefit from HFT in that these patients are much more sensitive to changes in dead space. However, cannula flow rates needed to maximize efficacy typically begin at greater than 3 L/min.

Summary

HFT is a unique noninvasive respiratory support modality in the NICU. It is based on the concepts of dead space elimination for breathing efficiency and the delivery of ideally conditioned respiratory gases to an already fragile lung. A misconception that stifles the adaptation of HFT is that it is an uncontrolled form of CPAP. The mechanistic literature, however, does not support this presumption and a significant amount of clinical data suggests that pressure is not a concern when HFT is applied correctly. Importantly, the neonatal community would benefit from the uniform adaptation of a definition that is based on research and guides the cannula design aspects and flow requirement. These studies suggest that cannula fit should not occlude more than 50% of the nares and that flows should be between 3 and 8 L/min.

References

1 Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev 2011:CD006405.

2 Campbell DM, Shah PS, Shah V, Kelly EN. Nasal continuous positive airway pressure from high flow cannula versus Infant Flow for Preterm infants. J Perinatol 2006;26:546-9.

3 Frizzola M, Miller TL, Rodriguez ME, et al. High-flow nasal cannula: Impact on oxygenation and ventilation in an acute lung injury model. Pediatr Pulmonol 2011;46:67-74.

4 Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. Respir Med 2009;103:1400-5.

5 Dewan NA, Bell CW. Effect of low flow and high flow oxygen delivery on exercise tolerance and sensation of dyspnea. A study comparing the transtracheal catheter and nasal prongs. Chest 1994;105:1061-5.

6 Shepard JW, Jr., Burger CD. Nasal and oral flow-volume loops in normal subjects and patients with obstructive sleep apnea. Am Rev Respir Dis 1990;142:1288-93.

7 Greenspan JS, Wolfson MR, Shaffer TH. Airway responsiveness to low inspired gas temperature in preterm neonates. J Pediatr 1991;118:443-5.

8 Saslow JG, Aghai ZH, Nakhla TA, et al. Work of breathing using high-flow nasal cannula in preterm infants. J Perinatol 2006;26:476-80.

9 Spence KL, Murphy D, Kilian C, McGonigle R, Kilani RA. High-flow nasal cannula as a device to provide continuous positive airway pressure in infants. J Perinatol 2007;27:772-5.

10 Wilkinson DJ, Andersen CC, Smith K, Holberton J. Pharyngeal pressure with high-flow nasal cannulae in premature infants. J Perinatol 2008;28:42-7.

11 Hasani A, Chapman TH, McCool D, Smith RE, Dilworth JP, Agnew JE. Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis. Chron Respir Dis 2008;5:81-6.

12 Mahmoud RA, Roehr CC, Schmalisch G. Current methods of non-invasive ventilatory support for neonates. Paediatr Respir Rev 2011;12:196-205.

13 Verder H, Robertson B, Greisen G, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. N Engl J Med 1994;331:1051-5.

14 Woodhead DD, Lambert DK, Clark JM, Christensen RD. Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal extubation: a prospective, randomized, masked, crossover trial. J Perinatol 2006;26:481-5.

15 Martin RJ, Herrell N, Rubin D, Fanaroff A. Effect of supine and prone positions on arterial oxygen tension in the preterm infant. Pediatrics 1979;63:528-31.

16 Wolfson MR, Greenspan JS, Deoras KS, Allen JL, Shaffer TH.

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High Flow Therapy and Heliox

For neonates with severe obstruction, heliox in conjunction with high flow nasal cannula therapy can be very helpful. The Precision Flow Heliox is the only FDA cleared device for high flow nasal cannula heliox delivery. High flow nasal cannula therapy with heliox provides all the benefits of high flow therapy with the added benefit of reducing airway resistance and further decreasing work of breathing.[1] In addition, this device can be used to provide non-invasive heliox support instead of using a critical care ventilator, freeing up valuable equipment for the patients who need it most.

1. Migliori C, Gancia P, Garzoli E, Spinoni V & Chirico G. The Effecst of Helium/Oxygen Mixture (Heliox) Before and After Extubation in Long-term Mechanically Ventilated Low Birth Weight Infants. Pediatrics 2009. 123, 6; 1524-28.

Surfaxin and RDS

Les Plesko

The journal Expert Reviews – Clinical Pharmacology recently published a paper, Lucinactant for the Prevention of Respiratory Distress Syndrome in Premature Infants.* The authors discussed lucinactant, the peptide containing synthetic surfactant developed and marketed as SURFAXIN by Discovery Labs.

Lucinactant is the first non-animal derived, synthetic surfactant, containing sinapultide, a peptide that mimics SP-B. The authors noted that a long term follow up study evaluating outcomes of infants treated with lucinactant, as well as the comparator products, through one year corrected age, "demonstrates that lucinactant is as effective as animal-derived surfactants in preventing RDS in premature neonates, and in vitro studies suggest it is more resistant to oxidative and protein-induced inactivation." The authors added, "Its synthetic origin confers lower infection and inflammation risks as well as other potential benefits, which may make lucinactant an advantageous alternative to its animal-derived counterparts."

Background

The authors noted that the use of surfactant replacement therapy was introduced in 1980s and formalized in 1990. Since then, half the decrease in infant mortality in the US is attributable to its use.

Surfactant comprises phospholipids and proteins produced by type II alveolar pneumocytes which begin to be detectable at 22 weeks' gestation. The phospholipids acting with the proteins give surfactant the ability to lower surface tension. The most important protein for lowering alveolar surface tension is SP-B, in that it enables the even distribution of lipids across the alveolar surface. As such, the lipid monolayer allows for resisting alveolar collapse at end expiration.

The first FDA-approved surfactant was colfosceril palmitate (Exosurf), a protein-free synthetic surfactant that reduced neonatal mortality from RDS. Research suggested, however, that animal-derived surfactants might be even more effective. This turned out to be the case, and four protein-containing surfactants were approved by the FDA (Infasurf, Survanta, Curosurf and Surfaxin). These surfactants combine lipids and proteins and as such are more like human surfactant.

The use of animal-derived surfactants demonstrated faster response than the no-protein surfactant and animal-derived surfactants became the standard treatment.

According to the authors of the article, "Animal-derived surfactants have both practical and theoretical disadvantages. The most worrisome potential problems include the transmission of infectious agents and the delivery of potentially immunogenic substances, which could worsen inflammation in the neonatal lung and sensitize an impressionable immune system. In addition, animal-derived surfactants have been shown to be susceptible to inactivation by plasma proteins, reactive oxygen species and meconium… Potential quality control issues and batch-to-batch variation have been associated with the animal-derived surfactants. Furthermore, both neonatologists and parents are concerned about cultural and religious conflicts created by the use of bovine, porcine or human proteins."

Definition and Administration

Here are the highlights of authors Jordan and Donn's definition and description of lucinactant (the description is abridged): Lucinactant is a synthetic surfactant containing a mixture of phospholipids and fatty acids, to which sinapultide, a bioengineered 21 amino acid peptide designed to mimic the carboxyl-terminus of SP-B, has been added. Its lipid content is primarily dipalmitoyl phosphatidyl choline but also contains lesser amounts of palmitoyloleoyl phosphatidyl glycerol and palmitic acid. The peptide content is comprised entirely of sinapultide.

The authors explained: Lucinactant functions primarily at the air-liquid interface of the alveolar membrane, mimicking endogenous surfactant by forming a phospholipid monolayer that lowers the surface tension at the low lung volumes typical of end expiration. Sinapultide assists with the distribution and stabilization of the phospholipid monolayer in a dynamic fashion throughout the respiratory cycle in a manner similar to SP-B. Lucinactant is administered directly to the trachea beneath the vocal cords and is delivered to the distal alveoli by gravity, bulk diffusion and positive pressure ventilation.

The recommended dosing for lucinactant is 5.8 mL/kg of birthweight. [According to the manufacturer, before use, the vial should be warmed for 15 minutes in a preheated dry block heater set at 44° C. After warming, the vial should be vigorously shaken until the SURFAXIN is a uniform and free-flowing suspension. The temperature of the product will be approximately 37° C or less after the product is drawn into a syringe for administration.] Each dose should be divided into four equal aliquots, each

Les Plesko is editor of this journal.

delivered intratracheally, while maintaining positive airway pressure of 4-5 cm H2O. The infant should be positioned with its head elevated to 30° and placed in the right lateral decubitus position for the delivery of the first aliquot. Once the infant has been checked for stability, it should be repositioned in the left lateral decubitus position for delivery of the second aliquot, and this procedure should repeated for the third and fourth aliquots that complete the dose; four doses may be administered at 6 hour intervals as needed.

Clinical Trials

Lucinactant's safety has been evaluated in two phase III trials involving 1,500 preemies. Common side effects were transient hypoxia and pallor related to endotracheal tube reflux and obstruction, and interrupted doses during administration. These side effects, the authors noted, were the same as for animal-derived surfactants. Adverse outcomes were the same as with beractant and poractant alfa, and the trials found no contraindications for the use of lucinactant. In vivo trials with animals didn't identify any systemic toxicity, and in vitro, lucinactant didn't induce reversion mutations or induce chromosomal aberrations. The authors referenced in vitro studies in human cell lines demonstrating that lucinactant is absorbed by fetal type II alveolar pneumocytes without affecting endogenous surfactant protein synthesis.

Various studies have demonstrated the efficacy of lucinactant. The SELECT trial compared lucinactant and beractant to colfosceril, and the STAR trial compared it to poractant alfa.

The authors explained that SELECT was a multicenter double-blinded randomized trial that involved 1,294 infants at less than 32 weeks gestation who weighed between 600 and 1,250 g at birth and who required endotracheal intubation. Results showed that lucinactant decreased the incidence of RDS at 24 hours, RDS-related mortality at 24 hours, and death at 14 days. Comparing lucinanctant to beractant, according to the authors, "The SELECT study showed a statistically significant decrease in RDS-related mortality at 2 weeks for infants treated with lucinactant (4.7%) compared with beractant (10.5%)."

The STAR study compared lucinactant to poractant alfa and included 252 infants at 24-28 weeks' gestation, weighing 600-1250 g at birth. The authors noted, "Because of the ethical dilemma involved in undertaking a placebo-controlled study in the face of substantial evidence of the benefit of protein-containing surfactants, the STAR study was designed as a noninferiority trial based on the hypothesis that infants treated with lucinactant would do no worse than those treated with poractant alfa in its placebo-controlled trial." In this study, "lucinactant was shown to be noninferior to poractant alfa, and similar complication rates were observed for both treatments. The hypothesis that lucinactant is superior to poractant alfa could not be tested by this study design." The authors added that no differences were found in the primary outcomes, including mortality and chronic lung disease, but that "a statistically significant decrease in risk of necrotizing enterocolitis was noted in infants treated with lucinactant despite the fact that neither study was powered to detect this difference. Together, the SELECT and STAR studies suggest that lucinactant is as effective as animal-derived surfactant preparations for the primary prevention of RDS."

The future

The authors pointed out that at the present time, lucinactant is only available as an intratracheal suspension and is indicated for the prevention of respiratory distress sydrome (RDS). Though lyophilized lucinactant is under development, it has yet to be approved for use. They noted that "aerosolization of surfactant has been an attractive but an elusive proposition. Attempts to aerosolize or nebulize animal-derived surfactants have been unsuccessful. The energy required to create the aerosol denatures the proteins. In perhaps the most exciting area of new research in RDS, lucinactant was recently shown to remain functional in an aerosolized form. The ability to reaggregate at the alveolar membrane and regain surface tension-lowering function after aerosolization appears to be a uniquely beneficial property of lucinactant, not shared by its animal-derived counterparts… If this formulation and mode of delivery are borne out in larger clinical trials, the benefits of delivering surfactant without the potential complications of intratracheal instillation would likely be substantial."

The authors concluded, "The future of SRT will probably see the development of novel uses for the peptide-enhanced synthetic surfactants. Lucinactant, which appears to resist inactivation by serum proteins and reactive oxygen species better than other surfactants, may be better suited than animal-derived surfactants to treat meconium aspiration syndrome, cystic fibrosis and acute RDS in older pediatric patients and adults. Another intriguing possibility is the use of surfactants as a vehicle to deliver other medications directly to the lung with avoidance of systemic side effects."

**Lucinactant for the prevention of respiratory distress syndrome in premature infants. Expert Rev Clin Pharmacol 6(2), 115-21 (2013), Brian K. Jordan and Steven M. Donn. The authors are with the Department of Pediatrics and Communicable Diseases, Division of Neonatal-Perinatal Medicine, CS Mott Children's Hospital, University of Michigan Health System, Ann Arbor, MI.*

Benefits of the Neo-Tee versus the Self Inflating Resuscitation Bag in the Delivery Room and NICU

Kennard Chandler

The self inflating resuscitation bag is unable to provide the neonate continuous positive airway pressure (CPAP). In addition, the self inflating resuscitation bag is unable to maintain end expiratory alveolar volume, which may lead to alveolar collapse and loss of alveolar recruitment. This may be overcome if a PEEP valve is incorporated into the self inflating resuscitation bag. However the self inflating resuscitation bag is often used without this PEEP valve.

The Neo-Tee (Mercury Medical) is able to provide the neonate with CPAP. As simple as this sounds, Neo-Tee's ability to provide CPAP is the tremendous benefit of the Neo-Tee over the self inflating resuscitation bag.

The only strategy that has proven to promote alveolar stability and enhance alveolar recruitment in the delivery room and the NICU is CPAP in one form or another. CPAP also prevents the loss of end expiratory alveolar volume thus maintaining alveolar stability and alveolar recruitment.

During a positive pressure breath the variation of lung volume depends on the compliance of the alveolar structures and the amount of pressure used to produce that change. The normal lung at birth does not present pure elastic behavior across the vital capacity range. Even in the normal lung at birth there are regional and postural variations in how fast or slow lung units will fill or empty along the vital capacity range.

When the lung is subjected to a pressure change, time is needed until a volume change will occur. The time necessary to inflate an alveolar structure to 63% of its volume is called a "time constant." This concept is extremely important when trying to understand the challenges of the neonate's pulmonary mechanics during the transition to breathing air. Time constants refer to the speed at which the alveoli will fill or empty. In the normal or near normal lung the alveolar time constants will vary based on the resistance and compliance of the lung structures. Some alveoli will fill or empty faster while others are slower to fill or empty. During transition many factors may unfavorably alter the regional time constants immediately after birth. Understanding these challenges and regional differences in time constants is essential in the delivery room and the NICU.

The successful transition from fetal circulation to pulmonary circulation depends on the neonate's ability to achieve a stable functional residual capacity (FRC) immediately following birth. The challenge in these neonates is to achieve and maintain an adequate FRC allowing alveolar stability and optimizing alveolar recruitment. Achieving alveolar stability means that the spontaneous breath must be able to open or recruit as much of the available alveoli as possible. Maintaining alveolar stability also means that there is adequate end expiratory alveolar volume to prevent alveolar collapse and loss of alveolar recruitment.

As stated earlier, the only strategy that has proven to promote alveolar stability and enhance alveolar recruitment in the delivery room and the NICU is CPAP in one form or another. CPAP also prevents the loss of end expiratory alveolar volume, thus maintaining alveolar stability and alveolar recruitment. The Neo-Tee provides CPAP and will assist the transition process from fetal to pulmonary circulation by providing a dynamic FRC immediately following birth. The self inflating resuscitation bag does not provide a dynamic FRC.

Maintaining end-expiratory alveolar stability and alveolar volume is the function of the amount of the positive-end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) that is applied. Adding PEEP to a self inflating resuscitation bag requires the addition of a special PEEP valve to the self inflating resuscitation bag. Without this PEEP valve the end expiratory airway pressure will be allowed to return to zero after each positive pressure breath. This may cause a decrease in the FRC and loss of alveolar stability resulting in alveolar collapse and a loss of alveolar recruitment. Maintaining alveolar stability using a self inflating resuscitation bag without a PEEP valve may be impractical or impossible.

CPAP is able to achieve and maintain alveolar stability because the airway pressure never falls below the lower inflection point, preventing alveolar collapse. Keeping these alveoli inflated (dynamic FRC) and continuously participating in gas exchange is the unique secret of CPAP.

Therefore the benefit of the Neo-Tee is the ability to provide CPAP, providing a dynamic FRC and alveolar stability and optimizing alveolar recruitment which will enhance the transition from fetal to pulmonary circulation in the newborn.

This review was written by Chandler, who is solely responsible for its content. This review would not have been possible without the suggestions and the unwavering support of Ed Golden RRT, Director of Pulmonary Services, Manatee Memorial Hospital. Chandler is a staff Respiratory Therapist who is currently employed at Manatee Memorial Hospital. He has been involved in respiratory care for the past 44 years.

Upping the "A-Game"

Deb Discenza

Neonatal Intensive Care Units (NICUs) are always looking toward the future, toward new developments and best practices to provide better and more advanced care for fragile newborns. Inova Children's Hospital's NICU, nestled in the suburbs of the Washington, DC metropolitan region has always shown its "A-Game." Back when the current NICU opened in 1992 it was state-of-the-art in its technology and layout. In talking with neonatologist Robin Baker, MD, I learned about this unique NICU environment and how they have achieved exceptional outcomes. They are presently planning to combine their solid best practices of the present with that of the new layout of the future, commonly referred to as "Mother-Centered Care."

What is it that sets your NICU apart from the others, regionally and even nationally?

Our main focus in the NICU has always been on delivering high quality care and with that goes data collection and attention to detail. In order to accomplish this goal, we have continually collected and analyzed data on ourselves and used this data to compare our outcomes to an outside benchmark, which for neonatology is the Vermont Oxford Network (VON). A lot of people claim to deliver "quality care" but in order to prove that, you must actually compare yourself to an outside benchmark and make improvements when appropriate. Over the past 25 years we have been collecting information on almost every infant that goes through our NICU. I can tell you when we start and stop feeds, what respiratory problems they may have had, infections, O2 exposure, and the list goes on and on. I can tell you almost everything about these newborns. We analyze this data yearly, monthly and weekly so we get a sense in real time of how we are doing and where we can improve. It is our ongoing data analysis that drives our quality improvement efforts.

A couple of years ago we had a few infants with borderline hypoglycemia after delivery. Upon further examination we discovered that OB had made slight adjustments to the fluids they were giving the mothers just before delivery. This was noted after only a few days – and the problem was immediately corrected. We also implemented a policy to give antibiotics within 60 minutes of an infant's admission to the NICU and have almost eliminated perinatal infections. Finally, we have used our data to track the incidence of necrotizing enterocolitis after making changes to feeding regimens and blood transfusions. Our changes appear to be having a positive influence.

But data is only helpful if you consistently practice the same way. If you have many different treatments for a certain disease, then analyzing your data is irrelevant. I think we are unique as a group in that we have created protocols that almost every physician agrees to and follows so our care is less physician-dependent. There will always be some variability but we try to adhere to our protocols. It is also better for the parents because they know what to expect regardless of what physician is on duty that day. I feel it is very difficult for parents if the care of their infant changes daily depending on who the physician may be. In addition to protocol agreement, we have a five-week NICU rotation. This further solidifies our "consistency of care." During those 5 weeks, you really get to know the infant and the parents. When they go home they are almost like family – and some might say we see them more than our own families during those 5 weeks! There aren't many NICUs that provide 24/7, 365 attending level care. And we are at the bedside from the time the infant is born until discharge.

You have the March of Dimes "NICU Family Support Program" here. Please tell me about it.

March of Dimes was huge addition for us because they do such a great job of working with the parents under extremely stressful situations. They have a scrapbooking night, a Pizza Night, a Pie Night during Thanksgiving and a very active parent support group where parents can speak with other parents who are or have had similar NICU experiences. The purpose is to ease the enormous amount of stress and strain the parents are experiencing. As another benefit, the March of Dimes had a whole curriculum that some of our staff went through related to bereavement.

Parent of a former patient and premature infant with Inova Children's Hospital's Dr Robin Baker.

Deb Discenza is the mother of a 30-weeker preemie now 9 years old and the author of The Preemie Parent's Survival Guide to the NICU available at www.PreemieWorld.com.

A mom and her preemie.

What other types of programs do you have in place to help advance care?

We have numerous committees and each focuses on a particular area. For example, we have infectious disease, respiratory, feeding, bereavement, and a delivery room resuscitation committee. Most meet on a monthly basis to evaluate pressing problems. Ten years ago we had what we felt was a high incidence of central line infections. Through meticulous attention to detail and a number of changes, last year we went over 300 days without a central line bloodstream infection [CLBSI] which is notable when you consider the size and complexity of the infants under our care. In addition, it makes a difference on costs and long-term as CLBSI adds another $30,000 to $40,000 in medical fees, increases the length of stay of the hospitalization as well as the potential for morbidities. Our feeding committee (and as well as our entire NICU) is focused on using nothing but breast milk for most infants. If we don't have breast milk, we may use donor breast milk. We also have the ability to pasteurize the breast milk if needed. Through the bereavement committee, our nurses have learned how to create mementos for the families after the loss of a child. With the respiratory committee there is a strong focus on oxygen exposure and as a result the incidence of retinopathy of prematurity has decreased since we implemented certain protocols. Behind the scenes, everything that comes in contact with the infant or protocols that are or have been implemented are fully evaluated and vetted before they are used. Once they are implemented, we track the effects. Again, it is all about quality, data and our quest to deliver the best possible care.

Another very important piece of our improvement model is we have created a system where everybody on the team feels empowered to "enforce the rules." In one example, consultants usually come in with lab coats but before they can touch an infant, the nurse will remind them to take their jackets off, wash their hands, and remove all jewelry. So this is not hierarchical care; instead, everyone has complete control and is empowered to help "police" the rules. If there is an infection, everyone feels it. In another example, unit secretaries were asked about admissions and how we can get the infants admitted quicker. Now that we are on EPIC they must make sure the infant is admitted promptly because no orders can be placed until the infant is admitted. So we have tried to empower everybody in this NICU to understand it is their NICU. Everyone is the same. Yes, there are some with more responsibility but in the end, it is everyone's NICU.

How is this NICU using developmental care to complement the medical care?

We do a lot to help these babies thrive. First, the babies are swaddled in developmentally appropriate positions. Second, we have "Serenity Hour" from 3 to 4 pm each day where we turn the lights down and try to minimize stimulation during this time. Third, Kangaroo Care is encouraged when the infants are stable, even if they are on ventilators. Fourth, we have monitors in place that monitor noise levels. But in the current ward-based environment, though, it is tough. In our new NICU we will strive for more "mother-centered" care. The mother can stay at the bedside and deliver almost all of the routine care, which increases bonding and decreases the feeling of detachment that many NICU moms develop. However, we must be careful in the new NICU because we don't want to go too far the other way. Some stimulation is appropriate.

Finally, we're one of the few practices that actually follow our newborns post-discharge. What we have noticed over the years is that our infants tend to do better neurologically and have less morbidity than predicted. We believe it is secondary to the very structured and meticulous approach we have developed and continually refine. Every little piece of the puzzle is important and they all affect each other.

So talk about this new NICU launching in 2016. What will it be like?

There is no doubt that the new unit will be more mother/baby-friendly. As stated before, this will lead to less stimulation, Kangaroo Care earlier, and hopefully better breast milk production for the moms. We will have a family-friendly parent room that will include showers so they can refresh themselves and relax a bit. Many families and specifically moms helped with the design. Even the colors will be more mom-friendly! Having a premature infant and spending days and weeks at the hospital is incredibly stressful and our goal is to decrease this stress by making it feel less like a hospital and increase the maternal contact. So it was designed around the mother. We are continually tweaking our plans as we talk with other NICUs that have already implemented single family rooms. One of the concerns is related to in-room communication. If a monitor on the baby goes off, how do you know it is a true alarm and how do you decide who is responding? How are they alerted? Communication techniques are continually changing and improving. So in order to decrease the isolated feeling one might get in a single family room, we have designed "neighborhoods" with a nursing station and sight lines into each room. No mom wants to feel stranded in a room and this design will allow for safe single family, mother-centered care.

Even before the new NICU is in place, your team has created quite a complex model that focuses on helping these babies and these families thrive.

Yes it has been and continues to be a huge undertaking. There is nothing that comes into contact with the newborn that we haven't thoroughly analyzed, researched, tested, implemented and re-analyzed. For all of our efforts, we were the first NICU in the nation to receive the Joint Commission's Gold Seal of Approval for Prematurity. We were also recently listed in the top 50 neonatal units in U.S. News & World Report. I can confidently say, we don't do it for the awards or the Gold Seals, we do it for the newborns and will always be searching for a ways to improve.

Inova Children's Hospital's NICU, while maintaining a high level of care in their current unit, is already shifting gears as the new unit prepares to open. With a solid focus on the new mother-centered care, this NICU maintains its "A-Game" and strives for an "A+-Game" as it continues to focus on what truly matters most to the patients and their families – quality care that provides the best possible outcomes.

NICU snapshot

Name: Inova Children's Hospital

Level: Level IV

Beds: 75-bed unit

Awards: • First in the nation to receive the Joint Commission's Gold Seal of Approval for Prematurity; • 2013 Top 50 NICUs, U.S. News & World Report

Other: • Largest subspecialty NICU in Northern Virginia; • Among the lowest neonatal mortality rates in the nation

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Effect of position on the mechanical interaction between the rib cage and abdomen in preterm infants. J Appl Physiol 1992;72:1032-8.

17 Danan C, Dassieu G, Janaud JC, Brochard L. Efficacy of dead-space washout in mechanically ventilated premature newborns. Am J Respir Crit Care Med 1996;153:1571-6.

18 Dassieu G, Brochard L, Agudze E, Patkai J, Janaud JC, Danan C. Continuous tracheal gas insufflation enables a volume reduction strategy in hyaline membrane disease: technical aspects and clinical results. Intensive Care Med 1998;24:1076-82.

19 Benditt J, Pollock M, Roa J, Celli B. Transtracheal delivery of gas decreases the oxygen cost of breathing. Am Rev Respir Dis 1993;147:1207-10.

20 Miller TL, Blackson TJ, Shaffer TH, Touch SM. Tracheal gas insufflation-augmented continuous positive airway pressure in a spontaneously breathing model of neonatal respiratory distress. Pediatr Pulmonol 2004;38:386-95.

21 Numa AH, Newth CJ. Anatomic dead space in infants and children. J Appl Physiol 1996;80:1485-9.

22 Morly C. Continuous distending pressure. Arch Dis Child Fetal Neonatal Ed 1999;81:F152-6.

23 Spentzas T, Minarik M, Patters AB, Vinson B, Stidham G. Children with respiratory distress treated with high-flow nasal cannula. J Intensive Care Med 2009;24:323-8.

24 Lampland AL, Plumm B, Meyers PA, Worwa CT, Mammel MC. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. J Pediatr 2009;154:177-82.

25 Kahn DJ, Courtney SE, Steele AM, Habib RH. Unpredictability of Delivered Bubble Nasal Continuous Positive Airway Pressure Role of Bias Flow Magnitude and Nares-Prong Air Leaks. Pediatr Res 2007;62:343-7.

26 Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? Pediatrics 2008;121:82-8.

27 Holleman-Duray D, Kaupie D, Weiss MG. Heated humidified high-flow nasal cannula: use and neonatal early extubation protocol. J Perinatol 2007;27:776-81.

28 Shoemaker MT, Pierce MR, Yoder BA, DiGeronimo RJ. High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study. J Perinatol 2007;27:85-91.

29 Collins CL, Holberton JR, Barfield C, Davis PG: A Randomized Controlled Trial to Compare Heated Humidified High-Flow Nasal Cannulae with Nasal Continuous Positive Airway Pressure Postextubation in Premature Infants. J Pediatr 2012.

30 Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S: Heated, Humidified High-Flow Nasal Cannula Versus Nasal CPAP for Respiratory Support in Neonates. Pediatrics 2013, 131(5):e1482-1490.

How to Feed Small for Gestational Age Newborns

Giovanni Barone, Luca Maggio, Annalisa Saracino, Alessandro Perri, Costantino Romagnoli, Enrico Zecca

Abstract

Feeding small for gestational age (SGA) newborns is extremely challenging and the neonatologist should be brave and cautious at the same time. Although these babies have a high risk of milk intolerance and necrotizing enterocolitis, enteral feeding guidelines are not well established and practice varies widely among different neonatal units. Currently available studies on this topic include extremely and very low birth weight neonates, but are not focused specifically on small for gestational age infants. This review analyzes papers focused on feeding interventions in order to provide the best available evidences about the optimum timing for introduction of enteral feeding, how fast feed volume can be advanced, which milk and which feeding method is more appropriate in SGA infants.

Background

The term "small for gestational age" (SGA) is used to describe newborns whose birth weight and/or crown-heel length is less than expected for their gestational age and sex. Traditionally, the term SGA has been used to describe a neonate whose weight and/or length at birth is at least 2 SD below the mean for the infant's gestational age, equivalent to the 2.3 percentile, based on the data derived from an appropriate reference population.[1] Some publications define SGA newborns as those with birth weight or length below the 3rd, 5th, or 10th percentiles for gestational age.[2] The first definition was chosen by the international SGA advisory panel because it likely includes the majority of patients with impaired fetal growth.

However, this definition of SGA is inaccurate because it is not able to exclude the constitutional smallness, which is not pathological.[3] The term intrauterine growth retardation (IUGR) suggests diminished growth velocity in the fetus as documented by at least 2 intra-uterine growth assessment. Therefore SGA and IUGR are not synonymous. IUGR indicates the presence of a pathological process occurring in utero that inhibits fetal growth. Being born SGA does not necessarily mean that an intrauterine growth retardation has occurred and infants who are IUGR are not inevitably SGA at birth.

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There are several causes for being SGA. Exposure of the fetus to toxins (smoking, alcohol, drug abuse), chromosomal anomalies (trisomy 13, Edward Syndrome, Turner Sydrome, Prader-Willy Syndrome etc), congenital infections (toxoplasmosis, rubella, cytomegalovirus), metabolic disorders, maternal factors (both young and advanced age, maternal hypertension, placental and uterine abnormalities etc.). However the most common etiology of being born SGA is placental insufficiency that impairs growth particularly during the last trimester of pregnancy leading to IUGR.[4-6] Below we discuss the most severe and important complication for these neonates, with pathophysiological considerations.

NEC

Necrotizing enterocolitis (NEC) is a severe inflammatory disorders in which prematurity and enteral feeding seems the major predisposing factors. It occurs in up to 7% of very low birth weight infants, with a mortality rate of 15-30%, inversely related to birth weight and gestational age.[7] Garite et al. in a retrospective study including 29.916 premature newborns found that both SGA and IUGR were independently associated with an increased risk of NEC[8] By the physiological point of view growth restriction modifies the developmental pattern of intestinal structure. The intestine of SGA neonates has reduced weight, length, wall thickness, villous weight, and crypt depth.[9,10] Furthermore these infants have intestinal dysbiosis and an alteration of the proliferation-apoptosis homeostasis which leads to a reduced surface of intestinal exchange.[11] These alterations could be responsible for the higher gastro-intestinal morbidity, feeding intolerance and impaired nutrient absorption.

However recently much attention was focused on those infants born prematurely with IUGR and abnormal blood flow on antenatal Doppler studies.[12] Increased placental resistance in the presence of placental failure leads to a reduction in end diastolic blood flow through the umbilical arteries, progressing to absent (AEDF) or reversed flow (AREDF).[13] Pathophysiology of fetal adaptation to chronic hypoxia involves preferential shunting of blood to the brain at the expense of the splanchnic circulation. It was shown that severe prenatal Doppler abnormalities are associated with poor fetal outcome,[14,15] but it is still debated if they increased the risk of neonatal NEC.

Some studies have demonstrated a close association between AEDF or AREDF and NEC, which appears to be independent of other factors such as degree of growth retardation, prematurity and perinatal asphyxia,[16,17] while others have not confirmed

these findings.[18,19] A meta-analysis of 14 observational studies demonstrated an increased incidence of NEC in preterm infants who had suffered fetal AREDF compared with controls, with an odds ratio of 2.13 (95% CI 1.49 to 3.03).[20] Nine of the included studies showed an excess of NEC in the AREDF infants; eight studies classified NEC using the stricter definition of radiological or surgical confirmation, of which six showed an excess of confirmed NEC in the AREDF group. Overall, confirmed NEC was not significantly increased in these studies (OR 1.6, 95% CI 0.9 to 2.8), but the six studies examining confirmed NEC in preterm infants with IUGR showed greatly increased odds of confirmed NEC in infants with fetal AREDF (OR 6.9, 95% CI 2.3 to 20). In many of the studies, fetuses with AREDF required earlier delivery than controls so it could be argued that the higher risk of NEC in these studies was primarily related to the lower gestational age and birth weight; nevertheless, the excess of confirmed NEC was also found in the two series that matched controls for gestation and weight (OR 5.5, 95% CI 1.1 to 28).[16,21] A more recent study confirmed the results of this meta-analysis demonstrating a strong relation between AREDF and subsequent development of NEC (OR: 5.88, 95% CI: 2.41 to 14.34) also after adjustment for gestational age at birth (OR: 7.64, 95% CI: 2.96 to 19.70,) and after adjustment for birth weight for gestational age z-score (OR: 6.72, 95% CI: 2.23 to 20.25).[22]

All the previous studies examined only the role of umbilical arteries Doppler flows. When Manogura et al.[23] investigated a more comprehensive fetal Doppler assessment that provided greater circulatory details (umbilical artery, middle cerebral artery, ductus venosus, and umbilical vein) the association between NEC and AREDF was lost. In this study, a multinomial logistic regression with NEC as dependent variable failed to demonstrate a relationship between placental resistance and the risk of NEC, and found that birth weight and base deficit at birth were the independent risk factors for NEC. These results have raised some doubts on the reliability of all the evidences suggesting a causal relationship between NEC and abnormal placental resistance. Moreover, many studies were underpowered given the overall low incidence of NEC, and the metabolic status at birth was not taken into consideration by any of these studies. If it is plausible that placental insufficiency predisposes to, but does not initiate, the cascade of events that lead to NEC, it is more likely that the limitations of prematurity define the origins of this disease.

The questions about feeding SGA infant

Enteral feeding guidelines are not well established in preterm SGA neonates, and there is a lack of published information about best feeding regimen. Practice varies widely among different neonatal units as shown by a survey carried out in two different English Health Regions, but a policy of delayed and careful introduction of enteral feeding is often chosen in order to prevent NEC.[20] We now analyze the best current evidences on feeding SGA infants.

What milk

Human breast milk would be expected to protect against NEC for its antimicrobial and anti-inflammatory characteristics. However, proving efficacy in randomized clinical trial has been challenging because of 2 main reasons. First of all, the difficulty of recruiting infants to a randomized trial about human milk when mothers have strong preferences, secondly the lack of standardized definitions of what human milk comprises (maternal or donor, fortified or unfortified, human milk alone or human milk plus formula).

In 1990 Lucas and Cole demonstrated a reduction in the incidence of NEC among preterm infants who received only human milk when compared with infants who received bovine milk–based formula.[24] Two meta-analysis of several small randomized controlled trials reported a lower incidence and severity of NEC in infants fed with an exclusively human milk diet.[25,26] A recent trial randomized 207 premature infants with a birth weight between 500 and 1250 grams to receive fortified human milk or bovine-milk based products and confirmed earlier data finding that the rates of NEC and NEC requiring surgery were markedly lower in the first group. The number of infants needed to treat (NNT) with an exclusively human milk diet to prevent 1 case of NEC was 10 and NNT to prevent 1 case of surgical NEC or death is 8.[27]

Early vs delayed

Early enteral feeding is advantageous because it improves the functional adaptation of the gastrointestinal tract by stimulating hormone secretion and gastrointestinal motility.[28] It also decreases the need of total parenteral nutrition and its associated complications, such as catheter related sepsis, cholestasis, cardiac tamponade, osteopenia of prematurity and other metabolic disturbances.[29,30] Despite this, early enteral feeding is often delayed in high risk infants because it has been thought to be associated with an increased risk of NEC. A meta-analysis of five RCTs conducted on preterm infants did not detect a significantly different risk of NEC between infants randomized to delayed feeding (defined as introduction of enteral feeds as later than day 5–7 after birth) and infants randomized to early feeding (defined as less than 4 day after birth); RR 0.89 (95% CI 0.58 to 1.37).[31] The two largest trials in that meta-analysis[32,33] recruited only SGA infants with abnormal fetal circulatory distribution or flow. For these reasons, data from these trials do not provide sufficient evidence that delayed introduction of enteral feeding in SGA neonates reduces the risk of NEC, even if 95% CI for the pooled estimates of effect is wide and consistent with more than 40% reduction in the risk of NEC and death in newborns who have delayed introduction. Given this level of uncertainty these findings should be applied cautiously.

Minimal enteral feeding

An alternative approach to delaying feeding is the minimal enteral feeding (MEF). MEF (also known as "trophic feeding," "gut-priming," "non nutritive feeding" and "hypocaloric feeding") is conventionally defined as giving small volumes of milk (typically 12 to 24 ml/kg/ day every 1-3 hours) starting within the first few days after birth without advancing the feed volumes during the first week of life.[34] Enteral fasting during the early neonatal period has potential disadvantages for premature infants, because gastrointestinal hormone and motility are improved by enteral milk. Delayed enteral feeding could impair the functional adaptation of the gastrointestinal tract leading to intestinal dismotility and consequent feeding intolerance.[35,36] A systematic review published in the Cochrane Library[37] did not detect a statistically significant effect on the incidence of NEC between very low birth weight newborns randomized to MEF and to no enteral feeding (RR 1.07 95% CI 0.67 to 1.70). Substantial clinical uncertainty remains about the effect of MEF on SGA infants because most of the trials on this topic specifically exclude infants who were SGA at birth. The only one including 56 babies with birth weight below 2000

grams and below 10th per-centile for gestational age failed to demonstrate significant differences between newborns fed with trophic feeding or no feeds for the first five days of life in the primary outcome of intestinal permeability measured by the sugar absorption test.[38] There were also no differences in feeding tolerance, growth and incidence of NEC between the two groups.[38]

How to advance feed volume

The rate of advancement of enteral feeding is another area of uncertainty. Retrospective studies have found that those neonatal centers where enteral feeding is introduced earlier and feeding volume advanced faster have higher incidences of NEC.[39] On the other hand, slow advancement of enteral feeding delays the establishment of full enteral nutrition and extends the duration of total parenteral nutrition with its associated risks,[40] that may have adverse consequences for survival, growth and development.[41] A meta-analysis of four trials (496 very low birth weight infants) showed no differences in NEC rates comparing rapid (as 30 to 35 ml/kg/day) versus slow (as 15 to 20 ml/kg/day) advancement feeding strategies (RR 0.91 95% CI 0.47 to 1.75).[42] Infants fed at faster rate reached the full enteral feeding about two to five days earlier than infants fed slowly, but they did not have a higher risk of NEC. However, these findings should be applied with caution to SGA newborns because the vast majority of the studied infants were appropriate for gestational age. Only in the trial performed by Salhotra et al[43] more than 95% of the 53 participants were SGA. In this trial, the fast enteral feeding group reached the full enteral feed significantly earlier (mean 10 days) than the slow advancement group (mean 14.8 days), and there were two cases of NEC in the fast advancement group. To date there are no trial that compare slow versus fast feeding regimen in a selected population of SGA newborns.

Mode of feeding

To date there are no studies focused on SGA newborns and the best mode of feeding. The few available data concern premature infants born < 1500 grams that are not able to coordinate sucking, swallowing, and breathing. A systematic review of seven trials published in the Cochrane Library[44] did not detect a statistically significant effect between continuous versus intermittent milk feeding methods in time to achieve full enteral feeding, in feeding intolerance, in somatic growth and in incidence of NEC. At the present time practice appears to be based more on individual assessment rather than on scientific evidence. Continuous feeding may reduce energy expenditure[45] and improve feeding tolerance, nutrient adsorption and growth;[46] on the other hand, intermittent bolus method may be more physiologic, promoting the cyclical pattern of release of gastrointestinal hormones, which are important for gut development.[47]

Feeding intolerance

Feeding intolerance is usually characterized by gastric residuals before feeding, emesis and abdominal distention. The gastric residual volume (GRV) is the element of feeding that can be measured and compared most easily. Several authors suggested to use GRV as a marker of feeding intolerance, in order to make early detection of NEC.[48-50] Qualitative and quantitative evaluation of gastric residuals can be performed. To date is difficult to assess a tolerance threshold of GRV beyond which enteral feeding should be withdrawn. Mihatsch et al[48] tolerated GRV up to 2 mL in newborns ≤ 750 grams and up to 3 mL in newborns from 750 to 1000 grams in their protocol, but concluded that additional research is required to evaluate if GRV threshold could be increased up to 5 ml/kg body weight. Cobb et al[49] found that GRV > 3.5 mL or 33% of a single meal may be associated with a higher risk for NEC while a GRV <1.5 mL or 25% of a meal is probably normal. Finally the available data on qualitative evaluation of gastric residuals suggest that infants with blood stained or hemorrhagic residuals were at higher risk of NEC, whereas bile stained residuals are not a risk factor by themselves.[50]

Quality of the evidence

Being born SGA does not necessarily mean that IUGR has occurred, and infants who are IUGR are not inevitably SGA at birth. Unfortunately, the terms IUGR and SGA have been used interchangeably, creating confusion on the topic. In the absence of congenital malformations or chromosomal abnormalities, small fetal size could be the consequence of two distinct processes: constitutional smallness or pathological growth restriction. Distinguishing one process from the other is challenging, but such distinctions have profound implications toward understanding quality and robustness of evidence provided by available trials. Patients enrolled in the studies are usually selected according to their birth weight (below the 10th or the 3rd percentile) without checking if a growth restriction really occurred. So SGA is a term that is often used as a proxy for restricted growth, thereby combining both constitutionally small and pathologically growth restricted fetuses. It is known that growth restricted fetuses are small because of some underlying pathological conditions (smoking during pregnancy, uteroplacental dysfunction, hypertensive disorders, etc.), and they are therefore at increased risk for neonatal morbidity and mortality. On the other hand, constitutionally small infants can easily have morbidity and mortality very similar to appropriate for gestational age, and considerably lower than pathologically growth restricted ones.[51]

Conclusions

There is limited evidence on which to base feeding policy in SGA newborns. Currently available studies on this topic include extremely and very low birth weight neonates, but are not focused specifically on SGA infants. Furthermore there are not RCTs that make a clear distinction between SGA and growth restricted neonates. Future randomized trials on feeding intervention should be targeted on IUGR infants, excluding constitutionally small newborns, in order to provide robust evidence concerning the optimum timing for introduction of enteral feeding, how fast feed volume can be advanced and which feeding method is more appropriate. To date, however, no trials showed any benefits of delayed enteral feeding or slow advancement of enteral feed volumes. Growth restricted newborns are a nutritional emergency that will result in serious short and long term detrimental effects, when left untreated.

References

1 Lee PA, Chernausek SD, Hokken-Koelega AC, Czernichow P, International Small for Gestational Age Advisory B: International Small for Gestational Age Advisory Board consensus development conference statement: management of short children born small for gestational age, April 24-October 1, 2001. Pediatrics 2003, 111:1253–1261.

2 Saenger P, Czernichow P, Hughes I, Reiter EO: Small for gestational age: short stature and beyond. Endocr Rev 2007, 28:219–251.

3 Gardosi J: New definition of small for gestational age based

on fetal growth potential. Horm Res 2006, 65(Suppl 3):15–18.
4 Thompson JM, Clark PM, Robinson E, Becroft DM, Pattison NS, Glavish N, Pryor JE, Wild CJ, Rees K, Mitchell EA: Risk factors for small-for-gestational-age babies: The Auckland Birthweight Collaborative Study. J Paediatr Child Health 2001, 37:369–375.
5 Bryan SM, Hindmarsh PC: Normal and abnormal fetal growth. Horm Res 2006, 65(Suppl 3):19–27.
6 Ahluwalia IB, Merritt R, Beck LF, Rogers M: Multiple lifestyle and psychosocial risks and delivery of small for gestational age infants. Obstet Gynecol 2001, 97:649–656.
7 Berman L, Moss RL: Necrotizing enterocolitis: an update. Semin Fetal Neonatal Med 2011, 16:145–150.
8 Garite TJ, Clark R, Thorp JA: Intrauterine growth restriction increases morbidity and mortality among premature neonates. Am J Obstet Gynecol 2004, 191:481–487.
9 Baserga M, Bertolotto C, Maclennan NK, Hsu JL, Pham T, Laksana GS, Lane RH: Uteroplacental insufficiency decreases small intestine growth and alters apoptotic homeostasis in term intrauterine growth retarded rats. Early Hum Dev 2004, 79:93–105.
10 Xu RJ, Mellor DJ, Birtles MJ, Reynolds GW, Simpson HV: Impact of intrauterine growth retardation on the gastrointestinal tract and the pancreas in newborn pigs. J Pediatr Gastroenterol Nutr 1994, 18:231–240.
11 D'Inca R, Kloareg M, Gras-Le Guen C, Le Huerou-Luron I: Intrauterine growth restriction modifies the developmental pattern of intestinal structure, transcriptomic profile, and bacterial colonization in neonatal pigs. J Nutr 2010, 140:925–931.
12 Baschat AA, Hecher K: Fetal growth restriction due to placental disease. Semin Perinatol 2004, 28:67–80.
13 Baschat AA: Fetal responses to placental insufficiency: an update. BJOG 2004, 111:1031–1041.
14 Gilbert WM, Danielsen B: Pregnancy outcomes associated with intrauterine growth restriction. Am J Obstet Gynecol 2003, 188:1596–1599. discussion 1599–1601.
15 Aucott SW, Donohue PK, Northington FJ: Increased morbidity in severe early intrauterine growth restriction. J Perinatol 2004, 24:435–440.
16 Malcolm G, Ellwood D, Devonald K, Beilby R, Henderson-Smart D: Absent or reversed end diastolic flow velocity in the umbilical artery and necrotising enterocolitis. Arch Dis Child 1991, 66:805–807.
17 Bhatt AB, Tank PD, Barmade KB, Damania KR: Abnormal Doppler flow velocimetry in the growth restricted foetus as a predictor for necrotising enterocolitis. J Postgrad Med 2002, 48:182–185. discussion 185.
18 Karsdorp VH, Van Vugt JM, Van Geijn HP, Kostense PJ, Arduini D, Montenegro N, Todros T: Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. Lancet 1994, 344:1664–1668.
19 Adiotomre PN, Johnstone FD, Laing IA: Effect of absent end diastolic flow velocity in the fetal umbilical artery on subsequent outcome. Arch Dis Child Fetal Neonatal Ed 1997, 76:F35–F38.
20 Dorling J, Kempley S, Leaf A: Feeding growth restricted preterm infants with abnormal antenatal Doppler results. Arch Dis Child Fetal Neonatal Ed 2005, 90:F359–F363.
21 Wilson DC, Harper A, McClure G: Absent or reversed end diastolic flow velocity in the umbilical artery and necrotizing enterocolitis. Arch Dis Child 1991, 66:1467.
22 Kamoji VM, Dorling JS, Manktelow B, Draper ES, Field DJ: Antenatal umbilical Doppler abnormalities: an independent risk factor for early onset neonatal necrotizing enterocolitis in premature infants. Acta Paediatr 2008, 97:327–331.
23 Manogura AC, Turan O, Kush ML, Berg C, Bhide A, Turan S, Moyano D, Bower S, Nicolaides KH, Galan HL, et al: Predictors of necrotizing enterocolitis in preterm growth-restricted neonates. Am J Obstet Gynecol 2008, 198:638. e631-635.
24 Lucas A, Cole TJ: Breast milk and neonatal necrotising enterocolitis. Lancet 1990, 336:1519–1523.
25 Boyd CA, Quigley MA, Brocklehurst P: Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2007, 92:F169–F175.
26 McGuire W, Anthony MY: Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review. Arch Dis Child Fetal Neonatal Ed 2003, 88:F11–F14.
27 Sullivan S, Schanler RJ, Kim JH, Patel AL, Trawoger R, Kiechl-Kohlendorfer U, Chan GM, Blanco CL, Abrams S, Cotten CM, et al: An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. J Pediatr 2010, 156:562–567. e561.
28 Burrin DG, Stoll B: Key nutrients and growth factors for the neonatal gastrointestinal tract. Clin Perinatol 2002, 29:65–96.
29 Camara D: Minimizing risks associated with peripherally inserted central catheters in the NICU. MCN Am J Matern Child Nurs 2001, 26:17–21. quiz 22.
30 Schutzman DL, Porat R, Salvador A, Janeczko M: Neonatal nutrition: a brief review. World J Pediatr 2008, 4:248–253.
31 Morgan J, Young L, McGuire W: Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev 2011, (3):CD001970.
32 Karagianni P, Briana DD, Mitsiakos G, Elias A, Theodoridis T, Chatziioannidis E, Kyriakidou M, Nikolaidis N: Early versus delayed minimal enteral feeding and risk for necrotizing enterocolitis in preterm growth-restricted infants with abnormal antenatal Doppler results. Am J Perinatol 2010, 27:367–373.
33 Leaf A, Dorling J, Kempley S, McCormick K, Mannix P, Linsell L, Juszczak E, Brocklehurst P, Abnormal Doppler Enteral Prescription Trial Collaborative G: Early or delayed enteral feeding for preterm growth-restricted infants: a randomized trial. Pediatrics 2012, 129:e1260–e1268.
34 McClure RJ: Trophic feeding of the preterm infant. Acta Paediatr Suppl 2001, 90:19–21.
35 Lucas A, Bloom SR, Aynsley-Green A: Gut hormones and 'minimal enteral feeding'. Acta Paediatr Scand 1986, 75:719–723.
36 Berseth CL: Neonatal small intestinal motility: motor responses to feeding in term and preterm infants. J Pediatr 1990, 117:777–782.
37 Bombell S, McGuire W: Early trophic feeding for very low birth weight infants. Cochrane Database Syst Rev 2009, (3):CD000504.
38 Van Elburg RM, van den Berg A, Bunkers CM, Van Lingen RA, Smink EW, Van Eyck J, Fetter WP: Minimal enteral feeding, fetal blood flow pulsatility, and postnatal intestinal permeability in preterm infants with intrauterine growth retardation. Arch Dis Child Fetal Neonatal Ed 2004, 89:F293–F296.
39 Uauy RD, Fanaroff AA, Korones SB, Phillips EA, Phillips JB, Wright LL: Necrotizing enterocolitis in very low birth weight

infants: biodemographic and clinical correlates. National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr 1991, 119:630–638.
40 Flidel-Rimon O, Friedman S, Lev E, Juster-Reicher A, Amitay M, Shinwell ES:Early enteral feeding and nosocomial sepsis in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2004, 89:F289–F292.
41 Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, Higgins RD, National Institute of Child H, Human Development Neonatal Research N: Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004, 292:2357–2365.
42 Morgan J, Young L, McGuire W: Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev 2011, (3):CD001241.
43 Salhotra A, Ramji S: Slow versus fast enteral feed advancement in very low birth weight infants: a randomized control trial. Indian Pediatr 2004, 41:435–441.
44 Premji SS, Chessell L: Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. Cochrane Database Syst Rev 2011, (11):CD001819.
45 Grant J, Denne SC: Effect of intermittent versus continuous enteral feeding on energy expenditure in premature infants. J Pediatr 1991, 118:928–932.
46 Toce SS, Keenan WJ, Homan SM: Enteral feeding in very-low-birth-weight infants. A comparison of two nasogastric methods. Am J Dis Child 1987, 141:439–444.
47 Aynsley-Green A, Adrian TE, Bloom SR: Feeding and the development of enteroinsular hormone secretion in the preterm infant: effects of continuous gastric infusions of human milk compared with intermittent boluses. Acta Paediatr Scand 1982, 71:379–383.
48 Mihatsch WA, Von Schoenaich P, Fahnenstich H, Dehne N, Ebbecke H, Plath C, Von Stockhausen HB, Muche R, Franz A, Pohlandt F: The significance of gastric residuals in the early enteral feeding advancement of extremely low birth weight infants. Pediatrics 2002, 109:457–459.
49 Cobb BA, Carlo WA, Ambalavanan N: Gastric residuals and their relationship to necrotizing enterocolitis in very low birth weight infants. Pediatrics 2004, 113:50–53.
50 Bertino E, Giuliani F, Prandi G, Coscia A, Martano C, Fabris C: Necrotizing enterocolitis: risk factor analysis and role of gastric residuals in very low birth weight infants. J Pediatr Gastroenterol Nutr 2009, 48:437–442.
51 Harkness UF, Mari G: Diagnosis and management of intrauterine growth restriction. Clin Perinatol 2004, 31:743–764. vi.

The Model of Palliative Care in the Perinatal Setting: a review of the literature

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Abstract

Background: The notion of palliative care (PC) in neonatal and perinatal medicine has largely developed in recent decades. Our aim was to systematically review the literature on this topic, summaries the evolution of care and, based on the available data, suggest a current standard for this type of care.

Methods: Data sources included Medline, the Cochrane Library, CINAHL, and the bibliographies of the papers retrieved. Articles focusing on neonatal/perinatal hospices or PC were included. A qualitative analysis of the content was performed, and data on the lead author, country, year, type of article or design, and direct and indirect subjects were obtained.

Results: Among the 1558 articles retrieved, we did not find a single quantitative empirical study. To study the evolution of the model of care, we ultimately included 101 studies, most of which were from the US. Fifty of these were comments/reflections, and only 30 were classifiable as clinical studies (half of these were case reports). The analysis revealed a gradual conceptual evolution of the model, which includes the notions of family-centered care, comprehensive care (including bereavement) and early and integrative care (also including the antenatal period). A subset of 27 articles that made special mention of antenatal aspects showed a similar distribution. In this subset, the results of the four descriptive clinical studies showed that, in the context of specific programs, a significant number of couples (between 37 and 87%) opted for PC and to continue with the pregnancy when the fetus has been diagnosed with a lethal illness.

Conclusions: Despite the interest that PC has aroused in perinatal medicine, there are no evidence-based empirical studies to indicate the best model of care for this clinical setting. The very notion of PC has evolved to encompass perinatal PC, which includes, among other things, the idea of comprehensive care, and early and integrative care initiated antenatally.

Background

The modern concept of palliative care (PC) has been gaining momentum in recent decades, especially since the 1960s, in response to a realization that end-of-life issues for seriously ill patients have been inadequately addressed with traditional approaches. The focus on adult PC has reached such relevance that it has become a global public health priority.

Although in a slower fashion, the concept of PC has been gradually incorporated into neonatology. Only recently it has been accepted that pain and discomfort can affect newborns, whatever their gestational age, and even fetuses, despite the fact that attention was drawn to this issue already many years ago. Likewise, the experience gained in the development of hospices, once again initiated for adults and subsequently adapted to pediatrics and neonatology, has provided insights towards the PC model applicable to perinatal medicine. The variety of PC approaches has introduced complexity and depth to the concept of PC in perinatal care, which makes necessary some degree of standardization.

Therefore, the objectives of this study were: first, to systematically review the clinical literature on Neonatal Palliative Care (NPC) and Perinatal Palliative Care (PPC) to determine if there is a best model of care; second, to summarize the evolution of the main traits of PPC; and lastly, to identify the most relevant features of PPC currently offered around the world.

Methods

Criteria for including studies in this review: We aimed to include clinical trials in which an experimental model of care was compared to another model of care. We planned to include randomized controlled trials (RCTs), cluster RCTs and quasi-RCTs, and decided that if no RCTs and quasi-RCTs were available, then we would include controlled before-and-after studies. In the event that no experimental studies would fulfill these criteria, articles that met the remaining criteria would be classified and examined, regardless of the study design in order to perform a qualitative synthesis of them.

Participants in the included studies were to be the fetus, neonates and families who received care guided by a PC model. We did not place any restrictions on diagnosis or clinical setting (eg hospital, home or nursing home). We considered measures of the following types of outcomes: physical, psychological, quality of life, and any adverse effects. We excluded studies that focused only on a very

specific aspect of the care, such as treatment of pain or ethical decision-making, not specifically in the context of PC.

Search methods to identify studies: We searched the Cochrane Library, MEDLINE (through PubMed) and CINAHL. The search strategy was developed to comprise searches both for keywords and medical subject headings under existing database organizational schemes. The strategy for MEDLINE (PubMed) is presented in Table 1. No language restriction was considered. The timeframe covered for the databases used in the search was from their inception to May 2010. We searched the reference lists of all relevant reviews or other studies, and scanned paper issues of the journals relevant to our topic.

Selection of studies: Two review authors pre-screened all search results (titles and abstracts) for possible inclusion, and those selected by one or both authors were subject to full-text assessment. Disagreements over whether a study met the inclusion criteria were planned to settle through joint discussion among the members of the research team; although there were no discrepancies.

Data collection and analysis: We first drew up a classification to catalogue the articles found. The categories established were: 1) prospective quantitative clinical studies (including cohort studies and controlled trials); 2) qualitative clinical studies; 3) case-control studies; 4) cross-sectional studies (including surveys on attitudes towards hospices or related issues); 5) case reports and case-series; 6) articles designing, implementing or describing a palliative care program; 7) literature reviews (discerning narrative reviews from systematic reviews & meta-analyses); 8) guidelines (including evidence-based clinical guidelines, clinical protocols and consensus); 9) comments/reflections; and 10) cost-effectiveness analysis. Those articles that could have been placed in multiple categories were classified into the most appropriate one by consensus among the members of the research group. We agreed that new categories could emerge or that already classified articles could be subject to reclassification.

In addition to performing a qualitative analysis of the texts, the following data from each classified article were recorded on predetermined spreadsheet: lead author and country; year; type of article or design; main topic; direct subjects and number if appropriate; indirect subjects and number if appropriate; and job or position of the authors. A secondary analysis was planned for those articles that envisaged initiating early or prenatal PC, as well as standard care (ie perinatal palliative care [PPC]).

Results

In total, 1,558 titles and abstracts were retrieved and assessed; there was not a single experimental study that fulfilled the eligibility criteria. Therefore, we classified and examine all the articles that met the remaining criteria, regardless of the study design. The articles were classified according to type of article or design as follows: comments or reflections 50, clinical studies 30 (case reports 15, quantitative series 10, and qualitative series 5), guidelines/clinical practice proposals 11, papers designing/describing a PC program 5, and reviews 5. According to their place of origin 64 articles were from the US (mainly from California 11, and Wisconsin 7); 25 from Europe (mainly from the UK 11, France 4, and Germany 3) and the rest were from Australia and New Zealand 6; Canada 4; Hong Kong 1 and Saudi Arabia 1. No quantitative empirical research studies were found, whether experimental (eg randomized controlled trials) or observational (cohort, or case-control studies).

Qualitative analysis of the content of the articles showed that the concept of PC has developed gradually; over time, there is a progression in the characterization of the care and consideration of issues that had not been initially addressed. Although the development is not perfectly defined–the various aspects of PC are inter-related and overlap–it can be summarized as follows: a) pain relief; b) comfort (multisensorial context); c) maternal bonding (and other emotional aspects); d) family-centered care; e) comprehensiveness (including psychological, social and spiritual aspects); f) early start and integrative care (including bereavement); g) antenatal period.

The 27 articles that were considered to be about PPC (those that made explicit mention of preparing or initiating the program before birth) were subject to a secondary, manual analysis. The distribution of this subgroup by type of article or design (see Table 2) gave percentages that were very similar to those observed in the whole sample. There were eight clinical studies (30%), four of which were quantitative series, three case reports and one a qualitative study. Five (18%) were classified as guidelines/clinical practice proposals and one as designing/describing a PPC program. As in the whole sample, the highest percentage was for comments/reflections with 13 articles (48%). As far as the country of origin was concerned, the distribution was also similar to that of the sample as a whole: seventeen articles (63%) were from the US, followed by seven (26%) from Europe (the United Kingdom had the most), and three from Canada. In this subgroup, only four clinical studies were found to show the quantitative results of their programs.

Discussion

The field of neonatal and perinatal medicine has been affected by the general interest shown in PC. The first references in the literature referring to the concept as such date to 1982, although its origins actually go back to the reaction to therapeutic obstination with premature births at the limit of viability in the early 1970s. However, it should be pointed out that very few clinical studies can be found that can provide empirical data on PC in the perinatal setting. About half of the 101 articles identified were comments/reflections, and less than a third could be considered to be clinical contributions or studies, of which half were simply case reports. Of the clinical contributions, five were classified as primarily qualitative studies, although in some other articles qualitative techniques were used. It was finally decided to classify these five studies, despite the fact that their main aim was not to study PC but to analyze the decision-making process of couples faced with the diagnosis of an unhealthy or non-viable fetus. In contrast, three other qualitative studies by Swanson-Kauffman that focused on the experience of miscarriage and the caring needs of women who miscarry were not included in the classification.

Interest in neonatal/perinatal PC seems to be greater in the US (followed by Europe) than in other parts of the world, although this distribution may reflect a publishing bias that is influenced by the databases consulted and the lack of clinical literature from some parts of the world, such as Africa. However, it should be borne in mind that sociological and clinical practice differences may imply underlying different meanings regarding PC and end of life issues.

This study has certain limitations, the greatest of which is a lack of evidence-based empirical studies to identify the best model for perinatal PC. Much of the information has not been published in the traditional literature; rather, it is compiled in reports and protocols of clinical practice, which are not immediately available (except a few which are available online) and could introduce some level of publication bias. Given the nature of the articles and the lack of quantitative results, we did a consensus analysis which would allow us to summarize the evolution of PC.

The qualitative evaluation of these articles seems to show an evolution on PPC over time that includes some of the aspects that have also been developed in newborn care. In addition, the care provided has also been enriched by input from palliative care units for adults and children. So the initial care provided for the more physical aspects such as pain relief and comfort (in a multisensorial context) is immediately supplemented with the importance of maternal bonding and other emotional aspects. In this regard, the hospice model, as the precursor/pioneer of PC, has made a considerable contribution. Hospices emerged as a result of the work by Saunders with adults in the 1960s and were soon advocated for children by Saunders herself and then adapted for neonates by Whitfield. Experience has also shown that general care designed not only to minimize pain in neonates but also to make them more comfortable, promote individualized developmental care and facilitate bonding with the mother can also be of great relevance. The importance of family participation in the NICU, which found expression in the concept of "family-centered care" in the 1960s and 1970s also could have some influence on neonatal PC. Although PC emerged in close combination with the NICUs, to encourage incorporation of the process in the family environment, the possibility of PC taking place in the home (at least on a temporary basis) was considered. This option, however, would depend heavily on the professional support that could be provided and the changing circumstances of the patient and the family.

Recently, attention has been drawn to the need for "integrative care." Using this term, Milstein highlights the importance of introducing healing and palliation (when indicated) alongside curative measures as soon as any diagnosis, especially a critical one, is made as an integrative paradigm of care. He also points out that because loss can be experienced in many conditions, even in the absence of death, bereavement is represented as an on-going, continual process throughout a disease process.

In recent years, particular emphasis has been put on the importance of initiating PC early, even antenatally. Three general areas of implementation have been described: fetus/neonates with lethal congenital anomalies, neonates that are previable or at the limits of viability, and neonates that do not respond to aggressive medical management.

An excellent synthesis of the design and implementation of a program of this sort can be found in the document drawn up by the British Association of Perinatal Medicine, coordinated by Murdoch and entitled "Framework for clinical practice in perinatal medicine." It divides PC planning into eight stages: a) eligibility of fetus or baby for palliative care; b) family care (including psychological support, creating memories, support of spiritual/personal belief and social support); c) communication and documentation; and d) flexible parallel care planning. The next four stages represent points of care transition: e) pre-birth care; f) transition from active postnatal care to supportive care; g) end-of-life care; and h) post end-of-life care.

Early and/or antenatal palliative care: Initiating early PC in adult cancer patients has recently shown benefits not only in terms of quality of life but also in improving expected outcomes and even survival. In perinatal care, all this does not necessarily justify early initiation, which in this case would involve preparing/initiating the program antenatally. Recently, however, some have called attention to the importance of this early integrative care. Early initiation (starting from diagnosis) may make a great deal of sense to those parents who must cope with a tragic prenatal diagnosis. Although many institutions are able to provide this sort of care, in some cases it has been explicitly organized in the form of perinatal hospices or PPC programs. They have given special attention not only to the curative needs of the fetus and the mother (eg clinical complications in the pregnancy) but also to psychological, spiritual and social needs of the whole family. All these actions provided in the right time with coordination amongst all health professional implicated. A secondary analysis of the bibliography identified a subset of 27 articles that make explicit mention of this concept. The geographical distribution and the topics covered were very similar to those of the whole sample of articles. Once again, it is noteworthy that most of the articles can be classified as comments/reflections and that only 30% (8 articles) could be considered to be clinical studies. Of these, three were case reports, one was a qualitative study and four are the results of initiating programs of this sort. These programs were implemented in five different centers, four of which were in different states in the USA and one of which, from the United Kingdom. According to the data provided and in the context of the PPC program, the percentage of couples who decided to continue with the pregnancy despite an ominous prenatal diagnosis ranged from approximately 40% to 85%. These programs involved 124 pregnancies and there was no maternal morbidity. Those parents who chose this model of care gave positive feedback about their decision and the care provided. The sample probably presents biases, because the parents' choice of center was surely influenced by their a priori convictions. Nevertheless, the data highlights that this model of PPC is viable and that many families request it and are grateful for it. Besides the quality of clinical care given to the fetus/neonate, this fact might suggest that, by choosing PPC, parents do not have to cope with the consequences of voluntarily terminating the pregnancy. Parents and relatives would be able to cope better with bereavement because they might prepare for the death of the neonate and, even accompany the baby to his/her natural end. In any case, when trying to make a decision after a problem with the fetus has been identified, parents and patients should have all the appropriate information and support about possible treatments and palliative care.

Conclusion

In summary, in light of the significance and complexity of PC, it seems desirable for obstetric and neonatal units to have available an active and efficient PPC program. The current literature suggests that PC programs in perinatal medicine may be comprehensive, initiated early and be integrative. This comprehensiveness should take into account not only all the people involved (the patient as the center of the process, including the family and the professionals) but also the aspects to be treated (physical, psychological, spiritual and social, including bereavement). Furthermore, when necessary, palliative care should be planned and initiated before birth. These may be the initial steps towards a model which needs to be further developed.

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