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Editorial

Shame

An article on Huffington Post by Glenn D. Braunstein, MD, discussed the poor US infant mortality rate. Braunstein is Chairman of the Department of Medicine, Cedars-Sinai Hospital, Los Angeles. He writes: Every day the headlines are filled with breathtaking reports about the advances in American medicine. But even as it leads the planet in medical and scientific accomplishments, the United States also has some downright shameful disparities in its healthcare, and one of the worst is in the area of infant mortality.

Every year about 30,000 babies in our nation, a disproportionate number of them African Americans, die before reaching their first birthday. Last year, the infant mortality rate in the US was an estimated 6.06 deaths per 1,000 live births, just ahead of Croatia, but lagging behind all of industrialized Europe and Asia.

For African Americans, the rate is 13.3 deaths per 1,000 live births, compared to 5.6 for whites. Research shows that women's and infants' health are hugely affected by socioeconomic factors, such as family income, education, a lack of access to adequate care and the environmental, physical and mental conditions impacting both parents. Still, these factors don't entirely explain the persistent racial divide, as even African American women with graduate degrees are more likely to lose a child in its first year than are white women who did not finish high school… The prevalence of preterm births in the United States is the chief reason we rank so poorly compared to other wealthy countries. In Sweden, for instance, 6.3% of births were premature, compared with 12.4% in the US in 2005, the latest year for which international rankings are available. In the past three years, overall preterm births have declined in the US. However, the number of preterm births for African Americans babies has not. It remains substantially higher at 17.47 per 1,000 births… One factor [for preterm birth and low birth weight] is access to prenatal care. African-American women are 2.3 times less likely than white mothers to have seen a healthcare professional before their third trimester, or to have received prenatal care at all. The hurdles to prenatal care for some African-American women may include their higher uninsured rates, their working and living in areas with reduced access to medical facilities and their lesser income and education. Some African-American women also have expressed fear about mistreatment in the health care system… To close the racial gap, programs must address all aspects of women's lives, especially those unique to African-American women. [A recent study suggests that] chronic stress, precipitated by such factors as poverty, living in a dangerous neighborhood or racism, may trigger the release of a hormone called corticotrophin. CRH, produced by the brain and the placenta, is closely tied to labor. It prompts the body to release chemicals called prostaglandins, which help trigger uterine contractions. Researchers hope to learn more about these and other factors, including genetics, child rearing and exposure to chemicals, through the National Children's Study, an ambitious undertaking in which researchers are examining the lives of more than 100,000 children from before birth to age 21… To slash infant mortality, of course, we must tackle teen pregnancy prevention programs, family planning, full coverage of prenatal care and child health. We also need to step up our efforts to get pregnant women to stop smoking and abusing drugs. We need to ensure that the inequities surrounding infant mortality get fixed so we can be proud of not only our headline-grabbing, world-class, scientific and medical advances but also the health of each and every American newborn.

Les Plesko, Editor

The above is an edited version of a blog by Dr Braunstein that appeared on the Huffington Post website.

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News

MARATHON

Healthy Mom&Baby, the consumer magazine from the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN), says that pregnant women should view themselves as marathon runners who won't give up in the last moments of the race. The magazine has announced the launch of the "Go the Full 40" campaign, designed to help women understand the many reasons it's important for a mom to carry her baby to term. Through 40 reasons, Healthy Mom&Baby is busting the myth that it's OK for babies to be born just a little early. The "Go the Full 40" campaign is featured in the Winter 2012 issue of Healthy Mom&Baby, in its iPad app, and on its website, gothefull40.com.

HUGE

The Huffington Post reported that an Iowa woman gave birth to a boy weighing 13 pounds and 13 ounces, without the aid of surgery. The boy, born at Mercy Medical Center in Des Moines, measured 23 1/2 inches long. Just over a year previously, the boy's brother was born at 12 pounds and an ounce at birth. Only a tenth of 1% of all newborns weigh more than 11 pounds at birth. The boys' mother endured six hours of labor without an epidural injection. She said she and her husband wanted to avoid cesarean delivery because that wouldn't have been good for her or the baby.

BMC NEWS

BioMed Central has developed a concept document proposing standard terms to describe articles relating to clinical trials, to help put its Threaded Publications initiative into practice, potentially across multiple journals and publishers. BMC invited the clinical research and publishing communities to share their views on the concept… The Journal of Medical Case Reports recently published its 2,000th report… The European Journal of Medical Research has joined BioMed Central's portfolio of open access journals. The journal, launched in 1995 as a subscription publication, covers all aspects of medical research and will continue with its specific focus on clinical research… The journal Antimicrobial Resistance and Infection Control launched with BioMed Central. BMC noted: The spread of antimicrobial resistance and changes in health care systems are causing an increase in health care-associated infections. In addition, the rising popularity of international travel has made healthcare-associated infections a global challenge. Antimicrobial Resistance and Infection Control (ARIC) will therefore become a key tool to those working to counter the rise in healthcare infections by ensuring the global dissemination of the latest research in the field… BMC has also launched Systematic Reviews, the first open access journal to provide a

venue for systematic reviews in healthcare research. Systematic reviews are essential tools for evaluating bodies of evidence on the efficacy of healthcare interventions.

FRIENDLY

A "Baby-Friendly" designation has been awarded to MedStar Georgetown University Hospital. Baby-Friendly USA, Inc is the accrediting body in the United States for the Baby-Friendly Hospital Initiative (BFHI), a global program sponsored by the World Health Organization and UNICEF. The initiative encourages and recognizes hospitals and birthing facilities that provide an optimal level of care for breastfeeding mothers and their babies. The award is given after an on-site survey. Facilities must demonstrate that they have integrated all of the "Ten Steps To Successful Breastfeeding" into their practice for healthy newborns. Georgetown scored 100% on seven out of the ten steps and at least 90% on the remaining three steps. Currently there are 127 Baby-Friendly hospitals out of an estimated 31,000 birthing facilities in the United States. Approximately five percent of all births in the US occur in a Baby-Friendly hospital.

NEVER SAFE

Researchers at the California Teratogen Information Service (CTIS) Pregnancy Health Information Line have found new links between the timing of alcohol consumption during pregnancy and certain characteristics of Fetal Alcohol Syndrome (FAS). The study used data obtained by counselors at the CTIS Pregnancy Health Information Line, a toll-free service offering evidence-based clinical information about exposures during pregnancy and breastfeeding. It focuses on 992 California women. The study specifically examines the timing of the mother's reported alcohol exposure in relation to known physical features of FAS. All infants in the study, whether identified as exposed to alcohol or not, received a special screening for birth defects. Researchers found that every pattern of higher prenatal alcohol consumption, no matter the timing in pregnancy, was associated with an increased risk of having an underweight infant or one with a reduced birth length. There were also significant associations between higher alcohol consumption in the second half of the first trimester and certain facial features of FAS, in addition to lower birth weight and length. For every drink consumed, there was a 25% increased risk for smooth upper lip, a 22% increased risk for thin red portion of the upper lip border, a 12% increased risk for small head size, a 16% increased risk for reduced birth weight, and an 18% increased risk for reduced birth length. The researchers said their findings showed that there is no designated safe period for drinking alcohol in pregnancy.

COFFEE CLATCH

A new form of prenatal care is building on the theory that women are relational by nature, assumption with improved pregnancy outcomes. Traditional prenatal care includes a series of one-on-one visits between a woman and her healthcare provider. However, an article featured in the December/January issue of Nursing for Women's Health, the clinical practice journal published by AWHONN, presents an alternative to traditional prenatal care. "CenteringPregnancy: The Benefits of Group Prenatal Care," by Genie Rotundo, MS, RN, LCCE, FACCE, discusses the CenteringPregnancy model of prenatal care, including improved birth outcomes and increased patient and healthcare provider satisfaction. Some elements of the program are that health assessment occurs within a group, where
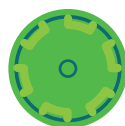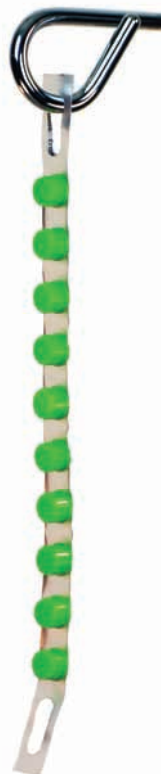
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women at the same stage of their pregnancy visit get together. Participants take an active role in their care by recording their own blood pressure, weight and gestational age with the assistance of a nurse committed to the group. Each group is led by co-facilitators who encourage and assist the pregnant women to teach each other and share their knowledge.

FACTS!

Research!America and March of Dimes developed a fact sheet on prematurity that illustrates how federally funded research has saved lives and reduced health care costs. According to the fact sheet, through research supported by the National Institutes of Health, scientists discovered that the hormone hydroxyprogesterone reduces the risk of preterm births by up to 42% in high-risk women and that a progesterone gel can reduce the risk of preterm births for women with a short cervix. Hydroxyprogesterone is also estimated to have saved more than $450 million in medical costs each year and may save more than $2 billion over the lifetimes of those babies who would have been born prematurely. NIH-funded research has also led to the development of noninvasive respiratory procedures for infants, such as CPAP.

BLOOD SPOTS

The Save Babies Through Screening Foundation (SBTS) reaffirmed its commitment to the public health value of retention and appropriate use of residual dried blood spot specimens. "Recent litigation efforts in Texas and Minnesota make clear the abundance of misinformation in circulation regarding the privacy and protection related to the use of newborn blood spots," said Jill Levy-Fisch, SBTS President. "Now more than ever, a public education campaign is needed to provide greater clarity about the benefits of retaining these samples as well as the privacy protections already in place in all states and afforded by the Genetics Information Nondiscrimination Act of 2008." Currently, laws regulating the retention and use of blood spot specimens differ from state to state. All states, however, have patient privacy protections in place. Strict state and federal rules and regulations govern the use of these specimens for research. Specimens can only be used for research without patient consent if all identifying information has been removed. Researchers must work through an Institutional Review Board (IRB) and state health institutions. Once approval is granted, researchers receive de-identified samples in order to ensure that privacy is protected. The SBTS said it recognizes the need for state public health departments to address public concerns about privacy and consent while at the same time clearly articulating the public health benefits of research using dried blood spots.

NEW STUDIES

Many new studies were presented at the Society for Maternal-Fetal Medicine's annual meeting, The Pregnancy Meeting, in Dallas. Researchers reported that early transplantation of human placenta-derived **mesenchymal stem cells** into the lateral ventricles of neonatal rats with birth-related brain damage is possible, and that the donor cells can survive and migrate in the recipient's brain. The study was undertaken to investigate the neuroprotective effects of mesenchymal stem cells therapy on postnatal rats, whose injury was designed to mimic brain injury in infants with a very low birth weight. In the study, donor cells survived, homed and migrated in the recipient brains and neurologic improvement was detected...

Researchers reported that massively parallel sequencing can be used to diagnose **fetal aneuploidies**, including Down syndrome, Edwards syndrome, Patau syndrome and Turner syndrome. The study demonstrated that it was possible to use massively parallel sequencing of maternal plasma DNA in combination with a proprietary algorithm to detect the three most prevalent fetal aneuploidies. With this clinical evidence, this prenatal test may be incorporated into routine prenatal care. Researchers sampled 2,882 women undergoing prenatal diagnostic procedures at 60 different US locations and identified 89 of 89 cases of trisomy 21 with 100% sensitivity and specificity, and had a 100% positive predictive value for the three most common autosomal aneuploidies, trisomies 21, 18, and 13. The study also detected Turner syndrome and other chromosome aneuploidies such as trisomies 16 and 20… Researchers found that the risk of obstetric intervention is lower for women who deliver or intend to deliver outside of hospitals, but there are some higher risks for newborns intended for **home births** compared to hospital births. The study, Neonatal Outcomes Associated with Intended Place of Birth: Birth Centers and Home Birth Compared to Hospitals, found that the risk of cesarean delivery was significantly lower for women who had or intended to give birth outside of hospitals; however, the risk of neonatal seizure and a 5-minute Apgar score of less than seven was much higher for intended home births… Researchers reported that induction of labor in patients who suffer a **rupture of membranes** between the 34th and 37th week of gestation does not reduce the risk of infection or respiratory problems in the newborn. In patients who underwent close monitoring versus those whose labor was induced, there was no difference in the risk for infection in the newborn, breathing problems in the newborn or cesarean section rates. The researchers observed more than 700 women at 60 hospitals. After 24 hours of ruptured membranes, patients were allocated to either immediate delivery or expectant management until 37 weeks of gestational age. Expectant management prolonged pregnancy for 3.5 days; the risk for neonatal sepsis was low, at 3.6%, and did not differ between treatment strategies; the risk for respiratory distress syndrome did not differ between treatment strategies; and cesarean section rates were equal in both treatment strategies… Researchers found that delivery by **cesarean section may not be protective** compared to vaginal deliveries for babies who are small for their gestational age born more than six weeks before their due date. The results indicate that delivery by cesarean section was not associated with decreased odds of any neonatal complications and was associated with significantly higher odds of respiratory distress syndrome in small for gestational age preterm newborns… Researchers found that **duration of stay in the US is associated with increased risk** of preterm birth for Hispanic women. For the study, researchers looked at 2,141 Hispanic women with a prior live birth who participated in the National Health and Nutrition Examination Survey and found that women living in the US for less than 10 years had a 3.4% frequency of preterm birth and women living in the US for 10 or more years had twice the risk of preterm birth and a 7.4% frequency of preterm birth. Furthermore, women born in the US had a 10% frequency of preterm birth and three-fold risk of preterm birth. The findings support the hypothesis that preterm birth is related to environmental factors… Researchers reported that **prescription medications** may affect the body's ability to metabolize 17-alpha-hydroxyprogesterone

caproate (17-OHPC), the only FDA approved medication for the prevention of recurrent preterm birth. Findings indicated that if a therapeutic level is defined for 17-OHPC, doses may have to be adjusted if certain other medications are also being taken… Researchers reported that, for children with **spina bifida**, surgery conducted while the fetus is still in utero as opposed to surgery on a newborn is more cost effective due to the costs associated with caring for a child with significant deficits… It was reported that **women who deliver their first baby early** are more likely to have a subsequent baby that is small for its gestational age, even when the second pregnancy is carried to term. Researchers looked at the Missouri state birth certificate records of 197,556 women who were pregnant between 1989 and 2005. They included women younger than 45 who gave birth between 20 and 44 weeks of gestation. These women had "normal" pregnancies that were without medical complications such as hypertension, preeclampsia, diabetes or renal disease. The resulting babies were not breach births and did not have birth defects. The findings indicate that if a mother delivered her first baby prematurely her second one is more likely to be small for gestational age, even if that baby arrived at the normal time and the pregnancy was normal and uncomplicated… Researchers reported that for women with **prior delivery via cesarean section** the optimal timing of elective delivery for mother and baby is 39 weeks even after consideration of the risk with continuing pregnancy. It was found that elective repeat cesarean deliveries at a later gestational age were associated with significantly lower rates of composite adverse neonatal outcomes when compared with 37 and 38 weeks deliveries. Moreover, adverse neonatal outcomes were significantly more frequent in pregnancies continued beyond 39 weeks versus elective cesarean at 39 weeks. On the other hand, maternal outcomes tended to be better with continued pregnancy rather than elective cesarean at 37 or 38 weeks, but the difference was significant only at 37 weeks. Composite maternal outcomes were significantly worse for later deliveries compared with elective cesarean at 39 weeks. All the information above was provided by The Society for Maternal-Fetal Medicine. For more, contact smfm.org or visit the organization on Facebook.

RAVE ON

Ecstasy and pregnancy: now there's been a study by Case Western Reserve University to gauge the drug's effect. Researchers found that chemical signaling that determines gender is affected, and that the drug contributes to developmental delays. Ninety-six participants were recruited and surveyed. Most reported taking the drug before and during pregnancy. Women who used ecstasy experienced more negative social consequences, such as health, job and social problems. The drug also seemed to result in the birth of more males than would be statistically expected. The study results as far as baby growth and development suggested the drug's neurochemical effects. Infants

exposed to ecstasy demonstrated poorer quality of coordinated movement and lower milestone attainment at four months. Ecstasy can deplete serotonin levels. Information reported by Petra Rattue, in Medical News Today, copyright Medical News Today.

GET THE LEAD OUT

St Louis has a new initiative that tests homes for lead hazards before a child's birth. The homes of pregnant women on Medicaid were targeted by the city's Heavy Metal Project. Researchers collected blood samples from 60 kids and found that the average blood lead level was 2.70 micrograms per deciliter compared with 3.63 µg/dL for controls. In 13.3% of study participants and 22.5% of controls, the researchers found blood lead levels more than 5 µg/dL. In the study, 62.5% of the homes underwent remediation. Information is from Medical News Today, written by Grace Rattue, copyright Medical News Today.

GUTS

Prebiotic ingredients in infant formula help colonize the newborn's gut with a stable population of bacteria, and probiotics enhance immunity in formula-fed infants, according to a pair of University of Illinois studies. report. Researchers compared the effects of feeding pre- and probiotics with infants fed breast milk and control formulas, and also compared the enhanced formulas' effects in both vaginally and cesarean-delivered babies. In the probiotics study, scientists divided 172 healthy six-week-old infants into two formula-fed groups and a breast-fed group. At six weeks, the formula-fed groups received either a control formula or a formula that contained

Bifidobacterium animalis subspecies lactis (Bb12) for a six-week period. The infants receiving the probiotic formula had increased concentrations of secretory, anti-rotavirus, and anti-poliovirus-specific IgA. Fecal samples from babies receiving the probiotic formula revealed significantly heightened immunity, especially among C-section infants. In the prebiotic study, 139 babies were divided into three groups. Breast-fed infants were compared with babies fed either a control formula or a formula supplemented with galacto- and fructo-oligosaccharides for six weeks. Babies fed the prebiotic formula showed some improvement in the number of beneficial bacteria and decreases in the types of bacteria that are often associated with illness.

CLEAN IT UP
Clean delivery kits and clean delivery practices could lead to substantial reductions in neonatal mortality in infants born at home, according to researchers at University College London, who analyzed the links between neonatal mortality, the use of clean delivery kits, and individual clean delivery practices in almost 20,000 home births in India, Nepal, and Bangladesh. The researchers found that use of the birth kits was linked to a 48% drop in neonatal mortality, with an additional 16% drop in mortality with each additional clean delivery practice. Researchers noted that the kits are cheap, about 40 cents, but that this was still too expensive for the people in the region.

SUPPLEMENTS
Babies whose moms were given micronutrient supplements had gene modifications at birth and at 9 months, according to researchers at the University of Cambridge. Such methylation had previously been associated with the development of the immune system. Researchers said the mechanism by which micronutrients influence methylation changes was still to be worked out. In the study, Gambian women trying to get pregnant were given micronutrients or a placebo until their pregnancy was confirmed.

MIGRAINES AND COLIC
Mothers with migraines are more likely to have babies who have colic, according to researchers at UC San Francisco. The researchers looked at more than 150 mothers and their babies. Mothers who had a history of migraines were two and a half times more likely to have babies with colic, than those who did not have migraines. Twenty-nine percent of the infants had colic when mothers had a history of migraines, and only eleven percent of babies had colics when their mothers didn't have migraines. Reported by Rupert Shepherd in Medical News Today, copyright Medical News Today.

GRANTED
The Association of Women's Health, Obstetric and Neonatal Nurses announced that Philips Healthcare has renewed a one-year educational grant to support AWHONN's Intermediate and Advanced Fetal Heart Monitoring (FHM) courses. The Philips grant will support AWHONN's work to continue providing important fetal heart monitoring education to approximately 13,000 perinatal clinicians each year. This year, Philips will profile three nurses in its "Sharing Success Stories" campaign. The nurses' stories will showcase how the FHM program has made a positive impact on the care they provide. Visit awhonn.org/fhm.

IDENTIFYING DOWNS
The risk of a fetus having chromosomal abnormalities that cause Down syndrome and Edwards syndrome can now be identified by using a noninvasive test on maternal blood that involves a novel biochemical assay and a new algorithm for analysis. As such the test can also reduce amniocentesis or CVS. Doctors had formerly employed MPSS, massively parallel shotgun sequencing to examine cell-free DNA (cfDNA) from the mother's plasma for fetal conditions to identify trisomy 21 pregnancies. While MPSS can accurately detect these conditions by analyzing the entire genome, it requires DNA sequencing large amounts and therefore its clinical usefulness is limited. The new assay, called Digital Analysis of Selected Regions (DANSR), was developed by Aria Diagnostics in San Jose, CA. It sequences loci from only those chromosomes under investigation, so the test requires 10 times less DNA sequencing as compared with MPSS. Researchers assessed 123 normal pregnancies, 36 T21, and 8 T18 pregnancies to check the performance of the assay and found that it managed to identify all 36 cases of T21 and 8 cases of T18 as having a risk of more than 99% for each trisomy. Reported by Petra Rattue in Medical News Today, copyright Medical News Today.

PRODUCTS

SURFACTANT BENEFITS
Cornerstone Therapeutics announced a new analysis published in the eFirst Pages section of the Pediatrics website reporting significant benefits in mortality rate and the need for redosing when treating neonatal respiratory distress syndrome (RDS) with Cornerstone's CUROSURF (poractant alfa) Intratracheal Suspension.[1] The objective of the independently performed meta-analysis was to compare the efficacy of CUROSURF versus Survanta (beractant) and Infasurf (calfactant) with respect to clinical outcomes among preterm infants with RDS. The analysis was led by Neetu Singh, MD, at Dartmouth Hitchcock Medical Center. Researchers included the data following a systematic literature search. As a result, five published randomized controlled trials (RCTs) comparing CUROSURF and Survanta were included in the analysis, enrolling a total of 529 infants. There were no trials that met the designated criteria comparing Infasurf to CUROSURF. In this review, it is important to note the initial surfactant dose administered to infants in each included RCT. (The FDA approved initial dose for CUROSURF is 200 mg/kg versus 100 mg/kg for Survanta. Two of the five RCTs included a subgroup of infants that received a low initial dose of CUROSURF (100 mg/kg). This dose is not approved in the United States therefore the results of that subgroup are not reported here.) Following the analysis, authors concluded that the 200 mg/kg initial dose of CUROSURF may result in superior short-term clinical outcomes, compared with Survanta, when used for the treatment of preterm infants with established RDS. There were no significant differences in respect to complications of prematurity between CUROSURF and Survanta. Key findings of the subgroup comparing the 200 mg/kg initial dose of CUROSURF to the 100 mg/kg of Survanta included: A significant reduction in mortality rates was found in infants treated with the 200 mg/kg initial dose of CUROSURF compared with those treated with the 100 mg/kg initial dose of Survanta. Those treated with CUROSURF experienced a relative risk reduction of 70% (RR: 0.29 [95 percent CI: 0.12-0.66], p=.004). The need for redosing was significantly lower with the 200 mg/kg initial dose of CUROSURF, with a relative risk reduction of 36 percent compared with the 100 mg/kg initial dose of Survanta (RR: 0.64 [95 percent CI: 0.53-0.83]; p=0.0008). As with any meta-analysis, there are a few important limitations to

note. This systematic review yielded a small number of relevant articles on surfactants that were considered sufficiently rigorous to be included (7 of the 92). In addition, each study included a relatively small patient population. Due to this, the largest study (Ramanathan R, et al 2004) contributed approximately 55% of all patients included in the analysis, as well as most of the weight and average of the summary treatment effect. Lastly, the included studies analyzed clinical outcomes only until hospital discharge and did not examine long-term outcomes such as neurodevelopmental outcomes. The authors also noted that the results of this systematic review and meta-analysis are consistent with previously published reviews on this subject. Most recently, a retrospective study compared all-cause, in-hospital mortality in more than 14,000 preterm infants with RDS.[2] This retrospective study found that the group receiving a 200 mg/kg initial dose of CUROSURF was associated with a significantly reduced likelihood of death compared to Infasurf and a trend toward reduced mortality when compared with Survanta. (The 100 mg/kg initial dose is not approved for use in the US. Per the product labeling, the approved initial dose for CUROSURF is 200mg/kg.) [References: 1. Singh, N, et al. Pediatrics. 128(6): December 1, 2011; e1588 -e1595; 2. Ramanathan R, et al. Journal of Perinatology. Advance online publication: September 1, 2011. Cornerstone licensed CUROSURF US rights from Chiesi Farmaceutici S.p.A. (Parma, Italy) as part of a broader transaction it completed with Chiesi in May 2009. CUROSURF is a registered trademark of Chiesi Farmaceutici, S.p.A. Survanta is a registered trademark of Abbott Laboratories, Inc. Infasurf is a registered trademark of ONY, Inc.]

NEW GENERATION

GE Healthcare, Inc is introducing a new generation of its Electronic Fetal Heart Rate (FHR) Monitoring program for physicians, midwives, nurses and other clinical staff in obstetrical care. This interactive, web-based education program now features recently updated clinical analysis and consensus statements on FHR patterns, and directly links clinical data to terminology, interpretation and management for greater standardization. In addition, a case study provides opportunity to apply learning in a real life scenario. This interactive, web-based education program using the National Institute of Child Health and Human Development (NICHD) standardized definitions provides accurate, consistent interpretation of FHR patterns to facilitate interdisciplinary communication and reduce risk during labor and delivery. The program now features updated analysis and data on FHR patterns and incorporates consensus statements from NICHD, the American Congress of Obstetricians and Gynecologists (ACOG) and other clinical organizations to standardize terminology and interpretation. With this standardization, training modules reinforce data points with appropriate clinical interventions, identifying certain FHR patterns with issues such as interruption of the oxygen pathway to provide learners with new models for patient care. The training program provides clinicians with standardized knowledge and communication tools to enhance care management with clear, consistent checklists that facilitate optimal patient safety and clinical efficiency. The program now also includes new features offering users "real-world" case study exercises to model use of FHR pattern information in the clinical setting, offering a highly interactive learning experience. Enhanced graphics and animation as well as a comprehensive post-test following the four modules help learners visualize information and test understanding of content. Visit gehealthcare.com/fhr.

FEEDING

Acacia Neonatal is dedicated to designing and producing the best neonatal products to reduce infection, provide the safest enteral feeding and increase medication safety. In light of these goals, we have created the NuTrio Enteral Feeding System, a comprehensive system including gravity feeding, extension sets, feeding tubes and syringes which feature the ever reliable TwistLok connection. This system is a locking system that eliminates misconnections and disconnections, two goals we know are vital to the care of those in the NICU environment. We have recently added a critical component to the NuTrio Enteral Feeding System in the form of our NuTrio SimpleFeed Infusor. This enteral feeding delivery product has been designed around three key safety principals: to look, act and feel

different than standard electro-mechanical infusion pumps. Rather than rely on medication delivery pumps repurposed for enteral feeding, this infusor offers the safety benefit of being different than a pump used for medication delivery. It requires no software updates, nor a plug for electricity. The first of its kind, the NuTrio SimpleFeed Infusor is the safety inspired, neonate-centered, economically sound infusor that offers convenient access and easier transitions throughout your unit while providing the safest enteral feeding to your patients. The infusor utilizes a special SimpleFeed restrictor tubing set to determine the rate of the feed being delivered. Sets are available for the most common delivery rates, including 0.5ml/min, 1.0ml/min and 2.0ml/min. A color-coded system is clearly outlined on the infusor itself and tagged on the tubing for quick and easy visual confirmation of the proper set. The NuTrio SimpleFeed Infusor can be used with the pole mounted holder for easy relocation and operation throughout your NICU, or hung from an IV pole for added flexibility. For instant preparation, the winder tightens the spring-loaded infusor in seconds, with no hand operation required. Alone, the NuTrio SimpleFeed Infusor offers increased safety, added convenience and reduced capital investment. As part of the NuTrio Enteral Feeding System, it complements the world's only complete enteral feeding system, available only from Acacia Neonatal. Our products are created to deliver a safer enteral feeding experience because we are proudly dedicated to making the lives of neonates healthier. We know your heart is in neonatology, and ours is too.Contact acacianeonatal.com/nutriosimplefeed or call (800) 486-6677.

ON THE GO

Philips Respironics, a unit of Royal Philips Electronics is introducing its latest advancement in oxygen therapy. SimplyGo is the only portable oxygen concentrator (POC) to offer continuous flow (up to 2 liters per minute) and pulse-dose delivery in a single device weighing 10 pounds or less. With this combination of capabilities, the SimplyGo POC helps homecare providers manage the therapy and lifestyle needs of nearly all oxygen users. SimplyGo is different from smaller devices because it is also capable of delivering oxygen continuously, similar to stationary concentrators used at home. With oxygen output of up to four times that of some lightweight POCs, SimplyGo can meet the portable needs of nearly all oxygen users including those who are highly active or require continuous flow. Philips designed its latest

portable oxygen concentrator with a long-life compressor, high-impact resistant design and oversized cart wheels. SimplyGo was tested and subjected to extreme conditions, including impacts, vibrations and temperatures, to deliver reliable performance day in and day out in real-life conditions experienced by oxygen users. Contact philips.com/simplygo.

RADIOMETER NEWS

Radiometer's accredited webinar series continued in 2012 with a session on bilirubin. The company received many positive comments on its Radiometer University webinar series. PACE and AARC contact hours were available for the free event, which was titled: Shedding light on bilirubin: Definition, dangers, detection and decisions, presented by Dennis Dietzen, PhD, DABCC, FACB… Radiometer's **ABL90 FLEX** delivers fast results on small sample volumes. Get results for all acute care parameters in just 35 seconds on only 65 microliters of blood. The ABL90 FLEX, Radiometer's newest cassette-based analyzer, delivers fast results on small sample volumes, processing up to 44 samples per hour. Time and labor-saving features enable the caregiver to spend more time caring for the neonatal, pediatric or adult patient. The **ABL800 FLEX** offers tBil, small sample volumes and micromodes for the NICU. The ABL800 FLEX analyzer offers whole blood total bilirubin, making it well suited to use in the NICU. In addition, analyzer micromodes ensure accuracy of samples as small as 35 mL, and a unique FLEXMODE provides the highest accuracy for the smallest capillary blood sample. In addition to whole blood total bilirubin, the ABL800 FLEX also offers a comprehensive panel for acute care testing that includes blood gases, CO-oximetry, electrolytes, metabolites (creatinine, lactate) and pleural fluid pH… **TCM3/30** customers: Radiometer makes it easy to upgrade. Radiometer is pleased extend its trade-up promotion, offering a $3,000 credit for every TCM3/30 monitor you replace with a TCM4 Series or TCM TOSCA/CombiM monitor. This represents a 40% savings on a new TCM4 Series/TOSCA/CombiM unit. The versatile TCM4 platform may be used in a variety of clinical applications, including the sleep lab, wound care and hyperbarics, the ICU and NICU/PICU. Contact (800) 736-0600, radiometeramerica.com.

APPROVED

Discovery Laboratories, Inc announced that the United States Food and Drug Administration (FDA) has approved SURFAXIN (lucinactant) for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS. SURFAXIN is the first synthetic, peptide-containing surfactant approved for use in neonatal medicine. Discovery Labs anticipates that SURFAXIN will be commercially available in the United States in late 2012. The safety and efficacy of SURFAXIN for the prevention of RDS in premature infants was demonstrated in a large, multinational phase 3 clinical program that included 1294 patients. For more visit www.surfaxin.com.

SAFE FEEDING

DeRoyal Industries, Inc in partnership with Benlan, with a 39 year history of providing high quality products and innovative services to the healthcare industry, announces its entry into the global Enteral Safe Feeding Set market. Misconnection errors that continue to occur with significant frequency and, in a number of instances resulting in deadly consequences, have created an ideal environment for DeRoyal to enter the marketplace and address these issues head-on. The focus is to create a complete product offering which streamlines supply chain, reduces hospital spending, and provides a measure of safety to eliminate misconnections. DeRoyal recognizes that only physical barriers can truly prevent misconnections. The enteral only (enteral-safe) connectors on the DeRoyal line of products can only fit with other oral/enteral products but will not fit into standard IV luer access fittings. This system prevents the misconnection opportunity and maximizes patient safety. DeRoyal's Enteral Safe Feeding System is comprised of non-latex and DEHP free Polyurethane and PVC feeding tubes, extension sets, six different sizes of one piece enteral only syringes from BD, and milk straws. They all incorporate the industry accepted Orange color to signal Enteral Safe and come with advanced safety features that provide for more secure connections, reduced chance of clogging, and provide an overall higher level of confidence for the caregiver. Contact deroyal.com.

INNOVATIVE PRODUCTS

Respiralogics, based in San Marcos, CA and owned and operated by the management team of David Thompson and Beth Keifer, collectively brings more than 60 years of clinical, educational and technical expertise in the critical care field. The longtime partners' goal is to free clinicians to focus on patient care. The company's suite of products focuses on the respiratory care field. Respiralogics' product line includes: Babi.Plus Bubble nCPAP System for delivery of non-invasive respiratory support for premature and small infants; Sil.Flex Stoma Pad and Sil.Flex TC Pad, ergonomically designed cushions intended to redistribute pressure at stoma sites, improving patient comfort and minimizing skin breakdown; Danny Ties, unique tracheostomy tube holders with a softer and more comfortable fit around the neck for patients of all ages; and Venti.Plus Test Lungs and Babi.Plus nTest Lung, great tools to simulate the respiratory system that demonstrate mechanical ventilator applications and perform ventilator circuit testing prior to clinical use. (Babi.Plus, Sil.Flex and Venti.Plus are trademarks of A Plus Medical. Danny Ties is a trademark of Leckie Medical Products, Inc.) Visit www.respiralogics.com.

INCUBATE

Siemens Healthcare has joined with LMT Lammers Medical Technology GmbH to exclusively offer the nomag IC – LMT's MR Diagnostics Incubator System for the transport of newborns and premature babies[1] – as an add-on to Siemens' 1.5T and 3T MR systems, including the MAGNETOM Aera and Skyra systems. The nomag IC enables newborns and premature babies to be examined after birth with magnetic resonance imaging (MRI) via optimal, noninvasive diagnostics. The incubator facilitates safe, convenient transport from the neonatal intensive care unit (NICU) to the MRI department with an MR-conditional trolley, MR-conditional gas and power supply, and attendant conditional accessories. The nomag IC incubation system optimizes thermoregulation during the MR examination, reduces the need for sedation and eliminates the need for general anesthesia; and facilitates access to diagnostic imaging that is free of ionizing radiation. The nomag IC also reduces examination time and enables more examinations due to the improved workflow. It's compatible with Siemens' MAGNETOM TIM Symphony, MAGNETOM Avanto, MAGNETOM Espree and MAGNETOM Area 1.5T systems as well as Siemens' MAGNETOM Trio with Tim, MAGNETOM Verio and MAGNETOM Skyra 3T units. (1. MR scanning has not been established as safe for imaging fetuses and infants less than 2 years of age. The responsible physician must evaluate the benefit of the MRI examination in comparison to other imaging procedures.) Contact siemens.com/healthcare.

Advanced Instruments

Booth 835

Advanced Instruments invites you to learn more about the Advanced Model 3320 Osmometer. Place it in the NICU or dietary department to rapidly monitor the osmolality of feeding solutions including infant formula, human milk, and additives such as fortifiers, or pharmaceutical medications.

The Lactoscope FTIR Advanced from Delta Instruments provides accurate analysis of protein, fat and lactose levels in human milk samples, allowing you to determine the exact nutritional content of breast milk samples. The system is self cleaning and provides fast, accurate results in seconds using a small sample volume. The Lactoscope utilizes proven Mid-IR technology which has been an established component analysis technique in the dairy industry for well over 25 years. The Lactoscope ensures optimal performance and low cost of ownership backed by a worldwide service and support network.

Cincinnati Sub-Zero

Booth 1022

What products will you be featuring?
Cincinnati Sub-Zero will be featuring the Blanketrol 3 Hyper-Hypothermia system with our Kool-Kit and Kool-Kit Neonate, for whole body temperature management.

What educational or training materials will you be offering?
Cincinnati Sub-Zero will have brochures and literature on all of its products at the PAS conference. We also offer studies and articles that support CSZ and the therapies that we provide as well as clinical support upon request.

Why should our readers visit your display?
Cincinnati Sub-Zero is a leader in neonatal whole body cooling which is shown to improve outcomes for newborns meeting the requirements for HIE. Cincinnati Sub-Zero's Blanketrol III with its "Gradient Technology" and the Kool-Kit Neonate provide accurate and safe patient temperature management. This system offers the ability to reach and help the maintain goal temperature, as well as provide controlled re-warming for the patient. CSZ also offers a wide range of hyper-hypothermia kits and blankets for adult and pediatric patients as well.

Cornerstone Therapeutics

Booth 422 and 424

What products will you be featuring?
Cornerstone Therapeutics will be featuring CUROSURF (poractant alfa) Intratracheal Suspension.

What educational or training materials will you be offering?
Our booth will offer visitors the most recent clinical literature

on CUROSURF, as well as dosing cards, wall charts and other educational tools.

Why should our readers visit your display?
Readers can stop by to learn more about CUROSURF and programs Cornerstone has put in place to support units and staff nationwide.

Fisher & Paykel
Booth 534

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

What educational or training materials will you be offering?
Come and experience hands-on training with the Neopuff Infant T-Piece 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.

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 PAS Conference in Boston at booth 534 for a complete review and demonstration of all Fisher & Paykel Healthcare products.

GE Healthcare
Booth 101

GE Healthcare provides transformational medical technologies and services that are shaping a new age of patient care. Our "healthymagination" vision for the future invites the world to join us on our journey as we continuously develop innovations focused on reducing costs, increasing access and improving quality around the world.

Centricity Perinatal, GE Healthcare's clinical information system designed for the perinatal department, helps clinicians deliver more of their best care to every mother and baby for quality outcomes from L&D through the NICU or the Nursery. Our consolidated solution interfaces with all major EMRs and has been created with critical user input and evidence-based research to optimize ease of use.

Built on more than 22 years of industry experience, Centricity Perinatal has helped deliver more than 35 million babies in the US. Learn how our NICU solution can help advance care in your NICU.

Join us in Boston for the Pediatric Academic Societies (PAS) meeting to find out how GE Healthcare's Centricity Perinatal solution can help provide prompt access to information, more efficient documentation and enhanced care coordination in the NICU.

Grand Rounds Software
Booth 827

Crib Notes from Grand Rounds Software: Today's IT environment is driving hospitals to use the "big box" EMR in all departments. It is clear to clinicians that these systems do not meet the specialized needs of departments like the NICU.

Grand Rounds Software will be presenting the Crib Notes electronic documentation system for the NICU. Crib Notes is

a fully integrated physician and nursing information solution engineered specifically for the NICU. The program has an easy-to-use interface for the entire staff, and is focused on helping to improve the quality of patient care in your NICU.

Crib Notes supports efficient and thorough documentation, communication among all care-givers, patient safety, regulatory compliance, and decreased medical-legal risk. Crib Notes integrates seamlessly with the hospital's IT infrastructure and systems.

Stop in to our booth and see why Crib Notes meets your needs and how the system can work within your current hospital EMR system.

Mennen Medical MTRE Products
Booth 434

What products will you be presenting?
Criticool Systems for therapeutic hypothermia

What educational or training materials will you be offering?
Brochures and PPTs.

Why should our readers visit your display?
Latest technology for pediatric cooling for TBI, post cardiac arrest, etc.

Mercury Medical
Booth 105

What products will you be featuring?
Mercury Medical will be exhibiting the new Neo-Tee with in-line adjustable PIP controller. It's the industry's first disposable Infant T-Piece Resuscitator with Built-In Pressure Relief and Color-Coded Manometer on the Tee. Secondly, Neo-StatCO2<Kg, the first CO2 detector specifically designed for tiny babies with an expanded patient weight range of 0.25kg to 6kgs. The air-Q family of Masked Laryngeal Airways will now include infant sizes 1.0, 1.5 and 2.0. Mercury is the only company with three types of resuscitation systems, CPR, Hyperinflation and now a T-Piece.

What educational or training materials will you be offering?
Full product training will be provided at the booth by Mercury Medical Product Specialists. We will provide Neo-Tee product information brochures with specifications and offer free samples. The samples will be provided by fully trained sales representatives who will provide full product in-servicing at the attendees' facilities. Mercury also offers a T-Piece CE web course through Innovative Respiratory Concepts.

Why should our readers visit your display?
Due to the changing NRP guidelines, it will be important for clinicians like RT Directors and NICU nurses to visit our display as they are actively looking for neonatal resuscitation devices that meet these NRP guideline requirements. For instance, the Neo-Tee offers more consistent inspiratory and expiratory pressure than other devices. It is affordable for use at every NICU, L&D and ED bedside. One of the latest requirements is that every NICU stock "size one" laryngeal mask for rescue airways. air-Q is the infant rescue airway solution for meeting

this requirement. Furthermore, NRP recommends using a colormetric CO2 on the supraglottic airway connector to ensure proper placement with rapid color change. Mercury provides the only disposable CO2 detector solution for premature infants below 1 kg with the New-StatCO2.

NeoMed, Inc
Booth 1029

NeoMed, Inc is a leading provider of neonatal and pediatric enteral delivery systems and specialty catheters. During the PAS conference, we will exhibit our Enteral Safety System, NeoBottle, SafeBaby Breast Milk Tracking System, and Specialty Kits and Catheters.

At the core of our Enteral Safety System is an extensive line of sterile and non sterile oral/enteral syringes, feeding tubes and extension sets. NeoMed is known for providing innovative products that feature an enteral delivery system with "enteral only" connections that are not compatible with luer connectors on IV devices and pump compatible enteral syringes that ensure proper dosing and validated volumes. All of our enteral products are designed to deliver enteral nutrition safely and effectively to the patient, mitigating misconnection, contamination and feeding errors.

Our commitment to improve outcomes is showcased by NeoMed's new Closed System NeoBottle. It is the first collection, storage and delivery system for both human breast milk (HBM) and formula that maintains a closed system and aseptic barrier from breast to baby. The NeoBottle also allows for fortification within the closed system and may reduce the need for freezing in some NICU settings. When used in conjunction with the SafeBaby Breast Milk Tracking System, NeoMed offers a complete solution to collection, storage and tracking of HBM.

NeoMed also features catheters and a broad range of specialty kits for Lumbar Puncture, Catheterization and Closed System Urinary Collection. Our kits include the Fenestrated NeoDrape to provide effective thermoregulation and translucent barrier protection during sterile procedures for patients in Labor and Delivery and the NICU.

A Challenging Patient: approaches to controlling FiO2 during highly unstable oxygen saturation

Maria Wilińska, MD, PhD; Anna Wasco, MD

Following the critical phase of their care, some infants experience frequent episodes of significant oxygen desaturation. Maintaining good control of SpO2, while at the same time weaning oxygen, can be most challenging. We present this case study of such an infant. We include information on the relative effectiveness of a new closed loop FiO2 control system (Avea-CLiO2, CareFusion Yorba Linda CA) and two manual FiO2 titration approaches. While this infant was unusually challenging, we have been using CLiO2 routinely for about 1 year and have found it to be very effective in a broad range of patients. Based on this general clinical experience and on our controlled trial,[1] we have found Avea-CLiO2 to likely be more effective than the best manual care and to result in a significant reduction in nursing labor.

This female was born at another hospital at an estimated gestational age of 27 weeks, weighing 800 grams. Having experienced intrauterine asphyxia, she required cardiopulmonary resuscitation in the delivery room. Subsequently after not responding to NCPAP, she was intubated and transferred to our center at 4 hours of age. Upon arrival she was stabilized with surfactant but required an FiO2 of 80%.

Her primary diagnosis was RDS with grade II IVH and hypothermic syndrome. The early course of treatment was complicated with a PDA and hemodynamic instability, both treated medically. By the 10th day of SIMV (20/5 rate 50) her FiO2 had been weaned to below 30%, but she was experiencing frequent severe episodic desaturation spells (9/hour < 80% SpO2). For this reason she was placed on the Avea-CLiO2 ventilator with automated FiO2. Two days later she was enrolled in a study[1] to compare automated CLiO2 control to two protocol-driven FiO2 adjustment strategies implemented by a dedicated operator to CLiO2 for approximately 7.5 hours. As can be seen in Figure 1 during CLiO2 use, SpO2 control was much more effective than during the periods of manual adjustment. The frequency and severity of episodes of severe hyper and hypoxemia were markedly reduced with CLiO2. Following this study period, she was placed back under CLiO2 FiO2 control, and the course over the next 14 hours is documented in Figure 2. During this period her SpO2 remained very unstable but FiO2 was, nevertheless, automatically weaned. She remained on Avea-CLiO2 until she was extubated 9 days later. She was then placed on SiPAP and weaned to NCPAP over the next 11 days. She was discharged home without the need for supplemental oxygen, mild BPD and grade II ROP.
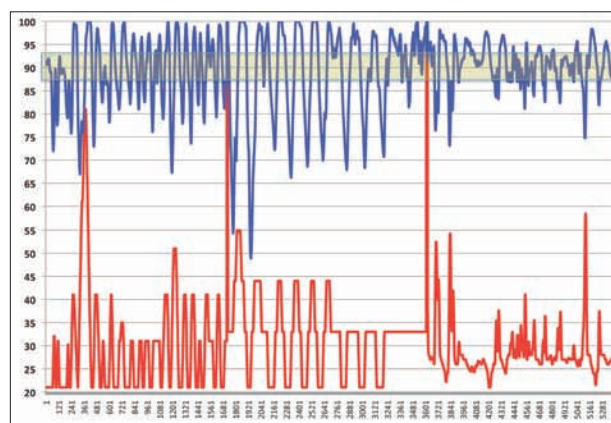
Figure 1. Comparison of CLiO2 and Two Methods of Manual FiO2 Control – 7.5 hours. The chart shows the FiO2 (red) and SpO2 (blue) based on 1 minute rolling averages of 5-second data points. Each tick on the time axis represents 10 minutes. The vertical red bars represent the 2.5 hour time demarcation between the three FiO2 control approaches. (Attentive, Routine, and CLiO2, respectively). The yellow horizontal band represents the intended target range (87%-93% SpO2). The FiO2 adjustments in response to desaturations during manual control, regardless of the strategy, were larger and longer compared to the faster more proportional control of CLiO2. During Attentive control the swings in saturations were more frequent but of shorter duration than during Routine control. The difference in overshoot of SpO2 in response to FiO2 increases is also markedly less during use of CLiO2. CLiO2 also found a baseline FiO2, in which to return to after desaturations of about 25%, which was apparently an FiO2 that better suited the infant's needs.

The authors are with the Center for Postgraduate Medical Education, Warsaw, Poland.

CLiO2 Theory of Operation

CLiO2 utilizes a sophisticated patented control system. While monitoring SpO2 virtually continuously, CLiO2 compares the SpO2 to the clinician selected target range. Every 1 second CLiO2 considers a change to the FiO2. If the SpO2 is outside the target range, the FiO2 change is based not only on the duration and magnitude/depth of the episode but also on the trajectory of the SpO2.

CLiO2 considers a baseline FiO2 level to facilitate returning to the target range as quickly as possible and minimizing overshoot beyond the target range. The baseline FiO2 is initially set by the clinician and updated automatically based on the infant's course. The time constant of the update is based on the infant's SpO2 stability. That is, the more stable the more quickly the baseline is changed.

In addition, when the SpO2 is within the upper half of the desired target range, the FiO2 is slowly weaned down to bring it to the mid-point of the desired range. Furthermore, even when in the target range, CLiO2 identifies rapid changes in SpO2 and responds in anticipation of a significant excursion.

Finally, in addition to traditional SpO2 alarms, CLiO2 also offers two other safety features. First, should CLiO2 need to increase FiO2 significantly to maintain SpO2 in the target range, an alert is provided to the clinician. Second, should the oximeter signal drop out, or be of poor quality, CLiO2 returns the FiO2 to the clinician set backup FiO2 or the most recent FiO2, whichever is higher.

CLiO2 has been shown in two controlled trials,[2,3] when compared to routine care, to markedly increase time in intended SpO2 target range, to reduce time in severe hyperoxemia without increasing time in severe hypoxemia and to reduce the level of inspired oxygen.
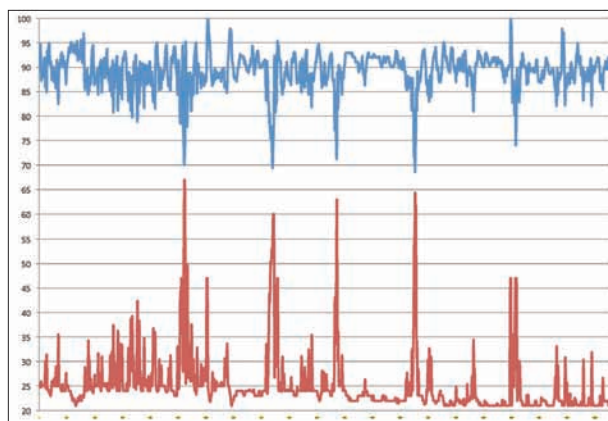
Figure 2. Subsequent CLiO2 Control – 14 hours. The chart shows the FiO2 (red) and SpO2 (blue) based on 1-minute rolling averages of 5-second data points. Each tick on the time axis represents 45 minutes. In this chart CLiO2's response to acute hyper and hypoxemia episodes remains apparent, but the longer period of time also affords the opportunity to see CLiO2's response to less acute trends in SpO2. In the early part of this period, at a time when the SpO2 was relatively stable but drifted above the control range, the FiO2 was reduced to 21%. Immediately following this, the FiO2 was increased when the SpO2 deteriorated. Over this 14-hour period of time, however, CLiO2 automatically reduced the FiO2 from a baseline of 25% to 21%.

References

1 Wilinska M, Bachman T, Swietlinski J, Wasco A. Comparison of different FiO2 adjustment strategies in ventilated preterm infants: a pilot study. Abstract:752789, SPR/PAS 2012.

2 Claure N, Bancalari E, D'Ugard C, Nelin L, Stein M, Ramanathan R, Hernandez R, Donn SM, M. Becker M, Bachman T. Automated adjustment of inspired oxygen in mechanically ventilated preterm infants: a multicenter crossover trial. Pediatrics 2011; 127(1): e76-e83.

3 Claure N, D'Ugard C, Bancalari E. Automated adjustment of inspired oxygen in preterm infants with frequent fluctuations in oxygenation: a pilot clinical trial. J Pediatr 2009; 155:640-5.

Feed Me Only When I'm Cueing: Moving Away From a Volume-Driven Culture in the NICU

Catherine S. Shaker, MS/CCC-SLP, BRS-S

Abstract
The adverse feeding outcomes of NICU graduates and their enduring feeding problems suggest a need to critically look at "the culture of feeding" in the NICU. It is a pivotal factor in how the preterm experiences feeding, how parents develop their working model of the feeding relationship, and how the NICU team communicates about, and attempts to support, feeding skills needed for discharge to home. These cultural underpinnings can affect caregiving, both adversely and positively, and, therefore, the emergence of safe and successful feeding and swallowing. An "infant-driven" (Ludwig & Waitzman, 2007) culture of feeding, which embraces the infant as a co-regulatory partner, versus a more traditional "volume-driven" feeding culture, which focuses on emptying the bottle, is suggested as essential for a true cue-based feeding approach, which optimally supports the preterm infant's developmental strivings and long-term well-being.

The Impact of Prematurity
More than a half million infants are born preterm each year in the United States and subsequently admitted to the Neonatal Intensive Care Unit (NICU) (National Center for Health Statistics, 2009). Medical advancements over the last decade have increased survival rates of preterm infants, particularly those for extremely low birth weight (ELBW) infants, defined as weighing less than 1000g (Hack, Friedman & Fanaroff, 1996). In addition, over 40,000 infants born each year in the United States (approximately 1% of live births) are extremely preterm (EP), defined as less than 28 weeks gestation at birth (Hamilton, Martin & Sutton, 2004). The majority of these very small and extremely preterm infants survive. However, improved survival rates bring an increased risk for nutritional, growth, motor and sensory problems (Hack, Taylor, Drotar, Schluter, Cartar, Andreias et al, 2005; Hack, Friedman & Fanaroff, 1996; Msall &Tremont, 2002; O'Shea, Klinepeter, Goldstein, Jackson & Dillard, 1997; Vohr, Wright, Dusick, Mele, Verter &Steichen et al, 2000). There is growing concern and effort to reduce the stress of the preterm care environment, while encouraging and facilitating the infants' emerging competence, particularly with respect to feeding. Early feeding difficulties that arise with the transition from tube feeding to oral feeding are prominent and may persist beyond discharge to home. Indeed, the delay in acquiring feeding skills is the

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most frequent cause of prolonged hospitalization in the NICU (Bakewell-Sachs et al, 2009).

Feeding Outcomes after Neonatal Intensive Care
While most infants are discharged from the hospital to home taking full breast or bottle feedings, many of these infants over time show negative feeding behaviors and slow velocity in their growth (Ross, 2009). While Kirkby and colleagues (2007) found that less than one percent of preterm infants required supplemental tube feedings at the time of discharge from the NICU, Hawdon and colleagues (2000) found that over 50% of parents report problematic feeding behaviors in former preterms at the age of 18-24 months. The incidence of feeding problems in EP infants after discharge has been reported to range from 19-80% (Cerro, Zeunert, Simmer & Daniels, 2002; Mathisen, Worrall, O'Callahan, Wall & Shepherd, 2000; Sweet, Hodgman, Pena, Barton, Pavlova & Ramanathan, 2003; Wood, Costeloe, Gibson, Hennessy, Marlow & Wilkinson, 2003). The risk of poor feeding outcomes appears to increase as gestational age decreases (Cerro et al, 2002). Of ELBW (extremely low birth weight) infants born at 600 grams or less, 62% had continued feeding problems at 2 years corrected age and 29% had gastrostomy tubes (Sweet et al, 2003). While extreme immaturity alone may be sufficient to alter the typical path to learning feeding skills and predispose the infant to later feeding problems, the role of experience cannot be discounted. Too often, the preterm may be bombarded during feeding by sensory stimulation that is overwhelming and stress producing. Yet the preterm's neuronal circuits are being organized and aligned in response to this stimulation during feeding (Graven & Browne, 2008). It is critical to consider how the preterm infant experiences feeding early on, and the conditions and strategies that may serve to be protective from developing a feeding problem that endures (Thoyre, 2007).

The Culture of Feeding in the NICU
The pressure to get the infant home can often overshadow a more developmentally supportive focus on pleasurable feeding experiences that minimize stress during feeding (Ludwig & Waitzman, 2007). How might the infant's experience during feeding affect the ability to eat both in the NICU and after discharge? In examining the culture of feeding in the NICU, one might begin by asking: Is feeding task oriented or relationship-based in our NICU? Is success defined by volume, rate of intake, time and weight gain, or does it include the quality of the feeding, a positive experience by the infant? Is the focus on the preterm feeding "well" (quality) or "well enough" (intake)? Is learning to feed viewed as a "light bulb" phenomenon, ie the infant all of a

sudden "figures it out" and therefore then "knows how to feed," or is feeding viewed as a developmental process that requires carefully titrated support from moment to moment?

Even at the time of discharge, preterm infants may be "sufficient" feeders (able to take in adequate volumes) but they are not skilled feeders. They lack consistent and stable feeding skills across the day, and are unable to flexibly adapt their feeding skills to changing conditions (Thoyre, 2003). As with other developmental skills, there is variability, and therefore the need to support the infant based on his continuous feedback during each feeding. The "environment of feeding" provided by the caregiver, and the interactions between the infant and caregiver, may promote or constrain the infant's development of feeding skill and feeding safety (Thoyre, 2003). Caregivers include nurses, parents, other family members and therapists. In dynamic systems theory, the caregiver system includes: how caregivers view feeding, cues they monitor during feeding, what meanings they ascribe to the infant's cues, their beliefs about their own ability to influence feeding, their ability to take the perspective of the infant and to provide sensitive care giving.

Sensitive caregiving (Thoyre, 2003) involves recognizing and attending to the infant's cues to determine when protection and support are needed, knowing when to allow the infant to regulate his own feeding behaviors, proactively structuring the feeding from moment to moment to support safety, and intervening during feeding contingent on cues from the infant signaling inability to self-regulate (Thoyre, 2003; Shaker, 1999). Is the caregiver's goal a successful "feeding" or supporting the infant to become a successful "feeder?" (Shaker, 1990). Focusing on a successful feeding suggests it is all about the caregiver's skill and often about the volume of intake, "getting it in" the infant. On the contrary, a focus on the infant as a successful feeder means the infant is supported in its own efforts to achieve adequate intake and feed safely, even if the volume is small. There is likely a difference in the stress the infant experiences depending on how the goal for the feeding is viewed.

How the Preterm Experiences Feeding
Sensitive indicators of the preterm infant's ability to cope with the stress of feeding include heart and respiratory rates, oxygen saturations, temperature, sleep-wake state, digestion, and suck-swallow-breathe synchrony. The challenge of feeding can quickly trigger changes in these indicators. The caregiver must utilize watchful vigilance to avoid potentially serious consequences of subsystem instability (ie, apnea, bradycardia, tachypnea, color change, and loss of state arousal and/or postural control). If feeding provides too great a challenge to physiologic stability, it can have a negative effect on the control of the larynx, pharynx and esophagus. The consequence of this deterioration is the potential for laryngeal penetration or indeed aspiration. In addition, the potential for silent aspiration is heightened in this fragile population (Arvedson, Rogers, Buck, Smart & Msall, 1994; Shaker, 1999; Thoyre, Shaker & Pridham, 2005) Therefore, the impact of feeding on the stability of the physiologic, motor and state systems must be assessed continuously during feeding. A disruption that negatively affects the infant's respiratory system may, for example, cause the infant to compensate through the motor system with changes in the sucking pattern (Ross & Brown, 2002). The preterm may also compensate through the state system, by moving to a lower state, which is not optimally supportive of successful feeding (McCain, 1997) or of active learning on the infant's part. In an attempt to keep the systems in

balance, the infant may use adaptive strategies to reduce bolus size, such as limited jaw and tongue excursions, compression-only sucking or purposefully expelling excess fluid out of the oral cavity (Eishima, 1991; Ross, 2008). These adaptive strategies may be perceived by caregivers as sucking problems if they are not viewed in the context of dynamic systems (Goldfield, 2007). Recognizing and conceptualizing disruptions in infant system synergy increases the likelihood of addressing the underlying issue, versus applying an arbitrary intervention that may actually over-ride the infant's own beneficial compensatory mechanism (Ross & Brown, 2002). For example, an infant with difficulty coordinating swallowing and breathing may move to a lower sleep state, accompanied by loss of postural control, particularly in the oral area. A well-intentioned caregiver may increase the flow rate to "help" the infant, either by using a faster flow nipple, or providing cheek or jaw support, which can result in a large uncontrolled bolus moving passively toward the airway. As the infant then "fights the flow" to breathe, decreases in oxygenation may compromise the infant's physiologic stability, with a resulting loss of coordinated feeding behaviors, as the infant attempts to protect his airway (Ross & Brown, 2002). This compromise in physiologic stability may lead to apnea and/or bradycardia (Mathew, 1991). Accumulation of these responses to physiologic instability, in turn, may provide negative feedback leading to stress and feeding refusal behaviors early on (Blackman, 1998). A good example of this is seen with infants who have chronic lung disease. These infants have more feeding refusals and negatively perceived feeding behaviors, which may be a reflection of the struggle to safely coordinate when swallowing and breathing compete (Martin & Pridham, 1992). If the focus is primarily on intake, the infant's behaviors may take on a different meaning or not be understood. Well-intentioned caregivers may "feed through" the infant's stop signs. It is critical to appreciate that infants are establishing their learned experiences with feeding; therefore every feeding experience, regardless of how brief, must be as positive as possible (Ross, 2009). A focus on emptying the bottle, or defining an empty bottle as "success," may alter the preterm's experience and potentially have deleterious effects on neuromaturation and on feeding outcomes.

The Impact of Neurodevelopmental Vulnerability
There is increasing evidence that many preterm infants have long-term alterations in brain development (Als et al, 2004; Graven & Browne, 2008). Positive experience and positive sensory input is essential for neuromaturation and development. Input that is unexpected, intense or out of order is detrimental to the progression of brain development (Aucott et al, 2002; Butler & Als, 2008). Preterms are at risk for adverse feeding outcomes because they are wiring their brains outside of the womb, in the NICU, which often provides sensory overload. Indeed, the NICU environment is their foundation for feeding development (Ross, 2009). Preterms begin to develop feeding skills when they are also in the process of developing motor and sensory neuropathways (Thoyre, 2007). They are born with a central nervous system given less time to mature within a protected intrauterine environment. The external NICU environment, unlike the uterine environment, involves absent postural containment typically provided by the uterus and amniotic fluid, aversive and painful stimuli, irregular patterns of handling from multiple caregivers and unfiltered noise and light (Sweeney, Heriza, Blanchard, & Dusing, 2010). In addition, initial subsystem interactions, whether positive or negative, create not only the context in which, but also affect how, the brain is "wired"

(Shore, 1997). Caregiving experiences, especially those during feeding, may also affect developing brain structure (Als, Duffy, McNulty, Rivkin, Vajapeyam & Mulkern, 2004). The combination of physiologic instability during feeding and a sensory-motor system that is undergoing rapid development in an unpredictable and often overwhelming environment may be a potential risk factor. Adverse stressful experiences during feeding may lay down altered sensory-motor pathways in the brain, and affect the ability and desire to eat both in the NICU and after discharge (Ross, 2009; S. M. Thoyre, personal communication, October 23, 2009).

Dynamic Systems Theory Applied to the Preterm's Experience of Feeding

Challenges with learning to feed successfully and safely are known to often result in delay in discharge to home. (Lau, Smith & Schanler, 2003). To accomplish safe and successful feeding, the preterm infant must be capable of sustaining attention to the task of feeding for the duration of the feeding, controlling and coordinating the postural, oral, and upper airway motor systems during the physiologic demands associated with feeding; and protecting the airway from compromise by fluid (Thoyre, 2003). This requires the dynamic integration, maturation and coordination of multiple subsystems, both internal and external. In a dynamic systems model, physiologic stability is considered as the foundation for organizing movement, behavioral state, attention/interaction and self-regulation. These systems support the infant's posture, oral structures, upper airway, arousal and physiologic regulation, and suck-swallow-breathe patterns. For the preterm infant, these subsystems are in the process of maturing along convergent, but not always synchronous, time lines (Thoyre, 2003). The infant's responses and behaviors guide the caregiver in understanding its thresholds of stress versus stability. Interventions contingent on the preterm infant's communicative behaviors are used within a problem-solving framework to enhance self-regulation, development and coping skills. A feeding approach based on dynamic systems theory might include (1) observing the infant continuously during feeding for cues of stress versus stability related to swallowing, breathing, physiologic stability, postural control and state regulation; (2) modifying the feeding approach through individualized interventions contingent on the infant's cues, to help the infant maintain or regain stability (Shaker, 1999). It is the critical responsibility of the caregiver to identify the infant's behaviors or cues and use them as a guide to supporting the infant in a positive, non-stressful experience during the work of feeding.

The Impact on Parent-Infant Well-Being

The technology of the NICU, attention to numbers rather than infant behaviors, and the non-individualized ways in which care is often delivered, has led to what has been termed the "medicalization" of families (McGrath, 2007). The importance of the feeding relationship and the infant's positive experiences may get lost in the "numbers," when the focus is on emptying the bottle to get home. In addition, parents often evaluate their own competency as parents before discharge by their ability to feed their infant (Thoyre, 2000). As such, they will especially benefit from an approach to feeding their infant that minimizes infant stress and optimizes co-regulation between infant and caregiver. Understanding the infant's behavioral communication that reflect the preterm's capabilities and challenges during feeding is essential. Parents learn by observing, and form their working model about feeding by watching in the NICU. How the nurse

feeds the infant has been shown to have a profound impact on mother-infant feeding interactions following discharge to home (Pridham, Brown, Sondel, Green, Wedel & Lai, 1998). Ideally, parents should learn while in the NICU to modify their own expectations of successful feeding away from a sole focus on the amount the infant is fed, to the quality of the feeding. Depending on the culture of feeding in each NICU, this may or may not happen. The nurse's working model, or paradigm, about feeding is a critical factor. Feeding may be viewed as either supporting an infant in a learning opportunity or something one does to the infant. The nurse's definition of success with feeding may be an empty bottle, or an infant who feeds without color change or other adverse overt behaviors. What is the nurse's perception of her relationship to the infant's success? It may be all about the caregiver: "I am a successful nurse if I can get it all in." Or, a focus on the infant as a co-regulatory partner: "I support the infant to feed safely based on his continuous feedback." If parents, based on the nurse's example, see the goal of a feeding as emptying the bottle, or "getting it in" the infant, they may not correlate feeding behaviors with physiologic instability, may not identify adverse events as problematic, may not recognize infant "stop" signs, and may not view feeding their infant as a positive, relationship-based experience. If parents observe a sensitive caregiver who provides an interactive fit with their infant, known as co-regulation (Thoyre, 2003), they will more likely view, and, therefore, demonstrate, feeding as relationship-based and focus on the infant as an active participant in the feeding. This co-regulated approach recognizes the impact of the caregiver's decisions on the infant's experience of feeding (S. M. Thoyre, personal communication, October 23, 2009), and views the infant as a co-regulatory partner with an individual agenda (Ross, 2008) and emerging skills. In this synergistic relationship, the caregiver, often the parent, learns to modulate their approach during feeding based on the infant's communication. This co-regulation between preterm and parent is the foundation for strong parent-infant attachment, and is formed most often during feeding experiences in the NICU. Providing parents with skills to co-regulate with their infant during feeding, as contrasted to showing them how to empty the bottle, is likely to support improved neurodevelopmental and feeding outcomes (Als et al, 2004; McAnulty et al, 2009). When the unique behavior of an infant is understood as a communicative attempt, and parents know how to respond to it effectively, feeding is both more successful and less stressful, and the attachment relationship tends to strengthen, while parental anxiety tends to diminish (Ross & Philbin, 2011; Pridham et al, 2001).

A Volume-Driven Culture of Feeding in the NICU

Traditional NICU feeding practice is grounded in the medical model in which a successful feeding is measured by volume intake, regardless of infant behaviors or caregiver manipulation of the bottle during feeding (Ludwig & Waitzman, 2007). This may lead to increased stress during feedings (McGrath & Braescu, 2004). While it is essential that the preterm ingests the volume and calories needed for growth, a focus on volume alone does not consider or support the preterm in the context of its developmental strivings. In a volume driven model of feeding, preterm infants are often encouraged to eat even when they are indicating that they are too fatigued or not behaviorally or physiologically ready for eating (Thoyre & Brown, 2004). The focus is on what is or is not in the bottle. Emptying the bottle becomes the goal. How fast the infant feeds becomes a measure of success, along with intake/volume. "Getting it in the baby" is the language one might hear, which minimizes, or

does not recognize, the active role of the infant. Infant cues of stress versus stability during feeding may not be recognized, not fully understood or misinterpreted. The caregiver may feed past the "stop" signs in an effort to assure volume is ingested. In the volume driven approach, the caregiver often uses well-intentioned strategies. For example, increasing flow rate to "help" the infant empty the bottle and increase intake which can cause the infant to struggle as he "fights the flow" to breathe; prodding the infant, which takes away his active sensory-motor control over feeding; putting the infant's head back to use gravity to help empty the bottle, which increases risk for bolus misdirection and airway compromise; unswaddling the infant to "keep it awake," which actually takes away critical postural support for the swallowing mechanism. The infant may indeed be asked to continue feeding despite subtle signs of physiologic instability, behaviors that suggest swallowing and breathing are becoming uncoupled, for example, such as drooling, gulping, the lack of a regular series of deep breaths, chin tugging, and changes in eye gaze pattern (Shaker, 1999). While signs of engagement, such as rooting, have meaning in a volume driven approach, signs of disengagement, ie "I want to stop, I am done" often do not. These signs may include pushing the nipple out, pulling off the nipple, no active rooting or sucking, arching, shutting down/inability to re-alert, or purposeful use of a weak suck on the infant's part to signal a preference for return to only pacifier sucking. The infant's communication is likely to not be perceived and feeding is continued. While intake is achieved and caregivers may express pride in being able to "get it in the baby," what is the long-term implication for the preterm of the experience the infant has endured? The infant's undue stress may set it up for safety issues as well as long-term learned refusals. Having a greater emphasis on achieving adequate intake/volume and less on competence with feeding is quite problematic (Thoyre, 2003). If the focus of the feeding is solely on volume (total intake or volume per minute), the feeder may not consider the infant's physiologic stability, and the feeding may be counterproductive (Ross, 2008). Repeated negative experiences during feeding may lead to aversions, as neuronal mapping is occurring rapidly during this time (Edelman,1987). The potential relationship of a volume driven culture in the NICU to the adverse long term feeding outcomes is quite concerning.

An Infant-Driven Culture of Feeding in the NICU

In an infant-driven approach (Ludwig & Waitzman, 2007), the aim is to help infants learn to feed, not to get them to eat or "get it all in." Safety becomes the primary goal. That includes: avoiding aspiration with feeding, avoiding passive manipulation of the nipple, and using a flow that is controllable for the infant (Ludwig & Waitzman, 2007). Recognition of the developmental nature of acquisition of feeding skills, and not pushing the infant further than he or she is developmentally capable of at any given time, is an essential component (Browne & Ross, 2011). Quality of feeding, positive infant experience and behaviors, and swallowing safety drive our conversations at the bedside when we discuss feeding progress. Feedings are designed to be nurturing, and a relationship-based experience with the caregiver, whether parent or nurse. The goal is an infant who is engaged in feeding without signs of distress, even if the feeding only lasts for as long as a few sucks. Feeding is stopped when the infant communicates being done, or the inability to continue for whatever reason, in lieu of the caregiver's doing whatever is necessary to empty the bottle (Shaker, 1999). The focus is not on intake. Intake will improve with development, if the infant's communicative behaviors are respected as signals to initiate

and terminate feeding experiences. Co-regulation during feeding becomes the focus, such that the infant's signs of stress versus stability specific to feeding and swallowing, from moment to moment, guide the caregiver (Shaker, 1999).

What feeding strategies are infant driven? The literature suggests the following strategies: choosing a more controllable flow rate to protect the immature preterm infant (Al-Sayed, Schrank & Thach, 1997; Chang, Lin, Lin & Lin, 2007; Gewolb & Vice, 2006; Goldfield, Richardson, Lee & Margetts, 2006; Lau, Sheena, Shulman & Schanler,1997; Lau & Schanler, 2000; Matthew, 1991; Shaker, 1999); considering a sidelying position (Debra Beckman, personal communication, March 21, 2002; Clark, Kennedy, Pring & Hird, 2007; Shaker& Thoyre, 2011; Shaker, 2011); providing supportive swaddling to optimize postural stability and control (Wolf & Glass, 1992; Shaker, 1999); providing anticipatory external pacing during feeding to avoid uncoupling of swallowing and breathing (Jordan, 1998; Law-Morstatt, Judd, Snyder, Baier & Dhanireddy, 2003; Shaker, 1999); supporting state regulation through re-arousal or calming (McCain, 1997); avoiding prodding (Brown & Ross, 2002; Shaker, 1999) and using a developmentally-supportive approach to feeding with preterms and their families (Shaker, 1999; Ross & Philbin, 2011). As the quality of a feeding takes priority over the quantity ingested, feeding skill develops pleasurably and at the infants' own pace and intake improves as a result. In an infant driven feeding culture, caregivers support feeding success by using the infant's communication to inform their feeding decisions and actions (Ross & Philbin, 2011).

Summary

Feeding preterm infants is often considered a routine task rather than a critical element of NICU care. Yet, infant feeding, by its nature, is an interactive developmental task (Thoyre & Brown, 2004). Research in preterm infant feeding shows that the ability to feed well is closely related to the caregiver's ability to understand and sensitively respond to the infant's physiology and behavioral communications (Thoyre & Brown, 2004; Pickler, 2004). Yet, the dynamic interaction amongst the preterm infant, the care providers and the culture of feeding in each NICU remains an unpredictable, and often, precarious, influence. In a volume-driven culture in the NICU, a successful feeding is measured by volume intake, regardless of infant behaviors or caregiver manipulation of the bottle during feeding. It leads to increased stress for the preterm during feeding, due to the caregiver's tendency to feed "past the infant's stop signs," resulting in maladaptive feeding behaviors on the infant's part, learned feeding refusals, and long term feeding aversions; most importantly, the parent-infant relationship, which is established early on in the NICU through co-regulated and communicative feeding interactions that build trust, can be affected negatively. This is not to say that volume is not one of the important measures of feeding integrity required for discharge from the NICU. However, volume must be viewed in the context of the infant's developmental strivings, and as the byproduct of a quality feeding, in which the infant's cues of both engagement and disengagement, despite the volume, are respected and honored. An infant-driven approach in the NICU provides this co-regulation through gentle feeding opportunities based on the infant's continuous feedback. As such, it is an essential component of a cue-based feeding approach in the NICU. The preterm's experience of feeding is strongly influenced by the assessments, decisions, and actions of NICU caregivers, and their support of the infant's individual manner and pace of acquiring feeding abilities (Ross & Philbin, 2011) Through their embracing,

modeling and coaching high-quality feeding interactions, NICU caregivers can build confidence and competence for parents, and establish feeding as a pleasurable relationship-based experience for the preterm. Moving away from a volume driven approach toward an infant-driven approach in the NICU is essential for improving feeding outcomes, the infant's well-being, and the parent-infant relationship both during and well beyond discharge from the hospital.

References

- Als, H., Duffy, F.H., McNulty, G.B., Rivkin, M.J., Vajapeyam, S. & Mulkern, R.V. (2004). Early experience alters brain function and structure, Pediatrics, 113, 846-857.
- Al-Sayed, L., Schrank, W., and Thach, B. (1997). Ventilatory sparing strategies and swallowing pattern during bottle feeding in human infants. Journal of Applied Physiology, 77, 78-83.
- Arvedson, J., Rogers, B., Buck, G. , Smart, P., & Msall, M. (1994). Silent aspiration prominent in children with dysphagia, International Journal of Pediatric Otorhinolaryngology, 28, 173-181.
- Aucott, S., Donohue, P.K., Atkins, E., & Allen, M.C. (2002). Neurodevelopmental care in the NICU. Mental Retardation and developmental Disabilities Research Reviews, 8, 298-308.
- Bakewell-Sachs, S., Medofff-Cooper, B., Escobar, G.J., Silber, J.,H., & Lorch, S.A. (2009). Infant functional status: The timing of physiologic maturation of premature infants. Pediatrics 123(5):e878-e886.
- Blackman, J. A. (1998). Children who refuse food, Contemporary Pediatrics, 15, 198-216.
- Browne, J.V. & Ross, E.S. (2011). Eating as a neurodevelopmental process for high risk newborns. Clin Perinatol 38, 731-743.
- Butler, S. & Als, H. (2008). Individualized developmental care improves the lives of infants born preterm. Acta Paediatrica 97, 1173-1175.
- Cerro, N., Zeunert, S., Simmer, K.N. , & Daniels, L.A. (2002). Eating behavior of children 1.5-3.5 years born preterm: parent's perceptions, Journal of Paediatrics and Child Health, 38, 72-78.
- Chang, Y.J., Lin, C.P., Lin, Y.J. & Lin, C.H. (2007). Effects of single-hole and cross-cut nipple units on feeding efficiency and physiological parameters in premature infants, Journal of Nursing Research, 15, 215-223.
- Clark, L., Kennedy, G., Pring, T., & Hird, M. (2007). Improving bottle feeding in preterm infants: investigating the elevated side-lying position, Infant, 3, 154-158.
- Edelman, G.M. (1987) Neural Darwinisim: The theory of neuronal group selection. New York: Basic Books, Inc.
- Eishima, K. (1991). The analysis of sucking behaviour in newborn infants, Early Human Development, 27, 163-173.
- Gardner, S.L., & Goldson, E. (2002) The neonate and the environment: Impact on development. In S.L. Merenstein & G.B. Gardner (Eds.), Handbook of neonatal intensive care (5th ed., pp 219-282). St. .Louis: Mosby.
- Gewolb, I.H. & Vice, F.L. (2006). Abnormalities in the coordination of respiration and swallow in preterm infants with bronchopulmonary dysplasia, Developmental Medicine and Child Neurology, 48, 595-599.
- Goldfield, E.C. (2007). A dynamical systems approach to infant oral feeding and dysphagia., Ecological Psychology , 19, 21-48.
- Goldfield, E.C., Richardson, M.J., Lee, K.G., & Margetts, S. (2006). Coordination of sucking, swallowing and breathing and oxygen saturation during early infant breast feeding and bottle feeding, Pediatric Research, 60, 450-455.
- Graven, S.N. & Browne, J.V. (2008). Sensory development in the fetus, neonate and infant: Introduction and overview. Newborn & Infant Nursing Reviews, 8, 169-172.
- Hack, M., Taylor, H.G., Drotar, D., Schluchter, M., Cartar, L., Andreias, L. et, Wilson-Costello, D., & Klein, N. (2005). Chronic conditions, functional limitations, and special health care needs of school-aged children born with extremely low birth weight in the 1990's. JAMA:The Journal of the American Medical Association, 294, 318-325.
- Hack, M., Friedman, H., & Fanaroff, A.A. (1996). Outcomes of extremely low birth weight infants. Pediatrics, 98, 931-937.
- Hamilton, B.E., Martin, J., & Sutton, P.D. (2004).Births: Preliminary data for 2003. National Vital Statistics Reports, 53, 1-20.
- Hawdon, J.M., Beauregard, N., Slattery, J., & Kennedy, G. (2000). Identification of neonates at risk of developing feeding problems in infancy. Developmental Medicine and Child Neurology, 42, 235-239
- Jordan, S. (1998). The controlled or paced bottle feeding, Neonatal Network, 3, 21-24.
- Kirkby, S., Greenspan, J.S., Kornhauser, M., & Schneidermann, R. (2007). Clinical outcomes and cost of the moderately preterm infant. Advances in Neonatal Care, 7(2), 80-87.
- Lau, C., Smith, E.O., & Schanler, R.J. (2003). Coordination of suck-swallow and swallow respiration in preterm infants, Acta Paediatrica, 92, 721-727.
- Lau,C. & Schanler, R.J. (2000). Oral feeding in premature infants: advantage of a self-paced milk flow, Acta Paediatrica, 89, 453-459.
- Lau, C., Sheena, H.R., Shulman, R.J., Schanler, R.J. 1997. Oral feeding in low birth weight infants, Journal of Pediatrics, 130, 561-569.
- Law-Morstatt, I., Judd, D.M., Snyder, P., Baier, R.J., & Dhanireddy, R. (2003). Pacing as a treatment technique for transitional sucking patterns, Journal of Perinatology, 23, 483-488.
- Ludwig, S. & Waitzman, K.A. (2007). Changing feeding documentation to reflect infant-driven feeding practice, Newborn and Infant Nursing Reviews, 7,155-160.
- Martin, R. & Pridham, K.F. (1992). Early experiences of parents feeding their infants with bronchopulmonary dysplasia, Neonatal Network, 11, 23-29.
- Mathew, O.P. (1991). Breathing patterns of preterm infants during bottle feeding: role of milk flow, Journal of Pediatrics, 119, 960-965.
- Mathisen, B., Worrall, L., O'Callaghan, M.O., Wall, C. & Shepherd, R. W. (2000). Feeding problems and dysphagia in six-month old extremely low birth weight infants, Advances in Speech-Language Pathology, 2, 9-17.
- McAnulty,G., Duffy, F.H., Butler,S., Parad, R., Ringer, S., Zurakowski, D., & Als, H. (2009). Individualized developmental care for a large sample of very preterm infants: Health, neurobehaviour and neurophysiology, Acta Paediatrica, 98, 1920-1926.
- McCain, G.C. (1997). Behavioral state activity during nipple feedings for preterm infants, Neonatal Network, 16, 43-47.
- McGrath, J.M. (2007). Family: Essential partner. In C. Kenner & J. Lott (Eds.) Comprehensive neonatal care: An interdisciplinary approach (3rd ed., pp 491-509). Philadelphia: W.B. Saunders Co.
- McGrath, J.M., Braescu, A.V.(2004) State of the science: Feeding readiness in the preterm infant. J Perinat Neonatal Nurs, 19, 265-272.

- Msall, M.E. & Tremont, M.R. (2002). Measuring functional outcomes after prematurity: developmental impact of very low birth weight and extremely low birth weight status on childhood disability, Mental Retardation and Developmental Disabilities Research Review, 8, 258-272.
- National Center for Health Statistics (2009, May 18).National Vital Statistics Report (Vol 57, No.12).
- O'Shea, T.M., Klinepeter, K. L., Goldstein, D.J., Jackson, B.W., Dillard, R.G. (1997). Survival and developmental disability in infants with birth weights of 501to 800 grams, born between 1979 and 1994, Pediatrics, 100, 982-986.
- Pickler, R.H. (2004) A model of feeding readiness for preterm infants. Neonatal Intensive Care (17) 31-36.• Pridham, K., Lin., C.Y., Brown, R. (2001) Mother's evaluation of their caregiving for premature and full-term infants through the first year: Contributing factors. Res Nurs Health 24:157-169.
- Pridham, K., Brown, R., Sondel, S., Green, C., Wedel, N.Y. & Lai, HC. (1998). Transition time to full nipple feeding for preterm infants with a history of lung disease, Journal of Obstetric, Gynecologic and Neonatal Nursing, 27, 533-545.
- Ross, E.S. & Philbin, K. (2011) Supporting oral feeding in fragile infants: An evidence-based method for quality bottle-feedings of preterm, ill and fragile infants. J Perinatal and Neonatal Nursing 25 (4): 349-357.
- Ross, E.S. (2009, July). Don't be a "babies R us" therapist: Thinking past the bottle in the NICU. Pediatric Feeding and Dysphagia Newsletter, 9(5),1-4.
- Ross, E.S (2008, October). Feeding in the NICU and issues that influence success, Perspectives on Swallowing and Swallowing Disorders (Dysphagia), 17, 94-100.
- Ross, E.S. & Brown, J.V. (2002). Developmental progression of feeding skills: an approach to supporting feeding in preterm infants, Seminars in Neonatology, 7, 469-475.
- Shaker, C.S.(2011) "Feeding and Swallowing in the NICU and After Discharge" Presented at Scripps Medical center, San Diego, CA.
- Shaker, C.S. & Thoyre, S.M. (2011) "NICU Feeding Frustrations: A Cue-Based Approach for the Entire Team" Presented at Dell Children's Medical Center, Austin TX.
- Shaker, C.S. & Woida, A.M. (2007). An evidence-based approach to nipple feeding in a level III NICU: Nurse autonomy, developmental support and teamwork, Neonatal Network, 26, 77-83.
- Shaker, C.S. (1999). Nipple feeding preterm infants: an individualized, developmentally supportive approach, Neonatal Network, 18, 15-22.
- Shaker, C.S. (1990). Nipple feeding premature infants: A different perspective. Neonatal Network, 8, 9-16.
- Shore, R. (1997). Re-thinking the brain: new insights into early development. New York, NY: Families and Work Institute.
- Sweeney, J.K., Heriza, C.B., Blanchard, Y. & Dusing, S.C. (2010). Neonatal Physical Therapy. Part II: Practice frameworks and evidence-based guidelines, Pediatric Physical Therapy, 22, 2-16.
- Sweet, M.P., Hodgman, J.E., Pena, I., Barton, L., Pavlova, Z. & Ramanathan , R. (2003). Two-year outcomes of infants weighing 600 grams or less at birth and born 1994 through 1998. Obstetrics and Gynecology, 101, 18-23.
- Thoyre, S.M. (2007). Feeding outcomes of extremely premature infants after neonatal care, Journal of Gynecologic and Neonatal Nursing, 36, 366-376.
- Thoyre, S.M., Shaker, C.S., & Pridham, K.F. (2005). The early feeding skills assessment for preterm infants, Neonatal Network, 24, 7-16.
- Thoyre, S.M & Brown, R.C. (2004). Factors contributing to preterm infant engagement during bottle feeding, Nursing Research, 53, 304-313.
- Thoyre, S.M. (2003). Developmental transition from gavage to oral feeding in the preterm infant. In J.J. Fitzpatrick (Series Ed.), M. Miles & D. Holditch-Davis (Vol.Eds.), Annual review of nursing research:Vol.21. Research on child health and pediatric issues (pp. 61-92). New York: Springer.
- Thoyre, S.M. (2000). Mothers' ideas about their role in feeding their preterm infants. J Obstet Gynecol Neonatal Nurs 29(6): 613-24.
- Vohr, B.R., Wright, L.L., Dusick, A., Mele, L., Verter, J., Steichen, J.J., Simon, N.P., Wilson, D.C., Broyles, S., Bauer, C.R., Delaney-Black, V., Yotton, K.A., Fleisher, B.E., Papile, L.A. & Kaplan, M.D. (2000). Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network 1993-1994. Pediatrics, 105, 1216-1226.
- Wolf, L.S. & Glass, R.P. (1992). Feeding and Swallowing Disorders in Infancy: Assessment & Management. Tucson, AZ: Therapy Skill Builders.
- Wood, N.S., Costeloe, K., Gibson, A.T., Hennessy, E.M., Marlow, N. & Wilkinson, A.R. (2003). The EPICure study: growth and associated problems in children born at 25 weeks gestational age or less, Archives of Disease in Childhood, Fetal and Neonatal Edition, 88, F492-500.

American Academy of Pediatrics & American Heart Association Neonatal Resuscitation Program Guidelines: A Review

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Introduction

The intention of this article is to present a concise review for healthcare professionals involved in the resuscitative care and management of the neonate in the delivery room (DR) and Neonatal Intensive Care Unit (NICU) in regards to the American Academy of Pediatrics (AAP) and American Heart Association (AHA) latest guidelines for neonatal resuscitation. Most recent guidelines for 2011 have focused on several major areas that include resuscitation training methodology, team approach to resuscitation, airway suctioning, temperature control, use of oxygen, administration of air vs supplemental oxygen, and drugs used during resuscitation. Emphasis remains on the team approach to newborn resuscitation. We will discuss each component providing the contrasting previous guidelines with changes advocated in the new recommendations. As with all guidelines, the intent is to provide the health care professional caring for neonates with an understanding and rationale but should not replace clinician judgment at the bedside.

Suctioning in the DR

Suctioning of the oropharynx/airway has historically been a key component of the newborn DR care. There is sufficient evidence to support that oropharynx/airway suctioning can cause bradycardia and pulmonary decompensation in addition to a reduction in cerebral blood flow in intubated patients. However, suctioning of secretions can clear the airway and decrease resistance.

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(a) When the amniotic fluid is clear:
Previous NRP guidelines recommended that secretions from the mouth and the nose be removed by wiping the mouth and the nose in the same order using towel or bulb suction. The infant was then positioned with the head to the side if no meconium was present.

Current recommendations:
Suctioning immediately following birth (including suctioning with a bulb syringe) of clear fluid should be reserved for babies with obvious airway obstruction or for the infant who will require positive pressure ventilation (PPV).

(b) When meconium is present:
Previous NRP guidelines recommended that in case of meconium stained amniotic fluid at delivery, suctioning the airway should be performed only if the infant was non-vigorous (depressed infant). Intrapartum suctioning of the mouth and the nose by the obstetrician after delivery of the head was no longer recommended.

The infant is considered vigorous at birth if he has
• Normal respiratory effort
• Normal muscle tone and
• Heart rate >100 bpm

The vigorous infant should be provided routine care and remain with the mother. An infant who was vigorous at birth, but had copious secretions with meconium noted in the oropharynx, required suctioning of the mouth and then the nose with bulb suction or a large bore suction catheter avoiding deep suctioning until after the infant was five minutes old.

The infant is considered to be non-vigorous (depressed) at birth with:
• Depressed respirations
• Depressed muscle tone and
• HR < 100 bpm

Depressed infants were not to be stimulated and to be provided with direct endotracheal suctioning using a meconium aspirator before the first breath after delivery. A repeat procedure could be performed if necessary, provided prolonged hypoxia was avoided during the procedure. All infants with meconium stained amniotic fluid were to be observed in the first few hours after birth with close monitoring of vital signs.

Current recommendations:
Current recommendations advocate for similar management but also stress that after unsuccessful intubation and meconium aspiration attempts in a depressed infant one should consider PPV especially when associated bradycardia [HR < 60 beats per minute (bpm)] is present.

Temperature control in the DR
Temperature control is very important as all newborns are at risk for hypothermia after birth due to the relatively cool environment and high surface area to volume ratio. In particular, babies less than 1500 grams are at markedly increased risk of hypothermia in the DR. Hypothermia can lead to significant neonatal morbidity and mortality. In the prior guidelines, methods to maintain newborn temperature were suggested as follows:
• Increase the temperature in the DR to 26°C
• Pre-heat the radiant warmer well before the infant is born
• Pre-warm all blankets, linens, and mattress
• Use food grade polyethylene bag by placing the baby's body below the neck without drying for all infants less than 28 weeks' gestational age.
• Cover the head with a cap
• Pre-warm the transport incubator to maintain the temperature en route to the NICU
• On all term babies who are not in distress, place the baby on the mother's chest (skin to skin contact) and also cover the baby with the blanket

Current recommendations:
Major changes are to increase the temperature of DR resuscitation area to approximately 25°C to 26°C, use of the polyethylene wrap for babies delivered at less than 29 weeks' gestation (or 28 weeks and less), and placement of a portable warming pad under layers of towels on the resuscitation table. The emphasis remains on monitoring of the infant's temperature to maintain normothermia, preventing both hypothermia and hyperthermia, when these techniques are used in combination. Iatrogenic hyperthermia may also occur in infants born to febrile mothers and rigorous temperature control and monitoring in these infants is essential.

In instances of perinatal depression and concern for hypoxic ischemic encephalopathy in an infant > 36 weeks of gestational age, NICU therapeutic hypothermia should be considered after initial stabilization in the delivery room but within six hours of birth. NRP is clear that such a treatment should only be instituted by experienced centers with a strict protocol.

Use of oxygen in the DR
Prior guidelines recommended 100% supplemental oxygen use when infant is cyanotic or PPV is required. Although several authors suggested resuscitation with 21% oxygen (room air), the position of NRP remained that the evidence was not sufficient to recommend 21% oxygen use. An oxygen blender was recommended for use in the preterm birth to guide oxygen delivery from 21% to 100% while maintaining the infant's oxygen saturation between 90 to 95%.

Current recommendations:
Assessment of oxygen need is important as a compromised infant may have blood oxygen levels well below recommended values. Skin color assessment is a poor indicator of

oxyhemoglobin saturation as has been determined in several studies. Oxygen management is of prime importance in neonatal resuscitation as there is strong evidence that either insufficient or excessive oxygen administration can be harmful to the newborn. Pulse oximetry is a better indicator than skin color to assess oxyhemoglobin saturation. Newer probes designed for newborns can provide accurate assessment of oxyhemoglobin saturation as early as within the first 1-2 minutes of life. Oximetry is recommended in situations where resuscitation is highly anticipated, when positive pressure is administered for more than a few breaths, when cyanosis is persistent, or when supplementary oxygen is administered.

Use of air vs oxygen is another area well addressed in the new guidelines. Most information is based on either 21% (room air) or 100% oxygen in term infants and it is difficult to provide an accurate fraction of oxygen to be administered. Currently, it is recommended that one should aim for an oxygen saturation value in the interquartile range of preductal saturations regardless of delivery at term vs. preterm. The pulse oximetry probe should be placed in the right hand or wrist for detection of preductal oxygen saturation. Here are the recommended oxygen saturation ranges at different time intervals;
• 60-65% at one minute
• 65-70% at two minutes
• 70-75% at three minutes
• 75-80% at four minutes
• 80-85% at five minutes
• 85-95% at ten minutes

The clinician can initiate resuscitation with blended oxygen and titrate to attain desirable oximetry reading. If blended oxygen is not available then use air. If the baby is bradycardic (HR <60 bpm) after 90 seconds of resuscitation with a lower concentration of oxygen, oxygen concentration should be increased to 100% until recovery of a normal heart rate.

Use of positive end expiratory pressure (PEEP/CPAP)
Use of PEEP/CPAP is a new section addressed in the current guidelines.

Current recommendations:
Current recommendations state that CPAP by a mask may be beneficial, particularly if the baby is preterm with respiratory distress. CPAP can also be used in term infant with labored respirations.

Endotracheal intubation in the DR
Intubation in the DR is suggested when
• An infant is depressed as in the settings of meconium stained amniotic fluid
• An infant who do not respond to PPV
• An infant who requires chest compressions
• An infant who is premature requiring mechanical ventilation
• An infant who requires surfactant administration
• An infant with diaphragmatic hernia

Current recommendations:
Current ET intubation guidelines remain unchanged except for added recommendations for use of a laryngeal mask airway (LMA). Ventilation of the newborn can be performed effectively with a flow-inflating bag, a self-inflating bag, or a pressure limited T-piece resuscitator. All endotracheal

(ETT) intubations require the use of carbon dioxide (CO_2) detector for confirmation of the ETT placement. In addition, the clinician should auscultate for bilateral air entry, assess bilateral chest rise, absence of gastric distention, vapor condensing on the side of the tube, and improvement of heart rate, color and oxygen saturation.

When endotracheal intubation is unsuccessful or not feasible due to orofacial/tracheal abnormalities and positive pressure with a face mask fails to achieve effective ventilation, a laryngeal mask can be used to provide PPV. The laryngeal mask has not been evaluated in the setting of meconium stained amniotic fluid, during chest compressions, or for administration of emergency intratracheal medications.

Chest compression in the DR

Another major change from prior guidelines is the initiation of chest compressions. Chest compressions are now recommended when the infant's heart rate is less than 60 bpm despite 30 seconds of effective positive-pressure ventilation. Effective ventilation is defined by bilateral breath sounds and chest movement when the clinician is providing PPV by bag-mask or via endotracheal intubation (intubation is strongly recommended). During chest compressions oxygen concentration should be increased to 100% and the compressions should be continued for at least 45-60 seconds before heart rate check which differs from every 30 seconds check previously.

Methods to implement chest compressions remain the same and include placement of two fingers on the lower third of the sternum above the xyphoid with opposite hand supporting the infant's back or the two-thumb technique with hands circling the infant's chest. Both methods must ensure adequate compressions by depressing on the lower third of the sternum to a depth of approximately one third of the anterior-posterior diameter of the chest. Chest compressions must be coordinated with ventilations to allow for adequate chest expansion and exhalation with a ratio of 1 breath to three compressions or 120 events per minute.

Medications in the DR

(a) Epinephrine

Epinephrine is used as the first line drug in neonatal resuscitation. It is indicated when heart rate is less than 60 bpm despite adequate ventilation and chest compressions. It is a cardiac stimulant and increases the strength and rate of cardiac contraction and cardiac output. In addition, via its vascular constriction effects, it leads to aortic constriction and increases coronary blood flow. Prior guidelines recommended use of epinephrine via intravenous (IV) access or ETT, although IV route was preferred. IV dose was 0.1-0.3 mg/kg/dose given rapidly followed by saline flush. ETT route dose was 0.3-1 mg/kg/dose given directly to ET tube followed by PPV to disburse the medication. The dose could be repeated every 3 to 5 minutes while providing PPV via ET with chest compressions.

Current recommendations:
Newer guidelines recommend use of epinephrine only when hear rate of < 60 bpm despite 30 seconds of effective ventilation (preferably via endotracheal tube) followed by at least 45-60 seconds of coordinated chest compressions. The recommended IV dose is 0.01 to 0.03 mg/kg/dose. While access is being obtained, administration of a higher dose (0.05 to 0.1 mg/kg) through the ETT may be considered, but the safety and efficacy

of this practice has not been established. The concentration of epinephrine for either route should be 1:10,000 (0.1 mg/ml). Additional need of volume expansion, treatment of acidosis, hypoglycemia and pressure agents should be considered if resuscitation is prolonged.

(b) Volume Expansion:

Use of volume expansion (whole blood, isotonic crystalloid) was considered when there was known or suspected blood loss, prolonged resuscitation or an inadequate response to prior resuscitative measures.

Current recommendations:
Volume expansion should continue to be utilized in resuscitation with the same considerations.

(c) Naloxone Hydrochloride:

Previously, use of naloxone was limited to infants with a history of maternal narcotic administration four hours before delivery after establishment of PPV.

Current recommendations:
Currently, administration of naloxone is not recommended as part of initial resuscitation efforts in the DR for newborns with respiratory depression. Heart rate and oxygenation should be restored by supporting ventilation in these infants.

(d) Sodium bicarbonate:

Use in neonatal resuscitation is controversial. Severe acidosis at birth and/or a prolonged resuscitation may build up acids causing poor myocardial contraction and pulmonary vascular constriction. This can result in hypoxia, asphyxia and pulmonary hypertension. While ventilating the baby, if the serum pH is low and base excess (BE) is high, one should consider bicarbonate administration by using a diluted 4.5% solution at a dose of 1-2 ml/kg/dose IV given by slow infusion over 10-20 minutes. In preterm infants, the use of bicarbonate is limited because of potential side effects.

Current recommendations:
Role of sodium bicarbonate is not well elaborated in the current guidelines and its use should be limited as previously recommended.

(e) Glucose:

Glucose administration has not been considered first line of resuscitation but can be considered in prolonged resuscitation.

Current recommendations:
As before, treatment or prevention of hypoglycemia during any prolonged resuscitation should always be a consideration for any infant. Administration of intravenous (IV) glucose via the umbilical vein (UV), peripheral vein or intraosseous (IO) route should be performed as soon as able.

Vascular access in the DR

Establishing vascular access has always been an essential part of newborn resuscitation. Use of the umbilical vein has always been recommended by NRP given the ease of access ability.

Current recommendations:
In addition to previously established vascular access of peripheral or umbilical venous (UV) use, temporary intraosseous (IO) access to provide fluids and medications to resuscitate

critically ill neonates may be indicated. Access with the IO route can be attempted following unsuccessful attempts to establish UV or peripheral access or when caregivers are more skilled at securing IO access.

Role of ethics
There are no federal laws in the United States which mandate DR care of an infant in all circumstances. On the other hand there may be laws specific to the area where practice is being done. Therefore the provider should know the local laws and prescribe to the NRP and the American Medical Association (AMA) code of Medical Ethics. Meeting with parents before a high-risk delivery should be done in the presence of obstetric provider. The specifics of ethical issues which can arise are delivery are beyond the scope of this review and readers are directed to AAP NRP textbook and also advised to review state and local laws.

Standard precautions in the DR
Current recommendations:
The NRP stresses the importance of maintaining standard contact precautions to prevent exposure to infection by following universal infection control in handling the infant in the delivery room.

Teamwork and communication
Teamwork and communication remain an integral part of neonatal resuscitation guidelines. Recognized as essential for each team member that comprises a functioning team for effective resuscitation are ten key behavioral skills which include knowing one's environment, anticipation and planning, taking the leadership role, effective communication, optimal delegation of workload, wise use of attention, use of all available information and resources, know when to call for help, and to maintain professional behavior.

Simulation based learning and certification
This is another area of a major change. Neonatal provider course now includes limited to no lectures and the course time is used for hands-on learning. Current focus of NRP is to provide simulation based learning and training followed by constructive debriefing which is essential at the time of certification or recertification. Healthcare providers should read the AAP NRP book and take an online examination by them rather than administered by an NRP instructor. They should then demonstrate NRP skills in simulation based scenarios to get certified. Specifics can be obtained from the AAP NRP 6th edition textbook.

Summary
Provided was a brief and concise summary of the latest AHA and AAP NRP guidelines. The article provides a quick review for the expert audience well adept with the neonatal resuscitation. We recommend readers to review current NRP principles to remain current with the latest evidence based resuscitation recommendations. It is also of utmost importance to remain familiar with local hospital and state regulations for health care practice. Decisions should be made with the best intent and knowledge of each clinician involved in the resuscitation.

Suggested Reading
1   American Academy of Pediatrics and American Heart Association; John Kattwinkel, MD, FAAP (ed). 2010 American Academy of Pediatrics and American Heart Association Guidelines for Neonatal Resuscitation. Neonatal Resuscitation (NRP) Textbook - 6th Edition (English version). eISBN 9781581106305; ISBN 13: 9781581104981. Publish Date 2011-05-17.
2   Kattwinkel, J., J. M. Perlman, K. Aziz, C. Colby, K. Fairchild, J. Gallagher, M. F. Hazinski, L. P. Halamek, P. Kumar, G. Little, J. E. McGowan, B. Nightengale, M. M. Ramirez, S. Ringer, W. M. Simon, G. M. Weiner, M. Wyckoff, and J. Zaichkin. 2010. "Neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care." Pediatrics 126(5): e1400-13.
3   Perlman, J. M., J. Wyllie, J. Kattwinkel, D. L. Atkins, L. Chameides, J. P. Goldsmith, R. Guinsburg, M. F. Hazinski, C. Morley, S. Richmond, W. M. Simon, N. Singhal, E. Szyld, M. Tamura, and S. Velaphi. 2010. "Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations." Pediatrics 126(5): e1319-44.
4   Kattwinkel J, Perlman J. The Neonatal Resuscitation Program: the evidence evaluation process and anticipating edition 6. NeoReviews. 2010;11:673–680.
5   American Academy of Pediatrics/ American Heart Association. Zaichkin, J. (ed). (2011). Instructor Manual for Neonatal Resuscitation - 5th Edition. ISBN 13: 978-1-58110-188-1.

NICU Support of the Breastfeeding Mother of Twins and Higher Order Multiples

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Introduction

Human milk (HM) feeding has long been recognized as the optimal method of feeding for nearly all infants. For the subset of infants hospitalized for prematurity, the receipt of HM may be crucial. Human milk plays a significant role in decreasing morbidity and improving gastrointestinal function, absorption of nutrients, visual acuity and long-term neurodevelopmental outcomes. Mothers of premature infants are often challenged in their attempts to provide HM for their infants. Therefore, premature infants are at greater risk than their full term counterparts of not being fed enough human milk or not being fed human milk at all.

A group of mothers known to be at high risk for premature delivery are those experiencing multi-fetal pregnancy. Due to a myriad of conditions, these mothers are at greatest risk for delayed onset of lactogenesis II, insufficient milk supply and even lactation failure. Breastfeeding and lactation support becomes critical in assisting mothers to provide human milk for their infants.

It is imperative that health care professionals in the antenatal healthcare and neonatal intensive care settings be knowledgeable and supportive of breastfeeding and human lactation. In addition to providing guidelines, this paper will address the unique challenges faced by health care professionals as they educate and support the breastfeeding mother of twins and higher order multiples (HOM).

Background

Multiples births were steady at about 2% of all births in the United States from about 1915 through the 1970s.[1,2] Beginning in the early 1980s, the incidence of twin, triplet and HOM birth escalated dramatically.[3,4] This may be due to a number of factors including an aging population and artificial reproductive technology. In its January, 2012 Data Brief, the National Center for Health Statistics reported that in 2009, 1 in every 30 babies was a twin compared to 1 in every 53 babies in

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1980.[5] Triplet /+ births have been reported at just over 150 per 100,000 births.[6] Some have called this "an epidemic of multiple pregnancies."[7] The rise in the proportion of infants born prematurely or at low birth weight has become a significant public health concern. (Table 1.) Because they comprise a much larger portion of infants born prematurely and at lower birth weights, twins, but not triplets, have impacted trends of perinatal health indicators.[8]

Table 1. Gestational age and birthweight characteristics by plurity: United States, 2009*

	All Births	Singletons	Twins	Triplets	Quadruplets	Quintuplets and higher order multiples[1]
Number	4,130,665	3,987,108	137,217	5,905	355	80
Percent very preterm[2]	2.0	1.6	11.4	36.8	64.5	95.0
Percent preterm[3]	12.2	10.4	58.8	94.4	98.3	96.3
Mean gestational age in weeks (SD)	38.6 (2.5)	38.7 (2.4)	35.3 (3.6)	31.9 (3.9)	29.5 (4.0)	26.6 (4.6)
Percent very low birthweight[4]	1.5	1.1	9.9	35.0	68.1	86.5
Percent low birthweight[5]	8.2	6.4	56.6	95.1	98.6	94.6

*Adapted from the 2009 CDC/NCHS, national vital statistics System[6]
1 Quintuplets, sextuplets, and higher order multiple births are not differentiated in the national data set.
2 Very preterm is < than 32 completed weeks of gestation.
3 Preterm is < 37 completed weeks of gestation.
4 Very low birthweight is < 1,500 grams.
5 Low birthweight is < 2,500 grams.

Evidence for HM feeding of premature and low birth weight infants is overwhelming. The use of HM in the NICU has been prioritized by major organizations including The American Academy of Pediatrics, The National Institutes for Child Health and Development, and The Academy of Breastfeeding Medicine. Percentages of infants receiving any breastmilk during their NICU stay and of those being discharged receiving any breastmilk are now benchmarked in hospital NICUs. Given the rise in multiple birth and prematurity, health care professionals can do much to support and guide these high-needs infants and their mothers to initiate and sustain HM feeding.

NICU Support During the Antepartum

A number of support measures can be provided during the antepartum by NICU staff and other health care professionals. Many mothers of multi-fetal pregnancies are hospitalized on bed rest for extended periods during the antepartum. These mothers often beseech interaction, thus providing abundant opportunities for perinatal education.

Because hospitalization often occurs in high risk settings where neonatal intensive care services are readily available and strategically located, NICU clinicians who will care for these infants have relatively easy access to the mothers and their families. A multidisciplinary team comprised of NICU and antenatal unit staff, neonatologists, lactation consultants, perinatal educators, occupational therapists and registered dietitians may be assembled to assess medical and educational needs. A systematic approach to the delivery of healthcare education geared specifically to individual and family needs may significantly improve outcomes. Expectations for delivery, early infant care and feeding are topics that should be addressed. If possible, a trip to the NICU with explanations of equipment and procedures may be very helpful to select mothers when performed in a gentle and thoughtful manner.

There is a wide variation in populations relating to rates of breastfeeding initiation in multiples. These range from 40-90% in twins alone.[9] Mothers expecting multiples may not consider breastfeeding purely due to logistical concerns. Therefore, research-based information about the importance of human milk-feeding should be provided. Breastfeeding education during the antepartum will allow mothers of multiples to make informed decisions and to approach infant feeding with more confidence.

Mothers of multiples are more likely to become pump-dependent. Therefore, preparation and anticipation for milk expression should be addressed. Pump-dependent mothers of premature infants are at risk for low milk volumes and discontinuation of HM feeding.[10,11] Preparation for HM feeding might include discussion and demonstration of hospital grade electric breast pumps and accessories, frequency and duration of milk expression, expectations of volume, storage, transport and feeding of HM to premature infants. Becoming familiarized with these elements prior to the birth of their babies will reduce fear and facilitate more positive outcomes.

Along with education regarding breastfeeding and infant nutrition, an assessment of maternal prenatal nutrition should be conducted. Mothers of multigestional pregnancies should have specific goals for daily caloric and nutrient intake given that they are at greater risk of micronutrient deficiency.[9] Attention to specific nutritional needs during multi-fetal pregnancies has been associated with improved neonatal outcomes[12] and increased initiation of breastfeeding.[13]

Early Postpartum: The First Few Days

Mothers of multiple infants are faced with all of the usual challenges experienced by mothers of singletons. However, a unique set of impediments affect multiples over singletons. Coupled with the increased potential for prematurity and its associated feeding difficulties, mothers of multiples often must deal with a variety of physical and psychological issues.

In the early postpartum, a mother may be besieged with infirmity related to pregnancy or the intrapartum. Serious illness (such as pregnancy-induced hypertension or HELLP syndrome), weakness due to heavy blood loss or bed-rest induced cardiovascular / muscular de-conditioning, surgical recovery, medication therapy and other physical stressors are often the case.

The psychological impact of caring and concern for multiples may be more than a mother can handle in the first few days and weeks. Mothers may be troubled with issues of separation, anxiety, grief and indecision. For example, the process of maternal / infant attachment may be at risk due to geographic separation. Mother is separated from her infants and her infants may be separated from one another due to differing needs in the level of intensive care.[14]

In situations where there has been a loss of one or more of the infants, a bereaved mother of multiples must cope with making decisions about disposition of remains. Concurrently, she may be struggling with anxiety, worry and conflict regarding attachment to the surviving infant(s).[15] Feelings of guilt often plague newly delivered mothers as they question whether there might have been something more they could have done to extend the gestational period.

Because these physical and psychological issues are associated with poor milk production and late onset of lactation, breastfeeding support provided by post-partum and NICU caregivers must begin as soon as possible after birth.

Begin Lactation Support as Soon as Possible after Delivery

For all mothers, the first 14 days post delivery is a critical period for the establishment of milk production.[16] It is imperative that pumping and manual expression of milk be initiated ASAP after delivery of premature infants. The combination of hand (manual) expression with breast massage and pumping has been shown to increase milk production and is highly recommend by practitioners[17] and by the Human Milk Banking Association of North America (HMBANA) as best practice.[18] Use of a hospital grade pump with small collection containers (such as those manufactured by Medela) will allow for optimal collection of milk. Although there are several types of hospital grade pumps, one in particular is able to provide a specific pattern of stimulation known to be closely associated with optimal subsequent milk volumes when used in the post delivery stage of lactogenesis I.[10,16] In situations where mother is too weak or ill, hands-on pumping support may be required to facilitate early initiation. Caregivers may hold breast shields in place and operate the pump. This may be done easily while mother is resting in side-lying position.

As soon as even a few drops of colostrum can be obtained, it should be fed to the infants orally by any means appropriate to their care. Ideally, colostrum should be given in the order it was expressed. Oropharyngeal administration of colostrum should be considered for those infants of extremely low birth weight who are not yet able to begin enteral feeding.[19,20] Mothers may be instructed on this relatively simple yet extremely important method of providing care to the baby. Not only is frequent oral mucosal coating of colostrum medically significant in reducing or avoiding intestinal inflammation, but also psychologically important to the mother in terms of her ability to care, interact and bond with her babies. Skin-to-skin mother care initiated as soon as possible after delivery will also facilitate milk production and attachment for these at-risk mothers.

Later Post-partum: The First Few Weeks

Mothers of multiples are often breast pump dependent for several weeks or even months. A hospital grade electric breast pump is recommended for long-term breast milk expression.[21] Insurance companies will often pay for the rental of a hospital-grade breast pump during the infant's hospitalization and until direct breastfeeding is well established. Intensive support for human milk feeding will be required during the infants entire hospital stay.[22] Following maternal discharge from the hospital, the role of the NICU staff becomes the primary source of education and support for the family of multiples. The family may be struggling with time constraints, stress, challenging infant feeding schedules and the psychological implications discussed earlier.

One of the obstacles of HM feeding for mothers of multiples vs singletons, is the distribution of expressed breast milk to their infants in cases where maternal milk supply is an issue. Mothers may have difficulty determining whether to give all HM to the sickest infant, to rotate exclusive HM feedings or to distribute available milk evenly amongst all. The NICU staff can assist mother in making these often difficult and critical decisions. An inverse dose-response relationship between the amount of human milk received and short or long-term morbidity has been demonstrated. The higher the doses of human milk, the lower the risk of health problems to the infant.[10] Furthermore, there is evidence of critical periods for human milk feeding where infant formula should be avoided. These may be the first 14 or 28 days of extra-uterine life, depending on the gestational age of the infant.[10] NICU staff diligence in supporting the breastfeeding mother of multiples can reduce the need for having to make these tough decisions regarding milk distribution.

Another decision that NICU staff can assist mother in making is the dietary choice of HM fortifier. If the infants are at very low birth weight and extremely premature, chances are that HM fortifier will be necessary. The NICU team should consider the use of human milk-based HM fortifier for these infants. Exclusive HM infant diets are associated with less morbidity and significantly lower rates of necrotizing enterocolitis (NEC) compared to those diets which include bovine milk-based products.[23] Furthermore, the use of human milk-based HM fortifier may reduce the cost of medical care by preventing NEC.[24] Although expensive, mothers may wish to consider this option and should be educated about its benefits and availability.[25]

There are a number of other measures NICU staff may employ to support mothers of multiple premature infants in their effort to provide human milk over the weeks of hospitalization.
- Have a NICU policy in place that will guide the staff in supporting these mothers. The staff needs to be consistent in giving advice.
- Encourage mothers to provide as much infant care as possible when they are visiting the NICU.
- Keeping the infants together in a cluster may help with attachment. If possible, co-bedding may facilitate attachment for the mother and reduce the level of stress for the infants. This may improve physiologic stabilization and assist with the initiation of breastfeeding.[26]
- Encourage mother to pump near her babies; create a cozy environment (low lights, relaxed positioning).
- Encourage skin-to-skin positioning in dark quiet areas where mom and babies can relax. When an infant is quiet and alert, encourage mother to hand express drops of milk onto its lips and tongue.
- Keep an eye out for post partum depression. These mothers are at greater risk.
- Be sure there is a support network available to her. Emphasis must be placed on intensive support and encouragement for the continuation of HM feeding throughout an infant's hospital stay.[22] Consider a support group for breastfeeding in the NICU.
- Recommend upper body massage therapy. This may facilitate milk ejection, thus greater volume when performed during milk expression.
- Lactation consultant services should be available daily and milk volume assessments should be monitored. Check function of mother's breast pump periodically.

Approaching Discharge

Length of hospitalization is a risk factor for HM feeding of premature babies. In one study, length of stay was found to be the most important factor influencing breastfeeding in premature singletons. The longer the hospitalization, the more likely the infant would be discharged formula feeding.[27,28] However, in a subgroup of multiples, lower gestational age (and thus longer hospitalization) significantly increased the probability of being breastfed.[27] Another study determined that multiple birth was a predictor of human milk feeding discontinuation by post-partum week 12.[28]

Pump dependency may last well beyond hospital discharge. Breastfeeding mothers need to know that their infants may not be fully capable of efficient milk transfer via exclusive direct breast feedings until they are close to or even beyond the time when they would have reached full term gestational age. Mothers will need help in planning for continued milk expression at home while bottle or alternate methods of feeding will likely be required for some or all of the infants.

As the infants approach hospital discharge, it is important for NICU staff to recognize additional challenges faced by mothers of multiple premature infants. These challenges can affect HM feeding outcomes. Infants of multiple gestations are often staggered in their hospital discharges. This can place emotional and physical strain on the mother and her family. Travel to and from the hospital coupled with the fatigue associated with full time infant care may wear a mother down. Fear of emotional disconnect in claiming the infants as her own may also complicate the process and anticipation of discharge for mother.[14] NICU staff must recognize these feelings and be able to address them with mother. The need for help and assistance at home should be emphasized.

Resources for Patient and Staff

There are a number of breastfeeding and general resources available for mothers of multiples and healthcare professionals alike. These include, but certainly are not limited to, the following:
- Twins to Quints: The Complete Manual for Parents of Multiple Birth Children, Edited by Rebecca L. Moskwinski, MD, (2002, Harpeth House Publishing)
- National Organization of Mothers of Twins Clubs, Inc. (A support group for parents of twins and higher order multiples), http://www.nomotc.org
- Multiples: More of Everything. Two volume video set, Injoy Birth and Parenting Education, 2009. 7107 La Vista Pl. Longmont, CO 80503

- Human Milk Banking Association of North America (HMBANA), https://www.hmbana.org

In Conclusion

NICU staff is in a unique position of influence over new parents whose infants are hospitalized for extended periods. The provision of HM is a critical element in the health and health care of infants, yet it remains a highly vulnerable matter. Knowledge and support of breastfeeding and human lactation should be a basic requirement for all members of hospital and community healthcare teams. During the Third Annual Summit on Breastfeeding, it was suggested that The Joint Commission, the largest health care accrediting body in the United States, require all hospitals who provide perinatal care, to meet the UNICEF/World Health Organization's Ten Steps to Successful Breastfeeding.[29] Although neonatal intensive care units may be exempt from some of its elements, patient and staff appreciation of the ten steps would undoubtedly spill over and influence best practice of human milk feeding in the NICU.

References

1 National Center for Health Statistics. Vital Statistics of the United States, 1917–1993. Available from: http://www.cdc.gov/nchs/products/vsus.htm.

2 National Center for Health Statistics. Vital statistics rates in the United States, 1940–1960. Washington, DC: U.S. Department of Health, Education, and Welfare, Public Health Service. 1968.

3 Taffel SM. Health and demographic characteristics of twin births: United States, 1988. National Center for Health Statistics. Vital Health Stat 21(50). 1992.

4 Martin JA, Park MM. Trends in twin and triplet births: 1980–97. National vital statistics reports; vol 47 no 24. Hyattsville, MD: National Center for Health Statistics. 1999.

5 Martin JA, Hamilton BE, Osterman MJK. Three decades of twin births in the United States, 1980–2009. NCHS data brief, no 80. Hyattsville, MD: National Center for Health Statistics. 2012.

6 Martin JA, Hamilton BE, Ventura SJ, et al. Births: Final data for 2009. National vital statistics reports; vol 60 no 1. Hyattsville, MD: National Center for Health Statistics. 2011.

7 Newman RB, Luke B. Multifetal pregnancy: A handbook for care of the pregnant patient. Philadelphia, PA: Lippincott William & Wilkins. 2000.

8 Blondel B, Kogan MD, Alexander GR, Dattani N, Kramer MS, Macfarlane A and Wen SW. The impact of the increasing number of multiples births on the rates of preterm birth and low birthweight: an international study. Am J Pub Health 2002;92(8):1323-1330.

9 Flidel-Rimon O, Shinwell ES. Breast feeding twins and high multiples. Arch Dis Child Fetal Neonatal Ed. 2006 Sep;91(5):F377-80.

10 Meier PP, Engstrom JL, Patel AL, Jegier BJ, Bruns NE. Improving the use of human milk during and after the NICU stay. Clin Perinatol. 2010 Mar;37(1):217-45.

11 Hill PD, Aldag JC, Chatterton RT, Zinaman M. Comparison of milk output between mothers of preterm and term infants: the first 6 weeks after birth. J Hum Lact. 2005 Feb;21(1):22-30.

12 Goodnight W, Newman R; Society of Maternal-Fetal Medicine. Optimal nutrition for improved twin pregnancy outcome. Obstet Gynecol. 2009 Nov;114(5):1121-34.

13 Friedman S, Flidel-Rimon O, Lavie E, Shinwell ES. The effect of prenatal consultation with a neonatologist on human milk feeding in preterm infants. Acta Paediatr 2004;93:775-8.

14 Leonard LG. Breastfeeding higher order multiples: enhancing support during the postpartum hospitalization period. J Hum Lact. 2002 Nov;18(4):386-92.

15 Pector EA. How bereaved multiple-birth parents cope with hospitalization, homecoming, disposition for deceased, and attachment to survivors. J Perinatol. 2004 Nov;24(11):714-22.

16 Meier PP, Engstrom JL, Janes JE, Jegier BJ, Loera F. Breast pump suction patterns that mimic the human infant during breastfeeding: greater milk output in less time spent pumping for breast pump-dependent mothers with premature infants. J Perinatol. 2012 Feb;32(2):103-10. Epub 2011 Aug 4

17 Morton J, Hall JY, Wong RJ, Thairu L, Benitz WE, Rhine WD. Combining hand techniques with electric pumping increases milk production in mothers of preterm infants. J Perinatol. Nov 2009;29(11):757-764.

18 Jones F. Best practice for expressing, storing and handling human milk in hospitals, home, and child care settings. Fort Worth, Texas: HMBANA;2011.

19 Rodriguez NA, Meier P, Groer M, and J Zeller. Oropharyngeal administration of colostrum to extremely low birth weight infants: Theoretical perspectives. J Perinatol. 2008;29:1-7

20 Spatz D and T Edwards. The use of Colostrum and Human Milk for Oral Care in the Neonatal Intensive Care Unit. Accessed in 2012 from http://www.Medela.com .

21 Sisk P, Quandt S, Parson N, Tucker J. Breast milk expression and maintenance in mothers of very low birth weight infants: supports and barriers. Journal of human lactation : official journal of International Lactation Consultant Association. Nov 2010;26(4):368-375.

22 Ackerstom S, Asplund I, Norman M. Successful breastfeeding after discharge of preterm and sick newborn infants. Acta Paediatr 2007;96:1450-4.

23 Sullivan S, Schanler RJ, Kim JH, Patel AL, Trawöger R, Kiechl-Kohlendorfer U, Chan GM, Blanco CL, Abrams S, Cotten CM, Laroia N, Ehrenkranz RA, Dudell G, Cristofalo EA, Meier P, Lee ML, Rechtman DJ, Lucas A. 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 Apr;156(4):562-7.

24 Ganapathy V, Hay JW, Kim JH. Costs of necrotizing enterocolitis and cost-effectiveness of exclusively human milk-based products in feeding extremely premature infants. Breastfeed Med. 2012 Feb;7:29-37.

25 Prolacta Bioscience. 605 E. Huntington Dr., Ste. 101, Monrovia, CA 91016 www.prolacta.com.

26 Nyqvist K, Lutes L. Co-bedding twins: a developmentally supportive strategy. J Obstet Gynecol Neonatal Nurs. 1998;27:450-456.

27 Kirchner L, Jeitler V, Waldhör T, Pollak A, Wald M. Long hospitalization is the most important risk factor for early weaning from breast milk in premature babies. Acta Paediatr. 2009 Jun;98(6):981-4.

28 Hill PD, Aldag JC, Zinaman M, Chatterton RT. Predictors of pre-term infant feeding methods and perceived insufficient milk supply at week 12 postpartum. J Hum Lact 2007;23:32-8; quiz 39-43.

29 Third Annual Summit on Breastfeeding. First Food: the Essential Role of Breastfeeding. Breastfeed Med 2011;6:243-366.

St Alexius Meets Needs of Delivery Unit with Informatics System

St. Alexius Medical Center, located in Hoffman Estates, IL and part of Alexian Brothers Health System, is a 330-bed community hospital that performs over 3,000 births per year. This past October, St. Alexius delivered the 35 millionth baby (Kithana Vasana Syharath) using GE Healthcare's Centricity Perinatal system, an electronic clinical information system that tracks crucial patient data from the expectant mother's first prenatal visit to post-delivery. Today, three out of every five babies in the US are born using Centricity Perinatal.*

Ensuring a healthy start
Expectant moms usually receive lots of advice to ensure healthy pregnancies, but it's often the doctors' and nurses' "behind the scenes" work and advances in medical technology that keep both mom and baby safe. With Kithana, Centricity Perinatal was used to keep track of her and her mom from the moment they settled down on a bed in the labor and delivery unit. She was first observed through a fetal monitor by clinicians, as data was recorded in the system. Although the data was displayed at a monitor at her mom's bedside, it was also accessible remotely to doctors and nurses across the hospital campus. Kithana's and her mom's record was being updated throughout her birth and their entire hospital stay until they were both ready to go home for the first time as a family.

The paperless system can also be used in neonatal intensive care units (NICUs). It can do so because it is scalable and clinicians can implement changes quickly as care situations evolve. Since all data is entered, stored and accessed electronically, the system can help reduce discrepancies that may lead to errors.

Informatics for better patient care
As a level 3 NICU with a high volume of annual deliveries, St Alexius counts on a robust informatics system to manage patient health and keep up with department workflows. Christine Van Duys, St Alexius' RNC and system manager, said St Alexius implemented Centricity Perinatal for labor and delivery in 2000, then for the NICU in 2010. According to Van Duys, some of the biggest benefits of using the system include automatic vital sign capture and ease of use.

"With GE's system, vital signs are automatically captured; patient monitors are interfaced into the system. That's much less documentation that the nurses have to do," says Van Duys. She also notes that the system's fetal monitoring surveillance is

much more tuned to nurses' work needs, as you're able to view all the fetal monitoring strips at once. The hospital has already experienced a notable decrease in charting time, which allows the nurses and physicians to spend more time attending to patient care.

Due to the success the hospital has had with the perinatal system in labor and delivery and in the NICU, Van Duys says they hope to implement Centricity in St Alexius' mother-baby unit, which will fully utilize the functionality of the Centricity Perinatal Mother-Baby Link. The Mother-Baby Link automatically populates the infant's record with relevant maternal and delivery information including vital data from caregivers and records from other units. Neonatologists can document daily physical exams and narrative notes, while viewing relevant reports from nursing, all in a single screen. Data can also be entered manually and updated as necessary. The discharge summaries begin building upon admission, pulling vital data from nursing and combining it with neonatologists' assessments and notes.

At St Alexius, Centricity Perinatal is a crucial part of the hospital's plan to utilize health informatics in a way that ultimately makes a positive impact on the patient level. The system meets the demands of a high-performing perinatal unit and improves efficiencies across the entire department.

*Estimated US birth rate is based on data from Centers for Disease Control and Prevention (CDC) http://www.cdc.gov/nchs/births.htm and applicable customer data.

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Penile Cyst in a Neonate: Case Report and Review of Literature

Dinushan Kaluarachchi, MD; Andreea Marinescu, MD; Benamanahalli Rajegowda, MD

Abstract

Penile cysts in newborn infants are uncommon. They are benign, asymptomatic and are present at birth. Their appearance at the tip of the penis concerns the parents and medical care providers on its clinical significance as well as it's management. We report two cases presented within few weeks. In one infant (Case 1), the lesion fell off after a few weeks without any intervention, whereas in the other infant (Case 2), the cyst was removed during circumcision. The cyst was submitted for histopathological studies. It was reported as Epidermal Inclusion Cyst.

Introduction

Penile cysts in newborn infants are uncommon. Though uncommon, the most commonly occurring penile cyst in a newborn is an epidermal inclusion cyst. We report two cases presented within few weeks at Newborn Nursey of Lincoln Medical and Mental Health Center, NY, USA and a review of literature.

Case 1

A newborn male infant was noted at birth to have a cystic to firm lesion at the tip of the penis (Figure 1). He was born at full term by vaginal delivery to a 25 year old African-American mother. Pregnancy including prenatal sonograms and the delivery was uncomplicated. Newborn examination revealed faintly yellowish, cystic to firm lesion measuring 5 x 5 mm, rounded and situated at the tip of the penile portion of the prepuce skin. It was fixed, non-mobile, non-tender, without evidence of inflammation. The urethral meatus was barely seen anterior to the lesion. There was good urinary stream. There was no evidence of other congenital abnormalities and the rest of the examination was normal.

Figure 1. showing the cyst

Figure 1a. showing penile portion, the cyst fell off

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Infant was seen by a pediatric urologist, with diagnosis of penile inclusion cyst. Treatment options of surgical excision, circumcision, aspiration of the cyst and just observation were discussed. Parents decided to observe without any surgical intervention. Infant was followed up at outpatient clinic. According to mother, the cyst fell off after 5 weeks without any bleeding or infection, leaving an irregular prepuce skin with clearly seen meatal opening (Figure 1a). We couldn't secure the cyst for the histopathological studies which could have provided us the diagnosis and also help in differential diagnosis.

Case 2

A newborn male infant was noted to have a same type of cystic lesion at the tip of the penile portion of the prepuce, but smaller in size compared to previous case, with good urinary stream (Figure 2). He was born at full term by normal vaginal delivery to a 34 year old African mother. Prenatal sonograms were normal and the delivery was uncomplicated. In this case mother gave consent for circumcision. A piece of circumcised skin along with the cyst was submitted for histopathological studies, which revealed (Figure 2a) under the layers of cyst, pearls of keratinized material, stratified epithelial cells and dilated sweat glands suggestive of epidermal Iinclusion cyst. The diagnosis is epidermal inclusion cyst.
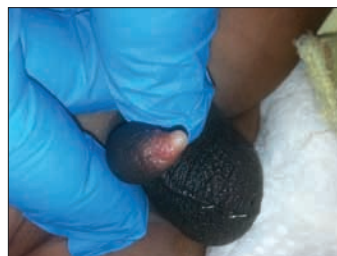
Figure 2. showing the cyst
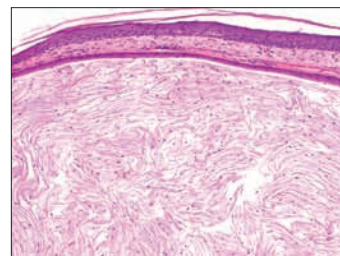
Figure 2a. showing histopathological picture

Discussion

In newborns, though uncommon, the most commonly occurred penile cyst is the epidermal inclusion cyst. These cysts are typically benign, occur all along the penile and the scrotal raphe, and most often are congenital and also acquired. In a congenital form it is presented at birth, though etiology is unknown, but it's believed to be an abnormal embryonic closure of the median raphe.[1] The definitive diagnosis is made by histopathological studies of the cyst. As demonstrated in our case in Figure 2a, demonstrating inclusion of dermoid elements in the cyst and

Universal Newborn Eye Screening

A paper was recently presented at the EPOS conference, Analysis of Universal Eye Screening in 3,573 Healthy Full-term Neonates, by Li-Hong, et al. In the abstract, the authors stated, the objective of their study was to establish the effectiveness of a newborn eye screening program for detecting ocular pathology in the healthy, full-term neonate. The authors said, It is anticipated that early detection may lead to treatments that can prevent blindness and visual disability. Methods: Neonates were screened within seven days after birth using flashlight, retinoscope, hand-held slit lamp microscope and wide-angle digital retinal image acquisition system (RetCam II). External eye, pupillary light reflex, red reflex, the opacity of refractive media, anterior segment, and posterior segment were examined. Results: A total of 3,573 healthy neonates were enrolled in the screening program, with detection of 848 abnormal cases (23.73%), including 769 retinal hemorrhage (21.52%). There were 215 cases of significant retinal hemorrhage (III degree), representing 6.02% of the total. In addition, 67 cases (1.88%) involved macula hemorrhage. The other 107 cases (2.99%) included: subconjunctival hemorrhage, lacrimal duct obstruction, congenital microphthalmos, congenital corneal leucoma, posterior synechia, persistent pupillary membrane, congenital cataract, enlarged C/D ratio, retinoblastoma, optic nerve defects, abnormal distribution of macular pigment, peripheral retinopathy, exudative retinopathy, and albino-like fundus changes. The authors concluded: Screening of all healthy newborns leads to detection of a significant number of ocular pathologies. RetCam photodocumentation is a safe, convenient, fast, and objective technique to screen newborns, leading to timely treatment and detailed follow- up observation of lesions.

The abstract noted: Clarity Medical Systems, Inc is the manufacturer of RetCam Ophthalmic Imaging Systems. Clarity had no knowledge, input, editorial review, etc over this article. Clarity is unaware of any risk or safety concern relative to the use of RetCam Ophthalmic Imaging systems in any use of this device reference in this article.

The RetCam Systems are FDA cleared for the following indications: • General ophthalmic imaging including retinal, corneal and external imaging; • Photodocumentation of pediatric ocular diseases including retinopathy of prematurity (ROP); • Screening for Type 2 pre-threshold retinopathy of prematurity (ROP) (zone 1, stage 1 or 2, without plus disease, or zone 2, stage 3, without plus disease) or treatment-requiring ROP, defined as Type 1 ROP (zone 1, any stage, with plus disease; zone 1, stage 3 without plus disease; or zone 2, stage 2 or 3, with plus disease) or threshold ROP (at least 5 contiguous or 8 non-contiguous clock
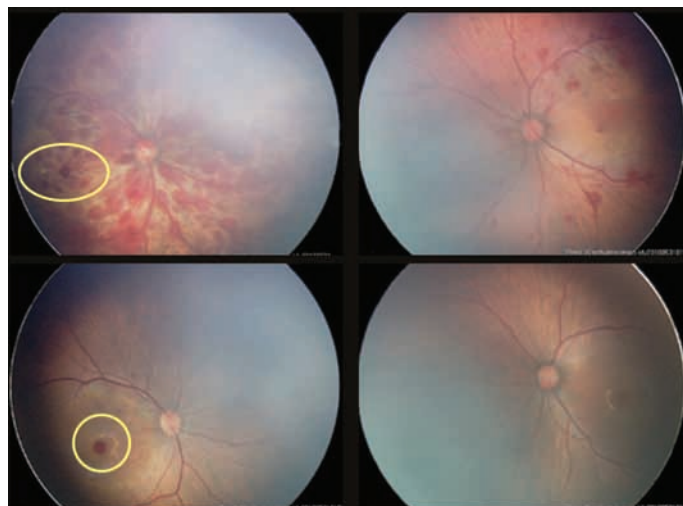
Fig. 1: Right eye, degree III retina hemorrhage extended to macula. Left eye, degree II retina hemorrhage. Follow up exam three weeks later, right eye macula hemorrhage not absorbed; left eye retina hemorrhage absorbed completely.
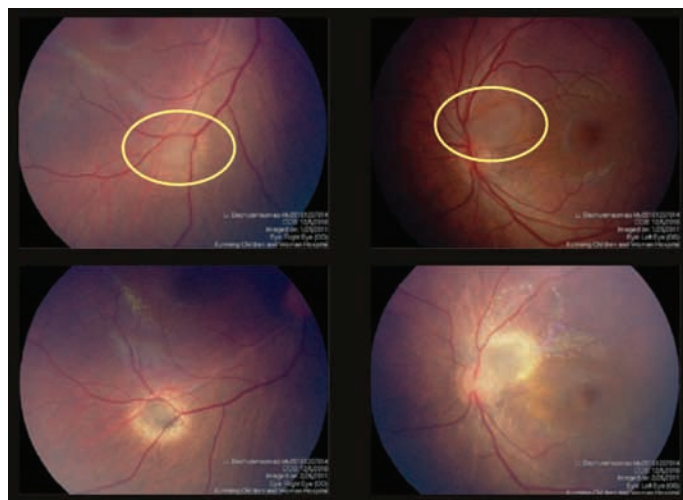
Fig. 2: Above graph: three days after birth during a routine screening, a retinoblastoma was found in both eyes.
Lower graph: A follow up exam using RetCam one month after birth, with a laser treatment 8 weeks after birth.

hours of stage 3 in zone 1 or 2, with plus disease) in 35-37 week postmenstrual infants.

References

1   Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. Archives of Ophthalmology 1988; 106(4):471-479.
2   Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity Randomized Trial. Archives of Ophthalmology 2003; 121(12):1684-1694.

The Evolution of Neonatal Resuscitation Devices

Kathleen Deakins, MSHA, RRT, NPS, FAARC; John Gallagher, BSHS, RRT-NPS

A small percentage of all infants require resuscitative measures during the transition to extra-uterine life. However for the 5-16% who do need intervention, ventilation is provided with the gold standard practice using bag and mask or similar resuscitation device.[1] Three types of resuscitation devices are used routinely to achieve the similar outcomes. The goal is to provide manual ventilation with positive pressure ventilation: by delivering peak inspiratory pressure (PIP) with or without positive end expiratory pressure (PEEP), continuous positive airway pressure (CPAP), oxygen, or sustained inflations.[2] Over the past five decades with advancement of medical technology, the inception of the Neonatal Resuscitation Program, and ongoing medical product development: self and flow inflating bags and t-piece resuscitators have evolved into the three primary devices used for neonatal resuscitation.

Today's newborn resuscitation and manual ventilation recommendations are defined in the American Academy of Pediatrics in the 6th Edition of Neonatal Resuscitation Manual. The type of resuscitation device chosen for use in clinical practice is dependent on many factors. The availability of equipment resources (interfaces), the skills and experience of trained caregivers, the availability of compressed gas and the estimated size of the patient may play a part in the decision to choose one device over another. Institutions around the globe are challenged by exposure to varying physical and economic resources and limitations that frequently drive their practices. It is practical to investigate different devices and techniques used to implement strategies to find out which one promotes the best outcomes. Because trends often influence regional preferences and result in adoption of specific devices, it is important to continue questioning what is the preferred method, device or practice that should be used to accomplish better-quality outcomes. Despite the growing research on resuscitation devices, no particular interface has proven to be superior to another.[3,4] The International Liaison Committee on Resuscitation advocates the use of guidelines and standards that incorporate using self inflating and flow inflating bags, while other regions prefer t-piece resuscitation devices if resources are available.[5] Regardless of the device chosen, the ability to provide PIP, PEEP, blow-by oxygen and CPAP and oxygen delivery and sustained inflations are important features to be considered when selecting a device for resuscitation.

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The positive and negative effects of resuscitation practices have been described in the literature for decades and continue to unfold over time. In earlier years, researchers confirmed that large tidal volumes delivered to premature lungs resulted in lung injury.[6] This led to the practice of controlling pressures with the hopes of decreasing delivered tidal volumes. Naik et al confirmed that cytokines were affected by positive pressure support with CPAP when applied to preterm lambs.[7] Jobe showed a reduction in acute lung injury in premature lambs when applying CPAP to infants at birth.[8] Despite the evidence surrounding benefits of CPAP or PEEP including stimulating surfactant production, improved lung mechanics, a decreased incidence of lung injury and the number of infants requiring intubation, there is not sufficient evidence to recommend it for use in every resuscitation.[1] By 2004, surveys related to resuscitation devices were being conducted to determine the mechanisms of breath delivery and consistency of pressures delivered by the three resuscitation devices.[9] While all devices used to manually ventilate infants are not created equal they do have one commonality: they are not entirely responsive to changes in compliance or resistance with or without consistent pressure and tidal volumes delivered may vary.[10] Based on evidence available, recommendations for the resuscitation device of choice continues to remain in the hands of the caregiver.

As early as ancient history, bag ventilation was simulated by forcing air into the lungs with a bellows device. By the mid 1950s, the concept and later evolution of the self inflating bag was developed. To date, self inflating manual resuscitators are used in routine practice in some delivery rooms and are fundamental resources found at every patient's bedside (for emergency use). They incorporate an already-inflated bag, a connector to attach a gas source, and a valve that releases gas to the patient's lungs with each squeeze. Gas enters the bag through a one-way valve which may entrain room air or mix with oxygen if attached to a gas source. The tidal volume delivered is dependent on the size of the bag, how much the bag collapses when compressed and how many fingers are used to squeeze the bag. The distinct advantage to using self inflating bags is that the bag maintains its shape without support and it can be used without a gas source and still function properly. The distinct drawbacks to self inflating manual resuscitators include the inability to provide a sustained inflation if desired, and failure to maintain positive end expiratory pressure (PEEP) without additional attachment of a flow resistor or PEEP valve.[1,11] Also the variability of the fractional delivered oxygen concentration (FDO2) measured

even at low flows (1-4 liters per minute) using a self inflating bag without a reservoir may result in higher-than-expected levels of oxygen being delivered under certain conditions which may create concerns during neonatal resuscitation.[12]

Flow inflating resuscitators are as beneficial for delivering sustained inflations, PIP, PEEP or CPAP during neonatal resuscitation.[10] A compressed gas source (flow) enters a collapsed bag, inflates the bag, and the amount of pressure is controlled by how much the bag is compressed, and an adjustable flow resistor or flow control valve located near a sealed patient connection. The bag (historically referred to as an anesthesia bag) remains inflated until it is squeezed, the flow source is disconnected, or the patient connection is broken. Upon squeezing a flow inflating bag over a specific period of time (inspiratory time), manual ventilation is accomplished with ease. Benefits of flow inflating bags include the ability to adjust PEEP and peak inspiratory pressure (PIP) with breath-by-breath pressure monitoring with a pressure manometer. Additionally, blow-by oxygen and CPAP can also be accomplished with simple adjustments. Historically, caregivers claimed that an "educated hand" could feel the compliance of the patient's lungs on the opposite end of the resuscitator in response to the change in the patient's compliance. This theory and practice has been handed down from caregiver to caregiver without sufficient validation. The tendency to create "excessive PEEP" or hyperinflation with higher pressures has been shown to result in iatrogenic lung injury defined by Salyer and colleagues.[13] This device, like others, requires practice and skill to accomplish targeted parameters. There is potential to achieve desired parameters through education, training and practice.

As early as the late 1980s, the t-piece resuscitator device evolved as the next generation of manual resuscitation devices with the promise of consistent delivery of PIP, PEEP, CPAP, and its ability to induce prolonged manual inflation. However it was not until 2004 that the American Academy of Pediatrics adopted its concept as an alternative device described in the neonatal resuscitation manual. By 2006 t-piece resuscitation gained popularity even though the most common resuscitation device in use across the US was the flow inflating bag; while in other areas the self inflating bags were still the prevalent.[14] T-piece resuscitation incorporates a gas source attached to portable resuscitator with adjustable PIP, and pressure relief setting. PEEP is adjusted on the circuit "T" closest to the patient connection. Pressures are displayed on the manometer of the face of the resuscitator. Manual ventilation, CPAP PEEP and free-flow/blow-by oxygen are available with simple adjustments in the setup. Researchers in the United Kingdom determined that the t-piece resuscitator was the most reliable device for delivering desired pressures at set times.[15] The most compelling benefit noted about the t-piece resuscitator was that it guarantees reliable and consistent ventilation pressures regardless of the specific medical discipline of the device operator.[16]

With each development of the resuscitation device came a comparison for consistency, accuracy and precision. In 2005, the t-piece resuscitator, flow inflating bag, and the self inflating bag were compared by evaluating each by different caregivers to determine which of three devices was more accurate, and which device had the ability to respond to adjusted target settings during use.[1] Bennett and colleagues found that the t-piece resuscitator when used on a patient model was superior

in its ability to achieve targeted pressures with precision and consistency when compared to the other two devices.[1] They also discovered that the operators' ability to adjust ventilating pressures took significantly longer with the t-piece resuscitator compared to the flow inflating bag and the self inflating bag . This was a critical finding because caregivers are frequently required to adjust ventilating pressures during neonatal resuscitation. Kelm et al found that the t-piece resuscitator could reliably provide the desired PEEP levels and do so with less variability than with flow inflating bags.[17] In Ireland, investigators compared the t-piece resuscitator, the flow inflating bag with a manometer, and the self inflating bag. Thirty-five subjects (physicians, nurses, and anesthetists), were asked to simulate ventilation by achieving target pressures.[18] Significant differences in the pressures were delivered by each device but no significant difference between the disciplines of providers was appreciated. The t-piece resuscitator and the flow inflating bag with the addition of a manometer provided accurate and reproducible pressures while the self inflating bag was not reliable. Furthermore, investigators cautioned the use of self inflating bags without a pressure manometer.[16]

The t-piece resuscitator has been found to operate with similar or improved precision and consistency when compared to other devices. A large multi-center National Institute of Child Health study targeted the use of CPAP in the delivery room and mandated that participants use a t-piece resuscitator for resuscitation.[19] Others set out to determine the tidal volume threshold for the efficacy of carbon dioxide detectors for its reliability during resuscitation using a t-piece resuscitator.[20] The t-piece resuscitator was gaining widespread use as a consistent means to achieving safe ventilating pressures.[21] As a review of literature dictates the basis for evidence, there is sufficient rationale to support using a t-piece resuscitator over other devices during the resuscitation of neonates if the equipment resources are available and proper training is completed. Industry leaders have identified important issues surrounding the variability of user-controlled nuances during manual ventilation. As cited by McHale and colleagues in the research regarding t-piece resuscitators, inspiratory time and ventilation rate are operator controlled and are susceptible to variation, especially because the t-piece resuscitator system does not need a built-in lag time to reset or refill (as in the case of hand-bag ventilation).[22] Careful consideration of these parameters is required to prevent excessive ventilation.

Neonatal resuscitation practices continue to evolve. With the development of each resuscitation device there have been improvements over the past several decades. Manual ventilation has accommodated and brought forth appropriately sized and better quality bags with valves, and masks. Evidenced by the number of flow or self inflating products, designs vary from simple bag-valve design to those with built-in pressure manometers and pressure relief valves. T-piece resuscitators have evolved into portable devices with adjustment in circuit length and improved design of the "t". Device hardware has also evolved and a simple completely portable flow driven t-piece resuscitator without hardware. Thus far, delivering consistent pressures during manual ventilation has been the focus during this evolution of manual ventilation during neonatal resuscitation. Opportunities for measuring the delivered volumes in the face of compliance and resistance changes is the next question to be answered that may impact the future of devices chosen and expected outcomes.

References

1. American Academy of Pediatrics. Special report neonatal resuscitation: American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatr 2010 126;5:1400-1413.

2. American Academy of Pediatrics. Special report neonatal resuscitation: American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatr 2010 126;5:1400-1413.

3. American Academy of Pediatrics. Special report neonatal resuscitation: American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatr 2010 126;5:1400-1413.

4. Ziderman DA, Bingham R, Beattie T, et al. Recommendations on resuscitation of babies at birth. Resuscitation 1998 37:103-110.

5. International Liaison Committee on Resuscitation. International neonatal resuscitation an excerpt from guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care: international consensus on science. 2000;106:E29.

6. Vyas h, field D, Milner AD, Hopkin IE. Determinants of the first inspiratory volume and functional residual capacity at birth. Pediatr Pulmonol 1986;2:189-193

7. Naik AS, Kallapur SG, Bachurski CJ, Jobe AH, Michna J, Kramer BW, Ikegami M. Effects of ventilation with different positive end expiratory pressure on cytokine expression in preterm lamb lung. Amer Journ of Resp and Crit Care Med 2001;164:494-8

8. Jobe AH, Kramer BW, Moss Tj, Newnham JP, Ikegami M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. Pediatr Research 2002: 52; 387-92

9. O Donnell CPF, Davis PG, morley CJ. Positive pressure ventilation at neonatal resuscitation: review of equipment and international survey of practice. Acta Pediatr 204;93:5 583-88.

10. Kattwinkel J, Stewart C, Walsh B, Gurka M, Paget-Brown A. Responding to compliance changes in a lung model during manual ventilation: perhaps volume rather than pressure should be displayed. 2009;123:e465-70.

11. American Academy of Pediatrics and the American Heart Association. Neonatal Resuscitation Textbook 6th Edition. 2011 75-78

12. Johnston KL, Aziz K. The self inflating resuscitation bag delivers high oxygen concentrations when used without a reservoir: implications for neonatal resuscitation. Respir Care 2009, 54;12:1665-1670.

13. Salyer J. Manual resuscitators some inconvenient truths Respir Care 2009 54;12:1638-1643.

14. Leone T, Rich W, Finer NN. Survey of delivery room resuscitation practices in the United States. Pediatr 2006;117:e164-e175.

15. Oddie, S., Wyllie, J., & Scally, A. (2005). Use of self-inflating bags for neonatal resuscitation. Resuscitation , Oct;67(1):109-12.

16. Roehr, C., Kelm, M., Fischer, H., Buhrer, C., Schmalisch, G., & Proquitte, H. (2010). Manual ventilation devices in neonatal resuscitation: tidal volume and positive pressure-provision. Resuscitation , Feb;81(2):202-5. Epub 2009 Nov 17

17. Kelm, M., Proquitte, H., Schmalisch, G., & Roehr, C. (2009). Reliability of two common PEEP-generating devices used in neonatal resuscitation. Klinische Padiatrie , Dec;221(7):415-8.

18. Hussey, S., Ryan, C., & Murphy, B. (2004). Comparison of three manual ventilation devices using an intubated mannequin. Archives of Disease in Childhood - Fetal & Neonatal Edition , Nov;89(6):F490-3.

19. Finer, N., Carlo, W., Duara, S., Fanaroff, A., Donovan, E., Wright, L., et al. (2004). Delivery roomcontinuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial. Pediatrics , Sep;114(3):651-7.

20. Garey, D., Ward, R., Rich, W., Heldt, G., Leone, T., & Finer, N. (2008). Tidal volume threshold for colorimetric carbon dioxide detectors available for use in neonates. Pediatrics , Jun;121(6):e1524-7.

21. Finer, N., Rich, W., Craft, A., & Henderson, C. (2001). Comparison of methods of bag and mask ventilation for neonatal resuscitation. Resuscitation , Jun;49(3):299-305.

22. McHale, S., Thomas, M., Hayden, E., Bergin, K., McCallion, N., & Molloy, E. (2008). Variation in inspiratory time and tidal volume with T-piece neonatal resuscitator: association with operator experience and distraction. Resuscitation, Nov;79(2):230-3. Epub 2008 Aug 8.

Maternal Intervention is Imperative for the Development and Maturation of the Preemie

Yamile C. Jackson, PhD, PE, PMP

For decades, the success of an NICU was measured by the survival rate of its patients. The healthcare team and the technology were responsible for providing (or not) all the medical, developmental, and nurturing care to the patient during hospitalization. If parents were "allowed" to visit, it was so they could foster a relationship with their baby, but only for few hours a day, because they were perceived as getting in the way of the job the healthcare team had to do.

Now the care has evolved to making sure that the baby has the best possible outcome when he or she survives prematurity. After an immense amount of work by researchers and professionals from diverse professional backgrounds globally, there is indisputable evidence that the parents, especially the mother, play a very important role in the medical and developmental outcome of the infant in the NICU.

While she's pregnant, the mother's womb meets four basic needs for her baby: breathing (oxygen), warmth, nutrition, and maturation/development. The absence of any of the first three is life ending so there is specific life-support provided by state-of-the-art technology for each need (ventilators, incubators, feeding pumps/IVs, etc). While development is a basic need it is not always life-threatening but defines the life conditions of the baby (and society at large) for a lifetime, including every degree of severity of many deficiencies that may surface years after leaving the NICU.

When the baby is born prematurely, the mother becomes the "technology" that works with the healthcare team to provide the fourth of the basic needs, enabling the baby to mature and develop as appropriately as possible. Contrary to previous belief, "building a relationship with her baby" is NOT the most important contribution that she offers to the convalescent infant. Her involvement, and that of the father, including holding the baby skin-to-skin, is proven to improve the physical, psychological, physiological and neurological development of the child, and has immeasurable benefits for the wellbeing of

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the adult. The relationship/bonding/attachment is crucial for both the baby and the parents, and is a natural result of proper and maximized parental involvement in the hospital and then at home.

Parents and the NICU staff are dealing with life and death situations and decisions every day and they are not necessarily worried about bonding or the long term consequences of prematurity at this time. Bonding is Love and a smooth transition into the new family, and these cannot be forced – they are fostered and happen naturally without much effort with the proper intervention. Each baby is born with a strong bond with the mother. The baby learned her scent through the amniotic fluid and recognizes her voice and the sounds heard in the womb. Detaching the baby from the mother and not introducing the father from birth deprive the baby from the only known source of comfort and protection leaving the child not only feeling lonely but in solitude.

The loaded question that new parents often ask (or should ask) is "what can I do to help my baby not only survive but develop all organs and systems including the proper maturation of the brain, while ensuring a loving relationship with me and smooth introduction into our family, so we can go home with the best possible future and in the shortest amount of time?"

The simplified answer is to work with the healthcare team and also practice Kangaroo Care as many hours a day as possible.

If Kangaroo Care were a medicine or a piece of equipment, every baby would already be prescribed this intervention, given the vast evidence of the benefits. In the US as in many industrialized countries, there is still the ill perception that Kangaroo Care is only beneficial in developing countries with limited access to high-tech equipment. In fact, babies receiving high-tech medical care also have to endure the stress conditions from which they were supposed to be protected by the womb, including noise, light, stress, pain, interruptions, invasive procedures, sleep cycles, etc. All these noxious stimuli affect the development of the neurological system, which is still immature, unable to adequately respond, and the foregoing can easily become threats that can leave short, medium and long term devastating and/or expensive consequences. It is the mother who can most effectively help the baby.

Kangaroo Care provides a kinder and gentler environment and is the most effective evidence-based intervention in terms of

Benefits of Kangaroo Care for the babies include:

- Less incidence and severity of infection (Charpak N, Ruiz-Pelaez JG, Figuero de Calume Z, Charpak Y., 1997).
- Accelerated autonomic and neurobehavioral development (Feldman R, Eidelman, 2003).
- Promotes self-regulation in premature infants: sleep wake cyclicity, arousal modulation, and sustained exploration (Feldman R, Weller A, Sirota L, Eidelman A., 2002).
- Consistently high and stable oxygen saturation levels, lower airway resistance, fewer apnea episodes, and an increased percentage of quiet sleep (Ludington- Hoe, Ferreira, & Goldstein, 1998).
- Stable temperature within normal thermal zone, heart rate, and respiratory rate (Ludington-Hoe et al., 2010).
- Reduced crying associated with painful procedures (Kostandy R, Ludington-Hoe SM, 2008).
- Breast milk is readily available and accessible, and strengthens the infant's immune system.
- The maternal contact causes a calming effect with decreased stress and rapid quiescence (McCain, Ludington-Hoe, Swinth, & Hadeed, 2005; Charpak et al., 2005).
- Reduced physiological and behavioral pain responses (Ludington-Hoe, Hosseini, & Torowicz, 2005).
- Increased weight gain (Charpak, Ruiz-Pelaez, & Figueroa, 2005)
- Enhanced attachment and bonding (Tessier et al., 1998).
- Positive effects on infant's cognitive development (Feldman, Eidelman, Sirota, & Weller, 2002).
- Less nosocomial infection, severe illness, or lower respiratory tract disease (Conde-Argudelo, et. al., 2003).
- Restful sleep (Ludington-Hoe et al., 2006).
- Earlier hospital discharge (London et al., 2006).
- Possible reduced risk of sudden infant death syndrome (SIDS) (see www.infactcanada.ca).
- Normalized infant growth of premature infants (Charpak, Ruiz-Pelaez, & Figueroa, 2005).
- May be a good intervention for colic (Ellett, Bleah, & Parris, 2002).
- Possible positive effects in motor development of infants (Penalva & Schwartzman, 2006).
- The critical stimuli to which the baby is exposed to during Kangaroo Care are:
  ◊ Vestibular: the chest movement of the breathing of the parent, and walking if allowed.
  ◊ Tactile: the skin and natural warmth of the parent.
  ◊ Olfactory: the scent of the parent and the maternal breast milk.
  ◊ Auditory: by the voices and heartbeat of the parent.

Benefits of Kangaroo Care for the parents include:

- Enhanced attachment and bonding (Tessier et al., 1998).
- Resilience and feelings of confidence, competence, and satisfaction regarding baby care (Tessier et al., 1998; Conde Agudelo, Diaz Rossello, & Belizan, 2003; Kirsten, Bergman, & Hann, 2001).
- Increased milk volume, doubled rates of successful breastfeeding and increased duration of breastfeeding (Mohrbacher & Stock, 2003).
- Physiologically her breasts respond to her infant's thermal needs (Ludington-Hoe et al., 2006).
- Profoundly beneficial for adoptive parents with critically ill preterm infant (Parker L, Anderson GC, 2002).

cost, sustainable results, and overall satisfaction. On the other hand, while it is a life-support necessity, there is no evidence that suggests that the incubator alone provides an appropriate overall environment for the developing infant.

What is Kangaroo Care?

The Kangaroo Care Method was invented in 1978 in Bogotá, Colombia, and consists of skin-to-skin contact between the adult and baby, from the time of birth when possible (from the delivery room or intensive, intermediate or basic care), and the nutrition based on breast milk. The US Institute for Kangaroo Care defines it as, "Kangaroo Care, Skin-To-Skin Contact, and Kangaroo Mother Care are terms that relate to the holding of a diaper clad infant bare-chest to bare-chest, ventral-surface to ventral-surface by the mother, father, or others" (www.usikc.org).

Skin-to-skin is not simply placing a stable baby on the chest of the mother or father. As with any other evidence-based medical intervention, the Kangaroo Care Method should not be left to the personal preference of the NICU staff but must be implemented as a standardized practice, with the necessary training of the staff and parents, including what it is, who can do it, what are the contraindications, warning signs, expected benefits, and recommended duration.

The newly formed United States Institute for Kangaroo Care is the primary source of information, resources and training in the US and it offers the Kangaroo Caregiver Certification Program that includes a 2 day intensive course in Kangaroo Care for professionals caring for pre-term and full-term babies. For more information visit www.usikc.org/events.html.

Kangaroo Position

It is standard practice in most NICUs to provide developmentally supportive positioning to the baby on the bed or in an incubator. For some reason, this is not always the case when the baby is placed in Kangaroo Care.

The basic component of the Kangaroo Position for the baby is specifically described in scientific literature. In the manual published by the World Health Organization in 2003 (http://goo.gl/9xJVU), it is explained as "strictly vertical with legs and arms outstretched and head in a lateral position on the mother's breast, to allow maximum exposure of the body area between the baby and mother or whoever is holding him/her." Known exceptions are those babies that are unable to be prone, so they may be positioned considering the individual circumstances.

Unfortunately, in the US the vast majority of the parents are unable to be present in the NICU around the clock, so the goal becomes to have every parent hold the baby in skin-to-skin contact for the length of the time they can be there, as long as the parent and the baby meet all the requirements. To achieve this, providing an ergonomic environment for the parent becomes just as important as the positioning of the baby.

The parent needs a comfortable chair (preferably one that reclines) with a foot stool. During the skin-to-skin session, parents are often asked to use their hands to hold the weight of the baby, ensure the proper posture of the baby for the length of the session, provide constant containment (ie, don't move your hands or the baby will wake up or become over-stimulated), provide boundaries, and make sure the leads/equipment/IVs are not dislodged and that the baby doesn't fall – then they are told

to relax and enjoy their special time with the baby. That is too much to ask from a parent when consistent and positive results are expected from periodic Kangaroo Care sessions. To support the parent to hold as long as possible, it is necessary to help them by providing a kangaroo wrap. The USIKC has compiled information about the different types of wraps that help facilitate Kangaroo Care (http://goo.gl/Sw3a8).

Duration of Kangaroo Care

For the baby and parent that have been given the green light to kangaroo, each session should be as long as possible and never less than one hour (one full sleep cycle) and may be offered by both parents several times a day. The great deal of scheduled nursing interventions may be performed while the baby is in kangaroo care, as well as breast feeding/pumping. In addition, and when appropriate, the professional knowledgeable in Kangaroo Care should help the parent learn to do the transfer alone while the nurse takes a supportive role.

According to the USIKC, preemies are "Kangarooed" for 6 months; therefore, parents must be fully trained in Kangaroo Care along with other interventions to be performed at home, before their baby is discharged from the NICU.

Dr Susan Ludington has compiled and annotated a biography that counts over one thousand entries in the area of Kangaroo Care and it is available in the USIKC website under "reference" (http://goo.gl/Ss9m3).

NICUs that practice Kangaroo Care in a consistent basis and with every baby/parent are not only providing the best possible care and outcome, but they are following the recommendation of The American Academy of Pediatrics, The Academy of Breast Feeding Medicine, UNICEF, the World Health Organization, the Neonatal Resuscitation Program, and the United States Institute of Kangaroo Care.

"Kangaroo Mother Care should begin as soon as possible after birth, be applied as continuous skin-to-skin contact to the extent that this is possible and appropriate and continue for as long as appropriate." (Nyqvist et al 2010 May Acta Paediatric) http://googl/luUpm.

dilated sweat gland. The acquired form has been identified in older children and adults with various sizes all along the penile and scrotal raphe. The acquired form also has been described as a complication of neonatal circumcision.[2] One should also consider mucoid cysts.[3,4] These cysts occurs when mucus secretions, smegma and squamous debris is entrapped between the inner tight prepuce skin of the penis under glans penis. It looks like a match stick, but it can be dislodged easily or sometimes it can be fixed, where as epidermal inclusion cysts are rarely dislodgable. Other conditions that must be diffentiated and to be ruled out are urethral diverticulum,[5] lipoma, dermoid cyst and occasionally, teratoma. The cysts don't cause any discomfort or obstruction to urinary passage. The appearance at birth is mostly cosmetic. Most of them will fall off without infection, as it occurred in our case number 1. Or it can be removed during circumcision after parental request. When it is done it should be submitted to histopathology to confirm the diagnosis, as shown in our case number 2. Parents should be reassured, however, if they have any concerns. Most pediatric urologists suggest circumcision to excise, surgical excision of the cyst or aspiration of the cyst. It is up to the medical care providers to explain to the parents of its benign nature and about providing non-intervention, ie, that time will take its course to solve the problem. If the problem persists, then the intervention is for the infant to be seen by the pediatric urologist, and further evaluation by them.

References

1   Suwa M, Takeda M, Bilim V, Takahashi K. Epidermoid cyst of the penis: a case report and review of the literature. Int J Urol 2000; 7: 431-3.
2   Okeke LI. Epidermal inclusion cyst as a rare complication of neonatal male circumcision: a case report. J Med Case Reports 2009; 3: 7321.
3   Cole LA, Helwig EB. Mucoid cysts of the penile skin. J Urol. 1976;115:397–400.
4   De Mendonca RP,Silva JL, Wroclawski ML, et al.Mucoid cyst of the penis: Case report and literature review. Can UrolAssoc J. 2010; 4: E155–E157.
5   Rawat J, Khan TR, Singh S, et al. Congenital anterior urethral valves and diverticula: Diagnosis and management of six cases. African Journal of Pediatric Surgery. 2009; 6: 102-105.

Milk Osmolality and Medications

The Journal of Perinatology recently published a paper, "Milk as a vehicle for oral medications: hidden osmoles" by Radmacher et al.* The authors said their objective was to measure the osmolality of common milk/medication combinations administered in the ICU, in that it is common to mix oral medications with milk feedings, and because many new milks and medications have entered the NICU since the 1980s, the last time the osmolality of oral and IV drugs were tested. Common milk/medication mixtures were analyzed for osmolality by freezing point depression. The authors found that only EleCare (30 kcal per oz) exceeded American Academy of Pediatrics recommendations for osmolality in its unadulterated states. The addition of multivitamins resulted in an osmolality that exceeded the recommended 400 mOsm kg^{-1} H2O. The cumulative addition of other medications resulted in some osmolalities >1000 mOsm kg^{-1} H2O. The authors concluded that the coadministration of medications with milk products should be evaluated as a potential contributor to gastrointestinal intolerance of feedings in preterm infants.

The authors obtained single bottles of 20, 22, 24 and 30 kcal per oz commercial formula. EleCare (Ross Products Division, Abbott Nutrition, Columbus, OH) was prepared from powder for 20 and 30 kcal per oz milks. Human milk samples were obtained and pooled for a representative specimen. Milk fortified to 24 kcal per oz with formula (Similac Special Care 30, also by Ross) was tested. A 20 ml volume of human milk or formula was chosen to simulate a feeding for a 1 kg infant at full volume feeds, and this volume was reduced to the working test volume.

Medications used for the ELBW patient were obtained and reduced to a quarter volume to match the feeding volume. The drugs, oral electrolytes such as sodium and potassium chloride, were tested for osmolality. The maintenance dose of caffeine was chosen, and aldactone and chlorothiazide were tested together.

The unadulterated milks were within the limits set by the AAP, except for EleCare 30, which had an osmolality of 565 mOsm kg^{-1} H2O. Many single medications had very high osmolalities, and the addition of liquid vitamins increased milk osmolalities well above the AAP's 400 mark. Sequential testing of milk with chronic diuretics, supplemental electrolytes and caffeine, revealed that all substantially exceed AAP recommendations. Phenobarbital was tested as a single drug additive in each milk and resulted in osmolalities from 644 to 776 mOsm kg^{-1} H2O. Milks with all additives resulted in osmolalities between 1500 and 2000 mOsm kg^{-1} H2O. Total osmolality of milks with added liquid vitamins was also past the recommended upper limit from the AAP.

The authors noted that infants in the NICU typically require more than one medication, and that almost all of them are prescribed vitamins on discharge. They also note that milk feedings are used to administer the medications. The authors note that feeding intolerance or NEC is associated with hyperosmolar feedings, and that high osmolar loads delay gastric emptying in LBW infants. The authors concluded: "In our study, the addition of vitamin drops, alone, sent all milks tested well over the AAP recommended osmolality limit of 400 mOsm kg^{-1} H2O. The multiple medication–milk mixtures tested were all well over 1000 mOsm kg^{-1} H2O. For infants receiving these mixtures, the risk for gastrointestinal compromise should be kept in mind… Infants that have experienced severe gastrointestinal complications may require the use of hydrolyzed milk products or elemental formulas for enteral nutrition. Additives to these formulas must be used cautiously owing to the effects each may have on the osmotic load. Healthcare professionals should consider options for dosing schedules, perhaps encouraging single medication administrations, so as few drugs as possible can be given in combination with feedings."

The Effects of Varying Protein and Energy Intakes on the Growth and Body Composition of Very Low Birth Weight Infants

Juan Antonio Costa-Orvay, Josep Figueras-Aloy, Gerardo Romera, Ricardo Closa-Monasterolo, Xavier Carbonell-Estrany.

Abstract

Objective: To determine the effects of high dietary protein and energy intake on the growth and body composition of very low birth weight (VLBW) infants.

Study design: Thirty-eight VLBW infants whose weights were appropriate for their gestational ages were assessed for when they could tolerate oral intake for all their nutritional needs. Thirty-two infants were included in a longitudinal, randomized clinical trial over an approximate 28-day period. One control diet (standard preterm formula, group A, n = 8, 3.7 g/kg/d of protein and 129 kcal/kg/d) and two high-energy and high-protein diets (group B, n = 12, 4.2 g/kg/d and 150 kcal/kg/d; group C, n = 12, 4.7 g/kg/d and 150 kcal/kg/d) were compared. Differences among groups in anthropometry and body composition (measured with bioelectrical impedance analysis) were determined. An enriched breast milk group (n = 6) served as a descriptive reference group.

Results: Groups B and C displayed greater weight gains and higher increases in fat-free mass than group A. Conclusion: An intake of 150 kcal/kg/d of energy and 4.2 g/kg/d of protein increases fat-free mass accretion in VLBW infants.

Introduction

The Nutrition Committee of the American Academy of Pediatrics suggests that, with optimal care and nutritional support, the growth rates of very low birth weight (VLBW) infants should be similar to those of fetuses of the same gestational age.[1] Nevertheless, despite advances in perinatal medicine and nutritional protocols,[2,3] it has not been possible to achieve this rate of growth in neonatal care units.[4-7] Postnatal growth restriction is associated with an increased risk of poor neurodevelopmental outcomes,[8-11] and inappropriate postnatal nutrition is an important contributor to growth failure.[12,13] The goal of obtaining appropriate intrauterine growth rates after birth has been successfully achieved with enriched diets, but these diets may lead to disproportionate increases in fat mass.[14] Energy supplied as carbohydrates is more effective than energy

supplied as fats in sparing protein oxidation in enterally fed low birth weight (LBW) infants.[15] At isocaloric intakes, carbohydrates are more effective than fats in enhancing growth and protein accretion in enterally fed LBW infants.[16] However, a diet with high-energy and high-carbohydrate content also results in increased fat deposition.[16]

To better define the macronutrient requirements of these infants, the increase in lean body mass should be taken into consideration in addition to weight gain. The ratio of lean body mass to fat mass in the weight gained depends on the protein and energy ratio in the diet. If energy and protein intakes are inappropriate, weight gain and the rate of increase in length and head circumference are reduced;[17] however, if protein intake is appropriate, a relatively higher energy intake may enhance the rate of increase in skinfold thickness,[17] which suggests that the excess energy is stored as fat.[18] However, Fairey et al.[19] did not show any difference in the proportion of fat to lean tissue gained in groups with a higher protein-to-energy ratio (3.2 g/100 kcal vs. 2.6 g/100 kcal).

Table 1 Baseline characteristics and complications prior to the beginning of the study

	Breastfed (n = 6)	Group A (n = 8)	Group B (n = 12)	Group C (n = 12)
Characteristics of the newborns				
Born in the hospital	5	8	11	9
Male gender	4	2	5	9
Cesarean section	4	7	11	8
1-min Apgar ≤4	1	3	2	2
5-min Apgar ≤8	3	4	2	2
Resuscitation (endotracheal intubation)	0	4	1	3
Prenatal corticosteroids	4	8	10	9
Complications of the newborns				
Respiratory distress syndrome	4	5	3	8
Mechanical ventilation	3	5	2	7
Patent ductus arteriosus	1	4	1	3
Sepsis	2	1	3	3
Necrotizing enterocolitis	2	0	0	0
Intraventricular hemorrhage	2	1	1	0
Parenteral nutrition > 7 days	2	3	3	3

The aim of this study was to explore the effects of high protein (4.2 to 4.7 g/kg/day) and high energy (150 kcal/ kg/day) intakes on the growth and body composition of VLBW infants. Our hypothesis was that supplemented formula would be well tolerated and would increase weight and lean body mass in preterm infants compared to newborns who did not receive supplementation.

Subjects and Methods

Subjects: Thirty-eight preterm (gestation of 32 weeks or fewer) newborns with weights below 1500 g and who were appropriate for gestational age were included in the study. The newborns were admitted to the neonatology ward of Hospital Clinic in Barcelona, Spain. Their baseline characteristics and complications of prematurity for each study group are shown in Table 1, while the compositions of the enteral diets of each study group are shown in Table 2. All of the newborns were free of any complications when they were enrolled in the study; further, they had recovered their birth weight and were gaining weight. At the beginning of the study, they received only enteral nutrition without IV perfusion.

Mechanical ventilation and parenteral nutrition were discontinued at least five days before the beginning of the study. Exclusion criteria were intrauterine growth restriction, chromosomal abnormalities, malformations, chronic diseases or need for oxygen treatment. Written informed parental consent was obtained prior to enrollment in the study. The Neonatology Ethics Committee of the Hospital Clinic approved the study.

Methods

Breastfed infants served as a reference group (group BM; n = 6). The macronutrient content of breast milk in this study (Table 2) was obtained using the reported data on milk from mothers of premature infants during early lactation.[20] Following the standard practice, the milk from the mother was enriched using Enfamil Human Milk Fortifier (Mead Johnson). Patients who were not breastfed were randomized to receive one of the three formulas detailed in Table 2. Randomization was performed by nurses who prepared the formula in the morning, using sealed envelopes, in blocks of 6. The nurses were the only individuals who knew the contents of the envelopes; however these nurses did not provide care for the infants. During the duration of the randomized trial, the blinding remained in intact, except for when sample sizes were calculated at the beginning of the study. Standard preterm formula, Alprem (Nestle), was given to the control group (group A; n = 8). The two experimental groups received high-energy and high-protein formulas with different energy-to-protein ratios: 150 kcal/kg/d with 4.2 g/kg/d of protein for group B (n = 12) and 150 kcal/kg/d with 4.7 g/kg/d of protein for group C (n = 12). ProMod (Abbott) and Duocal (SHS) were used to increase the protein and energy contents of the preterm formula.

The weight, length and head circumference of each infant were measured by the same investigator every week for four weeks (approximately 28 days). Electronic scales, accurate to 1 g, were used to weigh the subjects. Length and head circumference were measured using non-stretch tape. Z-scores were calculated for each infant, taking into account sex and post-menstrual age, by applying neonatal growth curves from Catalonia, Spain, which contain data obtained from more than 200,000 newborns.[21] Body mass index (BMI) was calculated using the following formula: weight (in kg)/length2 (in m).

Body composition was measured via total body electrical impedance analysis (BIA) and was performed by a single investigator. Impedance and resistance were measured using a

Table 2 Composition of enteral diets

	Diet	Protein (g/kg/d)	Protein/energy ratio (g/100 kcal)	Fats (g/kg/d)	Carbohy-drates (g/kg/d)	Energy (kcal/kg/d)
Breastfed (Group BM)	Breast milk 160 ml/kg/d + Enfamil® 4.5 g/kg/d	3.4	2.5	8.1	11.7	133: 10.2% protein 54.8% fat 35.2% carbohydrate
Group A	Alprem® 160 ml/kg/d	3.7	2.8	6.6	13.6	129: 11.5% protein 46.2% fat 42.3% carbohydrate
Group B	Alprem® 160 ml/kg/d + Promod® 0.66 g/kg/d + Duocal® 3.7 g/kg/d	4.2	2.8	7.5	16.3	149.5: 11.2% protein 45.2% fat 43.6% carbohydrate
Group C	Alprem® 160 ml/kg/d + Promod® 1.3 g/kg/d + Duocal® 3.3 g/kg/d	4.7	3.1	7.45	16.1	149.9: 12.5% protein 44.7% fat 42.8% carbohydrate

- Alprem (Nestlé): in 100 g = 506 kcal, protein 14.5 g, carbohydrate 53.6 g, fat 26.0 g.
- Enfamil Human Milk fortifier (Nutricia): 1 vial = 5 mL = 5 g = 7.5 kcal, protein 0.55 g, carbohydrate < 0.3 g, fat 0.55 g.
- ProMod protein powder (Abbott): in 10 g = 42.4 kcal, protein 7.6 g, carbohydrate 1.0 g, fat 0.9 g.
- Duocal MCT (Nutricia): in 10 g = 12.4 kcal, carbohydrate 1.8 g, fat 0.58 g.

Table 3 Analytical data by group

		Mean ± SD	p
Urea (mg/dl)	A	9.0 ± 1.9	0.032
	B	12.0 ± 6.6	
	C	17.2 ± 8.5	
Protein (g/l)	A	44.0 ± 2.0	0.755
	B	45.6 ± 5.6	
	C	46.9 ± 6.7	
Ammonia (mcg/dl)	A	114.4 ± 44.1	0.445
	B	112.3 ± 30.0	
	C	128.8 ± 28.5	
Triglycerides (mg/dl)	A	106.5 ± 58.9	0.930
	B	76.8 ± 16.3	
	C	72.7 ± 25.6	
Cholesterol (mg/dl)	A	102.9 ± 20.6	0.422
	B	115.1 ± 21.1	
	C	107.0 ± 21.4	
pH	A	7.38 ± 0.07	0.289
	B	7.39 ± 0.02	
	C	7.36 ± 0.05	
Base excess (mmol/l)	A	-0.14 ± 3.2	0.911
	B	0.23 ± 2.9	
	C	-0.38 ± 4.1	

Number of patients in each group: 8 in A, 12 in B and 12 in C.

One measurement was performed on one occasion for each patient in the 3rd week of the study.

Bioscan Spectrum (Biológica Tecnología Médica, Ltd., Barcelona, Spain). The clinical methodology followed the recommendations of Tang et al.[22] Skin electrodes were applied using the tetrapolar surface method. An 800-µA and 50-kHz alternating current was applied through these electrodes. The subjects were placed in a prone position with slight pelvic elevation, legs bearing weight through the anterior knees, with hips flexed at 30°. The knees were flexed at 30°, and the ankles were dorsiflexed at 70°. The arms were placed comfortably forward with forearms parallel to the long axis of the body. The arms were adducted at 45°, the elbows were flexed at 45° and the hands were comfortably extended. For distal limb positions, the voltage electrodes were placed so the lower edge of the electrode overlapped the proximal skin crease on the dorsal aspects of the wrist and ankle at the level of the styloid process and the medial malleolus, respectively. The current electrodes were positioned distal to the voltage electrodes at a center-to-center distance of 2 cm for the hand and 3 cm for the foot.

Total body water was determined using the equation described by Tang et al.:[22] Total body water = $(0.016 + 0.674 \times \text{weight} - 0.038 \times \text{weight}2 + 3.84 \text{ foot length}2)/\text{resistance}$. A fat-free mass (FFM) value was then obtained using the following equation: FFM = total body water/water percentage of the FFM. The water percentage of the FFM was based on the studies of Fomon et al.[23] and Ziegler et al.[24] Once the FFM was known, the fat mass (FM) was estimated as follows: FM = body weight - FFM.

Study design: A longitudinal, interventional, randomized clinical trial was used. At the beginning of the study, the weights, lengths and head circumferences of the subjects with the corresponding Z-scores were determined, along with their BMIs, FMs and FFMs. Data regarding anthropometric values, gestational age at birth and previous illnesses were obtained from hospital records. For

the four-week study period, the 32 patients fed artificial formula were randomly assigned to either high-energy and high-protein diets (groups B and C) or a standard energy and protein diet (group A). Serological control measures (serum glucose, protein, ammonia, pH, base excess, urea, cholesterol and triglyceride levels) were assessed once in each patient, during the third week of the study, to detect nutrition-related adverse effects in the three groups. The weights, lengths and head circumferences with their corresponding Z-scores, along with the BMIs, FMs and FFMs were determined on approximately Day 28 of the study and were considered the final values for the study.

Statistics: The sample size of each group was calculated according to the hypothesis that supplemented formula would increase FFM accretion. When the first five cases without supplementation (group A) and the first five supplemented cases (groups B or C) were analyzed on the 21st day of the study, their FFM accretions were 15.09+/-2.14 and 19.85+/-4.15 g/kg/day, respectively. Using these preliminary data, the sample size to compare two independently observed means by a bilateral analysis with 80% power and an a-risk of 0.05 was calculated to be 12 cases per group (10 cases plus 2 for possible drop-outs). Therefore, a sample size of 12 cases was considered suitable for each of the three groups.

All the variables displayed normal distributions. The results were expressed as the means ± SD. Cross-sectional differences in anthropometric and body composition measurements among all groups (A, B and C) were tested by analysis of variance (ONEWAY and Scheffé's test for multiple comparisons of at-birth and at-beginning variables, and UNIANOVA with covariates for comparisons of results at the end of the intervention). In the UNIANOVA, the factor was the group, and the covariates were the initial corresponding figure and the duration in days of the intervention. If the p-value of the factor group was < 0.1, the UNIANOVA with covariates tests were repeated to see if a significant difference existed between any of the three paired comparisons (group A versus group B, group A versus group C and group B versus group C). A chi-squared test was used to analyze the significance of the differences between qualitative variables. Statistical analyses were performed using SPSS 13.0 (SPSS, Inc., Chicago, IL). The results were considered statistically significant at p < 0.05.

Results

There were no significant differences between groups in baseline characteristics or in incidences of the following complications related to prematurity: patent ductus arteriosus, intracranial hemorrhage, hyaline membrane disease, sepsis and necrotizing enterocolitis (Table 1).

Energy intake up to 150 kcal/kg/d and protein intake up to 4.7 g/kg/d were well tolerated by all subjects from both the clinical and analytical points of view. Analytical data by groups are shown in Table 3. The only difference observed when comparing groups B and C with group A was that infants in groups B and C exhibited higher urea levels (p = 0.032).

The corrected ages of the preterm infants and measurements of the weights, lengths and head circumferences, along with the corresponding Z-scores, are shown in Table 4 and Figure 1. In addition, Table 4 and Figure 1 also show the FMs, FFMs and BMIs at birth and at the beginning and end of the study. Throughout the study, groups B and C exhibited increases in

Table 4 Characteristics of the infants at birth and at the beginning and the end of the study

		At birth	p *	At the beginning	p *	At the end	p **
Age (corrected gestational age, weeks)	BM	29.0 ± 1.7	——	32.2 ± 2.3	———	35.7 ± 1.94	——
	A	29.6 ± 1.6	0.683	32.8 ± 0.8	0.761	36.2 ± 0.60	0.406
	B	30.2 ± 1.4		32.6 ± 1.22		36.0 ± 1.02	
	C	29.8 ± 1.7		32.9 ± 1.70		36.4 ± 1.53	
Weight (g)	BM	1138 ± 173	——	1302 ± 173	——	1903 ± 223	——
	A	1196 ± 243	0.589	1452 ± 216	0.259	1967 ± 189	0.000
	B	1220 ± 221		1303 ± 213		1998 ± 146	A-B: 0.002
	C	1313 ± 336		1404 ± 189		2154 ± 202	A-C: 0.002
							B-C: 0.622
Weight (Z-score)	BM	-0.380 ± 0.918	——	-1.279 ± 0.984	——	-1.567 ± 0.738	——
	A	-0.368 ± 0.678	0.445	-1.170 ± 0.407	0.706	-1.501 ± 0.525	0.001
	B	-0.646 ± 0.476		-1.408 ± 0.639		-1.513 ± 0.605	A-B: 0.002
	C	-0.309 ± 0.819		-1.438 ± 0.970		-1.347 ± 1.091	A-C: 0.001
							B-C: 0.213
Length (cm)	BM	37.3 ± 2.2	——	39.7 ± 2.6	——	44.2 ± 1.52	———
	A	38.7 ± 2.7	0.750	41.5 ± 1.3	0.192	44.8 ± 0.91	0.715
	B	37.9 ± 3.1		40.4 ± 1.7		44.5 ± 1.24	
	C	38.8 ± 3.5		41.7 ± 2.1		45.6 ± 1.77	
Length (Z-score)	BM	-0.329 ± 0.903	——	-0.889 ± 0.972	——	-0.895 ± 0.845	——
	A	0.017 ± 1.260	0.386	-0.589 ± 0.272	0.784	-0.738 ± 0.354	0.700
	B	-0.619 ± 0.811		-0.807 ± 0.564		-0.537 ± 0.580	
	C	-0.215 ± 0.946		-0.642 ± 1.047		-0.441 ± 1.099	
Head circumference (cm)	BM	26.3 ± 1.3	——	28.0 ± 1.5	——	31.5 ± 1.28	———
	A	27.7 ± 1.7	0.615	29.2 ± 1.1	0.418	32.1 ± 0.55	0.077
	B	26.8 ± 1.8		28.5 ± 1.3		32.3 ± 1.18	A-B: 0.033
	C	27.8 ± 3.2		28.7 ± 1.3		32.3 ± 0.75	A-C: 0.097
							B-C: 0.744
Head circumference (Z-score)	BM	-0.297 ± 0.820	——	-0.907 ± 0.831	——	-0.654 ± 0.553	—
	A	0.311 ± 1.375	0.164	-0.689 ± 0.429	0.409	-0.331 ± 0.517	0.203
	B	-0.511 ± 0.583		-0.858 ± 0.556		-0.472 ± 0.639	
	C	-0.433 ± 0.857		-1.066 ± 0.761		-0.671 ± 0.777	
Fat mass (g)	BM	——	——	111.1 ± 61.7	——	202.4 ± 49.6	——
	A	——	——	140.3 ± 72.5	0.131	193.4 ± 49.6	0.182
	B	——		135.7 ± 50.3		208.1 ± 61.0	
	C	——		129.9 ± 56.5		219.3 ± 52.0	
Fat-free mass (g)	BM	——	——	1190 ± 204	——	1699 ± 206	——
	A	——	——	1311 ± 158	0.925	1773 ± 152	0.007
	B	——		1168 ± 180		1790 ± 127	A-B: 0.009
	C	——		1274 ± 151		1915 ± 199	A-C: 0.044
							B-C: 0.277
Body mass index (kg/m²)	BM	8.16 ± 0.53	——	8.26 ± 0.69	——	16.0 ± 0.74	——
	A	7.61 ± 1.00	0.195	8.41 ± 1.06	0.424	16.8 ± 1.18	0.472
	B	8.37 ± 0.78		7.93 ± 0.80		15.6 ± 0.80	
	C	8.49 ± 1.25		8.04 ± 0.78		15.2 ± 1.57	

Number of patients in each group: 8 in A, 12 in B and 12 in C.

Data are presented as the means ± SD

* ONEWAY, with the factor group

** UNIANOVA, with the factor group and adjusted for covariates (initial corresponding value and duration of the intervention). If the p-value of the group < 0.1, pair comparisons have been performed.
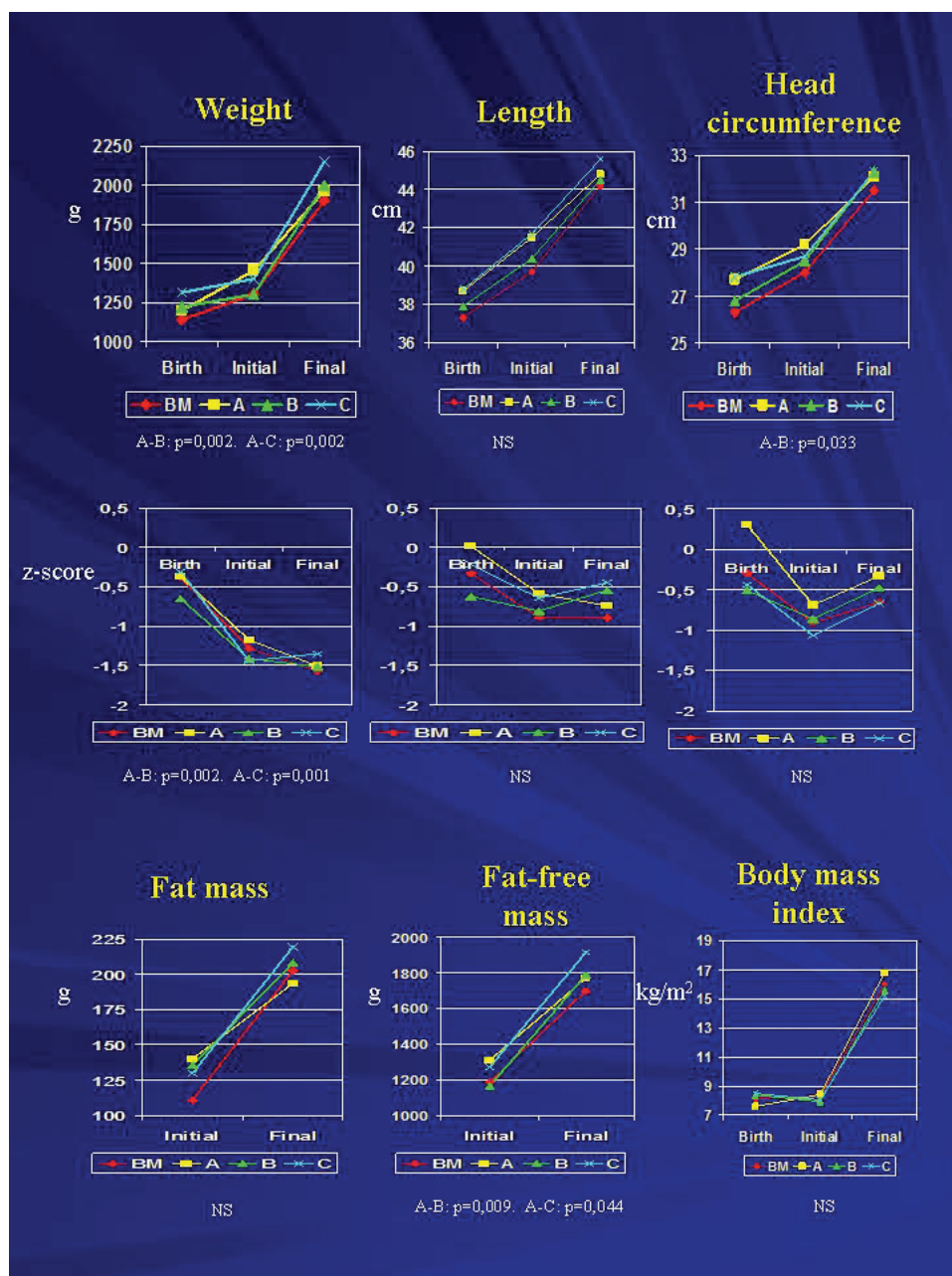
Figure 1 Anthropometric measurement means at birth and at the beginning and the end of the study

weight gain, Z-score of the weight gain, and FFM accretion. These changes were statistically significant for the factor group and for the covariates initial corresponding figure and duration of the intervention.

At the end of the study, weight gain was greater in groups B and C than in group A (p = 0.002 and p = 0.002, respectively). In addition, groups B and C exhibited significant increases in weight z-scores compared to group A (p = 0.002 and p = 0.001, respectively). Length gains and head circumference gains were similar in all groups, but final head circumference was significantly higher in group B than in group A (p = 0.033). The greater weight gains observed in groups B and C were related to greater increases in FFM, which were significantly higher than in group A (p = 0.009 and p = 0.044, respectively).

Despite the greater protein intake in group C versus group B, there were no differences in weight gain or FFM accretion between these groups. Therefore, intake consisting of 150 kcal/kg/d of energy and 4.2 g/kg/d of protein, with a protein/energy ratio of 2.8 g/100 kcal, was sufficient to achieve appropriate increases in weight and FFM in VLBW infants during their hospital stays.

Discussion
The breastfed group was regarded as a reference group for growth, FM accretion and FFM accretion. It was not considered in the statistical analysis because the intervention was only performed in formula-fed infants. Furthermore, the breastfed group happened to have the smallest children at birth. The weight differences at birth might have influenced the weight outcomes at the end of the study.

Our results show that an energy-enriched formula with a sufficient amount of protein increases weight gain with greater FFM accretion compared to normal formula in VLBW infants of

appropriate weight for gestational age. The results were obtained after controlling for the initial values of weight gain and FFM accretion and for the duration of the intervention. Bioelectrical impedance is a straightforward, non-invasive, relatively inexpensive and portable method for evaluating changes in body composition.[25] Body composition was measured using BIA. This is not a common methodology and is subject to some inaccuracies because of the assumptions that need to be made in the equations that relate impedance to water content, from which FFM is estimated. However, it has been proven to be a valid method for assessing body composition in neonates.[22,26]

The goal of nutrition in the VLBW infant is to optimize growth and neurodevelopmental outcomes while avoiding both short-term and long-term toxicity and adverse outcomes. Consistent with previous findings,[14,27,28] our study noted greater weight gains in patients receiving high-energy intake than in those receiving standard-energy intake. Previously, we reported that administering a high-energy diet without increasing the amount of protein led to a disproportion- ate increase in body FM.[14] Our new results show that adding both protein and energy to an infant formula increases weight gain and improves weight Z- scores and leads to greater FFM accretion, without short-term clinical or analytical adverse effects. The increase in urea levels in this study was proportional to protein intake and was not clinically relevant. The weight gain and FFM accretion rates observed in groups B and C are similar to the changes described in fetuses between 32 and 35 weeks of gestation by Ziegler et al.[24] Although the subjects in group C were fed more protein than those in group B (with protein/energy ratios of 3.1 g/100 kcal and 2.8 g/100 kcal, respectively), no improvement in terms of FFM accretion was observed. This observation was previously described by Fairey et al.[19] and could mean that protein intakes higher than 4.2 g/kg/d may exceed the capacity for protein utilization in VLBW infants, regardless of the accompanying energy intake; alternatively, higher energy intake may be required to improve protein utilization. Energy and protein intakes of 150 kcal/kg/day and 4.2 g/kg/day can be obtained with modular supplements added to a preterm formula, as we did in this study, or by increasing the volume or concentration of the product given to the infant.

In this early period of life, catch-up growth in head circumference was detected in each group, as indicated by the positive Z-score gains in all three groups. In addition, when the growth in head circumference was controlled for its initial value and for the duration of the intervention, it was statistically higher in group B than in group A. Postnatal head growth is an important clinical indicator of brain growth. In fact, poor postnatal head growth in preterm infants is strongly associated with poor neurodevelopmental outcomes and cerebral palsy.[29] Therefore, physicians caring for preterm infants should bear in mind that nutritional interventions aimed at limiting postnatal head growth restriction could improve neurodevelopmental outcomes.[10,11,30-32]

Catch-up growth in intrauterine growth-restricted infants may increase their risk of obesity, hypertension, impaired glucose tolerance and cardiovascular disease. Therefore, there is a concern that accelerated growth during a critical period in preterm infants could lead to long-term adverse metabolic effects. A strength of our study is the inclusion of infants whose growth was appropriate for their gestational age, as these infants are metabolically different from intrauterine growth-restricted

infants. The long-term effects of rapid growth of body weight on the onset of metabolic syndrome are relatively small compared to those of other risk factors (parental weight, lifestyle and growth later in childhood). These data suggest that the type and intake of nutrition needed by preterm infants with intrauterine growth restriction may be different from that of preterm infants with growth appropriate for their gestational age.[33,34]

The macronutrient composition of breast milk was based on reports rather than directly measured; therefore, there may be some error in the estimated macronutrient intakes. Although we had the appropriate number of newborns in the high-protein and high-energy groups (based on the calculations for sample size), the number of newborns in the control group was less because four newborns were withdrawn from the study at the request of the parents. In addition, we were wary of administering high levels of protein to preterm infants due to the potential future risk of overweight or obesity, as has been reported in healthy, formula-fed infants.[35] In a group of subjects being fed infant formula with higher protein content, a larger increase in weight during the first two years of life was identified, with no effect on length.[36]

Conclusions

This study suggests that higher protein and energy intake during a critical period is advantageous for preterm infant growth and body composition because it increases weight gain, weight z-score and FFM accretion. Energy and protein intakes of 150 kcal/kg/d and 4.2 g/kg/d, respectively, are sufficient to increase FFM accretion.

References
1   American Academy of Pediatrics: Committee on Nutrition. Nutritional needs of low-birth-weight-infants. Pediatrics 1985, 75:976-986.
2   American Academy of Pediatrics: Committee on Nutrition. Nutritional needs of preterm infants. In American Academy of Pediatrics. 6 edition. Edited by: Kleinman RE. Pediatric nutrition handbook. Elk Grove IL; 2009.
3   Canadian Pediatric Society: Nutrition Committee. Nutrition needs and feeding of premature infants. Can Med Assoc J 1995, 152:1765-1785.
4   Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA: Growth failure in the preterm infant: can we catch up? Semin Perinatol 2003, 27:302-310.
5   Heird WC: Determination of nutritional requirements in preterm infants, with special reference to 'catch-up' growth. Semin Neonatol 2001, 6:365-375.
6   Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, Verter J, Temprosa M, Wright LL, Ehrenkranz RA, Fanaroff AA, Stark A, Carlo W, Tyson JE, Donovan EF, Shankaran S, Stevenson DK: Very low birth weight outcome of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics 2001, 117(1):E1.
7   Clark RH: Extrauterine growth restriction remains a serious problem in prematurely born neonates. Pediatrics 2003, 111:986-990.
8   Ehrenkranz R, Dusick A, Vohr B, Wright L, Wrage L, Poole WK: Growth in the neonatal intensive care unit influences neuro-developmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006, 117:1253-1256.
9   Cooke RW, Foulder-Hughes L: Growth impairment in very

preterm and cognitive and motor perfomance at 7 years of age. Arch Dis Child 2003, 88:482-487.

10 Lucas A, Morley R, Cole TJ: Randomised trial of early diet in preterm babies and later intelligence quotient. BMJ 1998, 317:1481-1487.

11 Latal-Hajnal B, Von Siebenthal K, Kovari H, Bucher HU, Largo RH: Postnatal growth in VLBW infants: significant association with neurodevelopmental outcome. J Pediatr 2003, 143:163-170.

12 Ziegler EE, Thureen PJ, Carlson SJ: Aggressive nutrition of the very low birth weight infant. Clin Perinatol 2002, 29:225-244.

13 Embleton NE, Pang N, Cooke RJ: Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics 2001, 107:270-273.

14 Romera G, Figueras J, Rodriguez-Miguelez JM, Ortega J, Jiménez R: Energy intake, metabolic balance and growth in preterm infants fed formulas with different non-protein energy supplements. J Pediatr Gastroenterol Nutr 2004, 38:407-413.

15 Kashyap S, Towers HM, Sahni R, Ohira-Kist K, Abildskov K, Schulze KF: Effects of quality of energy on substrate oxidation in enterally fed, low birth weight infants. Am J Clin Nutr 2001, 74:374-380.

16 Kashyap S, Ohira-Kist K, Abildskov K, Towers HM, Sahni R, Ramakrishnan R,Schulze KF: Effects of quality of energy intake on growth and metabolic response of enterally fed low birth weight infants. Pediatr Res 2001, 50:390-397.

17 Kashyap S, Forsyth M, Zucker C, Ramakrishnan R, Dell Rb, Heird WC: Effect of varying protein and energy intakes on growth and metabolic response in low birth weight infants fed varying intakes of protein and energy. J Pediatr 1986, 108:955-963.

18 Kashyap S, Schulze K, Forsyth M, Zucker C, Ramakrishnan R, Heird WC: Growth, nutrition retention and metabolic response in low birth weight infants fed varying intakes of protein and energy. J Pediatr 1988, 113:713-721.

19 Fairey Ak, Butte NF, Mehta N, Thotathuchery M, Schanler RJ, Herid WC: Nutrient acretion in preterm infants fed with different protein:energy ratios. J Pediatr Gastroenterol Nutr 1997, 25:37-45.

20 Atkinson SA, Radde IC, Chance GW, Bryan MH, Anderson GH: Macro-mineral content of milk obtained during early lactation from mother of premature infants. Early Hum Dev 1980, 4:5-14.

21 Ramos F, Pérez G, Jané M, Prats R: Construction of the birth weight by gestational age population reference curves of Catalonia (Spain): Methods and development. Gac Sanit 2009, 23:76-81[http://scielo.isciii.es/ scielo.php?script=sci_ arttext&pid=S0213-91112009000100016&lng=es].

22 Tang W, Ridout D, Medi N: Assessment of total body water using bioelectrical impedance analysis in neonates receiving intensive care. Arch Dis Child 1997, 77:F123-F126.

23 Fomon SJ, Haschke F, Ziegler EE, Nelson SE: Body composition of reference children from birth to age 10 years. Am J Clin Nutr 1982, 35: S1169-S1175.

24 Ziegler EE, O'Donnell AM, Nelson SE, Fomon SJ: Body composition of the reference fetus. Growth 1976, 40:329-341.

25 Lukaski HC: Methods for the assessment of human body composition: traditional and new. Am J Clin Nutr 1987, 46:537-556.

26 Mayfield SR, Uauy R, Waidelich D: Body composition of low-birth-weight infants determined by using bioelectrical resistance and reactance. Am J Clin Nutr 1991, 54:296-303.

27 Carver JD, Wu PYK, Hall RT: Growth of preterm infants red nutrient- enriched or term formula after hospital discharge. Pediatrics 2001, 107:683-689.

28 Lucas A, Bishop NJ, King FJ, Cole TJ: Randomised trial of nutrition for preterm infants after discharge. Arch Dis Child 1992, 67:324-327.

29 Cheong JLY, Hunt RW, Anderson PJ, Howard K, Thompson DK, Wang HX, et al: Head growth in preterm infants: correlation with magnetic resonance imaging and neurodevelopmental outcome. Pediatrics 2008, 121:E1534-E1540.

30 Georgieff MK, Mills MM, Lindeke L, Iverson S, Johnson DE, Thompson TR: Changes in nutritional management and outcome of very-low-birth-weight infants. Am J Dis Child 1989, 143:82-85.

31 Brand I, Sticker EJ, Lentze MJ: Catch-up growth of head circumference of very low birth weight, small for gestational age preterm infants and mental development to adulthood. J Pediatr 2003, 142:463-468.

32 Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK: Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006, 117:1253-1261.

33 Greer FR: Long-term adverse outcomes of low birth weight, increased somatic growth rates, and alterations of body composition in the premature infant: review of the evidence. J Pediatr Gastroenterol Nutr 2007, 45:S147-S151.

34 Thureen PJ: The neonatologist dilema: Catch-up growth or beneficial undernutrition in very low birth weight infants- What are optimal growth rates? J Pediatr Gastroenterol Nutr 2007, 45:S152-S154.

35 Koletzko B, von Kries R, Closa-Monasterolo R, Escribano-Subías J, Scaglioni S, Giovannini M, Beyer J, Demmelmair H, Anton B, Gruszfeld D, Dobrzanska A, Sengier A, Langhendries JP, Rolland-Cachera MF, Grote V, for the European Childhood Obesity Trial Study Group: Can infant feeding choices modulate later obesity risk? Am J Clin Nutr 2009, 89(suppl):1502S-1508S.

36 Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, Beyer J, Demmelhair H, Gruszfeld D, Dobrzanska A, Sengier A, Langhendries JP, Rolland-Cachera MF, Grote V, for the European Childhood Obesity Trial Study Group: Lower protein in infant formula is associated with lower weight up to age 2 years: a randomized clinical trial. Am J Clin Nutr 2009, 89:1836-1845.

Evidence-based Guidelines for Use of Probiotics in Preterm Neonates

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Abstract

Background: Current evidence indicates that probiotic supplementation significantly reduces all-cause mortality and definite necrotizing enterocolitis without significant adverse effects in preterm neonates. As the debate about the pros and cons of routine probiotic supplementation continues, many institutions are satisfied with the current evidence and wish to use probiotics routinely. Because of the lack of detail on many practical aspects of probiotic supplementation, clinician-friendly guidelines are urgently needed to optimize use of probiotics in preterm neonates.

Aim: To develop evidence-based guidelines for probiotic supplementation in preterm neonates.

Methods: To develop core guidelines on use of probiotics, including strain selection, dose and duration of supplementation, we primarily used the data from our recent updated systematic review of randomized controlled trials. For equally important issues including strain identification, monitoring for adverse effects, product format, storage and transport, and regulatory hurdles, a comprehensive literature search, covering the period 1966-2010 without restriction on the study design, was conducted, using the databases PubMed and EMBASE, and the proceedings of scientific conferences; these data were used in our updated systematic review.

Results: In this review, we present guidelines, including level of evidence, for the practical aspects (for example, strain selection, dose, duration, clinical and laboratory surveillance) of probiotic supplementation, and for dealing with non-clinical but important issues (for example, regulatory requirements, product format). Evidence was inadequate in some areas, and these should be a target for further research.

Conclusion: We hope that these evidence-based guidelines will help to optimise the use of probiotics in preterm neonates. Continued research is essential to provide answers to the current gaps in knowledge about probiotics.

Background

Despite the advances in neonatal intensive care over past 20 years, the incidence of necrotizing enterocoli- tis (NEC) in preterm neonates has not changed significantly. The mortality (approximately 20 to 25%) and morbidity related to definite (greater than stage II) NEC, including prolonged hospitalization, survival with short-bowel syndrome and long-term neurodevelopmental impairment (NDI) continues to be high, espe- cially in preterm or extremely low birth weight (ELBW) (birth weight < 1000 g, gestation < 28 weeks) neonates needing surgery for this illness. Mortality reaches nearly 100% in children with extensive and full-thickness necrosis of the gut.

Antenatal use of glucocorticoids, with postnatally, preferential feeding with fresh human milk, aggressive prevention and treatment of sepsis, and a cautious uniform approach to enteral feeds are the strategies available to prevent NEC. Previous systematic reviews of randomized controlled trials (RCTs) showed that probiotic supplementation significantly reduces the risk of definite NEC, all-cause mortality and the time to reach full enteral feeds (~120 to 150 ml/kg/day of milk) in preterm neonates. Based on these results, reports have indicated that routine probiotic supplementation is justified, except for ELBW neonates, given the lack of specific data on this high-risk cohort. Our most recent updated systematic review and meta-analysis confirmed previous results, while improving their precision and reducing the likelihood of these being due to chance alone (Table 1). Moreover, trial sequential analysis (TSA) indicated that the results gave conclusive evidence of at least 30% reduction in the incidence of NEC. These conclusive results, along with those from observational studies on routine use of probiotics, their use in ELBW neonates, and their safety and possible benefits in terms of long-term NDI, justify a change in practice if safe and suitable probiotic products are available. Some have supported our views, but others cite difficulties such as problems in pooling data in the presence of clinical heterogeneity, reproducibility of the results in different studies, role of breast milk, pitfalls of TSA, lack of availability of safe and effective products, development of antibiotic resistance, cross-contamination and long-term adverse effects (AEs) as reasons for opposing routine use of probiotics in preterm neonates. We have previously addressed these concerns, and pointed out that probiotic research has completed a full

Table 1 Updated systematic review results (Pediatrics 2010)

Outcome	RR[a](95% CI)	P value	NNT[b] (95% CI[c])
NEC	0.35 (0.23 to 0.55)	0.00001	25 (17 to 34)
Mortality	0.42 (0.29 to 0.62)	0.00001	20 (14 to 34)
Sepsis	0.98 (0.81 to 1.18)	0.80	N/A[d]

[a]Relative risk.
[b]Confidence interval.
[c]Numbers needed to treat.
[d]Not available.

circle, from basic science and cohort studies, to conclusive meta-analysis, routine use, and long-term follow up. Many level III neonatal units in Japan, Italy, Finland and Columbia have been using probiotics routinely for over a decade, and have not reported any significant AEs. Based on the quality and totality of the evidence in the context of the related health burden and the lack of equally effective therapies, we believe that probiotics should be offered routinely to preterm neonates. Additionally, from the perspective of a preterm neonate or their family, there would need to be a good reason to ignore the evidence base for using probiotics to prevent NEC. Offering probiotics routinely, but still within a framework of research other than placebo-controlled trials, is the way forward to deal with the as yet unanswered questions. As the debate about the pros and cons of routine probiotic supplementation continues, many institutions are satisfied with the current evidence and wish to use probiotics routinely. Because of the lack of detail on many practical aspects of probiotic supplementation, clinician-friendly guidelines are urgently needed to optimize use of probiotics in preterm neonates.

Because of the vast scope of the field, we aimed to conduct a comprehensive rather than a conventional systematic review in order to develop evidence-based guidelines for using probiotics in preterm neonates, and we indicate areas for further exploration of this new frontier.

Methods

To develop the core guidelines for strain selection, age at start, dose and duration of the supplementation, we primarily used the data from RCTs of probiotics in preterm neonates from our recent updated systematic review.

For equally important issues such as strain identification, AEs, product format, storage and transport, regulatory issues, ethics and parent information, the relevant literature was searched in PubMed (1966 to October 2010) and EMBASE for the period 1980 to October 2010, and we also used the search engine Google.

PubMed was searched using the following terms: "Probiotics"[MeSH] AND "Culture Techniques"[MeSH]; "Probiotics"[MeSH] AND "Classification"[MeSH];

"Probiotics"[MeSH] AND "Bacterial Translocation"[MeSH]; "Probiotics"[MeSH] AND "Sepsis"[MeSH]; "Probiotics"[MeSH] AND "Informed Consent"[MeSH]; "Probiotics"[MeSH] AND "Legislation, Drug"[MeSH]; "Probiotics"[MeSH] AND ("Ethics"[MeSH] OR "Ethics Committees"[MeSH] OR "Ethics Committees, Clinical"[MeSH] OR "Codes of Ethics"[MeSH] OR "Ethics Committees, Research"[MeSH] OR "Ethics, Clinical"[MeSH] OR "Ethics, Professional"[MeSH] OR "Ethics, Medical"[MeSH] OR "Bioethics"[MeSH]); "Probiotics"[MeSH] AND Refrigeration"[MeSH] "Probiotics"[MeSH] AND "Quality Control"[MeSH]; "Probiotics"[MeSH] AND "Quality Assurance, Health Care"[MeSH].

EMBASE was searched using the following terms: probiotic.mp. or probiotic agent AND microbiological examination/or culture medium/or methodology/or culture methods.mp. or culture technique/or bacterium culture/; probiotic.mp. or probiotic agent AND antibiotic susceptibility.mp. or antibiotic sensitivity; probiotic. mp. or probiotic agent AND Sepsis; probiotic.mp. or probiotic agent AND bacterial translocation; probiotic. mp. or probiotic agent AND legislation.mp. or licence/ or law/; probiotic. mp. or probiotic agent AND informed consent; probiotics. mp. or probiotic agent AND temperature/or drug storage/or drug packaging/or cold chain.mp. or drug stability/or freezing/; probiotic.mp. or probiotic agent quality assurance.mp. or quality control/.

The search covered studies in the neonatal, pediatric and adult populations, and also in animal studies and in vitro studies. Cross-references from the relevant studies were also searched. Specific references that were used to develop the guidelines are quoted in the main manuscript of the review. All other essential or related references are included in the appendices, which also include the results of the PubMed and EMBASE search strategies.

An attempt to search Google search engine using the aforementioned terms was abandoned, as it resulted in hits ranging from 838 to 1,690,000. PRISMA guidelines for reporting the systematic review were followed where applicable.

When establishing guidelines, it is preferable to grade the level of evidence (LOE) depending on the type and the quality of study. However, we found that there are no validated and universally accepted methods for assessing the quality of studies) especially for studies other than RCTs), or for grading the LOE. Our core guidelines are based on the systematic review of RCTs of probiotic supplementation in preterm very low birth weight (VLBW) neonates. The quality of these trials was assessed by the method recommended by the Cochrane Neonatal Review Group and by Jadad scores, which are commonly used but have not been validated.

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

Figure 1 Designations of levels of evidence. Figure from *Merlin et al. BMC Medical Research Methodology* 2009: 34, doi:10.1186/1471-2288-9-34.

Table 2 Probiotic protocols from trials included in the updated meta-analysis

Study	Probiotic agent/s	Dose and duration
Kitajima 1997 [52]	*Bifidobacterium breve*	0.5×10^9 cfu[a] once daily from first feed for 28 days.
Dani 2002 [53]	*Lactobacillus rhamnosus* GG	6×10^9 cfu once daily from first feed until discharge
Costalos 2003 [54]	*Saccharomyces boulardii*	10^9/kg twice daily from first feed for 30 days
Bin Nun 2005 [55]	*Bifidobacterium infantis, Streptococcus thermophilus, Bifidobacterium bifidus*	0.35×10^9 cfu *B. infantis*, 0.35×10^9 cfu *S. thermophilus* and 0.35×10^9 cfu *B. bifidus* once daily from first feed to 36 weeks corrected age
Lin 2005 [56]	*Lactobacillus acidophilus, B. infantis*	1004356 *L. acidophilus* and 1015697 *B. infantis* organisms twice daily from day 7 until discharge
Manzoni 2006 [57]	*Lactobacillus casei*	6×10^9 cfu once daily from 3 days to 6 weeks of age, or discharge from NICU[b]
Mohan 2006 [28]	*Bifidobacterium lactis*	1.6×10^9 cfu once daily from day 1 to day 3; 4.8×10^9 cfu once daily from day 4 to day 21
Stratiki 2007 [59]	*B. lactis*	Preterm formula: 1×10^7 cfu/g started within 48 hours to 30 days
Lin 2008 [60]	*B. bifidus, L. acidophilus*	2×10^9 cfu daily for 6 weeks
Samanta 2009[61]	*B. bifidus, B. lactis, B. infantis, L.s acidophilus*	2.5×10^9 cfu daily until discharge
Rouge 2009 [62]	*Bifidobacterium longum, Lactobacillus* GG	1×10^8 cfu daily until discharge

[a]Colony-forming units.

[b]Neonatal intensive-care unit.

The development and reporting of crucial aspects of probiotics (for example, selection, manufacturing, transport, storage, quality control (QC), and regulation) has not necessarily followed the model of evidence-based medicine, making it difficult to apply the principles of LOE to every aspect of this intervention. It is also difficult to apply the conventional concept of study design and LOE for bench research to practical issues such as stability and taxonomy confirmation. We therefore adopted a simple method of grading the LOE, based on a pyramid of evidence hierarchy, with systematic reviews of RCTs being at the top (best evidence) and a case series being the bottom (Figure 1). We believe that this simple system for grading the LOE along with the judgment of the readers will be adequate to permit appropriate interpretation of the various aspects of the guidelines.

Results

Selection of strains: Bifidobacteria and lactobacilli are the species of choice in probiotics, given the evolution of the gut flora in preterm neonates. However, lactobacilli are a minor component of the intestinal microbiota. In terms of the rationale for species and strain selection, it is important to note that there are many different mechanisms producing the benefits of probiotics and there are also strain-specific effects. Bifidobacteria are the dominant strains in infancy, and the combination of lactobacilli and bifidobacteria is known to promote the growth of indigenous lactic-acid bacteria (bifidogenic effect) by formation of short-chain fatty acids as a product of the fermentation process.

Strains isolated from humans are preferable because of their natural occurrence, long-term record of safety in infants, and adaptability to both mucosal and dairy ecosystems. Researchers have generally selected strains belonging to bacterial species naturally present in the intestinal flora of the species to be targeted (in this case, humans), under the assumption that these bacteria have a better chance of out-competing resident bacteria and of establishing themselves at a numerically significant level in their new host. However, because humans have shared such strains with other mammals for millions of years, other researchers believe that their origin is difficult to trace as they are present everywhere: in human beings, animals, soil, food and water. Thus, bovine strains may also be used if they have a good record of safety and efficacy. It is the specificity of the action rather than the source of the microorganism that is important. The clinical significance of the origin of strains may be evaluated in future trials. The probiotic strains that have been used in various RCTs in preterm neonates are summarized in Table 2.

It is important to note that the probiotic effects are strain-specific, and cannot be extrapolated to other strains. The variability of the strains and protocols in the trials included in our meta-analysis indicates that the concept of strain-specific effects of probiotics may not be relevant to prevention of NEC by probiotics. Because of the various complex pathways involved in the pathogenesis of NEC, different strains may benefit by different pathways. The benefits of different probiotics in infective diarrhea indicate that

Table 3 Specific recommendations for major clinical decisions

Specific recommendations		LOE[a][reference]
Selection of strains	Combination containing *Lactobacillus* and at least one *Bifidobacterium* species is preferable. *Lactobacillus* GG alone may not be effective	I [14]; II [55,56,60]; III-[3,15]
Dose	3×10^9 organisms per day, preferably in a single dose	I [14]; II [55,56,60]
When to start?	When the neonate is ready for enteral feeds, preferably within first 7 days of life	I [14]; II [55,56,60]; III [3,15]
How long to continue?	At least until 35 weeks corrected age, or discharge	II [55,56,60]
Supplementation during acute illness	Stopping the supplementation during an acute illness such as sepsis, NEC[b]or perinatal asphyxia may be safe	IV [94-98]

[a]Level of evidence.

[b]Necrotising enterocolitis.

Table 4 Guidelines for other clinical and non-clinical issues[a]

Guidelines	References
1. Starting dose for ELBW[b]neonates: 1.5×10^9 cfu/day[c] until reaching 50-60 ml/kg/day feeds	[84] and authors' opinion
2. Osmotic load: solution should be diluted to keep the osmolality below 600 mOsm/L	[86,87]
3. Diluent: sterile water or breast milk	Authors' opinion
4. Volume for administration: 1 to 1.5 ml per dose	[86] and authors' opinion
5. Clinical monitoring: patients should be monitored for intolerance (abdominal distension, diarrhea, vomiting), probiotic sepsis, and adverse effects (flatulence, loose stools) of additives such as prebiotic oligosaccharides.	[95-101] and manufacturer recommendation
6. Ongoing laboratory surveillance: Expertise in taxonomy confirmation (16S rRNA sequencing and PFGE[d]), ruling out contaminants, recovering probiotic strains at low inoculums from sterile sites, familiarity with the Gram stain and phenotypic appearance of probiotics, and monitoring for antibiotic susceptibility/resistance and cross-contamination are crucial.	[107]
7. Cold chain: maintenance of cold chain should be checked. Refrigerate at 4 to 10°C	Manufacturer recommendation
8. Product stability: stability should be checked by regular microbiological tests	[51,67,112,151]
9. Leftover solution should be discarded after giving small doses as it may get contaminated	Manufacturer recommendation
10. Regulatory issues: importing may be easier for research than for clinical use. National regulations on drugs and food supplements and customs quarantine guidelines should be checked	[131,132]
11. Data monitoring: high-quality data monitoring and collaboration between regional neonatal networks is crucial for monitoring outcomes at a population level	[145,146]
12. Information for parents: parents should be kept well informed about benefits and adverse effects, including the possibility of cross-contamination	[18,24]
13. Other potentially useful strategies: early preferential use of breast milk, strategies for prevention of sepsis, standardised feeding protocols, avoidance of undue prolonged exposure to antibiotic	[137-142]

[a]Level of evidence was applicable to specific recommendations for clinical issues (Table 3) and not to other guideline components discussed in Table 4 above.
[b]Extremely low birth weight.
[c]CFU: Colony forming units.
[d]Pulsed-field gel electrophoresis.

although many probiotic effects are strain-specific, others may be similar for very different probiotic organisms. The variation in the immunomodulatory effects between species is generally larger than that between the strains of the same species. The rates of gut colonization by a probiotic strain also differ according to the age of the host.

Evidence indicates that the functionality of a multistrain or multispecies probiotic could be more effective and more consistent than that of a monostrain probiotic. Researchers have also investigated the adequacy of combinations of strains. Colonization of an ecosystem providing a niche for more than 400 species in combination with individually determined host factors is anticipated to be more successful with multistrain rather than monostrain probiotic preparations. The results of one review indicated that multistrain probiotics showed greater efficacy than single strains, including single strains that were components of the mixtures themselves. It was unclear whether this was due to synergistic interactions between strains or to the higher probiotic dose used in some studies. Based on the complexity of normal gut flora and of NEC pathogenesis, and the multiple beneficial mechanisms of probiotic strains, multistrain probiotics may be more effective than single-strain probiotics.

However, the report of a consensus meeting of experts states that a combination of probiotic strains in a product does not necessarily add to the benefits of each strain. A high number of different strains is not, in itself, indicative of greater efficacy than a lower number of strains. Clinical trials are needed to address the benefits of single-versus multistrain probiotic products in preterm neonates.

Our systematic review of RCTs indicates that the trials reporting a significant decline in NEC used multistrain products, whereas those reporting a lesser decline used a single organism, such as Lactobacillus rhamnosus GG. Failure of Lactobacillus GG to prevent NEC in the RCT reported by Dani et al and in the report of 12 years' experience by Luoto et al suggests that it may

be prudent to avoid the use of this single strain alone, pending further evidence. The potential of Bifidobacterium animalis (subspecies lactis) also needs to be explored.

Using more than two or three strains (each with an optimal mass) may result in higher risk of translocation because of the substantial increase in the total dose, especially in ELBW neonates; however, without an optimal mass of each component, a combination may not be effective in assuring survival and colonization by each strain of the supplement. It is better to avoid untested combinations, because strain combinations can be antagonistic, compatible or synergistic.

It would be reasonable to use probiotic products that have previously been shown to be effective in RCTs, provided the evidence indicates that there has been no change or compromise in the manufacturing technique.

Dose: An optimal mass or dose is essential for any probiotic strain to survive and colonize the gut. The concept of viability refers to the ability of the probiotic strain to survive and proliferate in adequate numbers to benefit the host. It is hence expected that there will be an optimal dose below which benefits may not occur, as survival and proliferation to adequate numbers, after overcoming the barriers such as gastric acid, bile and competing flora, is not ensured. Evidence indicates that to be functional, probiotics have to be viable and in sufficient dosage levels, typically 106 to 107 colony-forming units (cfu)/g of product.

Conventional dose-response studies could be conducted in preterm neonates; however the selected doses will be arbitrary, and only guessed from what is known about the gut ecosystem in preterm neonates. There is no data on the toxic or lethal dose of probiotics for preterm neonates, and extrapolating from studies in other populations and animal experiments is likely to be incorrect. An expert consensus report stated that "there is no standardized number of probiotic bacteria that would ensure an effect. The effective quantity, for a given effect and a given strain,

is the quantity which has demonstrated an effect in the relevant human intervention trial." In addition, live probiotics have the potential to replicate in the gut and lead to bacteremia. Judicious consideration is hence important in applying the principle of dose-response studies to this high-risk population with associated poor nutrition, impaired immune status and frequent exposure to infectious agents. Conducting crossover and forced-titration (stepwise dose-escalation) dose-response studies will also be difficult, as the incidence of NEC is known to fluctuate over time. As for parallel design, the definition of a target dose is subjective.

Based on the median dose used in the RCTs in preterm neonates (Table 2), we suggest that a daily dose of 3×10^9 cfu/day may be appropriate for neonates of less than 32 weeks gestation. Currently, there are no data available regarding a dose beyond which the risk of probiotic complications will be high in ELBW neonates. Until such data are available, we suggest that the starting dose should be 1.5×10^9 cfu/day for ELBW neonates until they reach enteral feeds of 50 to 60 ml/kg/ day. Halving the volume of the probiotic supplement should also benefit these neonates because they are often intolerant to large enteral volumes. The reduced dose is still expected to be beneficial, based on the lower clinically effective doses used in the trials in our updated meta-analysis.

Investigators of one recent trial suggested that the daily probiotic dose in malnourished children should preferably be given as a single rather than divided dose, in view of the rapid decline of the strain mass in vivo. The osmotic load, pH and volume of a single dose are crucial in ELBW neonates because of their inability to tolerate even very small volumes of milk feeds in the early days of life. The nature of diluent (dextrose, sterile water, saline, milk) and volume after dilution are also important practical issues. The currently recommended range of osmolarity of neonatal milk formulae is 246 to 320 mOsm/kg. The osmotic load of drugs and milk additives is a concern in high-risk neonates because of the risk of NEC. Adequate dilution is thus necessary to avoid undue hyperosmolarity.

When to start? Because of the importance of early establishment of commensal flora in preterm neonates, the probiotic supple-mentation should be started as early as possible before pathogens colonize or antibiotics destroy the prevailing commensals. The earliest reported age at start of supplementation was 4 hours of life, in the study by Satoh et al. Otherwise most of the investiga-tors assessed (7/ 11) started the supplementation when the neo-nates were ready for enteral feeds (Table 2). Clinical stability (for example, no sepsis, patent ductus arteriosus, inotropes or ileus) is desirable to ensure that the gut function has recovered after the initial illness, with minimal risk of intolerance or translocation. The optimal protocol for probiotic administration in ELBW neo-nates with intrauterine growth restriction needs to be confirmed.

When to stop? It is well known from animal and human (both adults and children) studies that shedding of probiotic organisms in the stool commonly stops about 2 to 3 weeks after the probiotic supplement is stopped. Hence continued administration is necessary to promote sustained colonization in preterm neonates until evidence is available for this high-risk population. Based on the published trials (Table 2) and the inverse relation of gestational age with NEC and all-cause mortality, it seems appropriate that supplementation could be stopped after reaching the corrected gestational age of 36 to 37 weeks, when the risk of these adverse outcomes is minimal.

Supplementation in the presence of potentially compromised gut integrity: The risk of probiotic translocation and sepsis is higher in critically ill and/or extremely preterm neonates with potentially compromised gut integrity, and may be higher in the presence of high doses of a single strain. The current evidence is inadequate to make clear recommendations in this area. Investigators reported increased mortality in recipients of probiotic (compared with placebo) in an RCT involving adults with acute pancreatitis. These findings may relate to non-occlusive mesenteric ischemia in critical illness, which is exacerbated by the added bacterial load itself or a pro-inflammatory response by gut epithelial cells. Extrapolating these findings to critically ill and/or extremely preterm neonates may not be appropriate, but stopping the supplementation during an acute illness (for example, proven or suspected sepsis, NEC, perinatal asphyxia) may be in the best interest of the child, pending further evidence. Studies are needed to identify the optimal use of probiotics in such neonates.

Clinical monitoring during supplementation: Intolerance (higher osmotic load causing abdominal distension, diarrhea or vomiting), probiotic sepsis and AEs (flatulence, loose stools) of additives such as prebiotic oligosaccharides need to be monitored. However, the significant overlap of features of ileus of prematurity, sepsis and NEC is expected to make this issue very difficult. Frequent clinical examinations and a cautious approach are desirable until enough experience is obtained with a probiotic product and protocol in this high-risk cohort.

Ongoing laboratory surveillance for safety: On-site expert microbiological support is vital for independent taxonomy confirmation, exclusion of contaminants and confirmation of colony counts in the reconstituted product. Microbiology laboratories should ensure that their culture media are capable of recovering the constituent bacterial species, especially at low inoculums from sterile sites. Additionally, they should be familiar with the Gram stain and phenotypic appearances of the probiotics in different media, and be aware of the possible need for extended incubation times in anaerobic conditions. In the few published reports of bacteremia with probiotics, there is scant detail about the blood culture manufacturer or system or the media used. Clinical isolates should be compared with probiotic strains using molecular methods such as 16S rRNA sequencing and pulsed-field gel electrophoresis. The possibility of cross-contamination, resulting in nosocomial acquisition of probiotic strains by other children in the neonatal unit, should not be for- gotten. Kitajima et al. reported colonization rates of 73% and 91% in their probiotic group versus 12% and 44% in the control group neonates at 2 and 6 weeks respectively. Costeloe et al reported cross-contamination rates of 35% in their pilot clinical trial. This possibility needs to be discussed with the parents of the children in neonatal units providing probiotic supplementation. It is important for researchers to note that cross-contamination in the control arm in an RCT is expected to underestimate the true effects of probiotics. Antibiotic susceptibility testing of probiotics by standardized methods should be undertaken to provide local guidance for empiric antibiotic prescribing. The frequency of in vivo transfer of antibiotic-resistance mechanisms is currently unknown. The role of routine fecal surveillance cultures to detect such transfer is also unknown, and is likely to be beyond the scope of routine laboratories. Other important issues are the stability of the probiotic on transport and shelf storage, ability of the laboratory to rapidly detect probiotic sepsis, and surveillance for the development of antibiotic resistance. Regular random stool cultures are beneficial but need extra resources. Compared

with lactobacilli, culturing bifidobacteria is difficult as it requires special media and expertise. The rarity of bifidobacterial sepsis in the literature could relate to failure to isolate these strains in blood culture by particular techniques. Newer nonculture methods are a better option. Extensive ongoing microbiological monitoring may not be necessary if the safety and quality (from manufacturing, transport and storage on-site to use in the neonatal unit) of the probiotic product is ensured.

Practical issues: Variations in the manufacturing process can significantly alter the properties of probiotic strains. Variations between batches in the quality of dietary supplements are also known to occur. Assurance of good manufacturing practices is thus important. The choice of the packaging material plays an important role in maintaining the viability of the probiotic strains at sufficiently high levels to ensure their therapeutic activity throughout shelf life. Probiotics, by current definition, are live microorganisms that survive in the anaerobic environment of the gut, and are sensitive to oxygen, moisture and heat. Their production and packaging should therefore involve limiting their exposure to oxygen by using barrier packages and eliminating oxygen by flushing with nitrogen. The support compounds should have minimal moisture. Refrigeration is important to protect the product from significant temperature fluctuations. The product format (dry powder, sachets, ready-to-use liquid, capsules, tablets) is an important issue, as we have recently reported poor viability of strains in probiotic tablets.

Based on the current understanding that viability (ability to survive, proliferate and benefit the host) is an important property of probiotic strains, the proportion of viable strains in a probiotic product will be an essential determinant of its clinical efficacy. This necessitates a high degree of stringency in the manufacturing process, as required by regulatory agencies. However, evidence indicates that dead or inactivated probiotic strains, or even their cellular components and culture broths, can still have beneficial effects. If further clinical research provides evidence to this effect, the proportion of viable strains in a probiotic product may not be a crucial issue. However, it is important to note that even if viability of the strains does not turn out to be a crucial issue in the future, the level of stringency required in the manufacturing process cannot be compromised, because there are other important issues involved, such as taxonomy confirmation and contamination. Wastage after administration of a small dose, and stability and contamination of the leftover dose are also practical issues, and availability of a product in different strengths may solve this problem. Assurance of regular supply and ready availability of a standby product is important in view of the ongoing need for routine use and research, and prevention of inflation in pricing due to the monopoly of one product.

Role of prebiotics in probiotic products: The coexistence of probiotics and prebiotics, as found in human breast milk, is known to be synergistic. Prebiotics have been shown to enhance the survival of endogenous probiotic organisms. Further research, such as RCTs of probiotics versus synbiotics, is necessary to evaluate whether addition of prebiotics improves the survival and/or efficacy of probiotic strains in preterm neonates.

Regulatory issues: There has been a poor track record of QC of some commercially available products, thus improvisation and standardization of the regulatory guidelines is urgently needed. The first option involves the central regulatory agencies (for example, in Australia, this is the Therapeutic Goods

Administration (TGA)) taking the responsibility of approving the QC and quality assurance (QA) practices in the manufacturing plant, and facilitating the development of a central QC laboratory for providing national backup services for independent ongoing confirmation of quality. However, this option runs the risks of administrative delays, overburdening of the central laboratory, and complete dependency of all neonatal units on its services. The second option involves development of a central QC laboratory for each state to supervise or assist the routine use of probiotics in the state neonatal units. The third option is for each institution to develop its own on-site expertise within the federal regulatory guidelines. In countries such as the USA, where probiotics ('intended to use to diagnose, cure, mitigate, treat or prevent disease and affecting structure or function of the body') are registered as drugs rather than food supplements, the regulatory restrictions on the access to probiotics will be considerable. Substantial delay in access to probiotics is inevitable in such countries if phase I, II and III studies are to be conducted before probiotics can be made easily available. Defining probiotics as "foods for specialized health use" as in Japan may overcome these difficulties. It is important to note that, although the regulatory restrictions will be more stringent if probiotics are regulated as drugs, the regulations will then at least be clear and consistently applied, and once licensed, probiotics will potentially be more accessible to consumers and physicians. Thus, in the longer term it may actually be in the patients' interest for probiotics to be regulated as drugs under some circumstances.

We believe that with cooperation between government, industry, scientists, and the International Probiotics Association, any one of these strategies could be easily adopted to increase the availability of high-quality probiotics if there is a political will to do so.

Other potentially useful strategies: Owing to the development of aberrant gut flora and delayed colonization by normal commensal strains in preterm neonates, early preferential feeding with breast milk and minimizing exposure to antibiotics are crucial to optimize the benefits of probiotic supplementation. Neonates given antibiotics at birth have been reported to retain abnormal microbial flora 4 weeks later, indicating the damaging effect of these agents. Strategies for preventing sepsis are also crucial in optimizing the benefits of probiotic supplementation, as sepsis needs treatment with antibiotics (anti-probiotics). The benefits of a standardized feeding protocol must not be forgotten if prevention of NEC and facilitation of enteral nutrition is the goal. Such a protocol will help in evaluation of the efficacy of probiotics in presence of different feeding policies. For neonatal units with donor milk banks, the effect of pasteurization on breast-milk probiotics needs to be studied, given the thermal sensitivity of probiotic strains. Breast-milk oligosaccharides are not affected by pasteurization.

Data monitoring: Probiotic supplementation is a new development in neo- natal intensive care. Hence, high-quality data monitoring is essential to evaluate population outcomes in this high-risk cohort. Monitoring data during routine use is similar to post-marketing surveillance, which has a higher rate of detection of AEs (including rare ones), and is helpful in comparing the benefits and risks in different populations with different management practices. Such data are essential to evaluate the effects of the intervention at a local level, and for planning future research. It is often a requirement of regulatory agencies

such as the TGA when an unlicensed drug is used. The need for post-marketing surveillance has been emphasized by expert committees. Collaboration between regional neonatal networks is crucial for linkage of databases.

Information for parents: Based on the current evidence, parents are unlikely to refuse probiotics, an intervention that substantially reduces the incidence of death and life-threatening diseases such as NEC. Because of the lack of significant experience with probiotics, especially in extremely preterm neonates, and the currently unanswered questions surrounding this intervention, it is important to ensure that parents are well informed about the benefits and potential AEs, both short and long-term. Honesty, clarity and transparency in sharing information with the parents, and respect for their autonomy are crucial. Informed consent may be required until sufficient experience has been obtained to provide probiotics as a routine therapy without hesitation. Continued vigilance, equivalent to post-marketing surveillance, and uniform reporting are necessary to gain more data and confidence with probiotic supplementation.

Role of placebo-controlled trials: The sum of the current evidence supports our view that the role of placebo-controlled trials is necessary only for the evaluation of new strains. From the purist's point of view, a large, definitive, placebo-controlled trial may be justified for ELBW neonates in a setting of low baseline risk, but given the current evidence and the difficulties in obtaining fully informed consent from parents, successful completion of such a trial in a realistic time frame will be difficult. We have pointed out that the issue of reproducibility in different settings has been addressed adequately. Placebo-controlled trials are not justified purely for evaluating the frequency and consequences of cross-contamination. Allowing access to a known, clinically effective, probiotic product also cannot be the justification for such a trial, especially when special regulatory schemes allow access to a life-saving intervention. For addressing other important issues such as defining the optimum intervention (which probiotic (s), what dose and timing), and assessing microbial adaptations and ecological consequences, interactions with other preventive interventions and the effect of probiotics on early development, other types of study designs such as head to head trials (comparing different products or protocols), cluster randomized and factorial trials, cohort studies and long-term follow-up studies are more suitable than placebo-controlled trials. The frequency of cross-contamination in the placebo arm of a RCT is important in this context. As for understanding the mechanisms of the benefits of probiotics in the prevention of NEC, it is important to note that the pathogenesis of NEC remains poorly understood despite extensive research for over three decades and that there are multiple pathways by which probiotic(s) can provide benefit. There is a wide range of possible mechanisms that need further investigation, and several clinical observations that cannot be satisfactorily explained at the cellular level. A large number of the mechanisms cannot be measured easily in humans for ethical or feasibility reasons (for example, access to tissue specimens).

Advancing knowledge by further research while not denying probiotics to preterm neonates High-quality definitive RCTs comparing issues such as low versus high doses, single versus multiple strains, live versus killed probiotic organisms, whole probiotics versus probiotic components, probiotics versus prebiotics, probiotics versus synbiotics, commencing supplementation very early (starting on day 1 of life if the severity of initial illness is not restrictive) versus starting as

early as possible (ready for enteral feeds), and enteral plus topical (oral spray) versus only enteral supplementation, will advance the knowledge in this area. A clear understanding of the benefits and risks of probiotics will also be facilitated by the advantages of prospective and robust data collection during such research. Long-term issues such as NDI, development of allergy, sensitization and altered immune responses also need to be monitored. The significance of exposure of preterm neonates to lactose, dextrin and cornstarch, which are used as carriers or substrates in probiotic products, needs to be evaluated.

Accessing probiotic products for research versus routine use Accessing a probiotic product (Table 2) may be relatively easy in research rather than routine use, at least until the regulatory issues are clarified. In Australia, importing a probiotic is possible with clinical trial notification approval from the TGA and a license to import a biological product from the Australian Quarantine and Inspection Services. It is also possible in Australia, with the local approval of the Drug and Therapeutics Committee and endorsement by the TGA of named clinicians as authorized prescribers, to obtain a probiotic under a special access scheme. A similar scheme is possible in the UK. For a new product or strain, a very thorough independent QA/QC process is needed before using it in this high-risk population. Small placebo-controlled trials (rather than observational studies) will be important to rigorously assess and confirm the ability of the new strains to colonize the preterm gut if the product is to be adopted for routine use. Even minor variations in the manufacturing process can compromise the safety and efficacy of the product.

Conclusion

We have provided evidence-based guidelines (Table 3, Table 4) for the use of probiotics in preterm neonates, as we believe that the current evidence justifies routine use of this intervention. These guidelines will also be helpful for optimal use of probiotics in research settings. We believe that probiotics should be offered routinely to all high-risk preterm neonates, taking into account the unaddressed issues. The best way forward could be to offer these products routinely but still within a research framework to cover the current gaps in knowledge. It is important to note that most of the unaddressed issues can be easily resolved by studies not requiring a placebo.

The benefits of probiotics may not be dramatic in neonatal units with a low incidence of all-cause mortality and definite NEC in preterm neonates for various reasons. Investigators have suggested that nutritional outcomes may be appropriate for probiotic research in such neonatal units, because of the beneficial effects of probiotics on the gastrointestinal tract.

Current evidence is inadequate in some areas of probiotic supplementation. We have erred on the side of safety in suggesting guidelines in these areas, taking into consideration the basic principle: first, do no harm. We wish to emphasize that "routine" does not equate to "blind" use of probiotics, a potentially powerful but double-edged weapon in this high-risk population. As the debate around routine use of probiotics in preterm neonates continues, countries such as Denmark have already issued guidelines for use of probiotics in preterm neonates. If prevention of death and disease and facilitation of nutrition is the goal, relying on a package of potentially better practices rather than on probiotics alone is essential.

Bowel Ischemia in a Baby with Unspecified Renovascular Hypertension

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Abstract

Introduction: Renovascular hypertension due to congenital multiple visceral arterial stenoses in neonates is rare. Management is challenging and has not been standardized. Medical control of blood pressure remains the first-line therapeutic approach. However, unwise control of blood pressure in such cases may lead to disastrous situations.

Case presentation: We present the case of an 18-day-old Saudi girl with hypertension due to unspecified vascular occlusive disease. The hypertension was managed medically by maintaining blood pressure at "near normal" levels, and this led to bowel ischemia. Our patient survived the short bowel syndrome and is now two years old. She is on full oral feeding and has reached acceptable growth parameters. Her blood pressure has stabilized at around 110/70 mmHg without anti-hypertensive drugs. She has good organ function and walks despite increased narrowing in stenotic areas and complete obliteration of her left iliac and femoral arteries as seen on follow-up computed tomography angiography.

Conclusions: We suggest keeping blood pressure at the highest levels permissible in similar clinical situations to prevent a state of bowel hypoperfusion. When alternative treatments for congenital multiple visceral arterial stenoses are not feasible, careful medical therapy and a waiting approach for collaterals to develop may be appropriate.

Introduction

Renovascular disease is an important cause of hypertension in children, and the incidence is reported to be 3% to 10%. Medical management remains the first line of treatment. However, unwise control of blood pressure (BP) may lead to disastrous situations. We present the case of a baby with congenital multiple visceral arterial stenoses in which medical therapy contributed to the development of bowel ischemia.

Case presentation

An 18-day-old full-term Saudi girl who had an unremarkable prenatal and family history (as obtained from the parents) and who was born via normal spontaneous vaginal delivery with

a birth weight of 2.5 kg was admitted to a provincial hospital with cardiogenic shock. High BP was diagnosed, and she was treated as a case of cardiomyopathy and was discharged home after 10 days on propranolol and captopril. Without a medical report from the previous hospital, her parents brought her to our pediatric emergency room at the age of 45 days with lethargy and poor oral intake. She looked malnourished and hypoactive. Her weight was 2.4 kg. She had a high systolic BP of 114 to 178 mmHg (normal values for this age and weight are from 70 to 80 mmHg) and a diastolic BP of 57 to 82 mmHg (normal values for this age and weight are from 30 to 40 mmHg).

She was admitted to the pediatric intensive care unit and required daily doses of 1.8 mg of hydralazine, 9 mg of propranolol, and 12 mg of captopril to keep her systolic BP in the range of 85 to 142 mmHg and her diastolic BP in the range of 43 to 75 mmHg. Laboratory studies showed the following: a white blood cell count of 32.8×10^9 cells/L, a hemoglobin level of 102 g/L, a platelet count of 804×10^9 cells/L, erythrocyte sedimentation rate of 2 mm/hour, normal renal and liver profile results, normal urine analysis results, a serum renin level of 625 nmol/L, a serum cortisol level of 526 nmol/ L, and a growth hormone level of 58 µg/L. An echocardiogram showed severe non-obstructive hypertrophy of both ventricles and normal cardiac function. A Doppler ultrasound of her renal arteries revealed severe bilateral renal artery stenosis with a peak systolic velocity of 250 cm/second and a resistive index of 0.89. A computed tomography (CT) angiography revealed multiple arterial stenoses involving both renal arteries near the ostium (Figure 1), the superior mesenteric artery (Figure 2), the celiac artery, the hepatic artery, and both femoral arteries.

Our patient was stabilized on daily doses of 6 mg of hydralazine and 9 mg of propranolol to keep her systolic BP in the range of 97 to 114 mmHg and her diastolic BP in the range of 39 to 54 mmHg. She was discharged home on these medications with a plan to undergo percutaneous transluminal angioplasty (PTA) of the stenosed arteries when she reached a weight of 5 kg. Two weeks after discharge, she presented to our pediatric emergency room with sepsis and greenish vomiting, rectal bleeding, and pneumoperitoneum. A laparotomy revealed bowel necrosis involving her ileum, cecum, and ascending colon. Her necrosed bowel was resected, and a jejunostomy with a mucus fistula at her transverse colon was created. The multidisciplinary team treating her included a pediatric surgeon, a pediatric intensivist, a pediatric nephrologist, a pediatric gastroenterologist, a pediatric geneticist, a pediatric rheumatologist, a pediatric

Figure 1 A computed tomography angiogram shows stenosis of both renal arteries near the ostium (arrows).

Figure 2 A computed tomography angiogram shows stenosis of the superior mesenteric artery (arrow).
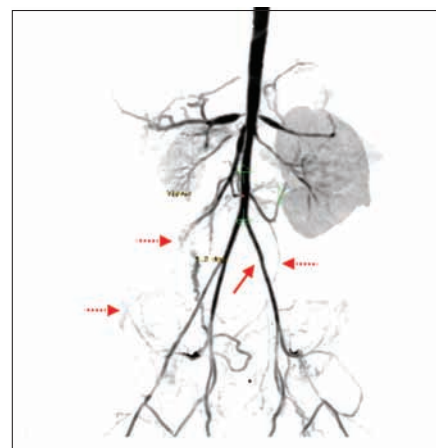

Figure 3 A follow-up computed tomography angiogram shows complete obliteration of the left external iliac and femoral arteries (arrow) and development of collateral circulation (dotted arrows).

radiologist, and an interventional radiologist. She stayed in hospital for about eight months. The results of a genetic analysis were normal, and metabolic disorders were ruled out. A skin biopsy was normal. The short bowel syndrome was managed successfully. The stoma was closed with a small bowel-to-transverse colon anastomosis. When she reached a weight of 5 kg, two attempts to perform PTA failed because of the very small caliber of her femoral arteries. During this eight-month period, all efforts were directed at keeping her systolic BP between 115 and 150 mmHg to prevent a further episode of bowel hypoperfusion. Later, she was discharged on full oral feeding and 2 mg of hydralazine orally every eight hours and 3 mg of propranolol orally every eight hours as needed if her systolic BP exceeded 150 mmHg.

At present, she is two years old and has normal cardiac, liver, and renal functions. She is on full oral feed- ing, and her weight is 11.5 kg. She has not required anti-hypertensive medications for the last six months. A recent CT angiography revealed increased narrowing of both renal arteries, her superior mesenteric artery, her celiac artery, and her hepatic artery and complete obliteration of her left external iliac and left femoral arteries. However, a good set of collateral vessels was seen during the evaluation (Figure 3).

Discussion

Renovascular hypertension in babies is caused by any one of a large group of vascular disorders. These disorders include renal venous thrombosis, thromboembolism of the renal artery, external compression of the renal artery, fibromuscular dysplasia, neurofibromatosis, Takayasu arteritis, Kawasaki disease, Williams syndrome, mid-aortic syndrome, idiopathic arterial calcification, and a so-called unspecified group of vascular occlusive diseases. The management of hypertension is individualized and depends primarily on the causative disorder. However, regardless of the causative disease, control of BP is a priority to prevent the possible complications of hypertension. Reproducible BP measurements above 90/60 mmHg are widely accepted as the definition of hypertension in the term neonate. Although many ill neonates are treated for hypotension and hypertension, the normal physiological BP to ensure appropriate organ perfusion is uncertain.[3] Intestinal angina in patients with multiple arterial stenoses is rare. Stanley and colleagues reported only two cases with classic intestinal angina out of 24 cases with

splanchnic arterial lesions. Sethna and colleagues reported only one case of bowel ischemia out of 102 cases of idiopathic mid-aortic syndrome. Our patient's condition belonged to the group of unspecified vascular occlusive diseases. Medical control of the BP with a PTA, or vascular reconstructive surgery at a later date, seemed to be an appropriate treatment strategy. The BP was brought to near normal levels. However, in the pre- sence of superior mesenteric artery stenosis, these 'near normal' levels were insufficient to ensure adequate bowel perfusion, and our patient developed bowel ischemia.

When she passed the critical period of sepsis and short bowel syndrome and reached a weight of 5 kg, she underwent two attempts to perform PTA. These attempts were unsuccessful because of the very small diameter of her femoral arteries. Open vascular surgery was unfeasible because of lack of experience. The only choice was to wait and see. Although a radiological follow-up showed increasing narrowing in the stenotic areas, our patient showed clinical improvement over time. This could be explained by the development of collateral circulation seen on follow-up Doppler ultrasound and CT angiography. Sethna and colleagues[7] reported oliguric renal failure in only 4% of 102 cases of idiopathic mid-aortic syndrome and stated that effective collateral circulation develops over time. Srinivasan and colleagues[10] documented the presence of collateral circulation in 51% of the 68 angiograms performed for 43 children with renovascular hypertension due to fibromuscular dysplasia and neurofibromatosis type 1.

Conclusions

In babies, the management of hypertension caused by unspecified vascular occlusive disease is challenging. A multidisciplinary approach is important. Although intestinal angina is a rare complication, doctors and parents should be aware of it. Parent education is essential to prevent late presentation. Keeping BP at 'high permissible' levels may prevent bowel hypoperfusion. Aggressive angioplastic interventions and open reconstructive surgeries are not indicated when the BP is medically controlled and the organs are functioning normally. Careful medical treatment and waiting for collateral circulation to develop may be appropriate in such difficult clinical situations.
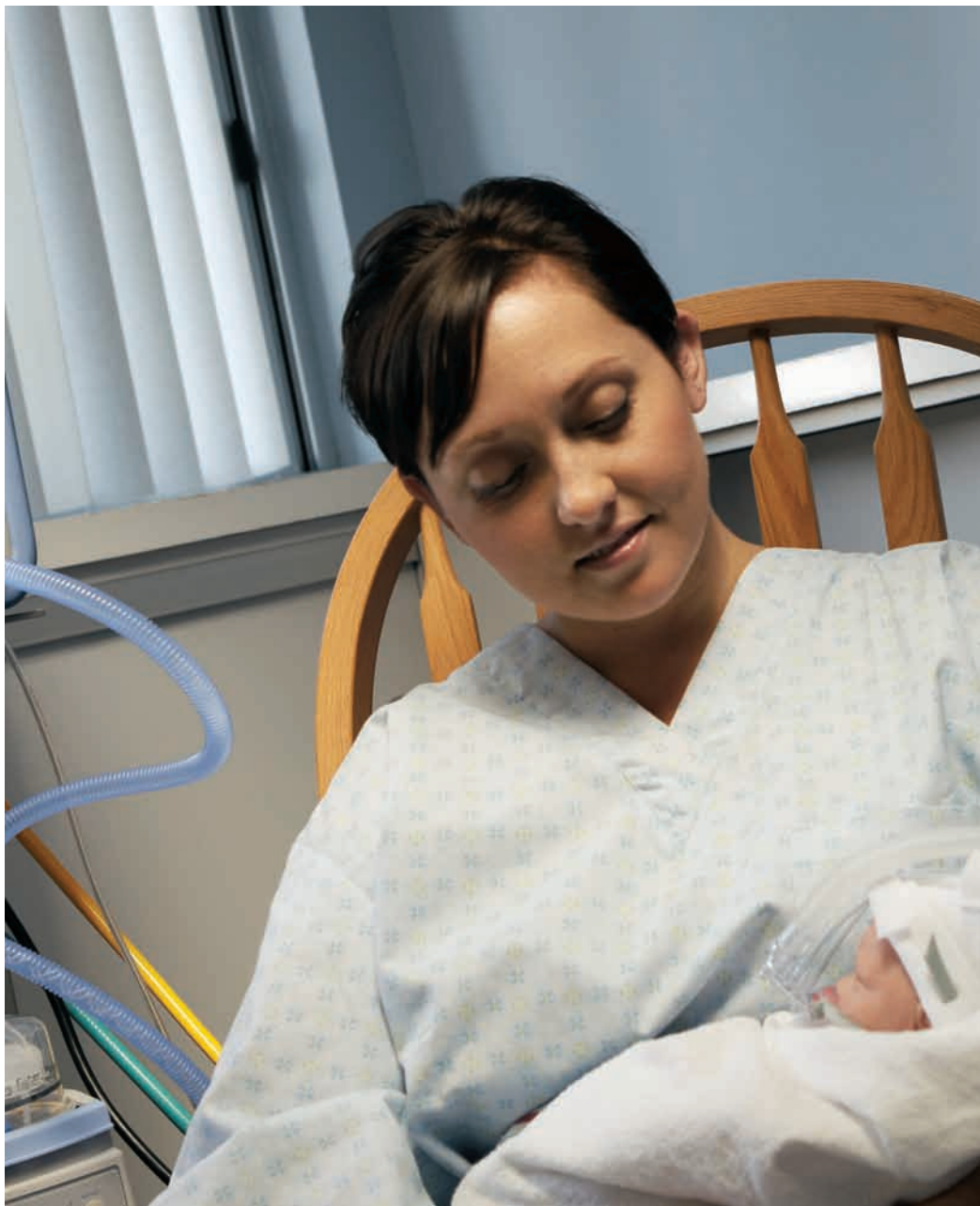
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