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November-December 2012

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The Journal of Perinatology-Neonatology

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References: 1. Rubin LP, et al. *Journal of Perinatology* advance online publication, 14 July 2011; doi:10.1038/jp2011.87. **2.** Kanako IN, et al. *Arterioscler Thromb Vasc Biol.* 2007;27:2555-2562. **3.** Canfield LM, et al. *Eur J Nutr.* 2003;42:133-141. **4.** Schweigert FJ, et al. *Eur J Nutr.* 2004;43:39-44. **5.** Patton S, et al. *Lipids.* 1990;25:159-165. **6.** Jewell VC, et al. *Proc Nutr Soc.* 2001;60:171-178. **7.** Connor SL, et al. *FASEB.* 2008;22:451-454.

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Editorial

Brave New World

Medical News Today recently reported on a scientific development which will surely impact parents' decisions about their babies: According to the news item, "With whole genome sequencing quickly becoming more affordable and accessible, we need to pay more attention to the massive amount of information it will deliver to parents, and the fact that we don't yet understand what most of it means, according to an article in the Hastings Center Report. Most analyses of the ethical issues raised by whole genome sequencing have been 'futuristic forecasting,' but the authors conclude that 'this is problematic given the speed with which whole genome sequencing is likely to be incorporated into clinical care,' as its price falls to under $1,000. Prenatal whole genome sequencing differs from current prenatal genetic testing practice in ethically relevant ways. Most notably, whole genome sequencing would radically increase the volume and scope of available prenatal genetic data. In contrast with current tests, which identify serious genetic conditions in fetuses at high risk for them, the new tests would likely be used by many more expectant parents and reveal a wide spectrum of genetic traits, including disease susceptibility. Some of the ethical challenges posed by prenatal whole genome sequencing arise from the uncertainty of what the information means. The function of more than 90% of genes in the human genome is unknown and as a result, the article says, 'much of the data generated from whole genome sequencing over the next few years (or even decades) will be of questionable utility.' After analyzing the kind of information that whole genome prenatal testing will yield, the authors conclude that most of it would probably not be as helpful as information uncovered by the current categories of prenatal tests. They noted that the quality and quantity of information may augment parents' anxiety. 'To the extent that parents now think of their child as a clean slate' during pregnancy, the prenatal image of a normal, healthy baby will be dramatically altered by this technology,' the authors write. The anxiety over the results and changing views of what is 'normal' could lead to an increase in pregnancy terminations. Apart from reproductive decisions, the authors also foresee whole genome prenatal testing having a negative impact on child rearing. For example, if parents were able to get genetic information suggesting that their child's predicted IQ may be low, they might not strongly encourage and support the child's efforts in school. Also, the new technology could increase the tension between the interests of parents and children. Although parents have a strong interest in getting information that informs their reproductive choices, children have a competing interest in not knowing certain kinds of information about themselves that could limit their autonomy as they grow into adulthood." The abstract of the referenced paper says: "Whole genome sequencing would radically increase the volume and scope of available prenatal genetic data. The wealth of new data could enhance reproductive decision-making, promoting parents' freedom to make well-informed reproductive decisions. We argue, however, that there is potential for prenatal whole genome sequencing to alter clinical practice in undesirable ways, especially in the short term. We are concerned that the technology could (1) change the norms and expectations of pregnancy in ways that complicate parental autonomy and informed decision-making, (2) exacerbate the deleterious role that genetic determinism plays in child rearing, and (3) undermine children's future autonomy by removing the option of not knowing their genetic information without appropriate justification." See The Hastings Center Report, July/August 2012, Prenatal Whole Genome Sequencing: Just Because We Can, Should We? by Donley, et al.

Les Plesko, Managing Editor

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News

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PETITION

Out of concern for the long-term health of premature babies, PreemieWorld, LLC has created a petition to ask the American Academy of Pediatrics (AAP) to revise its current Respiratory Syncytial Virus (RSV) guidelines so that all infants born prior to 37 weeks gestation automatically qualify for a full season of Synagis for at least one year. After almost a decade of providing guidelines that did recommend a full season of Synagis for all premature babies, in 2009 the AAP has dramatically changed its recommendations limiting doses for the majority of infants while disqualifying others altogether. In a typical season, premature babies would receive an injection every month. "Parents and professionals in the community are stunned by this change," commented Deb Discenza, Co-Founder of PreemieWorld, LLC. "Why would the medical community spend so much time and money saving and protecting that tiny baby only to send it home into a risky environment? RSV is a small cold to the average adult. To a premature baby with a fragile immune system it can spell grave illness, hospitalization and even death. If I thought that the AAP was providing real clinically-based evidence in these changes, then I would support it. However, noting that RSV can occur several times in one season and that they are not following proper labeling instructions as approved by the Food & Drug Administration tells me that the guidelines need to be reverted until full research can be done." Deb Discenza is the mother of a girl born at 30-weeks gestation. She is the author of The Preemie Parent's Survival Guide to the NICU, heads up PreemieWorld, LLC at www.PreemieWorld.com and is the moderator of a 12,000 member online social network for parents of premature babies at http://www.inspire.com/groups/preemie/. The petition may be found at http://bit.ly/RSVPetition.

BIG ADVANTAGE

It's really not unexpected news, but premature babies are more likely to survive when they are born in high-level neonatal intensive care units (NICUs) than in hospitals without such facilities, and this benefit is considerably greater than previously reported. A current study, the largest to date, revealed a stronger effect. Pediatric researchers who analyzed more than 1.3 million premature births over a 10-year span found that the survival benefits applied not only to extremely preterm babies, but also to moderately preterm newborns. The research team performed a retrospective study of all hospital-based deliveries of infants with a gestational age between 23 and 37 weeks in Pennsylvania, California and Missouri, a total of over 1,328,000 births. The study focused on preterm deliveries in high-level NICUs, compared to preterm deliveries at all other hospitals. "Prior studies from the early 1990s found increased survival rates of 30 to 50 percent among preterm infants delivered at high-level NICUs, compared to preterm infants delivered elsewhere," said study leader Scott A. Lorch, MD, a neonatologist at The Children's Hospital of Philadelphia. "However, our research found rates as high as 300 percent improvement, when our study design controlled for the effect of sicker patients who typically deliver at high-level NICUs." Complication rates were similar for both types of hospitals. The complete study, "The Differential Impact of Delivery Hospital on the Outcomes of Premature Infants," was published in the journal Pediatrics in July online and in print in August.

AWARDED

The Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) received its third consecutive designation of "Premier Program" by the American Nurses Credentialing Center (ANCC) for excellence in continuing nursing education (CNE). The 2012 Premier Program award recognizes "continuing nursing education providers that continually raise the bar for quality." AWHONN will be "expected to mentor other continuing nursing education organizations, to continually provide and disseminate best practices, to publish, and to assist ANCC in advancing high quality continuing nursing education activities," according to the ANCC. AWHONN CNE offerings span a range of topics, from childbearing and newborn care to women's health and professional nursing issues. AWHONN's biggest CNE program is its long standing fetal heart monitoring education program, which educates more than 10,000 participants annually. Particularly highlighted by ANCC for 2012 was AWHONN's Late Preterm Infant (LPI) Initiative.

A LITTLE LATE

In response to the growing number of late preterm infants and the data that clearly demonstrates the health risks of preterm birth, AWHONN launched its Late Preterm Infant Initiative in 2005 to help raise awareness of the special needs of this population of vulnerable newborns. As part of the LPI Initiative, AWHONN conducted a 14-hospital research-based practice project and subsequently released its Assessment and Care of Late Preterm Infant Evidence-Based Clinical Practice Guideline. Findings from the project included analysis of health risks experienced by infants in the study population. The article "Newborn Clinical Outcomes of the AWHONN Late Preterm Infant Research-Based Practice Project, notes that LPIs experience difficulty with basic life processes, such as breathing, feeding and maintaining a healthy body temperature. Furthermore, LPIs need to be observed for physiologic instability because they have a chance of developing problems that may require NICU treatment. Feeding challenges were among the most frequently observed complications in the study population.

RECOGNIZED

AWHONN, the Association of Women's Health, Obstetric and Neonatal Nurses, has awarded five recipients with the Fetal Heart Monitoring Instructor Recognition Award. Luann Beacom, FNP, CNS, MPH, MSN, works as a nurse practitioner in women's health as well as a perinatal clinical nurse specialist for Scripps Healthcare in San Diego, CA. Beacom has worked in perinatal nursing for 30 years, has been a fetal heart monitoring Instructor since 1995, and an Instructor Trainer since 1998. Donna Hintz, BA, RN, CLC, is a clinical nurse educator for The Birth Place at St Alexius Medical Center in Bismarck, ND. She has been a fetal heart monitoring site course administrator and Instructor for the

Intermediate and Advanced courses since 2006. Additionally, Hintz works as a staff nurse and teaches breastfeeding classes at St Alexius Medical Center. Tao Liu, RN, MSN, has been a fetal heart monitoring Instructor since 2008. In addition to her role as a fetal heart monitoring Instructor, Liu is currently an assistant director of nursing and an obstetrical nursing educator at the State University of New York Downstate Medical Center. Candace Rouse, RN, MSN, CSN-BC, is the clinical nurse specialist for perinatal services at Sinai Hospital of Baltimore, MD. She has been a fetal heart monitoring Instructor since 2008, and a Designated Instructor teaching both the Advanced and Intermediate courses since 2012. Deborah Schy, MSN, APN/CNS, RNC-OB, C-EFM, IBCLC, CIMI, has been a fetal heart monitoring Instructor since 1998 and an Instructor Trainer since 2007. Schy also works as a perinatal outreach educator at Advocate Lutheran General Hospital in Park Ridge, IL.

KEEP COOL

Texas Children's Hospital and Baylor College of Medicine announced the arrival of Dr Jeffrey Kaiser to lead the hospital's hypothermia program for newborns. Kaiser is an internationally recognized leader in neonatal neurology and a National Institutes of Health-funded researcher. An expert in hypoxic ischemic encephalopathy, Kaiser was the first physician in the world to use FDA-approved head-cooling equipment on an infant with HIE. Recent studies published in the New England Journal of Medicine and Pediatric Research suggested that babies with HIE who were cooled shortly after birth continue to benefit from the therapy at school age. Texas Children's Newborn Center, together with the hospital's new Pavilion for Women, houses the nation's largest level-III Neonatal Intensive Care Unit and is one of only two hospitals in the greater Houston area to offer whole body cooling treatments to prevent fatalities and severe neurological damage that can lead to mental retardation, cerebral palsy and epilepsy in full-term babies who are oxygen deprived at birth.

HIGHER RISK

Infants who are bottle-fed face a higher risk of developing pyloric stenosis. Researchers at the Statens Serum Institute in Copenhagen looked at the connection between bottle-feeding and pyloric stenosis using data on 70,000 infants to identify 65 who had to have surgery for pyloric stenosis. Of these infants, 29 had been bottle-fed. The researchers found bottle feeding increased the odds of developing pyloric stenosis 4.6-fold. The risk was seen even when the baby was breast-fed before being bottle-fed and it started within 30 days after bottle feeding began. Information is from HealthDay Reporter, from an article by Steven Reinberg, copyright HealthDay Reporter.

WATCH YOUR FINGERS

Evan Godt reported in Healthimaging.com that a significant number of adult fingers are exposed to radiation during NICU radiographs. Researchers at Royal University Hospital, Saskatoon, Saskatchewan, Canada, also noted that their numbers may be just the fingertip of the iceberg, so to speak, because radiograph images are often cropped. The researchers looked at 230 consecutive NICU chest radiographs at their facility. Thirty out of that number, or 13%, showed fingers directly in the x-ray beam and were visible on PACS. An additional 22 radiographs contained fingers that were cropped, and 44 radiographs contained fingers within the coned area. In all, 42% of images

contained extraneous adult fingers in at least one of the three areas.

NOURISHMENT

Resourceful bacteria in the baby microbiome can ferret out nourishment from a previously unknown source, possibly helping at-risk infants break down components of breast milk, according to researchers at UC Davis. Breast milk contains glycans (complex sugars) that infants cannot break down, so it promotes the growth of bifidobacteria that can process these glycans. While it is known that bifidobacteria avail themselves of the free glycans in breast milk, it was not known whether these bacteria could also obtain glycans that were linked to proteins. These glycoproteins are abundant in breast milk. The researchers found that specific strains of bifidobacteria possessed enzymes capable of removing glycan groups from glycoproteins, enabling them to use these glycans as an additional food source. One of the enzymes, EndoBI-1, was able to remove any type of N-linked glycan (glycans attached to proteins by the amino acid asparagine). This is unique among enzymes of this type and may provide a growth advantage for bifidobacteria in the infant intestine because the glycoproteins in breast milk have complex glycans attached.

CALL ME MAYBE

Telemedicine is making it possible to bring sophisticated medical care and technology to patients and their caregivers. With the placement of faster fiber-optic networks in areas away from metropolitan hubs, high-speed bandwidth is making it possible for physicians, physicians' assistants and nurses to offer a full range of treatment options and diagnostics to patients in rural or underserved areas. The North Country Telemedicine Project in upstate New York is such an example. Upon its completion, with the click of a mouse every healthcare facility throughout the North Country/Adirondacks will be able to connect with each other as well as with larger healthcare facilities in other regions. Tech Valley Communications is stringing more than 5,000 miles of cable in Saratoga County to that end at a cost in excess of $1 million, creating a fiber optic network allowing medical professionals to communicate with one another in real-time for any medical purpose.

BMC NEWS

BioMed Central's e-mail newsletter touted the impact of open access vs subscription journals. BMC noted: The scientific impact of articles published in open access and subscription journals are similar when journal discipline, location of publisher and age of publication are compared, which is particularly true in medicine and health, where open access journals founded in the last 10 years receive on average as many citations as subscription journals launched during the same time. See: Open access versus subscription journals: a comparison of scientific impact, by Bo-Christer Björk, David Solomon, BMC Medicine 2012, 10:73. According to the article abstract, "average citation rates, both unweighted and weighted for the number of articles per journal, were about 30% higher for subscription journals. However, after controlling for discipline (medicine and health versus other), age of the journal (three time periods) and the location of the publisher (four largest publishing countries versus other countries) the differences largely disappeared in most subcategories except for journals that had been launched prior to 1996. OA journals that fund publishing with article processing charges (APCs) are on average cited more than other OA journals. In medicine and health, OA journals founded in the last 10 years are receiving about as many citations as subscription journals launched during the same period. The results indicate that OA journals indexed in Web of Science and/or Scopus are approaching the same scientific impact and quality as subscription journals, particularly in biomedicine and for journals funded by article processing charges.

IQ AFFECTED

A study by researchers at Columbia Center for Children's Environmental Health has found a difference between how boys and girls respond to prenatal exposure to the insecticide chlorpyrifos. Exposed boys had greater difficulty with working memory than girls with similar exposures. On the plus side, having nurturing parents improved working memory, especially in boys, although it did not lessen the negative cognitive effects of exposure to the chemical. Recent research established a connection between prenatal exposure to chlorpyrifos and deficits in working memory and IQ at age 7. A follow-up study showed evidence in MRI scans that even low to moderate levels of exposure during pregnancy may lead to long-term, potentially irreversible changes in the brain. This latest study explored the impact of sex differences and the home environment on these health outcomes. The researchers studied a subset of 335 mother-child pairs enrolled in the ongoing inner-city study of environmental exposures, including measures of prenatal chlorpyrifos in umbilical cord blood. When the children reached age 3, the researchers measured the home environment using the Home Observation for Measurement of the Environment (HOME) criteria, including two main categories: 1) environmental stimulation, defined as the availability of intellectually stimulating materials in the home and the mother's encouragement of learning; and 2) parental nurturance, defined as attentiveness, displays of physical affection, encouragement of delayed gratification, limit setting, and the ability of the mother to control her negative reactions. The researchers tested IQ at age 7. While home environment and sex had no moderating effect on IQ deficits related to chlorpyrifos exposure, the researchers found that chlorpyrifos exposure had a greater adverse cognitive impact in boys as compared to girls, lowering working memory scores by an average of three points more in boys than girls (96.5 vs 99.8); and that parental nurturing was associated with better working memory, particularly in boys. The insecticide chlorpyrifos was widely used in homes until 2001. It continues to be present in the environment through its widespread use in agriculture, wood treatments, and public spaces such as golf courses, parks, and highway medians. People near these sources can be exposed by inhaling the chemical, which drifts on the wind. Low-level exposure can also occur by eating fruits and vegetables that have been sprayed with chlorpyrifos.

WEIGHT RELATIONS

Being overweight and pregnant can affect how children grow and develop. Researchers at the University of Iowa compared the weight and height of babies born to overweight and obese mothers with those born to normal-weight mothers. Contrary to expectations, babies of overweight/obese mothers gained less weight and grew less in length than babies of normal-weight women from just after birth to three months. The overweight/obese mother babies also gained less fat mass than those born to normal-weight mothers. Fat mass in infants is widely considered to be crucial to brain growth and development. The study implies that the obesity epidemic is harming children while they are still in utero and increases the importance of addressing the

risk of obesity before females enter the child-bearing years, where the negative effects can affect the next generation. Why is this happening? The researchers noted that fat cells that normally help suppress a person's immune system flare up when an adult is overweight. This state of warfare being waged in an overweight/obese pregnant mother's immune system may also inflame the fetus's developing immune system, diverting energy that otherwise would go to the baby's development. Also, researchers opined that the cosseted baby is getting so many free fatty acid-derived growth hormones from its overweight mother that the other growth generator, the pituitary gland, slows its production. When the baby is born and is cut off from the mother's growth line, the pituitary gland is not developed enough to pick up the slack, the researchers think. The study included 97 mothers, of whom 38 were overweight or obese. None was diabetic. The researchers found babies of overweight/obese mothers gained 11 ounces less than those born to normal-weight mothers from two weeks to three months. They also put on 0.3 ounces less fat mass and grew nearly a half-inch less.

EXPOSED

Pregnant women who are highly exposed to PFCs have babies that are smaller at birth and larger at 20 months of age, according to a study from Emory University. PFCs are found in protective coatings of packaging products, clothes, furniture and non-stick cookware. They've been detected in human sera, breast milk and cord blood. The study included 447 British girls and their mothers. The researchers found that even though girls with higher exposure were smaller than average (43rd percentile) at birth, they were heavier than average (58th percentile) by 20 months of age. The authors say this path may lead to obesity at older ages.

SIZE DOESN'T MATTER

Research at the University of Rhode Island suggests that the length of human pregnancy is limited primarily by a mother's metabolism, not the size of the birth canal. Scientists have previously posited that humans' short duration of gestation is so that babies are born before their heads get too big. As a result, human babies are relatively helpless and seemingly underdeveloped in terms of motor and cognitive ability compared to other primates. The study noted that the main problem with this theory is that there is no evidence that hips wide enough to deliver a more developed baby would be a detriment to walking, so that there's doubt that the size of the birth canal is limited by bipedalism. Plus, there is no solid evidence that human pregnancy is shortened compared to other primates and mammals. In fact, human gestation is longer than expected compared to other primates, and babies are larger, not smaller. The researchers posited that metabolism might be a better determinant of the timing of human birth. They came up with the theory of EGG, ie, energetics, gestation, and growth, and stated that under this theory, babies are born when moms can't put any more energy into gestation and fetal growth. Using metabolic data on pregnant women, the researchers showed that women give birth just as they are about to cross into a metabolic danger zone, the limit to how man calories a body can burn each day, and that women give birth right before they reach this zone.

AT RISK

Researchers at UCLA's Jonsson Cancer Center found that the children of US-born Latina women are at higher risk of having retinoblastoma. The study also found that offspring of older fathers were at greater risk for retinoblastoma, as were children born to women with sexually transmitted diseases and those born in multiple births, which may indicate an increased risk from in vitro fertilization. The research team used data from

the California Cancer Registry and examined all retinoblastoma cases reported from 1988 to 2007. Using California data allowed the researchers to cull information from a large and diverse population that included many Latinas. The risk is lower among mothers born in Mexico. The researchers surmised that Latinas born in the US are less likely to exhibit the healthy pregnancy behaviors found in foreign-born Latinas. They have poorer diets and are more likely to smoke and drink during pregnancy, which could contribute to the risks of retinoblastoma. The researchers noted that while immigrant women born in rural Mexico often have less education and lower socioeconomic status, they retain healthier diets and perinatal habits, which may be correlated to lower risk of disease in their children.

NAMASTE

University of Michigan researchers have found that pregnant women who were identified as high-risk for serious depression who participated in a 10-week yoga intervention saw significant reductions in their depressive symptoms. These mothers-to-be also reported stronger attachment to their babies in the womb. Women who showed signs of depression and who were between 12-26 weeks pregnant participated in 90-minute mindfulness yoga sessions that focused on poses for the pregnant body, as well as support in the awareness of how their bodies were changing to help their babies grow.

NO DIFFERENCE

Babies presenting vertex position born by vaginal delivery have equally successful birth rates as those born by cesarean delivery, according to researchers at the NIH. Medical News Today reported: the researchers noted, however, that preterm breech births by vaginal delivery are not successful, and C-sections are much more practical for these types of births. The authors analyzed data from the Consortium on Safe Labor (CSL), which includes information from over 200,000 deliveries from 2002 to 2008 which took place at 19 hospitals and 12 clinics all over the country. The researches analyzed 2,906 pregnancies, between 24 0/7 weeks and 31 6/7 weeks, which had the options of either vaginal or cesarean delivery. They compared planned cesarean delivery with vaginal delivery. The data was looked at by age blocks: 24 0/7 to 27 6/7 weeks and 28 0/8 to 31 6/7 weeks because the neonatal mortality seemed to occur at 24 0/7 to 27 6/7 weeks. Vaginal deliveries, with vertex presentation and attempted at 24 0/7 to 27 6/7, had no dramatic affect on neonatal mortality, and 80% of the births had positive outcomes. Breech presentation resulted in planned cesarean deliveries for the most part and of the vaginal deliveries performed, only 27.6% were successful. In deliveries during 28 0/7 to 31 6/7 weeks' gestation, for vertex presentation most deliveries were successful, with no difference found between planned cesarean deliveries and neonatal mortality rates. Neonatal mortality was 6% for vaginal deliveries and 1.5% of cesarean deliveries when the presentation was breech during the 28 0/7 to 31 6/7 weeks' gestation. Information for the above is from Medical News Today, written by Christine Kearney, copyright Medical News Today.

NATURAL CHILDBIRTH AND PTSD

A Tel Aviv University researcher has found that a third of all post-partum women exhibit some symptoms of PTSD, and a smaller percentage develop full-blown PTSD following the ordeal of labor. Of those women who developed post-traumatic symptoms, 80% opted for natural childbirth without pain relief. Other significant factors identified included the woman's body image, including discomfort with being in an undressed state for the relatively prolonged period of labor and undergoing elective cesarean sections, fear during labor, and complications in the present and earlier pregnancies and labors. Researchers interviewed 89 post-partum women between the ages of 20 and 40, first within 2 to 5 days after delivery and then again one month after delivery. They discovered that of these participants, 25.9% displayed symptoms of post-trauma, 7.8% suffered from partial post-trauma, and 3.4% exhibited symptoms of full-blown PTSD. Symptoms included flashbacks of the labor, the avoidance of discussion of the event, physical reactions such as heart palpitations during such discussions, and a reluctance to consider having another child. The most influential factor was pain management during delivery. Of the women who experienced partial or full post-trauma symptoms, 80% had gone through a natural childbirth, without any form of pain relief. Eighty percent of the PTSD group reported feeling discomfort with being unclothed, and 67% had previous pregnancies which they described as traumatic. Fear of the labor itself, both in terms of expected pain levels and danger to themselves and their children, was also influential. The researchers discovered that support during labor, in the form of a midwife or doula, had no impact when it came to avoiding post-traumatic symptoms. Factors such as socioeconomic and marital status, level of education, and religion also had no effect.

DEFECT

An increased production of a protein, HUEW1, has been found to likely be responsible for a genetic defect that leads to an intellectual disability, XLID, in 2-3% of infants. An intellectual disability is present in 2 to 3% of babies at birth, possibly by a genetic defect, but scientists have been unsure exactly what genes are responsible in 80% of these cases. According to researchers at VIB/KU Leuven, the cause in some patients is an increased production of the HUEW1 protein. HUEW1 regulates the dose of other proteins in the brain. The researchers concluded that further exploration is required in order to develop a new treatment for XLID. A better understanding is needed of the role of HUWE1 in the body, they explained, more specifically in the brain. Reported by Medical News Today, written by Sarah Glynn, copyright Medical News Today.

SEX NORMALIZATION

A paper from researchers at Northwestern University used Freedom of Information Act findings to detail off-label medical intervention employed in the US on pregnant women to intentionally engineer the development of their fetuses for sex normalization purposes. The pregnant women targeted are at risk for having a child born with congenital adrenal hyperplasia. Women genetically identified as being at risk are given the synthetic steroid dexamethasone starting as early as week five of the first trimester to try to "normalize" the development of those fetuses, which are female and CAH-affected. Because the drug must be administered before doctors can know if the fetus is female or CAH-affected, only one in eight of those exposed are the target type of fetus. The off-label intervention does not prevent CAH; it aims only at sex normalization. Like diethylstilbestrol, which is now known to have caused major fertility problems and fatal cancers among those exposed in utero, dexamethasone is known, and in this case intended, to cross the placental barrier and change fetal development. Experts estimate that the glucocorticoid dose reaching the fetus is 60 to 100 times what the body would normally experience. Medical societies have argued against this off-label intervention outside prospective clinical trials because it is so high risk

and because nearly 90% of those exposed cannot benefit. The researchers noted that mothers offered the intervention have been told it has been found safe for mother and child but there has never been any such scientific evidence. A recent study in Sweden has found a nearly 20% serious adverse event rate among the children exposed in utero. Clinical proponents of the intervention have been said to be interested in whether the intervention can reduce rates of tomboyism, lesbianism and bisexuality, characteristics they have termed "behavioral masculinization." The authors stated that the US systems designed to prevent another tragedy like DES and thalidomide involving de facto experimentation on pregnant women and their fetuses, appear to be broken and ineffectual.

UNAFFECTED

Researchers at Stanford University demonstrated that the fraction of fetal cell-free DNA (cfDNA) in maternal blood is unaffected by the mother's presumed risk for trisomy, offering support for the use of non-invasive prenatal testing (NIPT) for detecting genetic conditions such as Down syndrome in a broad patient population. Stanford's study showed that there were no significant differences in the fraction of fetal cfDNA in maternal blood in women who were stratified into three different trisomy risk groups based on maternal age, prenatal screening results or nuchal translucency measurement. Previous studies demonstrated that fetal fraction did not vary with race, ethnicity, maternal age, or trisomy type.

ABORTION AND BIRTHS

Researchers at the National Institute for Health and Welfare in Helsinki, Finland found that women who have had three or more abortions have a higher risk of some adverse birth outcomes, such as delivering a baby prematurely and with a low birth weight. The research found that among 300,858 Finnish mothers, 31,083 (10.3%) had had one induced abortion between 1996-2008, 4,417 (1.5%) had two, and 942 (0.3%) had three or more induced abortions before a first birth (excluding twins and triplets). Those who had had three or more induced abortions had a small, but statistically significant increased risk of having a baby with very low birth weight (less than 1500g), low birth weight (less than 2500g), or of a preterm birth (before 37 weeks), or very preterm birth (before 28 weeks), compared to women who had had no abortions. There was a slightly increased risk of a very preterm birth for women who had had two induced abortions. Most of the induced abortions (88%) were surgically performed and nearly all (91%) were performed before 12 weeks gestation. The risk of having a baby born very preterm appeared to increase slightly with each induced abortion, but only the risk from two abortions or more was statistically significant. Among women who had had three or more abortions, there was a statistically significant increased risk of a third (35%) having a baby born preterm (before 37 weeks), a two-fold (225%) increased risk of very low birth weight, and a two-fifths (43%) increased risk of low birth weight.

MILKING IT

Scientists at Duke University Medical Center have found that breast milk, but not infant formula, fosters colonies of microbiotic flora in a newborn's intestinal tract that aid nutrient absorption and immune system development. The researchers grew bacteria in samples of infant formulas, cow's milk and breast milk. For the infant formula, the researchers used three brands each of popular milk- and soy-based products, and they purchased whole milk from the grocery store. Breast milk was donated and processed to separate different components, including proteins, fats and carbohydrates. They also tested a purified form of SIgA. The infant formulas, the milk products and the SIgA were incubated with two strains of E. coli bacteria, which immediately began multiplying in all of the specimens, but there was an instant difference in the way the bacteria grew. In the breast milk, bacteria stuck together to form biofilms that serve as a shield against pathogens and infections. Bacteria in the infant formula and cow's milk proliferated wildly, but it grew as individual organisms that did not aggregate to form a protective barrier. The bacteria in SIgA had mixed results, suggesting that this antibody by itself isn't enough to trigger the beneficial biofilm formation.

DISCRIMINATION = LBW

Yale Researchers have found evidence that suggests discrimination on a regular basis against pregnant urban women can play a large part in increased risk of low birth weight among newborns. The researchers interviewed 420 black and Latina women between the ages of 14 and 21 during their second and third trimesters and again when their babies were 6 and 12 months old. Those who said they had been discriminated against the most had higher levels of depression and eventually had babies who weighed less at birth then the women who reported less. Reported by Christine Kearney in Medical News Today, copyright Medical News Today.

FAT DAD = WEAK SPERM

Obesity in dads negatively impacts sperm, which results in smaller fetuses, poor pregnancy success and decreased placental development, according to a team of experts at the University of Melbourne's Department of Zoology. In order to identify the effects of paternal obesity on embryo implantation into the mother's womb and fetal development, in vitro fertilization (IVF) was used on animals in the study. Embryos were generated from male mice that were normal weight and obese. For ten weeks, the obese mice were fed the equivalent of a western fast food diet. Results showed that the fetuses produced from obese fathers had delayed development. There was a 15% decrease in fetal development and the rate of embryo implantation in the womb. Information is from an article written by Sarah Glynn in Medical News Today, copyright Medical News Today.

NANN NEWS

News from smartbrief.com, NANN's aggregator news service: Moderately premature infants who had **hypoglycemia** after birth were more likely to suffer developmental delays as well as neonatal morbidities as they grew up, a Dutch study found. Researchers said the increased risk of developmental delays can be attributed to the brain injury risk posed by low blood glucose levels [The Inquisitr]… Receiving the H1N1 **flu vaccine** during pregnancy did not raise the risk of birth defects or pregnancy complications, according to Danish researchers [WebMD]… NANN's new 2012 **online product catalog** offers a variety of educational and professional development programs and resources to enhance nursing knowledge and provide valuable networking opportunities in neonatal nursing. NANN members receive a significant discount on products and many are available for free. To purchase NANN products, visit NANNstore.org… New Zealand researchers monitored the oxygen levels of 80 sleeping babies and found that **bed-sharing babies** had more oxygen desaturation and carbon dioxide rebreathing events compared with babies sleeping alone in cribs [Huffington Post]… **NAVA** can help protect the lungs of preterm infants needing

mechanical ventilation, according to researchers at Seoul National University College of Medicine. The study compared NAVA with synchronized intermittent mandatory ventilation with pressure support, and found it reduced peak inspiratory pressure, lessened the work of breathing and lowered peak electrical activity of the diaphragm [Medscape/Reuters]… The **Navigator Mentoring Program** is a peer mentoring program designed to provide support for novice nurses for six months beyond the orientation period. This product includes a book and CD-ROM discussing the development of the novice nurse's technical and critical-thinking skills and addressing the need for interpersonal skill development. Enter promo code SALE40 to receive discount at checkout… The Competencies and **Orientation Tool Kit** for Neonatal Nurse Practitioners covers NNPs skills, from novice to expert, using competencies as the basis of measurement or performance evaluations. When purchased, a complementary flash drive is included which contains 15 easy-to-use forms and tools that can be customized… Administering **corticosteroids** to pregnant women at high risk of preterm delivery can boost fetal lung development even after the recommended 34-week cutoff, Tel-Aviv University researchers said. Their study found that infants whose mothers were given betamethasone after 34 weeks had fewer respiratory problems than those whose mothers did not receive the treatment [Medscape/Reuters]… Some newborns may be treated as small or large for their gestational age because of **errors in neonatal growth charts**, McMaster University researchers reported. They found 14 of 16 studies used for developing birth-weight charts contained systematic plotting errors and estimated that 5% of newborns would be misclassified due to the errors. The researchers recommend plotting birth-weight values in the middle of the newborn's gestational week rather than at the beginning, which shifts the curve leftward [Medscape/Reuters]… Michigan's Munson Medical Center responded to an increasing volume of NICU patients by creating a **special caregiver team** comprising two neonatologists and four nurse practitioners that provides 24/7 in-house coverage specialized care for the unit [WPBN-TV/WTOM-TV]… **NANN's Career Center** is the place to see available opportunities. With more than 7,000 highly skilled and trained members, new opportunities are added frequently. Visit NANN Career Central... **Academic hospitals** had higher rates of adverse events among pediatric patients but fewer preventable complications than nonacademic hospitals, according to researchers at the Hospital for Sick Children in Toronto who examined data on Canadian hospitals. The study included academic centers with level 3 NICUs and community hospitals with a NICU or special-care nursery. Intensive care services accounted for 13.3% of adverse events overall [MedPage Today]… Belgian researchers assessed more than 100 small-for-gestational-age babies and found those who were **formula-fed** had higher endocrine levels of high-molecular-weight adiponectin and insulin growth factor-I than the breast-fed group. They noted the catch-up growth of SGA babies was mainly restricted to lean mass in the initial four months after birth, regardless of feeding type [PhysiciansBriefing.com/HealthDay News]… A 96-month retrospective study found that using **prophylactic antibiotics** an hour prior to cesarean delivery instead of after umbilical cord clamping decreased surgical site infections by 48% [Medscape]… The Ohio Perinatal Quality Collaborative used a **quality improvement program** to reduce medically unnecessary early deliveries by 60% in 20 participating hospitals [Reuters]… The Neonatal Intensive Care **Nursing Certification Review Course** helps to identify the special knowledge inherent in the role and function of the registered nurse preparing to become certified in neonatal intensive care nursing… "Double Trouble: The Effects of Multiple Gestations" reinforces a neonatal nurse's knowledge on the effects of **multiple pregnancies**. This module includes managerial strategies, ways to involve families, and areas for further research along with a fun crossword as a learning assessment tool (1 CNE contact hour; free to NANN members)… Women who were obese and developed **gestational diabetes** had the highest increase in risk for delivering large babies, per a study reported in Diabetes Care. Researchers noted increased risk for heavier babies among overweight and obese women even without gestational diabetes [WebMD]… Certification and Core Review for Neonatal Intensive Care Nursing, 4th edition, prepares nurses for the AACN's **CCRN-Neonatal exam** and the **NCC's Neonatal Intensive Care Nursing exam**, the two leading neonatal critical-care nursing certification examinations. This book reflects essential knowledge, latest evidence and best practices to offers excellent preparation for the certification exam… The NANN store also offers: Precepting the **Advanced Practice Nurse**: From Expert RN to Novice NNP, which discusses current theories and published evidence on the teaching and learning experience and offers practical examples and tools that will enhance the quality of preceptorships for both the preceptor and preceptee. Eligible for 4.0 CNE contact hours… A Johns Hopkins Children's Center survey of 100 mothers with babies in an NICU found 92% felt discussions with physicians, nurses and other caregivers were productive, yet many did not agree with a **doctor's opinion** concerning the severity of their child's condition. The study in the Journal of Perinatology found 63% of these mothers said their child was not as sick as the physician had stated and in some instances mothers of children with life-threatening conditions described their infants not being ill, being only somewhat ill or even "pretty healthy" [HealthDay News]… The Resource Guide for **Neonatal Cardiac Care** has been updated recently with 14 full-color labeled illustrations to show heart defects in an easy-to-open ring packet. This guide is a portable resource to share with a parent when discussing a neonate's care through the use of illustrations… Newborn screening effectively identifies **congenital hypothyroidism** but more work is needed to help children get treatment that prevents intellectual deficits. A Wayne State University team said many children stop treatment without medical supervision. Children who were underweight at birth or who had been admitted to a NICU were more likely to discontinue treatment [Medscape]… A survey revealed that 70% of more than 100 doctors surveyed reported that they found **mobile apps** were highly or very credible. Researchers also found that 76% of respondents felt similarly about **medical websites**. Nurses were more skeptical, with 46% trusting apps and 69% trusting medical websites [MobiHealthNews.com].

PRODUCTS

DISTRIBUTOR

MediPurpose announced KOL Bio-Medical Instruments, Inc as its Eastern US regional distributor for its new babyLance infant heel incision device. The company also announced that Kentec Medical of Irvine, CA will distribute babyLance heelsticks in 15 states throughout the Western United States. The babyLance will be distributed in Austria by Medikus. The new babyLance infant heel incision device is a fully redesigned iteration of MediPurpose's original heelstick device. The new babyLance features an ergonomic design to provide a secure and stable grip.

Combined with a redesigned trigger mechanism, the device is easy to activate, helping to deliver a consistent incision without touching the baby's tender nerve fibers. The babyLance BLN (Newborn) delivers an incision depth of 1.00 mm. The babyLance BLP (Preemie), delivers an incision depth of 0.85 mm. Contact medipurpose.com/babylance.

WHO'S LISTENING?
How secure is the smartphone, tablet or other mobile device that stores your important data? And what if you couldn't remotely erase or retrieve your data if the device were lost, stolen or invaded by hackers? For many who work in healthcare, there's often that worry. But now they'll have help. A company called CommandHub has developed and patented new tools with military-grade security for protecting sensitive data on mobile devices while allowing users to easily access and, if they choose, share their information with others. IT company NJVC announced it will be the preferred distributor of CommandHub. Contact njvc.com/commandhub.

GO WITH THE FLO
Maxtec, Salt Lake City UT, offers the newMaxFLO_2 air & oxygen mixer. The MaxFLO_2 offers an affordable method for mixing precise amounts of air and oxygen in high flow and low flow applications. Each MaxFLO_2 comes equipped with dual flow meters, a mixed gas analysis port for spot-checking or continuous monitoring of FiO2, and a pole mount. When combined with a Maxtec oxygen analyzer, the MaxFLO_2 provides a convenient gas mixing solution that provides users with immediate access to total flow rate and FiO2. Contact maxtecinc.com, (800) 748-5355.

TAKING NOTE
Grand Rounds Software, LLC (GRS), makers of the Crib Notes suite of EMR software for NICU, PICU, and Well Baby Nurseries announced the successful implementation of Crib Notes in the Level III Nursery at the South Jersey Healthcare (SJH) Regional Medical Center. Muhammad Anwar, MD, chief of Neonatology at SJH said, "In six months we were able to configure the system, train staff, and go live in our growing, busy NICU. We were live in one day for both nurses and clinicians with excellent adoption of the software and its capacities." The SJH Regional Medical Center has six licensed NICU beds in its nursery. All aspects of documentation for nurses, doctors, nurse practitioners and ancillary staff will be done in Crib Notes. Integration with the hospital's existing EMR ensures a complete, easily accessible patient record. And with the software being Meaningful Use certified it supports the federal mandates applied to hospital EMR system. Contact (800) 323-9167, cribnotes.com.

AARC PREVIEW

Neotech

Booth 528/530

What neonatal/perinatal products will you be presenting?
Neotech Products will be displaying our new interface designed for safe, gentle and comfortable delivery of NIPPV and NCPAP, the Neotech RAM Cannula. We will also be showing our Neotech ChinStrap for CPAP, the NeoSeal for CPAP and some of our other great products like the Little Sucker, Little Sucker Cover and EZCare Softouch Tracheostomy Holder.

Tell us about new products and R&D efforts you'll be highlighting.
We will be highlighting the new Neotech RAM Cannula, which is now being used in more than 250 hospitals in the United States and around the world. In a short time it has proven to be a safe, simple, effective and gentle way to deliver respiratory support to neonates.

Discuss education/training/support materials you'll be featuring.
We will be providing education and support materials for the Neotech RAM Cannula and will have clinicians at our booth available to discuss the product and answer questions.

What speakers, clinical papers or promotional items will you be presenting?
We will have product samples and will be highlighting new clinical papers as well as some of our products in development.

Why should our readers visit your display?
Stop by and meet our hardworking and dedicated staff, we want to hear your feedback and ideas. We are committed to creating more respiratory products for the NICU and PICU and we're excited to share our current products with you and give you a sample bag!

New Findings in the Science of Neurodevelopment, Cognition and Human Milk

Jean Rhodes, PhD, CNM, IBCLC

Introduction

Despite improvements in neonatal and perinatal medicine, infants born prematurely have a significantly higher risk of neurological disabilities when compared to infants born at term. According to a 2002 Agency for Healthcare Research and Quality report, half of all extremely low birth weight (ELBW) infants will have a least one significant neurodevelopmental impairment.[1] As with many neonatal outcomes, these risks are inversely proportional to the infant's birth weight and gestational age at birth: the smaller and more preterm the infant, the greater the risk.[1-4]

While effects of early infant nutrition may be subtle, with results not apparent for months or years, studies suggest early nutrition has the potential to influence cognition, behavior and educational performance.[3,5-13] Human milk contains a multitude of physiologically active factors, including essential fatty acids and their derivatives docosahexanoic acid (DHA) and arachidonic acid (AA). These fatty acids are recognized as critical elements in development of healthy cells and tissues in the human nervous system, cardiovascular system and eyes.[7,14-30] Other components of human milk such as growth factors, antioxidants, hormones, anti-infective/anti-inflammatory factors and cholesterol are also involved in healthy human neurological development.[10,12,13,19,31,32] In this article, we will explore some of the recent evidence related to the benefits of human milk in the neurological and cognitive development of infants, particularly preterm infants.

Studies of Cognitive and Neurological Development and Human Milk Feedings

Cognitive and behavioral benefits of human milk have been a subject of inquiry for many years. As early as 1929, Heofer and Hardy[33] evaluated the effects of infant feeding type and duration on physical and mental developmental differences in Chicago school children. Study methods and analyses differed from those seen today; however, results supported the benefits of 4-9 months of exclusive breastfeeding over infant formula feeds.

Researchers of lactation and human neurodevelopment are challenged by a number of methodological issues that influence outcomes, particularly those that influence intelligence measures. Therefore, results are not always consistent.[5,8,34-38]

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However, recent reports continue to add to the body of evidence that human milk improves mental capacity. In 2011 a study by Jedrychowski *et al*[8] reported IQ scores of children born >36 weeks increased with duration of exclusive breastfeeding when compared to partially breastfed children. This study followed subjects for seven years after birth. Intelligence measure gains – in the range of 2-3.8 IQ points, depending on the length of exclusive breastfeeding – were small but statistically significant.

In another study published in 2011, Quigley *et al*[10] evaluated the relationship of breastfeeding and human milk feeding on cognitive development in both term and preterm infants. In total, 11,879 infants were recruited and followed for five years. The authors adjusted for multiple confounders; beyond the standard confounders such as maternal age, education, socioeconomic status, infant gestational age and birth weight, the analysis adjusted for parents' parenting beliefs and the child's exposure to early learning opportunities.

Their findings suggested longer durations of breastfeeding/human milk feeding had positive effects on cognitive development, particularly in children born preterm. For example, in children born at term, the authors found a 1-2 point difference on three subtests of the British Ability Scales (Second edition) between children who were breastfed for 4-6 months and those who were never breastfed. Children born preterm who were breastfed or received breastmilk for at least 2 months had even greater improvements, with 4-6 point increases, when compared to children who did not receive mother's milk.

This very large study contributes significant weight to the argument that breastfeeding and human milk feeds contribute positively to infant intelligence and cognitive development. Like most studies, maternal IQ – an important variable in predicting a child's intelligence[35,39] – was not measured directly but inferred from maternal education and socioeconomic status. Unlike many previous reports, this study controlled for selected aspects of the home environment including parenting beliefs and the child's exposure to educational opportunities. Comparison of outcomes by gestational age at birth suggests greater cognitive effects of human milk feeds in infants born preterm.

Studies Specific to Preterm Infants

Two studies by Vohr and associates – published in 2006 and 2007[12,13] – followed extremely low birth weight infants until approximately 18 and 30 months corrected age. The authors' objective was to evaluate longitudinally the physical,

developmental, neurological, cognitive and behavioral effects (as measured by Bayley Scales of Infant Development) of breastmilk ingested in the NICU. Data were collected on multiple confounding variables including but not limited to socioeconomic status, maternal age, education, marital status, race/ethnicity, infant gestation, gender, and neonatal complications.

In these studies, children who received breastmilk during the NICU stay had better Bayley Scale outcomes at 18 and 30 months than children who were formula fed. Furthermore, after adjusting for confounding variables, analyses indicated that for every 10 mL/kg/day increase of breastmilk, infants demonstrated incremental improvements in Bayley subscale percentile scores and rehospitalization rates. Overall, any breastmilk volumes were better than none with cognitive results sustained if not improved between 18 and 30 months of age.

Previous studies, like those we have just examined, have associated breastfeeding with positive child cognitive development. Other research has suggested cognitive scores in preterm infants might be related to anatomical factors such as head circumference and brain size.[40] A 2010 study by Isaacs and colleagues[32] took the question a step further by examining the relationship between early human milk feeding, measures of intelligence, and brain growth and brain volume in preterm infants. The subjects in this study were part of a larger project conducted many years prior. From 1982-1985, Lucas and colleagues studied 502 NICU preterm infants over the first 30 days of life. All breastmilk feedings were documented then converted into percentages of infants' total feeding intake. Their results showed a dose-response benefit from human milk feeding on infant cognitive development at nine months,[41] 18 months,[42] and 7-8 years of age.[38]

In 2010, Isaacs and associates published a follow up study with 50 from the original 502 infant cohort, now in their adolescent years. All subjects were born at or less than 30 weeks gestation, were previously determined to be neurologically normal, and received primarily expressed mothers' breast milk in the first month of life with some variation as to type of supplement. The authors assessed cognitive and neurological development with Wechsler intelligence scales and brain MRI studies. MRI analysis included total brain volume as well as white matter and grey matter volumes.

Isaacs *et al* found subject mean IQ scores were close to the population average of 100 with no significant difference between girls and boys. However, boys – but not girls – showed a significant proportional relationship between percent expressed breastmilk and IQ scores. The higher the percent of expressed breastmilk, the higher the IQ scores. In addition, total white matter in boys increased with higher percentages of human milk feedings. The authors concluded that, "In all subjects, but most clearly in boys, the effects of breast milk were seen more strongly on white than grey matter in the brain. These data support the hypothesis that one or more constituents of mothers' breast milk promote brain development at a structural level." (p.6)[32]

Components of Human Milk that May Contribute to Improved Cognitive and Neurological Outcomes

Human milk contains a variety of medium and long chain fatty acids, including two essential fatty acids – linoleic acid (LA) and α linolenic acid (ALA) – the human body can't synthesize and must, therefore, get from dietary sources. Linoleic acid is the precursor for the omega 6 polyunsaturated fatty acids; α linolenic acid is the precursor for omega 3 polyunsaturated fatty acids.[43] Of the many fatty acids in human milk, arachidonic acid (AA) from linoleic acid and docosahexanoic acid (DHA) from α linolenic acid are the LCPUFAs most associated with brain, eye and cardiovascular development.[9,14,16-22,24,26,28-30,44-49]

During fetal development, the last 20 weeks of gestation is a critical period of human brain growth and development. Linear growth in brain weight follows a steep slope: approximately half of the brain's volume is obtained in the last 6 weeks of a 40-week gestation. Changes during this time period are dramatic. For example, at 26 weeks gestation the brain will weigh 30% of its expected weight at 40 weeks; at 34 weeks it will weigh 65% of term weight.[50]

Brain growth is concomitant with neurological structural maturation and organization. During the fetal period and extending into infancy, neurogenesis, synaptogenesis, dendritic arborization and neuronal connectivity occur as axons elongate to form the cerebral cortex.[24,50] Of interest to the discussion at hand, 60% of infant brain is lipid, mostly membrane lipid, which requires arachidonic acid (AA) and docosahexanoic acid (DHA) for growth and development.[14,17]

DHA and AA are integral components of brain and nervous system cell membranes. They are also abundant in retinal, endothelial and vascular cells.[19,21,23,24,28,29] During pregnancy, the placenta supplies LCPUFAs to the growing fetus, but after birth, the infant is dependent on exogenous nutritional sources for continued supplies. Preterm infants by nature of their interrupted gestation have the greatest need for LCPUFAs. As we have discussed, human milk is a natural source rich in DHA and AA and their precursors, the essential fatty acids. However, bovine milk has very few LCPUFA[43] and studies of the efficacy of infant formulas with added synthetically manufactured PUFAs are inconclusive at this time.[14,26,51-55]

By virtue of their unsaturated status, long chain polyunsaturated fatty acids are susceptible to oxidative degradation and the formation of eicosanoids associated with a cascade of inflammatory and immune responses. Antioxidants in human milk can suppress degradation of LCPUFAs and reduce inflammation associated with eicosanoids.[19] DHA also down-regulates inflammation associated with serious diseases in preterm infants such as necrotizing enterocolitis and bronchopulmonary dysplasia.[19] These components may work in concert with other anti-inflammatory agents in human milk – for example, interleukin-10 (an anti-inflammatory cytokine), lactoferrin, and epidermal growth factor – to reduce destructive up-regulated inflammatory immune responses in preterm infants.[56-58]

Vohr and colleagues,[12,13] Quigley *et al*[10] and Isaacs and associates[32] identified several components of human milk that may be involved in neurological and cognitive development, including LCPUFAs, growth factors and hormones. Of these, LCPUFAs are most often associated with infant central nervous system development. In addition, Isaacs *et al* also suggested the presence of cholesterol in human milk might contribute to brain development and intelligence. Dietary cholesterol is an important component in the development of myelin membranes and glial cells, both constituents of brain white matter.

Like DHA, cholesterol is an essential structural component of cell membranes in mammals. It is also the precursor of steroid hormones.[59] In human studies, plasma cholesterol levels have been shown to progressively increase in breastfeeding infants and are higher than cholesterol levels in formula-fed infants.[60] Therefore, in addition to brain cell development, there is speculation dietary cholesterol from human milk may program a more healthy cholesterol synthesis later in life.[61]

These findings lend support to the notion that breastmilk promotes brain development and that the mechanisms for this effect are probably related to the interactions between multiple human milk components – DHA, LCPUFAs, growth factors, hormones, cholesterol and others – with neural cell growth and development. Interestingly, at a fundamental level there seem to be differences in the neurocognitive development of preterm children determined by gender. As we noted in the results by Isaacs *et al*, girls and boys have different average brain volumes, different proportions of white and grey matter and different neurodevelopmental responses to human milk feedings.

Concluding Remarks

The science of human neurodevelopment, cognition, infant nutrition and gender intersected in this discussion of the use of human milk for preterm infants. Several recent studies demonstrate neurocognitive benefits of human milk feeds in the NICU for preterm infants and to a lesser extent, advantages for breastfeed term infants. These benefits increase as doses of human milk increase.

Of special interest in this discussion are the roles of LCPUFAs (especially DHA) and cholesterol in human milk. These substances, naturally abundant in breastmilk but not infant formula, are critical to the development of a functional central nervous system and along with other breastmilk components may be involved in suppressing inflammatory processes in vulnerable infants.

It would seem that the neurodevelopmental building blocks provided by human milk work to increase brain volume and thus may allow for increases in IQ and other neurodevelopmental outcomes so elegantly shown by Vohr and colleagues, Quigley and coworkers and many others before them. Thus the studies outlined in this article add to the growing body of evidence to support the use of human milk for preterm infants and begin to provide insights as to how these benefits are conferred to the infant.

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You Never Know

Kate Beevers

You just never know till you show up…

Attending Medica for the 6th year, I was approached by physician from Morocco interested in my products. Since I was sharing the booth with a large well known manufacturer I assumed he was interested in those products and so after a delightful conversation about clinical practice I directed him to my "booth buddies."

This was Dr Hassan Afilal and his lovely wife Veronic Landau. During our talk he invited me to visit his clinic… in Morocco. I reserve some time after Medica for clinical visits so I was interested. Dr Afilal offered to accommodate my husband and me in his home while I visited Morocco. "Come and visit… I guarantee you will fall in love with Morocco," he said.

Later he came back and was still asking for the samples out of my display. We arranged that at the show's end at 2 PM, he could get the entire product from the display. At 2:01 PM he reappeared and the samples were his.

Again Dr Afilal encouraged me to visit Morocco. So, being a pragmatist, I thought "well, if I wasn't supposed to go I wouldn't have been invited."

So, after visiting another distributor in Israel and a few days in Malaga, Spain, where we were assured in no uncertain terms that we would be robbed in Morocco if we weren't with a group, Tim and I set out, first to the ferry to Algiers (past the Rock of Gibraltar in the beautiful blue waters of the Mediterranean) where we were "detained" by authorities. They didn't seem to know what to do with us as we weren't with a tour group. Took about an hour but all was well. Then by train for three hours where the Moroccan landscape swept by, unending farms (how do they plow those steep hills? With oxen; the tractors are used on the flatter places, apparently) to Rabat where we were met late at night in the beautiful marble train station by Dr Afilal's assistant Aladdin and driven to his home in the "ambassador district" (the Chinese ambassador and the Korean ambassador were neighbors). Over the delicious evening repast we learned Dr Afilal studied medicine in Paris for years, where he specialized in neonatal medicine, and met his lovely wife. About 8 years ago he returned to his home in Morocco with his family of 6 children to start a clinic with an NICU. He chose Rabat, as it is between Casablanca and Tangiers, two of the largest cities in Morocco.

As he began this endeavor he realized he had to teach the nurses and fellow doctors the way he wanted to practice. This education fell squarely on his head. Hassan choose to train the nursing staff in their own common language to optimize their understanding.

The first infants transported to his clinic didn't always make the transport successfully, as the transporters were unfamiliar with the needs of ill premature babies.

Dr Afilal responded to this challenge by buying 6 specially equipped ambulances to go out and bring the babies back to the clinic. These are staffed by attendants trained by Dr Afilal. The number of babies making a successful transport has greatly improved.

The building that houses Morocco's first NICU is unassuming. It looks like an office, between a tailor shop and drug store. But surprise, after you get past the security in the lobby it's a 10-12 bed NICU with additional rooms for the less acute or chronic cases and beds for pediatric patients and their families. Everywhere I looked was an exam room, treatment room or consult room, no wasted space.

The NICU was bustling with gowned caregivers. I saw some tiny babies. Really huge 18x24 charts… good idea – no one would walk off with those charts!

Dr Afilal had a kind word or two for every mother we passed. He is unusual, as a practicing physician in the position of president of the Moroccan Pediatric Society, since most of these positions are held by academicians.

Dr Afilal was always on the move, attending to patients in clinic, on the phone with concerned parents by day, greeting his "fans" on our evenings out. Everyone seemed to know him. He says, "I have taken care of all their children… or their grandchildren."

His goal is to bring better care to his country. From the farmer to the financier. A significant portion of his practice is pro bono. "It's just right that we do things this way."

We spoke in the evenings about how to bring incrementally better care to any rural practice by implementing simple low tech improvements.

I am so excited to have met this doctor, Hassan Afilal, and had been able to share his energy and excitement for making neonatal practice better in Morocco. For him it's truly "all about the babies."

During clinic hours my husband and I toured Rabat, from street markets through narrow cobbled streets to the latest well

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appointed "mall." We drank the hot sweet mint tea as is custom and toured Roman ruins, Islamic mosques, listened to the haunting call to prayer over a stunning mausoleum overseen by imposing, elegantly uniformed guards. Our trip to the ruins was special as we got there just at dusk while the many storks were landing for the night. The noise they make clacking their beaks in greeting raises the hair on the back of one's neck. I think this noise was used in the "Beastmaster," a movie from years ago starring Mark Singer. Dashing for the exit gate in a sudden downpour, I heard the young group ahead of us singing in Arabic in the rain. I suppose the goodness or badness of a downpour is all in how you look at it.

Although there were not many signal lights, there was no deficit of traffic police. Snappy uniforms (including gloves and spats) by day; easy to see in their white coats by night.

Lots of fresh fruit at every meal (white pomegranates – I gotta get me some) and by tradition, couscous on Friday lunch. Plenty of couscous so the local "soup kitchen" gets plenty, too. Another, "it's right that we should do this."

The restaurants in Rabat have a serious French influence; an evening of quiet drinks watching the pale pink Moroccan sunset in the Hassan Hotel is something to experience.

I did, in fact, fall in love with the Morocco I saw. I look forward to returning and having many more collaborative discussions with Hassan Afilal, founder of one of Morocco's first NICUs.

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ROP Screening with the RetCam Shuttle: Sicilian Project

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Abstract

Purpose: A multicentered Sicilian Itinerant RetCam Project (SIRP) was conducted between October 2008 and November 2009. The Department of Ophthalmology of the University of Catania was the Reference Center. The project included 5 Neonatal Intensive Care Units in Sicily (NICU).

Methods: All premature babies born in participating NICUs were examined using a telemedicine approach and a RetCam Shuttle (RCs) (Clarity Medical Systems) to train the ophthalmologist with no experience in the treatment of Retinopathy of Prematurity.

Results: 366 neonates were examined over a 13 month period. The incidence of ROP Stage III Threshold (T) for the babies with a gestational age below 29 weeks was 9.53% and 0.33% for babies above 29 weeks. The incidence of ROP III T in babies with a birth weight lower than 1000 grams was 12.06%. No signs of ROP III T were detected for those who weighed above 1000 grams. Seven out of 366 premature neonates (1.9%) required treatment and were treated successfully (100%).

The percentage of correct diagnoses made by the NICU ophthalmologists and validated by the reference center specialists increased gradually over time. The result between the third and the fourth quarter vs the first one was chi squared p = 0.029 and p=0.001 respectively. False positives and negatives dropped significantly in the fourth quarter vs the first one with a chi square respectively of p=0.007 and of p=0001.

Conclusion: This study has demonstrated high reliability for identification of the cases of ROP requiring treatment. There were no adverse outcomes.

Introduction

Retinopathy of Prematurity (ROP) is a disease with severe consequences. Its main risk factors are a gestational age < 34 weeks and a low birth weight. The epidemiological data published by Kirchner[1] in 2005 indicate that the incidence of severe ROP in premature babies with a birth weight lower than 600 grams is approximately 43%, approximately 33% in the babies between 600 and 700 grams, approximately 26% for those between 700 and 800 grams, and only approximately 2% in neonates with a birth weight between 1400 and 1500 grams.

In a 2008 study, Mutlu[2] reported an incidence of ROP of 37.1% in neonates with a gestational age of 32 weeks or less. In a 2009 study, Lad[3] showed an incidence of about 15.58% in infants with the mean birth weight 1,186.9 grams and with a mean gestational age at birth of 28.9 weeks. In 2009 Austeng[4] demonstrated an incidence of 34.8% in infants born before 27 weeks gestation.

It is crucial, therefore, to carry out periodical follow-up[5] by qualified neonatal experts for babies with a birth weight below 2000 grams or with a gestational age less than 33 weeks, who are at risk for developing ROP. The aim of treatment is to diagnose the disease before it reaches an advanced stage and becomes difficult to treat or to obtain good therapeutic results. Our study was conducted between October 2008 and November 2009 in 5 Sicilian Neonatal Intensive Care Units (NICU) by an ophthalmologist dedicated to the diagnosis of ROP who was linked to our Reference Center. The study was designed to obtain data using telemedicine for all Sicilian NICUs on the retinal condition of premature babies to provide early diagnosis and prompt treatment of the disease, to train ophthalmologists with no experience of ROP and to obtain demographic data.

Patients and Methods

The multicenter RetCam Project (SIRP) was designed to allow the participating University Intensive Care Units (NICUs) to use a RetCam shuttle (RCs) weekly, which was operated free of charge by the Mobile Ophthalmic Unit of Unione Italiana Ciechi (Sicilian Association for the Blind) for the diagnosis, documentation and follow-up of ROP. The RetCam Shuttle (RCs) (Clarity Medical Systems), present some advantages compared with the traditional RetCam system (RC). The fact that it is smaller and therefore easier to move proved to be very useful for our study.

The Reference Center was the Ophthalmology Unit of the University of Catania for the NICUs in the following hospitals: Ospedale S. Giovanni Di Dio in Agrigento (168 Km from the Reference Center), Ospedale Cannizzaro in Catania (7.5 Km from the Reference Center), Ospedale Umberto I in Enna (86 Km from the Reference Center), Ospedale Civico in Palermo (212 Km from the Reference Center), and Ospedale M. Paterno' Arezzo Ragusa (108 Km from the Reference Center).

The project started with a month-long course in the use of the RC at the Ophthalmology Unit of the University of Catania

The authors are with the Department of Ophthalmology, University of Catania, Italy. No author has any commercial or proprietary interest in the product or company.

Table 1: Number of patients affected by ROP and percentage at the various stages according to gestational age

	23-29 week (average =26,76 week)	30-33 week (average = 31,59 week)
Number of Patients	63	303
Avascular	20 (31,75%)	228 (65,35%)
ROP I	28 (44,44%)	63 (30,69%)
ROP II	9 (14,28%)	11 (3,63%)
ROP III T	6 (9,53%)	1 (0,33%)

Table 2: Number of patients affected by ROP and percentage at the various stages according to gestational weight

	650-1000 gr. (average=786,7gr.)	>1000 gr. (average=1350,3gr.)
Number of Patients	58	308
Avascular	17 (29,32%)	235 (76,29%)
ROP I	24 (41,38%)	68 (22,08%)
ROP II	10 (17,24%)	5 (1,63%)
ROP III T	7 (12,06%)	0

Table 3: Number and percentage of false positives and negatives

Total Patients 366 pts.	I Quarter 94 pts.	II Quarter 89 pts.	III Quarter 78 pts.	IV Quarter 105 pts.
Correct Diagnoses	65 (69.15%)	63 (70.78%)	66 (84.63%)	99 (94.28%)
False Positive	18 (19.15%)	16 (17.98%)	8 (10.25%)	6 (5.72%)
False Negative	11 (11.70%)	10 (11.24%)	4 (5.12%)	0

Table 4 : Comparison between authors according to gestational age

	LORENZ	**LORENZ**	**LARSSON**	**LARSSON**	**AUSTENG**	**S.I.R.P.**	**S.I.R.P.**
	23-29 week	30-33 week	23-29 week	30-33 week	23-26 week	23-29 week	30-33 week
Number of Patients	478	440	162	91	506	63	303
Follow-up (years)	6	6			3	1	1
ROP II (No T)	45 (9,4%)	1 (0,2%)	39 (24%) (I – II)	7 (7,7%) (I – II)	115(22,7%)	9(14,3%)	11 (3,63%)
ROP III (T)	41 (8,6%)	1 (0,2%)	44 (27,1%) (III-IV-V)	2 (2,2%) (III-IV-V)	170 (33,5%)	6 (9,53%)	1 (0,3%)

Table 5: Comparison between authors according to gestational weight

	LORENZ	**LORENZ**	**LARSSON**	**LARSSON**	**S.I.R.P.**	**S.I.R.P.**
	<1000 gr.	>1000 gr.	<1000 gr.	>1000 gr.	<1000 gr.	>1000 gr.
Number of Patients	275	558	90	163	58	308
Follow up (years)	6	6			1	1
ROP II (No T)	42 (15,3%)	4 (0,7%)	26 (28,9%)	20 (12,3%)	1 10(17,2%)	5 (1,6 %)
ROP III (T)	38 (13,8%)	4 (0,7%)	39 (43,3%) (III-IV-V)	7 (4,3%) (III-IV-V)	7 (12,06%)	0

organized for the ophthalmologists of the participating NICU and also for experienced ophthalmologists to enable them to use the RC accurately. The ophthalmologists were considered reliable in ROP diagnosis only when 90% of their diagnoses using an indirect binocular ophthalmoscope and the RCs matched the findings of two specialists at the Reference Center.[6]

Protocol: In each participating unit, the protocol included the following visits: The first visit was undertaken at 3 weeks chronological or postnatal age or within the 29th week of gestational age. Follow-up visits for babies without ROP were every 15 days until the whole vascularization of the peripheral retina was observed (Stage 0). Babies with Stage I disease were seen every 2-3days. Those with Stage I-II, zone 2-3 were assessed every 7 days. Babies were assessed every 2-3 days for those with Stage III, according to the severity of the disease.

The examinations took place in the NICU and were designed allowing observation of the anterior segment with a focus light in order to assess corneal opacities, depth of the anterior chamber, presence of the tunica vasculosa lentis and its staging and lens opacities.[7]

The posterior segment was assessed after pupillary dilatation with phenilephrine 0.5% (Visufarma) and tropicamide 0.5% (Visufarma), which provided complete mydriasis. Following

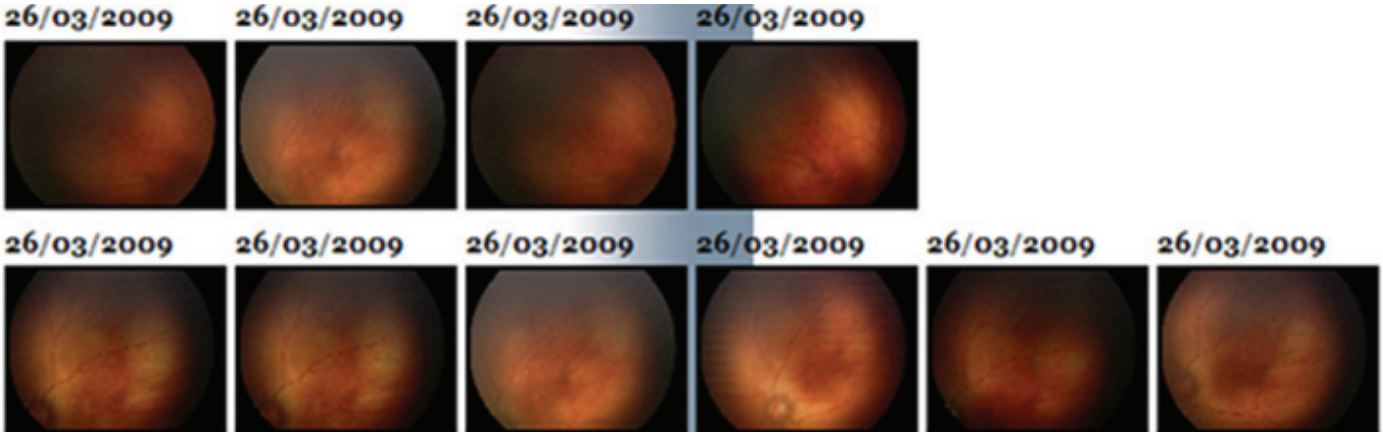

Figure 1: The images were sent via the Internet in this database

dilation a sterile blephorostat was applied to the eye. By means of an indirect binocular ophthalmoscope and scleral indentation, the ophthalmologists looked for signs of ROP and documented their findings according to the International Staging Standards. Patients were examined with the RCs every week. Before the exam, oxibuprocaine chloridrate (Novartis Farma S.p.a.), a topical anesthetic, was used in both eyes. This was followed by the application of a sterile speculum, which allowed adequate exposure of the surface to be photographed. Methyilcellulose 2.5% (Alfa Intes) was placed on the camera probe of the RCs[8] and on the patient's cornea. At least 5 images of the posterior pole at 130 degrees and the retinal periphery at 360 degrees were acquired.

The images were sent via the Internet from the peripheral NICU to the Reference Center in an ad hoc database (Fig 1), which was password protected with a unique password for each individual NICU. The name of the patient examined was then entered into the Registry, with data regarding gestational age, birth weight and case notes. The images were uploaded and were evaluated by two RC ophthalmologists experienced in ROP. These specialists made a diagnosis, which was then sent via telephone and e-mail to the reference NICU. This allowed for the evaluation of the treatment indicated and for any false positive and negative results. In the presence of ROP, the baby was treated either at the NICU or transferred to the Reference Center within 24 hours. The result of the treatment was considered to be positive if, in a period ranging from 7 to 18 days, the vessel congestion (plus) and the ridge had diminished or disappeared and initial peripheral retinal vascularization was observed.

Results

Between October 2008 and November 2009, a longitudinal prospective trial was conducted on 366 premature babies (732 eyes). Sixty-six were examined in Agrigento, 76 in Catania, 66 in Enna, 86 in Palermo and 72 in Ragusa.

All the premature neonates from the participating NICUs were seen at least once a week until the complete vascularization of their peripheral retina was seen. The average number of visits per baby varied according to the gestational age. Those below 29 weeks had an average number of visits equal to 8.3±2.1, while those above 29 weeks had an average of 5.8±1.6 visits. During each weekly visit and for each neonate, between 5 and 20 images were acquired with an average value of 10.3 and a median of 11.

The Reference Center evaluated the number and the percentage of correct diagnoses and false positives (diagnosis of ROP with a grade higher than the actual one) and false negatives (diagnosis of ROP with a stage lower than the actual one) in the four trimesters of the project period to check the reliability of the NICU ophthalmologists.

The patients included in the project were divided in two groups according to their birth weight and their gestational age. The first birth weight group was in turn subdivided in two groups: neonates with a birth weight between 650 grams and 1000 grams with a mean weight of 786.7 grams and those above 1000 grams with a mean of 1350.3 grams. The second gestational age group was subdivided in two groups: neonates between 23-29 weeks with a mean of 26.76 and those between 30-33 weeks with a mean of 31.59.

Out of all the premature babies studied, 7 required treatment, 5 at the Reference Center and 2 at the Catania Hospital Cannizzaro peripheral NICU. Of these, 6 had a birth weight lower than 1000 grams (mean 750 grams) and a gestational age below 29 weeks (mean 26.5). Only one had a birth weight lower than 1000 grams. and a gestational age of 30 weeks.

The incidence of ROP Threshold (T) was: 9.53% for babies with a gestational age below 29 weeks and 0.33 for those above 29 weeks. In the infants with a birth weight higher than 1000 grams, the incidence of ROP III T was 12.06%. The ophthalmologists at the Reference Center conducted all the treatments with a diode laser mounted on a cap according to the ETROP protocol (Early treatment for ROP 2003)[9] and used laser photocoagulation of the avascular retina or of the ischemic areas. The average number of laser spots was 850 ± 220 spots per eye. All the patients showed a regression of ROP and vascularization of the peripheral retina with a therapeutic success rate of 100%.

The gestational age at which treatment was administered was 34.5±2.5 weeks on average.

Tables 1 and 2 show that the percentage of ROP at the various stages is higher in infants with a low weight and gestational age with respect to those with a birth weight above 1000 grams and with a gestational age above 29 weeks where the percentage of ROP III T was 0% and 0.33% respectively.

Table 3 shows that, over time, the percentage of false positives and negatives dropped significantly. In the first quarter, the percentage of false negatives was 11.70%, while the percentage of false positives was 19.15%. Diagnoses were correct in 69.15%.

The percentage of errors diminished gradually up to the IV quarter when false negatives were 0% and false positives were 5.72% with 94.28% correct diagnoses. The percentage of the correct diagnoses significantly increased in the third and fourth quarter vs the first with a chi squared p=0.029 and p=0.001. The number of false positives and negatives dropped significantly in the fourth quarter vs the first, with a chi squared for the false positives of p=0.007 and for the false negatives of p=0.001.

Discussion

PRIS is one of the first studies to use RCs for the diagnosis and the follow up of ROP. This tool proved to be particularly useful because it is easy to handle and use and it is very portable and resilient (about 30000 kms of road transport during the project). These characteristics are combined with the RetCam 2, except for retinal fluorangiography.

Several studies are reported in the literature to evaluate the sensitivity and the specificity of ROP screening with RCs through a telemedicine approach. A first study by Yen[10] and colleagues compared the RetCam 120 system with indirect ophthalmoscopy and found an insufficient image sensitivity of 46-76% but a good specificity of 95-100%; another study by Sommer[11] and colleagues conducted a screening on 145 premature babies using the RetCam 120, which showed no false positives and more importantly, no false negatives; Wu and colleagues[12] reported a 100% sensitivity and 97.5% specificity, while Roth and colleagues[13] reported sensitivity of 82.4% and specificity of 93.8%. A study by Schwartz and colleagues[14] showed a 95% sensitivity. Chiang and colleagues[15] results showed 100% sensitivity and 93.3% specificity. Work by Ells and colleagues[16] instead, showed 100% sensitivity and 96% specificity. Other similar results were obtained by Murakami and colleagues[17-18] showing 100% sensitivity and 99.4% specificity.

The purpose of our study was not designed to compare indirect ophthalmoscopy and the RCs; however, very similar results between these two diagnostic tools were shown.[6]

The objectives of our project were fully achieved: in 13 months, 366 premature babies were examined (732 eyes) by the ophthalmologists from both the participating peripheral NICU and by those at the Reference Center. In 7 cases, laser treatment was necessary according to the International Protocol (ETROP 2003) and all cases were treated successfully. All the treated subjects had a birth weight between 650 and 1000 grams and a gestational age below 29 weeks except for one baby born at 29 weeks. This case strongly supports that babies with a higher gestational age also should be monitored closely.

In addition, our results show that the Sicilian ophthalmologists not experienced in ROP were adequately trained to perform the screening. In fact, in the observation period between the first and the fourth quarter, the false positives dropped by a statistically significant chi squared amount equal to p=0.007 and the false negatives by p=0.001. The percentage of correct diagnoses increased progressively by a statistically significant chi squared amount equal to p=0.029 between the first and the third quarter and equal to p<0.001 between the first and the fourth. Our epidemiological data are certainly supported with the current literature, with the incidence stated in the literature: 32.2% (our result in terms of ROP incidence). Moreover, our study showed that above 30 weeks gestation, the incidence was 24.75% and below 30 weeks it was 68.25%, Lorenz (2009) in Germany showed an incidence of 27.6% with a 6 year follow-up,[19-21] Larsson (2002) 36.4%,[22] Mathew (2002) 31.2%[23] and Chiang (2004) 24%.[24] Our epidemiological data percentage is in line with the recent epidemiological studies and enables us to determine the incidence of low birth weight and gestational age in premature babies in the participating NICU in Sicily (32.2%). This is relevant regarding the number of premature babies born after 33 weeks overall, but also for the babies born before 33 weeks gestational age, who have a high risk for developing ROP. These data suggest that it is necessary and important to conduct an ophthalmological examination and screening in these neonates to monitor, treat when necessary and to follow the evolution of ROP.

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Reinventing a Better babyLance Infant Heel Incision Device – Listening to End Users: Infant Heelstick Trigger Activation Survey at the 2011 NANN Conference

Abstract

In September 2011, medical device manufacturer and master distributor MediPurpose conducted a survey at the National Association of Neonatal Nurses' national convention in Orlando, Florida to gauge NANN members' preferences between MediPurpose's original babyLance infant incision device's "push-forward trigger" activation mechanism and a newly designed prototype's "pull trigger."

This white paper illustrates key findings from that survey, which indicated a majority preference for the new design's pull trigger, validating the company's decision to move forward with reinventing its heelstick device.

Introduction

After launching the highly successful and innovative SurgiLance safety lancet in 1999, medical product manufacturer and master distributor MediPurpose introduced a complementary product in 2010, the babyLance infant heelstick.

However, within a few months of launch, MediPurpose discovered that babyLance's innovative design was not fully meeting the preferences and expectations of users in the US market.

Although a number of US healthcare facilities expressed a desire to continue use of the product, feedback indicated that the device needed a number of modifications in order to fully satisfy customer demands. Trigger activation was among them – more specifically, an indicated preference for a "pull trigger" activation mechanism, rather than babyLance's "push-forward trigger."

MediPurpose elected not to withdraw the product from the market, but rather, it reduced its production and marketing programs for babyLance. The company then initiated a program to re-evaluate and redesign a device that, among other improvements, would be activated by a pull trigger.

Throughout a year-plus of intensive redesign and testing efforts, MediPurpose routinely gave prototypes of the reinvented babyLance to neonatal nurses around the country for evaluation, using their feedback for supplementary adjustments and modifications.

In October 2011, MediPurpose conducted a survey at the National Association of Neonatal Nurses' national convention in Orlando, Florida to gauge NANN members' preferences between the original push-forward trigger babyLance device and a newly designed pull trigger model.

Problem Definition

Within only a few months after launching its new babyLance infant heel incision device in 2010, MediPurpose soon discovered that the device was not fully meeting the preferences and expectations of users in the U.S. market. The device's "push-forward" trigger – a design change from the "push-down" or "pull" trigger mechanisms offered by some competing brands – was identified as one key issue.

This issue was further impacted by geography. In the United States, where heelsticks are commonly used for infant heel incisions, a limited range of heelstick device models had influenced users' preferences and expectations.

On the contrary, in Europe, where heel incisions are commonly performed with fingerstick devices, there was less demand for heelstick devices in general, with limited preference for a particular trigger style. Subsequently, the babyLance's "push-forward" trigger was more readily embraced.

In a market where heelstick users' preferences had been shaped by the existing competitors' "pull" or "push-down" triggers, MediPurpose needed to prudently conclude which trigger type it would use on its reinvented babyLance heelstick.

Surveying NANN Membership To Validate User Preference

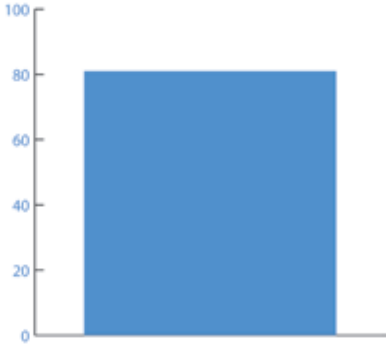
In its unambiguous mission of carefully listening to its customers and end-users throughout the babyLance infant heel incision device's reinvention process, MediPurpose conducted a survey at the National Association of Neonatal Nurses' national convention in Orlando, Florida in October 2011 to gauge NANN members' preferences between its original babyLance infant heelstick device's "push trigger" and a newly designed prototype's "pull trigger."

The survey of 142 participants indicated a convincing preference for the new pull trigger – both in regards to the trigger's activation mechanism and design.

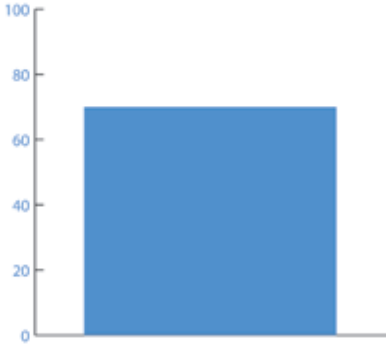
- Pull vs push trigger activation preference: 81% preferred the pull trigger activation

Further, participants indicated a significant preference for the

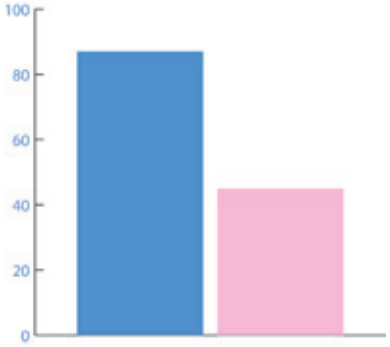
This article was provided by MediPurpose.



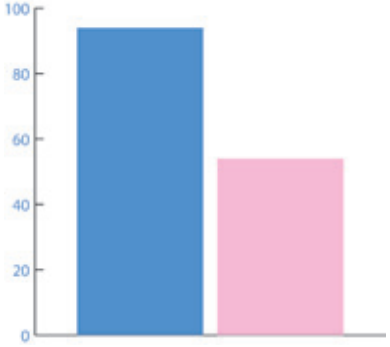
Criteria 1: Pull vs. push trigger activation preference
81% preferred the new pull trigger (blue area) to the original push-forward trigger



Criteria 2: Similarity to home facility device's trigger
70% said the new pull trigger most closely approximated their home facility device's trigger (blue area)



Criteria 3: Pull vs push trigger comfot
87% said the new pull trigger was comfortable to use (blue area), as compared to 45% that said the original push-forward trigger was comfortable (pink area)



Criteria 4: Pull vs push trigger ease of activation
94% said the new pull trigger was easy to activate (blue area), as compared to 54% that said the original push-forward trigger was easy to activate

pull trigger's comfort and ease of activation:

- Pull trigger comfort: 87% indicated the pull trigger was comfortable
  - As compared to push trigger: 45% indicated the push trigger was comfortable
- Pull trigger activation ease: 94% indicated the pull trigger was easy to activate
  - As compared to push trigger: 54% indicated the push trigger was easy to activate

Finally, the survey supported MediPurpose's presumption that users would prefer the trigger activation that was most similar to that being used at their home facility.

- Pull trigger's motion approximation to home facility's device: 70% indicated an approximation

Summary of Key Survey Results

MediPurpose's survey of 142 NANN members indicated a preference for the redesigned babyLance heelstick's "pull trigger" activation mechanism and design.

Benefits of Listening to End-Users When Reinventing the babyLance

After listening carefully to the end-users, MediPurpose launched a redesigned "pull trigger" babyLance infant heel incision device in August 2012 that will satisfy the unique needs of both its end-user customers and distribution partners.

The company's confidence is fostered by the knowledge that its new heelstick device:

- Is designed with intensive input from a diverse range of highly qualified users.
- Provides a preferred pull trigger activation mechanism that is comfortable and easy to use.
- Is assured to provide safety and quality from a proven and trusted manufacturer with worldwide distribution channels.

In addition, this interactive process further validates MediPurpose's medical product innovation process and capabilities.

For more information about babyLance, contact medipurpose.com/babylance.

How Does System Pressure Correlate with Nasopharyngeal Pressure in an Infant NCPAP In-Vitro Model?

Kate Beevers

Introduction

In the clinical setting the author noticed that, with sufficient flow a CPAP circuit didn't seem to "need" a baby to generate CPAP bubble.

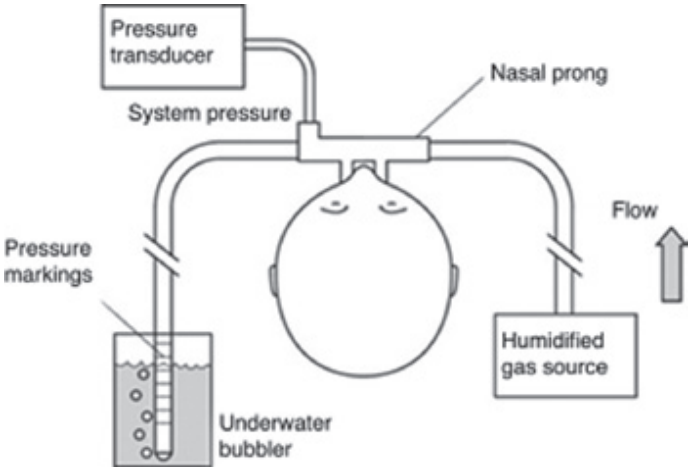


Figure 1: CPAP Diagram

The clinical model that is widely accepted for bubble CPAP is if there is a bubble, then the system is sufficiently pressurized to transmit therapeutic pressures to the baby.[1]

There are conflicting claims from many commercial product manufacturers which lead to confusion in this market area:

- Makers of HFNC (high flow nasal cannula) assure us that the high flows do not translate to the baby and do not provide positive pressure therapy.[2]
- Makers of CPAP generators describe the use of "leak compensation" to provide consistent pressures through the use of higher flows that continue to provide the baby with therapeutic pressures.

"To respond to changing respiratory requirements related to leaks and changes in breathing patterns, NeoPAP utilizes the Baby-Trak leak compensation algorithm. This leak compensation technology eliminates the need for a closely fitted interface seal and helps to reduce pressure on the infant's face. NeoPAP's Baby-Trak software allows the device to measure pressure at the patient's nose and manage it to the target CPAP level. The flow of the oxygen and air gas mixture is controlled to compensate for leaks, allowing a looser fit of the patient interface than if a seal were required."[3]

- CPAP works by maintaining positive pressure in the airway during spontaneous breathing, thereby increasing functional residual capacity and improving oxygenation in infants with RDS. CPAP does this by stabilizing the airspaces that have a tendency to collapse during expiration due to prematurity or surfactant deficiency. A variety of mechanisms of action of nasal CPAP have been proposed. These include:
  - Increase trans pulmonary pressure
  - Increase functional residual capacity (FRC)
  - Prevent alveolar collapse
  - Decrease intrapulmonary shunting
  - Increase lung compliance
  - Splint the airway
  - Splint the diaphragm
  - Stimulate lung growth
  - Possible high frequency effect[4] (with bubble CPAP)
- Effective CPAP allows oxygenation and ventilation without atelectasis or over-distension and no adverse side effects. No universal methods exist to find the "best" pressure. Physiological "PEEP" being about 3cm H2O. Pressures of 4-6cm H2O are commonly used.[5]
- For the CPAP system to be effective it must have the following characteristics:[6]
  - Be a low resistance delivery system
    The CPAP set up is designed to deliver through a low resistance system. The resistance in the circuit is directly proportional to the length of the circuit, inversely proportional to the fourth power of the radius of the tubing used. This means that doubling the length of the tube doubles the resistance of the tube, and halving the radius increases the resistance 16 times! Since the pressure that is delivered and ultimately reaches the lungs is directly related to the resistance of the delivery system and patient airway, it is imperative that every effort is made to minimize that resistance, ie large bore tubing and short wide connection to the baby
  - Fit appropriately and PREVENT pressure leaks (not "compensate for")
  - Snug fitting nasal prongs
  - Chinstrap in place and secure
  - Flow through an optimally maintained airway
  - Warmed humidified gas
- In addition, for effective CPAP
  - The baby's airway should be in optimally to give airway patency and developmental positioning
  - The caregiver should suction PRN q2-4 hrs as needed for secretion management
  - The caregiver should maintain the system with meticulous and consistent technique[7]

NCPAP is common in the NICU. It has largely replaced intubation as it gives acceptable results with fewer complications in general and none of the complications unique to intubation.

Two main types of patient interfaces are used: masks and short prongs.

Kate Beevers is President of Beevers Manufacturing.

Nasal and septal irritation, breakdown and erosion are frequently reported with both interface types.

High flow cannula manufacturers claim that increasing flow doesn't translate to higher patient pressures.[8] Manufacturers of flow generators, especially leak-compensated flow generators, claim that it does.[3]

Purpose

The purpose of this investigation was to measure, in a static model, the transmitted pressures from a CPAP set up to an infant head model with and without a pressure seal at differing flow rates using a variety of commercially-available patient interfaces.

Hypotheses: This begins a comparative analysis of two hypotheses.

Hypothesis One – In a CPAP system, minor leaks can be compensated for by increasing the flow till the system is pressurized. The baby will receive the transmitted pressure in the nasopharynx and it will be transmitted to the respiratory tract and provide the desired positive pressure to the respiratory units.

Ie, Minor system leaks can be compensated by increased flow and nasopharyngeal pressure will be maintained.

Hypothesis Two – An effective CPAP system must be sealed in order to transmit therapeutic pressures to the baby. Leak compensation and the like compensate the delivery system but do not transmit the pressure to the baby nasopharynx. A leak is a leak, is a leak. By definition the presence of a leak means the system is not sealed and therefore does not transmit pressure further down the system.

Ie, Flow-based leak compensation is not effective in maintaining nasopharyngeal pressures. For the positive pressure to be translated to the baby's nasopharynx there must be a sealed system, either through the use of snuggly fitting nasal prongs, mask or thru the use of a hydrocolloid seal either hand cut by clinicians or using a product such as Cannulaide.

Method

In the in-vitro study, we measured system pressure and flow, and the pressure inside the model (head pressure), with different patient interfaces and varying degrees of leak. See Figure 2.

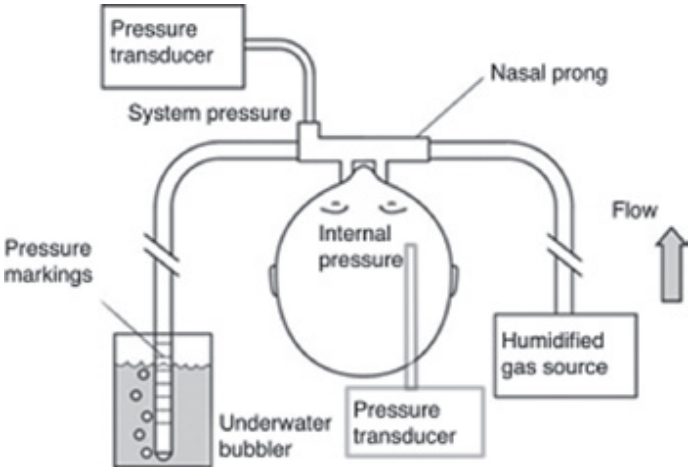


Figure 2: Experimental Schematic

PHASE ONE

Each interface was set up at 5 lpm to a simple calibrated bubble chamber. The pressure in the system was then noted. This phase was measured with no model infant head in the system.

The flow was then increased to allow a system pressure of 5cm H2O. This flow was noted.

- Simple HFNC in infant and pediatric sizes
- RAM cannula
- Hudson prongs 0,1,3,5
- INCA prongs 15

Flow is added till the 5cm H2O achieved this flow level is recorded.

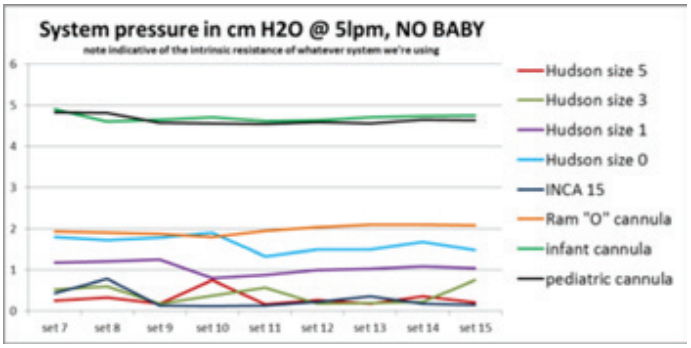


Figure 3: System pressure with no baby

PHASE TWO

The cannulas/prongs are inserted in the infant model head.

Flow is applied till the simple bubble chamber achieves 5cm H2O or the flow meter is >15 lpm.

This flow is recorded... In addition, the internal pressure is recorded.

Each cannula/prong is tested in the same fashion.

PHASE THREE – FINAL PHASE

A Cannulaide is added to the infant face and retested using RAM cannula, Hudson prongs, and Inca prongs.

The HFNC are omitted from this phase, as they are intended as a free flow circuit and not intended to provide pressure. The risk of barotrauma in this very premature population precludes the use of any system other than those with an adjustable pressure pop off.

Flows required to achieve 5cm H2O in the simple calibrated bubble chamber are recorded as are the communicated pressures on the cheek manometer (internal pressures).

Variables

Notes: It takes from 35-45 min to run through each test phase.

The pressure sensor is zeroed for each set.

A set includes testing flows on each Hudson 0, Hudson 1, Hudson 3, Hudson 5, INCA 15, pediatric HFNC cannula, infant HFNC cannula and the RAM orange.

The same baby head is used the same cannulas are used; a new Cannulaide is used for each set. The same water bottle and water is used. The variability I acknowledge is the variability in Cannulaide placement. This baby head model is well sized for size 2 Cannulaides; it is slightly big for ideal size 1 Cannulaide placement. I acknowledge some leakage that might not be present in a more ideal sized baby head model.

As a clinician, I found the INCA 15, Hudson 3, and Ram Orange to be a suitable size for this "infant" model.

Setup

To investigate this idea several flow circuit models were created using:

- A flow meter to provide air flow (in this case compressed air)
- A tubing array to transfer air from the flow meter through the prong set up and on to a simple calibrated bubble chamber
- an HFNC pediatric O2 cannula
- an HFNC infant O2 cannula
- Hudson CPAP prongs in size 0, 1,3 and 5
- RAM cannula orange
- Inca 15 CPAP prongs
- Cannulaide in size 1, 2
- an AMBU baby face with open nares and a pressure monitoring port on the cheek
- a dual channel digital manometer to register communicated pressures; this was placed distal to the flow meter and proximal to the prong set up.

Data analysis

From the Poiseuille equation we see the resistance to airflow is proportional to the length of the tube and inversely proportional to the 4th power of the radius of the tube.

$$R = \frac{Cl}{r^4}$$

Where C is a constant; l is the length of the tube, and r is the radius.

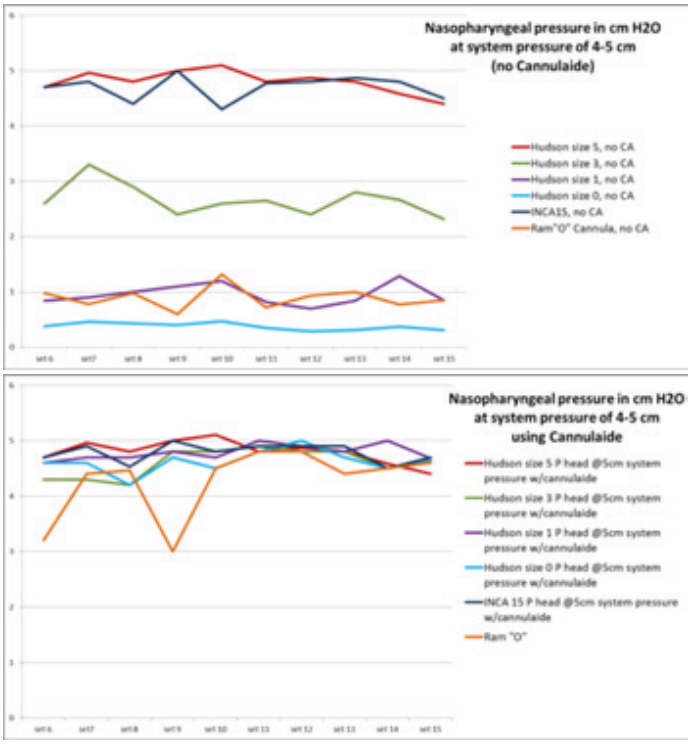
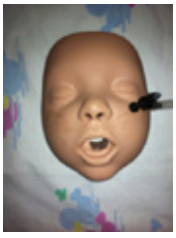


Figure 4: Head pressure before and after Cannulaide

Results

In the Phase One experiment it was observed that a bubble could be produced in some accessories with sufficient flow, indicating a pressurized system with no head model in place (see Figure 3). Even when the simple calibrated bubble chamber achieves 5cm H2O the communicated pressure to the model baby head may not be significantly pressurized unless the prongs tested are snuggly fitted. With the addition of a hydrocolloid seal in this case the Cannulaide the communicated pressures to the baby head are higher. Also noted, significantly less flow needed to achieve that 5 cm H2O pressure. Subsequent applications of the accessory to the baby head model did not result in significant transmitted pressure even when the flow exceeded 15 lpm.

Table 1: Experimental Equipment


Baby Head Model


Dual Port Manometer


Ram Orange


Pediatric HFNC


Hudson CPAP prongs (0,1,5)

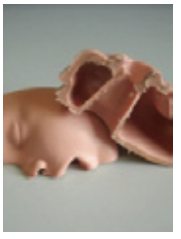

Infant HFNC


A-Plus CPAP Bubble Chamber (top view)


A-Plus CPAP Bubble Chamber (side view)


Cannulaide (Size 2)


Assembled test bed


Cross section of infant head model

Conclusion

- Maximizing the size of the flow delivery device minimizes the resistance issues.
- A leak, is a leak, is a leak.
- "Compensating" for a leak by increased flow does not significantly translate pressure to the baby head in this experiment.
- Extrapolating the pressure given the infants system is not necessarily effective or accurate.
- A good seal, making a complete circuit with minimal leaks, is necessary to provide airway pressure to the infant.
- A good seal can be accomplished by either, snuggly fitting prongs or TNBT a flexible hydrocolloid seal.
- In order to assist spontaneous breathing, avoid endotrauma and support many neonates that would otherwise fail CPAP, the use of CPAP or NIV (non-invasive ventilation) is recommended.
- In order for CPAP or NIV to work, a seal is required. Without a seal NIV is unable to sense respiratory efforts.

Discussion

Though higher flows result in increased system pressures, this system pressure is not transmitted to the infant model nasopharynx in the presence of air leaks.

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Development of Lung Function in Very Low Birth Weight Infants with or without Bronchopulmonary Dysplasia: Longitudinal assessment during the first 15 months of corrected age

Gerd Schmalisch, Silke Wilitzki, Charles Christoph Roehr, Hans Proquitté, Christoph Bührer

Abstract

Background: Very low birth weight (VLBW) infants (< 1,500 g) with bronchopulmonary dysplasia (BPD) develop lung damage caused by mechanical ventilation and maturational arrest. We compared functional lung development after discharge from hospital between VLBW infants with and without BPD.

Methods: Comprehensive lung function assessment was performed at about 50, 70, and 100 weeks of postmenstrual age in 55 sedated VLBW infants (29 with former BPD [O2 supplementation was given at 36 weeks of gestational age] and 26 VLBW infants without BPD [controls]). Mean gestational age (26 vs 29 weeks), birth weight (815 g vs 1,125 g), and the proportion of infants requiring mechanical ventilation for ≥7 d (55% vs 8%), differed significantly between BPD infants and controls.

Results: Both body weight and length, determined over time, were persistently lower in former BPD infants compared to controls, but no significant between-group differences were noted in respiratory rate, respiratory or airway resistance, functional residual capacity as determined by body plethysmography (FRCpleth), maximal expiratory flow at the FRC (V'max FRC), or blood gas (pO2, pCO2) levels. Tidal volume, minute ventilation, respiratory compliance, and FRC determined by SF_6 multiple breath washout (representing the lung volume in actual communication with the airways) were significantly lower in former BPD infants compared to controls. However, these differences became non-significant after normalization to body weight.

Conclusions: Although somatic growth and the development of some lung functional parameters lag in former BPD infants, the lung function of such infants appears to develop in line with that of non-BPD infants when a body weight correction is applied. Longitudinal lung function testing of preterm infants after discharge from hospital may help to identify former BPD infants at risk of incomplete recovery of respiratory function; such infants are at risk of later respiratory problems.

The authors are with the Department of Neonatology, Charité University Medicine, Berlin, Germany. The authors would like to thank Jessica Blank for assistance in data processing, and Dr Scott Butler of English Manager Science Editing, Sydney, Australia, for linguistic revision.

Background

Bronchopulmonary dysplasia (BPD) remains the most common long-term complication of very preterm birth,[1] despite the widespread use of prenatal steroids, exogenous surfactants, and minimally invasive strategies of respiratory support,[2-4] along with other advances in neonatal care.[5-7] In contrast to what was noted in the pre-surfactant era, when BPD was characterized by airway inflammation, fibrosis, and smooth muscle hypertrophy, the "new BPD" is associated with delayed alveolar and vascular development, resulting in simplification of alveolar structures, dysmorphic capillary configurations, and variable extents of interstitial cellularity and fibroproliferation.[8,9]

A considerable body of data has revealed that very preterm infants with "new BPD" exhibit abnormalities in lung function after birth,[10-12] during the first years of life,[13-17] throughout childhood,[7,18-23] and into early adolescence.[24] It is currently unclear whether survivors of BPD are at increased risk of developing a later COPD-like phenotype.[25]

Most previous studies of lung function in preterm infants with BPD have been limited by variations in methods, equipment, and outcome measures. Further, the lack of controls or appropriate reference data have hampered the interpretation and comparability of results.[26] Therefore, data are often inconsistent because of methodological differences among studies. Moreover, most lung function studies performed during childhood have focused primarily on assessment of small airway performance. However, BPD also arrests alveolar and vascular development, such that abnormalities subsequently develop in the distal lung

Table 1 Patient characteristics in the neonatal period, shown as means with SDs (in brackets) or as numbers with percentages (%).

	Without BPD N = 26	With BPD N = 29	*p*-value
Gestational age (weeks)	29.08 (2.12)	26.41 (2.19)	**< 0.001**
Birth weight (g)	1124.1 (248.3)	815.7 (243.1)	**< 0.001**
Birth weight < 1,000 g	7 (27%)	25 (86%)	**< 0.001**
Fetal lung maturation[1)]	14/19 (74%)	12/17 (71%)	1.000
Surfactant administration[1)]	18/20 (90%)	18/20 (90%)	1.000
Mechanical ventilation	15 (58%)	29 (100%)	**< 0.001**
Mechanical ventilation for ≥ 7 d	2 (8%)	16 (55%)	**< 0.001**

Statistically significant *p*-values are shown in bold

1) Total number is reduced because the some data of outpatients were incomplete

Table 2 Chronological and postmenstrual age on the day of lung function testing (LFT) (means with SDs in brackets; the *p*-values show the extent of statistical significance when data from the two patient groups were compared)

	1st LFT	2nd LFT	3rd LFT	*p*-value
Age (days)				
Without BPD	140.1 (48.5)	302.7 (77.7)	522.3 (128.6)	
With BPD	150.7 (49.1)	293.0 (115.2)	517.1 (155.5)	0.928
Postmenstrual age (weeks)				
Without BPD	49.0 (7.5)	71.3 (12.8)	100.4 (22.1)	
With BPD	48.4 (8.0)	70.0 (17.6)	101.4 (22.6)	0.944

parenchyma.[5] Despite the extensive literature on lung function in children that had BPD in infancy, little is currently known about either pulmonary growth in such children or the ability of the very immature lung to recover from BPD. It seems essential to determine the extent of possible catch-up growth, and, most importantly, to identify parameters of lung function that indicate the presence of BPD-specific impairment. Therefore, the aim of the present longitudinal study was to compare the development of lung function and somatic growth in very preterm infants with and without BPD during the first 15 months of corrected age.

Methods

Subjects: For the present retrospective analysis, we identified 55 preterm infants of birth weight < 1,500 g who had under-gone serial lung function testing (LFT) at three time points (at about 50, 70, and 100 weeks of postmenstrual age) in our outpatient lung function laboratory. Infants with congenital diaphragmatic hernia, congenital heart disease, neuromuscular disease, or thoracic wall deformities, were excluded from the study. Of the 55 infants born between October 1995 and February 2010, 29 had been diagnosed with BPD, based on a requirement for supplemental oxygen at 36 weeks of postmenstrual age. Written parental consent was obtained before LFT. The study was approved by our Institutional Data Safety Committee.

Lung function testing (LFT)

Measurements were performed on clinically stable children who had not experienced any respiratory tract infection over the 3 weeks prior to testing. Before LFT, body weight was measured to the nearest 10 g (Seca, Hamburg, Germany); body length from crown to heel was measured to the nearest 5 mm using an inelastic tape; and, (at the end of LFT), an arterialized capillary blood gas sample was taken (ABL800 FLEX Radiometer; Brønshøj, Denmark).

After temperature stabilization for at least 30 min, all equipment used was calibrated prior to each measurement according to the recommendations of the manufacturer. When LFT was planned, sleep was induced by oral administration of chloral hydrate (50 mg.kg-1) 15-30 min before testing. Each sleeping infant was placed in the supine position with the neck in a neutral position, supported by a neck roll. After a pause of 5-20 min, tidal breathing parameters [tidal volume (VT); respiratory rate (RR); and minute ventilation (V'E) were measured using the dead-space free flow-through technique employing customized equipment that has been described in detail elsewhere.[27] Next,

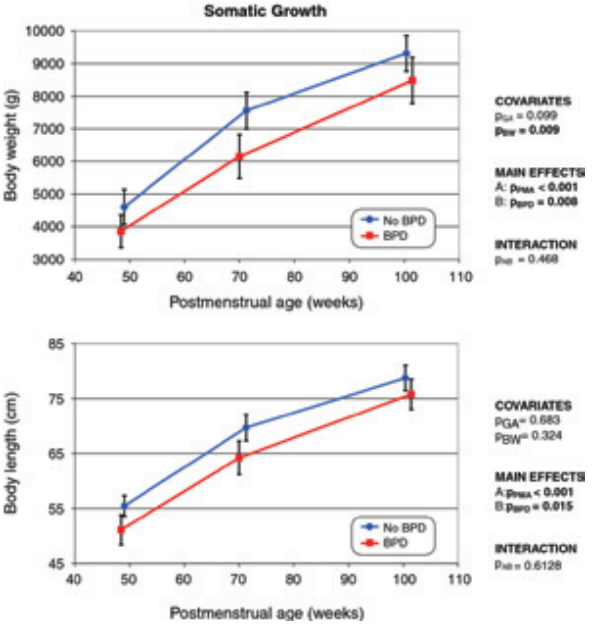

Figure 1 Changes over time in body weight (top) and body length (bottom) of infants with and without former BPD (means with 95% CIs) The *p*-values show the extent of statistical significance of the covariates gestational age (p_{GA}) and birth weight (p_{BW}); those of the main effects by postmenstrual age (p_{PMA}) and BPD (p_{BPD}); and that of the interaction (p_{AB}) of both factors. Statistically significant values are shown in bold.

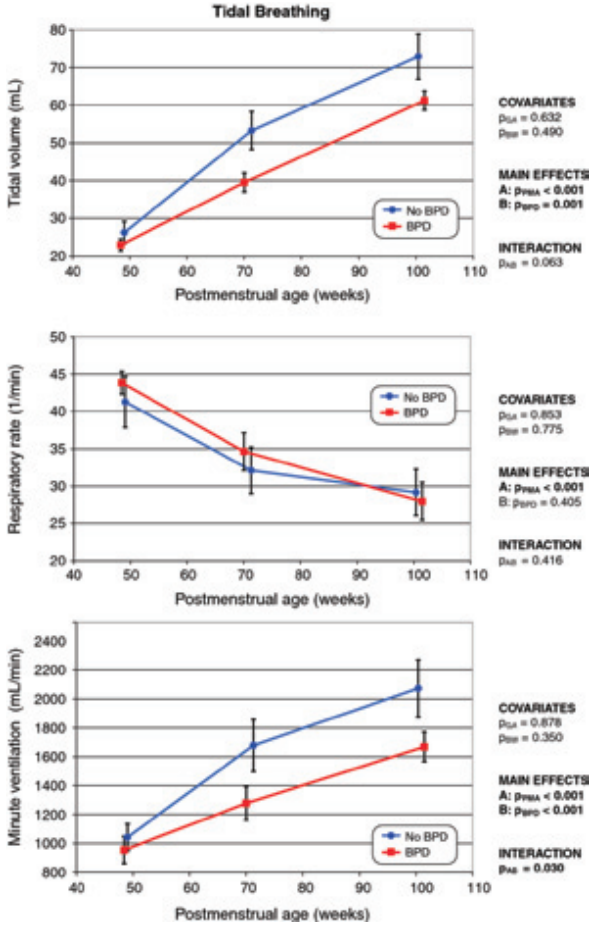

Figure 2 Changes over time in tidal (top), respiratory rate (middle), and minute ventilation (bottom) in infants with and without former BPD (the mode of presentation is the same as that of Figure 1).

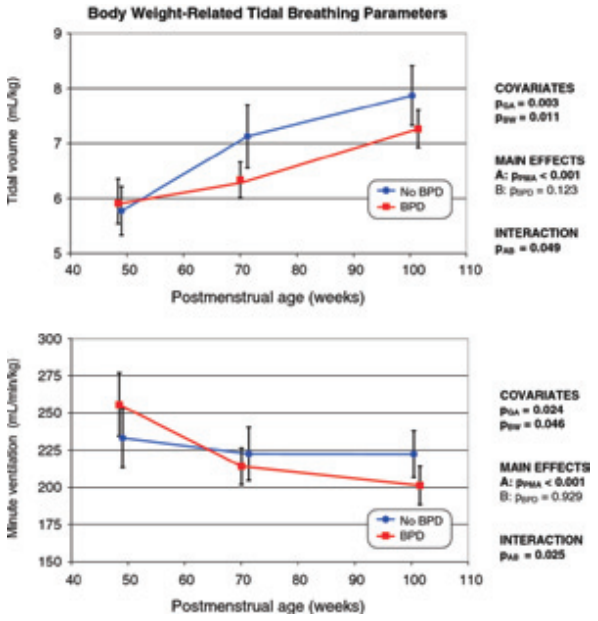

Figure 3 Changes over time in tidal volume (top), minute ventilation (bottom), normalized to actual body weight, in infants with and without former BPD (the mode of presentation is the same as that of Figure 1).

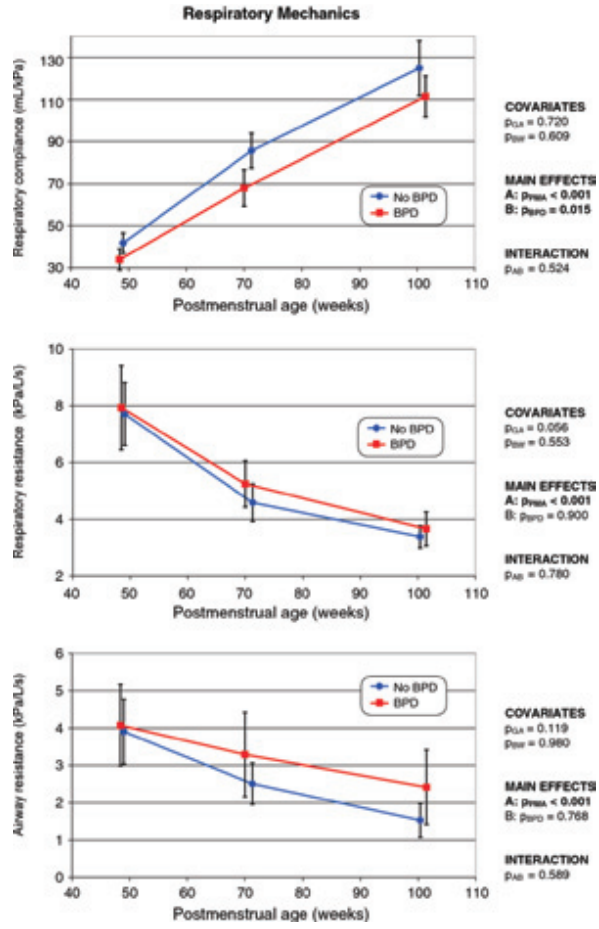

Figure 4 Changes over time in respiratory compliance (top), respiratory resistance (middle), and airway resistance (bottom), in infants with and without former BPD (the mode of presentation is the same as that of Figure 1).

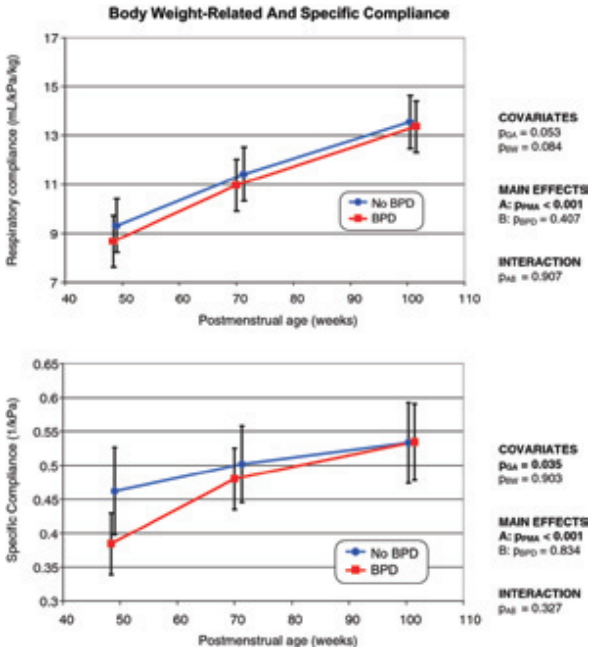

Figure 5 Changes over time in respiratory compliance normalized to actual body weight (top), and specific compliance (bottom), in infants with and without former BPD (the mode of presentation is the same as that of Figure 1).

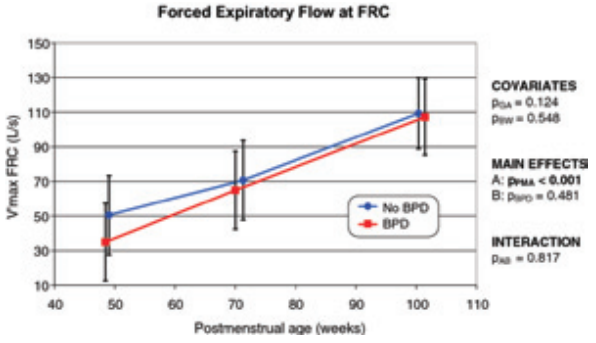

Figure 6 Changes over time in the forced expiratory flow rate, at the FRC, in infants with and without former BPD (the mode of presentation is the same as that of Figure 1).

lung mechanical parameters (respiratory compliance [Crs] and respiratory resistance [Rrs]) were measured using the occlusion test. Airway resistance (Raw) and functional residual capacity (FRCpleth) were assessed using a constant volume infant plethysmograph (Jaeger, Würzburg, Germany). Employing the same equipment, the maximal expiratory flow at the functional residual capacity (V'maxFRC) was measured using the rapid thoraco-abdominal compression technique, in line with international guidelines.[28]

Finally, multiple breath inert gas washout was performed using 5% (v/v) sulfur hexafluoride (SF6) (Ecomedics AG, Dürnten, Switzerland) as the tracer gas; this measured the proportion of the lung volume that participated in gaseous exchange (FRCSF6). During all pulmonary function tests, heart rate and oxygen saturation level were continuously monitored via pulse oximetry (N-200; Nellcor, Hayward, CA).

Statistical methods: Patient characteristics are presented as proportions (% values) or as means with standard deviations (SDs; in brackets) and were compared using Fisher's exact test

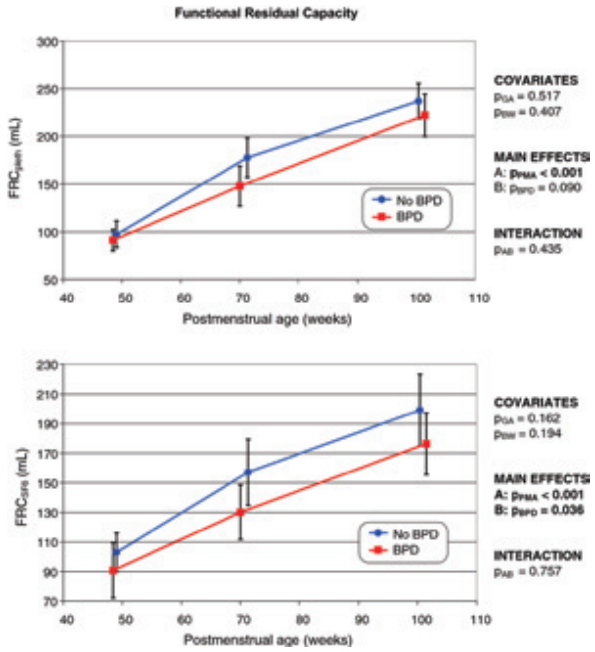

Figure 7 Changes over time in functional residual capacity as measured by body plethysmography (top), and the SF_6 multiple breath washout technique (bottom), in infants with and without former BPD (the mode of presentation is the same as that of Figure 1).

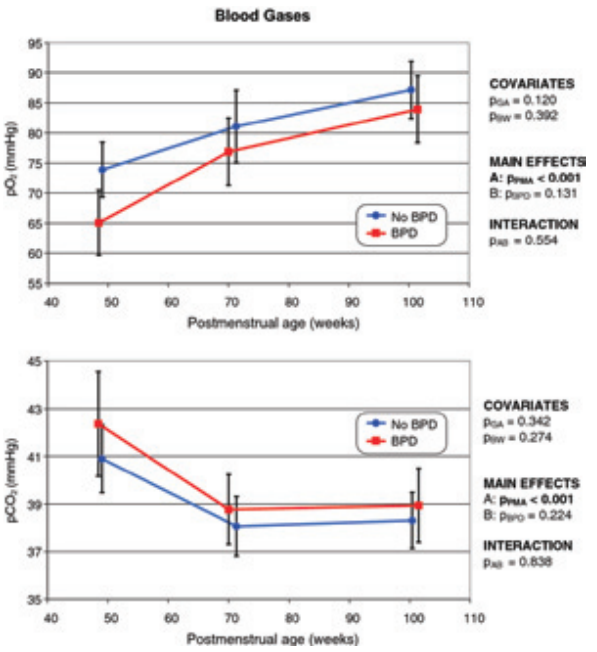

Figure 8 Changes over time in pO_2 (top) and pCO_2 (bottom) levels in infants with and without former BPD (the mode of presentation is the same as that of Figure 1).

or either the paired or unpaired t-test, as appropriate. Parameters of lung function are shown as group means, with 95% confidence intervals (CIs), in both the text and the Figures. The effect of BPD on development of lung function parameters was explored by multivariate analysis of variance (MANOVA); gestational age and birth weight were used as covariates. Statistical analysis was performed using SPSS (version 19; SPSS Inc. Chicago, IL). A p value of < 0.05 was considered to be statistically significant.

Results

Characteristics of the study population: Table 1 compares the characteristics, at birth, of infants with and without BPD. The former BPD infants were of lower gestational age and birth weight; the proportion of such infants that had an extremely low birth weight (< 1,000 g) was almost 3-fold higher than in the control group. The proportions of infants treated with surfactant, and the frequency of prenatal steroid administration, did not differ significantly between the two groups. All BPD infants required invasive mechanical ventilation (MV) during the neonatal period whereas only half of non-BPD infants were mechanically ventilated.

Somatic growth: Age at the day of LFT is shown in Table 2. No statistically significant difference was evident between the two groups in either chronological or postmenstrual age. In contrast, body weight ($p = 0.008$) and body length ($p = 0.015$) were lower in BPD infants than in controls (Figure 1). MAN-OVA revealed that birth weight significantly influenced the rate of gain of body weight over time ($p = 0.009$). The observed differences in body weight and length between the two groups remained constant at all three test time points. No statistically significant interaction was evident between BPD and PMA.

Tidal breathing: ll tidal breathing parameters (Figure 2) showed rapid development ($p < 0.001$) in both groups. In BPD infants, both VT and V'E were significantly lower ($p \leq 0.001$) than in non-BPD infants, but no statistically significant difference in the respiratory rate was evident. Neither gestational age nor birth weight significantly influenced the values of the tidal breathing parameters. However, V'E showed significant interaction ($p = 0.03$) with BPD and PMA: V'E increased more rapidly in non-BPD infants compared to those with former BPD. This was particularly evident when data from the first and second LFT session were compared.

After normalization of VT V'E to actual body weight (Figure 3), the between-group differences became statistically insignificant. However, gestational age and birth weight exerted statistically significant impacts on both weight-related parameters studied. Further, the interaction between BPD and PMA remained statistically significant upon normalization by body weight, indicating that the development, over time, of the weight-related parameters breathing parameters VT and V'E differed. As shown in Figure 3 V'E related to the body weight remained stable in non-BPD infants but decreased continuously in former BPD infants, because VT was lower in such infants.

Lung mechanics: As with the tidal breathing parameters, the development over time of all lung mechanical parameters differed significantly ($p < 0.001$) between the two groups (Figure 4), but the covariates did not significantly influence such variations. In former BPD infants, Crs was significantly lower than in non-BPD infants, but rose in parallel as PMA increased. After normalization of Crs values to actual body weight (Figure 5), the differences between the groups became statistically insignificant; both groups developed similarly. Specific compliance (CRS/FRC; the elasticity of a unit of lung volume) increased in both groups, but apparently more rapidly in former BPD infants (Figure 5). At 15 months of age, the specific compliance was nearly identical in either group.

Both Rrs and Raw (Figure 4) decreased with increasing age (p

< 0.001). Although the mean values of Rrs and Raw were always somewhat higher in former BPD infants compared to non-BPD infants, such differences never attained statistical significance.

V'maxFRC: In both non-BPD and BPD infants, V'maxFRC increased rapidly over time ($p < 0.001$); the value more than doubled between the first and third LFT sessions (Figure 6). At a PMA of approximately 100 weeks, the mean V'maxFRC of either patient group was near-identical.

Functional residual capacity: As PMA increased, a continuous rise ($p < 0.001$) in the end-expiratory lung volume measured either by body plethysmography (FRCpleth) or the SF6 multiple breath washout technique (FRCSF6) was evident in both groups (Figure 7). No statistically significant difference in FRCpleth was apparent when former BPD and non-BPD infants were compared, whereas FRCSF6 was significantly lower ($p = 0.036$) in the former BPD infants.

In both groups, normalization of FRCpleth and FRCSF6 values to actual body weight rendered the values of either group near-constant at each of the three measurement time points; no statistically significant between-group difference was evident. Also, when non-BPD and former BPD infants were compared, no statistically significant difference in mean FRCpleth values normalized to body weight was evident; the means (with 95% CIs) were 22.7 (21.9-23.4) mL/kg versus 22.8 (22.0-23.6) mL/ kg; $p = 0.855$. This was also true of the normalized mean FRC_{SF6} values: 21.3 (20.3-22.3) mL/kg versus 20.5 (19.5-21.4) mL/kg; $p = 0.401$.

Blood gas levels: The development over time of blood gas levels was comparable in either group (Figure 8); no statistically significant influence of gestational age or birth weight was evident. Whereas pO2 increased continuously ($p < 0.001$) as PMA rose, pCO2 decreased significantly ($p < 0.001$) from the first to the second LFT session and remained near-constant thereafter. Although the mean pO2 value of former BPD infants was consistently somewhat lower, and the pCO2 somewhat higher, than those of non-BPD infants, the differences did not attain statistical significance. No statistically significant interaction of BPD and PMA was apparent, indicating that differences between infants with and without BPD were constant over time.

Discussion and Conclusions

In the present study, we have shown that very low birth weight (VLBW) infants (birth weight < 1,500 g) with BPD exhibit reduced somatic growth (in terms of body weight and length) and impairment of some lung function parameters, compared to VLBW infants without BPD, when assessed at the same PMA. With the exception of the tidal breathing parameters VT and V'E, we found no evidence for catch-up during the first 15 months of life. This is in agreement with the data obtained from sequential lung function measurements performed at 6, 12, and 24 months after birth on 44 infants with moderate-to-severe BPD, which showed that lung function abnormalities persisted.[29] A study by Baraldi et al[13] of 24 VLBW infants with BPD showed that pulmonary mechanics improved during the first years of life but substantial airway functional impairment remained, as revealed by a low V'maxFRC The extent to which lung function in BPD survivors improves with age remains controversial.[24] Blayney et al[30] investigated 32 former BPD infants at mean ages of 7 and 10 years. Those with normal lung function at age 7 years demonstrated normal lung growth whereas those with evidence of impaired lung function at 7 years of age exhibited continued lung growth or repair, or both, during later school years. In another study, Koum-bourlis et al[31] performed repeated lung functional testing of 17 former BPD subjects between the ages of 8 and 15 years and found that although airflow obstruction may persist, this does not deteriorate later in life; an improvement in air trapping over time was evident. A more recent study by Doyle et al[24] on 147 former VLBW infants, of whom 33 formerly had BPD, showed that, at a mean age of 19 years, those with former BPD had poorer lung function than those without former BPD.

In the present study, the most significant lung function differences between the two patient groups were in the tidal breathing parameters (VT, V'E), lung compliance and end-expiratory lung volume. Whereas FRCpleth did not differ between former BPD and non-BPD infants, FRCSF6 (which measures the lung volume in actual communication with the airways) was significantly lower in former BPD compared to non-BPD infants. However, all differences in tidal breathing, lung compliance and FRC values disappeared after normalization of such parameters to actual body weight. This is attributable to the significant somatic growth retardation evident in former BPD infants. Normalization in terms of weight is usually performed after LFT of infants to reduce the extent of (the otherwise high) inter-subject variability. However, in infants experiencing growth retardation, such normalization may lead to overestimation of lung function. Hence, the results should be interpreted with caution. The reasons for the poor growth of preterm infants with former BPD remain unknown, but likely include dysfunction of various organ systems, decreased nutrient intake, and increased energy requirements.[31]

Immaturity and BPD independently impair postnatal lung function. Hoo et al[32] were the first to show that the V'maxFRC was reduced in preterm infants in the absence of any neonatal disease or therapy. The reduction was attributable to the arrest of lung and airway development. A preliminary study by Gappa et al,[33] measuring V'maxFRC in premature infants with and without BPD, suggested that prematurity per se may be a more important contributor to the observed impairment in lung function than is BPD. This may explain why we did not find any statistically significant difference in V'maxFRC values between preterm infants with and without former BPD.

Although the measurement of V'maxFRC is currently the most frequently used lung function test in infants who are unable to cooperate, the effect of the BPD on lung function can not only reduced on the assessment of the small airways. Hjalmarson and Sandberg[10] found in preterm infants with severe BPD a reduced FRC and increased inhomogeneity indices indicating an impaired alveolar gas mixing. Furthermore they found a reduced lung compliance and changes in the breathing pattern; the tidal volume was decreased and the respiratory rate increased. The differences between healthy pre- term infants and those with mild-to-moderate BPD were distinctly lower.

Several studies[12,17,34-36] using tracer gas techniques have shown that the FRC is reduced in former BPD infants, in good agreement with the findings of the present study. This reduction in FRCSF6 may not necessarily reflect a defect in lung development (the FRCpleth values were identical in either group) but rather a reduction in the proportion of the lung volume that participates in pulmonary gas exchange, in turn attributable to structural changes in the lung caused by BPD and

the use of mechanical ventilation. All of our BPD infants required invasive mechanical ventilation.

Consistent with the findings of the present study, Hjalmarson and Sandberg[10] found no significant difference in respiratory resistance between former BPD and non-BPD infants. Further, the variation in lung compliance did not persist after normalization to actual body weight. In contrast to studies from the presurfactant era, which predominantly investigated infants born at term,[37,38] no difference in the elastic performance of the respiratory system was evident between former BPD and non-BPD preterm infants. This may be explained by the fact that respiratory compliance after birth, in both groups, was very low, as a result of immaturity (as reflected by the low birth weights). Rapid catch-up growth during the first 15 months of life was evident; normal values of approximately 14 mL/kPa/kg[39] were eventually attained. Former BPD infants attained such values somewhat more slowly than did non-BPD infants (Figure 4, top). Baraldi et al.[13] also found that the respiratory compliance of VLBW infants with former BPD became normal at 2 years of age.

Catch-up growth in terms of lung compliance during the first year of life was reported in a study of BPD infants performed by Gerhardt et al[40] in the presurfactant era 25 years ago).

The cited authors speculated that, in former BPD infants, the increase in compliance evident upon aging was associated with lung growth, and more specifically to the formation of new alveoli. Specific compliance increased with age, as was also the case in our present work (Figure 5, bottom), supporting the interpretation of Gerhardt et al.[40]

As the lung grew, maturation of the breathing pattern was observed in both groups, as shown by an increase in tidal volume and a fall in the respiratory rate. However, a distinct delay in maturation was apparent in former BPD infants. Only a few studies have measured tidal breathing parameters in preterm BPD infants. Previously,[41,42] we found that BPD infants showed an increased respiratory rate and elevated minute ventilation, but no change in tidal volume, compared with healthy controls delivered at term. Similar results were obtained by Latzin et al,[12] who compared preterm former BPD infants with preterm healthy newborns at 44 weeks PMA. Hjalmarson and Sandberg[10] described a similar pattern in preterm infants with mild-to-moderate former BPD. Tidal volume (normalized to body weight) was significantly reduced in infants with severe BPD, compared to healthy preterm controls. Although the data did not attain statistical significance, we also noted increases in both respiratory rate and minute ventilation, normalized to body weight at term, in the present study. This breathing pattern is characteristic of stiff lungs and is energetically optimal.[43] However, with increasing age, a decrease in minute ventilation (normalized to body weight) was evident in former BPD infants. This was caused by a decrease in tidal volume. In non-BPD infants, minute ventilation per kilogram of body weight was near-constant. It remains unclear whether the decrease in minute ventilation in former BPD infants is attributable to impairment of respiratory mechanics resulting in a lower FRC, to the existence of a lower respiratory drive, or to a defect in respiration control.

The present study had several strengths and limitations. The strengths are the depth at which LFT was performed; we measured tidal breathing, respiratory mechanical parameters, lung volume, maximal respiratory flow, and blood gas levels. Also, all patients were examined by the same investigator, using the same equipment and protocol. Apart from the known inter-subject variability of several of the parameters that we measured, LFT remains highly device- and protocol- dependent. This poses major problems in multicenter studies.[17] The limitations of our study are the retrospective nature of our analysis, the small sample sizes of both groups (limiting our power to detect differences between former BPD and non-BPD infants with statistical significance), and the lack of a control group of healthy infants.[44] It is virtually impossible to recruit such a control group, for both practical and ethical reasons. Because our study was observational in nature, no causal relationships can be deduced from our findings.

In conclusion, the extent of somatic growth, and the evolution of some lung function parameters, of very preterm infants with former BPD lag behind those characteristic of preterm infants without BPD for the first 15 months of life. The differences between the groups in most lung function parameters disappear after the somatic growth retardation of former BPD infants is taken into account. Longitudinal LFT of preterm infants after discharge from hospital may help to identify those at risk of incomplete recovery of respiratory function, which can lead to development of respiratory problems in childhood and adolescence.

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Development of a Proxy-reported Pulmonary Outcome Scale for Preterm Infants with Bronchopulmonary Dysplasia

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Abstract

Background: To develop an accurate, proxy-reported bedside measurement tool for assessment of the severity of bronchopulmonary dysplasia (also called chronic lung disease) in preterm infants to supplement providers' current biometric measurements of the disease.

Methods: We adapted Patient-Reported Outcomes Measurement Information System (PROMIS) methodology to develop the Proxy-Reported Pulmonary Outcomes Scale (PRPOS). A multidisciplinary group of registered nurses, nurse practitioners, neonatologists, developmental specialists, and feeding specialists at five academic medical centers participated in the PRPOS development, which included five phases: (1) identification of domains, items, and responses; (2) item classification and selection using a modified Delphi process; (3) focus group exploration of items and response options; (4) cognitive interviews on a preliminary scale; and (5) final revision before field testing.

Results: Each phase of the process helped us to identify, classify, review, and revise possible domains, questions, and response options. The final items for field testing include 26 questions or observations that a nurse assesses before, during, and after routine care time and feeding.

Conclusions: We successfully created a prototype scale using modified PROMIS methodology. This process can serve as a model for the development of proxy-reported outcomes scales in other pediatric populations.

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Background

Bronchopulmonary dysplasia (BPD), or chronic lung disease (CLD), is one of the most common sequelae of preterm birth,[1] and its severity is an important predictor of long-term outcomes in premature infants.[2] The infants most vulnerable to BPD are those born before the 28th week of gestation (extremely low gestational age newborns, ELGANs). Compared to their peers without lung disease, ELGANs with BPD have increased mortality.[2,3] Those who survive with BPD have prolonged initial hospitalizations[4] and an increased risk of neurodevelopmental impairment such as mental retardation and cerebral palsy.[5-7] These BPD associated morbidities lead to increased family stress, economic hardship, and increased health care costs throughout childhood.[4,8,9]

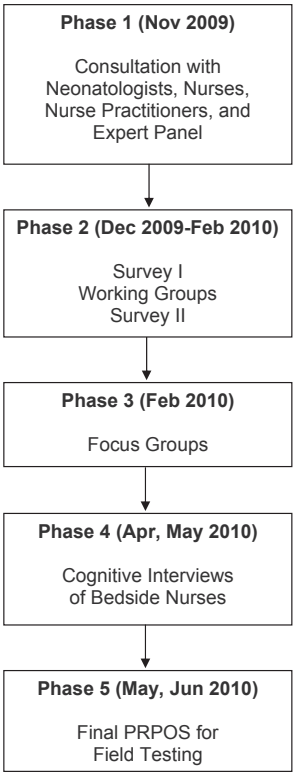

Figure 1. PRPOS development phases. Phases of development of the Proxy-Reported Pulmonary Outcomes Scale, from November 2009 to June 2010.

The most common definitions of BPD include the receipt of oxygen at 36 weeks post-menstrual age, with or without a physiologic test of oxygen dependency,[10,11] and the National Institutes of Health (NIH) consensus categorization of "none," "mild," "moderate," and "severe," which is based on the duration of oxygen therapy and the amount of oxygen received at 36 weeks.[12] These NIH categories help determine the effect of therapies designed to reduce the incidence of BPD in a clinical trial, but they are not useful to providers who are attempting to examine the day-to-day pulmonary function of an infant, and this

Table 1 Demographic information on participants in the modified Delphi process

	Survey 1	Working Groups	Survey 2
Total No. Participants	38	14	43
Missing data	3		1
Institution, n (%)			
UNC	13 (34%)	7 (50%)	9 (21%)
Duke	6 (16%)	7 (50%)	7 (16%)
Stanford	7 (18%)	0	9 (21%)
UAB	1 (3%)	0	3 (7%)
Iowa	8 (21%)	0	8 (19%)
Expert Panel	0	0	7 (16%)
Role, n (%)			
MD	10 (26%)	2 (14.3%)	14 (33%)
NP	9 (24%)	1 (7.1%)	10 (23%)
RN	10 (26%)	6 (42.9%)	13 (30%)
Specialist	6 (16%)	5 (35.7%)	6 (14%)
Years in Practice, mean*			
MD	14.7	12.3	11.4
NP	21.1	30	23.5
RN	18.8	15	20.1
Specialist	18.7	17.5	15.3

*Note: Years in practice have missing data for four cases in survey 1 and 16 cases in survey 2.

Table 2 Scenarios to describe level of CLD severity

Severity Level	Scenarios
No CLD	Baby Doe was extubated to CPAP and off supplemental oxygen by DOL[a] 22. He is now DOL 84 (36 weeks corrected age). Baby Doe has NO CLD.
Mild CLD	Baby Doe came off all oxygen on DOL 65. He is now DOL 84 (36 weeks corrected age). Baby Doe has MILD CLD.
Moderate CLD	Baby Doe is now DOL 84 (36 weeks corrected age) and on 0.1 lpm oxygen. Baby Doe has MODERATE CLD.
Severe CLD	Baby Doe is now DOL 84 (36 weeks corrected age) and on high-flow oxygen blended to an FIO2 of 0.65. Baby Doe has SEVERE CLD.

[a]DOL - day of life.

oxygen-based categorization does not capture the nuances of disease-related functional limitations.

A valid bedside assessment tool of pulmonary function will give clinicians and researchers a more effective way to test therapies by reliably identifying subtle effects on infant pulmonary function or by identifying subgroups of infants who respond to therapies such as diuretics or bronchodilators. Our goal was to develop a scale to assess the effects of lung disease on functional outcomes using proxy-reported measures. We adapted Patient-Reported Outcomes Measurement Information System (PROMIS) methodology, a widely recognized system of instrument item selection and refinement for patientreported outcomes,[13-18] to develop a parsimonious Proxy-Reported Pulmonary Outcomes Scale (PRPOS).

Our most significant adaptation of current PROMIS methods is our entire reliance on proxy-reported measures for this neonatal population because of their inability to report on their own.

The ultimate goal of PRPOS is to provide clinicians with a set of items and responses in various functional domains that can discriminate between infants with differing degrees of BPD severity. Our secondary goal is to present a model instrument development process that might be replicated for use in diseases of infancy. This paper describes the first five of six steps in the scale development process: (1) identification of domains, items, and responses; (2) item classification and selection using a modified Delphi process; (3) focus group exploration of items and response options; (4) cognitive interviews of proxy reporters on a preliminary scale; (5) final revision before field testing; and (6) reliability testing (for which analysis is ongoing).

Methods

We developed PRPOS in the five phases illustrated in Figure 1.

Phase 1: Identification of domains, items, and responses: We identified an appropriate set of activity domains and assessments for inclusion in the scale using face-to-face interviews with experienced neonatologists, nurses, and neonatal nurse practitioners at two academic medical centers (The University of North Carolina at Chapel Hill [UNC] and Duke University) and input from a panel of national experts in neonatology, pediatric pulmonology, feeding, and development.

We conducted interviews individually or in small groups using a "brainstorming" format. We asked respondents to use their clinical experience to identify characteristics of an infant diagnosed with BPD [CLD] at 36 weeks and any activities that precipitated these characteristics. During this phase of the process, items were included if at least two participants agreed on their discriminative utility, with the goal of identifying a complete set of potential items. The resulting set of activity domains and assessments, which grew in the course of the discussions from nine original "assessments and domains" to what began to be called 15 "qualities and conditions," was used in the next phase of the development process.

Phase 2: Item classification and selection: We used a modified Delphi process, a method of obtaining consensus on a subject matter from experts in the field through anonymous solicitation or polling of their opinions,[19] to identify, classify, review, and revise possible items and domains. Modified Delphi process participants included experienced neonatologists, nurses, and neonatal nurse practitioners, developmental specialists, and feeding specialists at five academic medical centers (UNC, Duke University, Stanford University, University of Alabama at Birmingham [UAB], and University of Iowa [Iowa]).

Our modified Delphi process included three steps: (1) a survey, (2) working group meetings, and (3) a second survey reflecting areas where consensus had not yet been achieved. The surveys were designed and administered using the web-based survey software Qualtrics (Provo, UT), and each respondent received a unique URL to the surveys. The entire process took place from December 2009 to February 2010.

We invited 59 clinicians from five academic medical centers to participate in the two surveys (Table 1); in addition, we asked our eight expert panel members to take the second survey.

The first survey (step one) had three parts. In part one, respondents described how certain qualities or conditions (alertness, tone of back/trunk, lower body, and upper body, eye

Table 3 Domains and behaviors used in survey 2

Domain	Behavior
Sleep	Interrupted sleep/restlessness
	Excessive sleepiness
	Sustained active or quiet sleep
Arousal/transition	Transitions well between states
	Arouses easily, but to agitation
	Arouses with difficulty
Awake state: General state during care time	Mainly quiet alert or active alert
	Wiped out, persistent drowsiness
	Restless, agitated
Awake state: Calming during care time	Calms, but with some difficulty
	Irritable, not easily calmed
	Calms with containment, voice soothing
Awake state: Eye appearance during care time	Eyes intermittently opened and closed
	Eyes tightly closed
	Engaged/alert
	Panicked/wide-eyed
	Glazed/blank
Awake state: Eyebrow appearance during care time	Raised
	Relaxed/neutral
	Furrowed
Awake state: Color change during care time	Mottled
	Pale
	Dusky
	None
Awake state: Tone during care time	Arched/shoulders elevated or retracted
	Floppy
	Mainly flexed/hands loosely flexed or opened and closed
	Some increased extensor tone, fingers splayed
Feeding mechanics: Rooting/feeding cues	Roots and initiates feeding cues independently
	Minimal cues/rooting
Feeding mechanics: Mouth/tongue position during first 5 minutes of feeding	Opened and rounded/seals on nipple spontaneously or with prompting
	Turns head away/hesitant to open mouth
	Refuses to eat
	Open mouth posture/tongue and chin positioned to open airway
Feeding mechanics: Tone during first 5 minutes of feeding	Floppy
	Mainly flexed/hands loosely flexed or opened and closed
	Arched/shoulders elevated or retracted
	Some increased extensor tone, fingers splayed
Feeding mechanics: Desaturation during first 5 minutes of feeding	Not able to accept nipple without desats
	Frequent breaks required for pacing
	Desats with sustained sucking; recovers with intervention
Feeding mechanics: Respiratory rate (RR) with feeding	RR above baseline during sucking pause periods/recovers slowly
	Tachypnea at onset of feeding only
	RR above baseline during sucking pause periods/recovers quickly
Respiratory: desaturation during care time	Severe or frequent
	Mild or intermittent or occasional
	Moderate or somewhat common
Respiratory: tachypnea during care time	Constant
	No tachypnea
	Occasional or intermittent

Table 4 Sample focus group questions from nine domains

Topic area	Sample questions
Arousal from sleep	How would you describe babies who 'arouse with difficulty'? What would that look like?
Calming	What would "may have trouble calming" look like if you were describing a baby with moderate CLD? What would someone observe? How about with severe CLD?
Agitation	How would you describe a CLD baby who is 'very agitated'? What are all the observations you might make about a baby at the far end of that spectrum (severe disease)?
Energy level/ activity	Describe a CLD baby in "a high energy" state. How, if at all, would an agitated baby look different from a baby in a state of high energy level/activity level?
Eye appearance	Is it helpful to include a 'glazed/blank' assessment of eye appearance? If so, is 'glazed/blank' on the spectrum from 'engaged' to 'panicked/wide-eyed' or is 'glazed/blank' indicating something different?
Color change	What color change do you observe in babies with CLD? What words best describe that color change?
Tone	What is a specific word or a modifier that describes a baby that has such bad lung disease and is so tired and wiped out that they become low-tone?
Desaturations	Do babies with no lung disease sometimes desat? Would 'normal' include an occasional desat?
Respiratory rate	How would you describe respiratory rate with feeding in a baby with no CLD?

appearance, eyebrow appearance, desaturations, presence of tachypnea, recovery time from tachypnea, retractions, and heart rate) appear in infants with four levels of BPD [CLD] severity–none, mild, moderate, severe–in three situations (e.g., at baseline before care, during care time, and during the first five minutes of feeding). Table 2 presents the scenarios used to describe level of CLD severity. Respondents also described the appearance of three feeding cues: opening the mouth, dropping the tongue, and the position of the chin. The survey provided three "other" categories where respondents could fill in additional characteristics they thought were important and describe the appearance of those characteristics in infants at each of the disease states.

In part two of the survey, respondents rated how well each of the observation domains and feeding cues would discriminate levels of CLD severity using a scale of 1 to 9, where 1=not at all well and 9=extremely well.

In part three, respondents provided open-ended feedback on the types of things that should be recorded before the assessment (e.g., whether a retinopathy of prematurity exam had taken place that day, or the timing of a furosemide dose) and made comments on other things we should consider in developing the scale.

Following the survey, we conducted three multidisciplinary workgroups (step two of the modified Delphi process) at UNC and Duke. At the start of the workgroups, we asked participants to score how well a set of items–quality of sleep; alertness, arousability, facial expression; disorganization; difficulty in calming; color change; tone; and feeding mechanics—reflects the severity of CLD in an infant during five states (sleep, transition, awake state, care time, and feeding) using a five point scale (0=no; 1=some; 2=moderately, 3=pretty closely; and 4=yes, very much). We then had guided discussions in which we asked participants to help refine our set of domains, narrow similar terms to a single, best descriptor, and clarify and simplify complex items. At the end of the workgroup, participants completed the score card again, and we determined whether discussion had changed preferences.

The feedback we received from the working groups contributed to development of our second survey (step 3), in which respondents estimated at what severity of lung disease they might observe a particular behavior or action and how well those items discriminate levels of CLD severity. Table 3 lists the five behavior domains. We also asked whether the following terms were familiar and useful in describing breathing: intercostal, subcostal, and substernal retractions; head bobbing; and nasal flaring. The survey included space for respondents to provide additional comments. At the conclusion of the modified Delphi process, we developed a preliminary scale.

Phase 3: Focus groups: In February 2010, we conducted two focus groups of bedside nurses, a physical therapist, and a developmental specialist to clarify domains, confirm item definitions, and refine the wording of potential scale items and corresponding response options.[13,20] An experienced

Table 5 Initial set of activity domains and assessments

Activity Domains	Assessments
At rest	Position: Tone (arched, relaxed)
Feeding by mouth	Pulse oximetry: Desaturation (length, depth)
Oro-gastric feeding	Retraction (subcostal, intercostal, head bob)
Handling/transitions/care time	Tachypnea (change in respiratory rate, time to baseline)
Family holding	Apnea (number, severity)
Noise	Heart rate (bradycardia)
Transition to awake	Alertness (engages, averts gaze, frantic)
Stooling	Circumoral cyanosis (presence of)
Sleep time (quiet alert/engaged periods versus prolonged sleep time)	Oro-motor dysfunction

Table 6 Survey 1 results of average ratings of appropriateness of CLD observation

Observation domain	MDs (n = 10)	RNs/NPs (n = 19)	Specialists (n = 6)
Alertness, mean (SD)	4 (2.03)	5 (2.29)	5 (2.48)
Tone:			
back/trunk	4 (2.12)	5 (2.03)	6 (2.77)
upper body	3 (1.77)	6 (2.02)*	6 (2.34)*
lower body	3 (1.81)	5 (1.76)*	4 (2.07)
Eyes	4 (2.20)	6 (1.97)	6 (2.51)
Eyebrows	4 (2.10)	6 (2.06)	6 (2.25)
Feeding cues:			
opens mouth	4 (1.98)	7 (1.46)*	6 (2.86)*
drops tongue	4 (1.81)	7 (1.73)*	6 (2.83)
position	5 (2.20)	7 (1.83)	6 (2.93)
Desaturation	8 (1.90)	8 (1.00)	8 (0.84)
Tachypnea:			
over baseline	8 (1.57)	8 (0.94)	9 (0.55)
time to recover	8 (1.51)	8 (0.61)	9 (0.55)
Retractions	8 (1.81)	8 (0.97)	9 (0.55)
Heart rate	6 (1.72)	7 (1.09)	7 (1.50)

*p < 0.05 vs MD responses (ANOVA with post-hoc analysis using the Student-Newman-Keuls all pairwise multiple comparison procedure)

focus group moderator conducted both focus groups, and members of the research team observed the discussions and provided background and clarification when necessary. The moderator used a semi-structured interview guide to elicit group participation and discussion on specific topic areas. We audio-recorded the focus group sessions and compared and collated notes taken by investigators in the group with the moderator's notes from the transcripts.

Each focus group was presented with the same scenario describing the clinical course of a premature infant at 36 weeks, and then asked to think about the infant in four disease states, no CLD, mild, moderate and severe CLD (see Additional File 1, Box S1). The focus group moderator instructed the participants to refer to the scenario throughout the discussion. Questions during the discussion centered on nine areas (Table 4).

Phase 4: Cognitive interviews: Following the focus groups, we conducted semi-structured cognitive interviews to obtain information about what items actually meant to potential respondents in terms of their comprehension of individual questions (ie, the question intent and meaning of terms), the sense of the questions overall, retrieval from memory of relevant information (ie, recallability of information and recall strategy), decision processes, response processes, and instructions for using the tool.[13,18,21,22]

The cognitive interviews were approved by the Institutional Review Board at UNC, and all interviewees gave their informed consent prior to the interview. The interviews took place in April and May 2010 and included bedside nurses from three academic medical centers (UNC, Stanford, and Iowa), chosen to elucidate possible regional differences in response to terms. In our cognitive interview process, a bedside nurse used the scale on an infant and then participated in a cognitive interview. The experienced cognitive interviewer followed a semistructured interview guide with questions about each item, the overall scale, and the directions.

Examples of the cognitive interview questions include:
- On a scale of 1 to 5, with 1 being easiest and 5 being hardest, how easy or hard was it to choose an answer?
- How sure are you of your answer? -or- How sure are you that it is [X]?
- Would it be easier for you if you could choose from fewer options? (If yes, probe: what response options would you eliminate?)
- Would it be easier for you if you could choose from more options? (If yes, probe: what other response options would you like to see here?)
- Is there another response that should be added that would more fully describe what you observe?
- Why do you say [X]? -or- Tell me why you chose [answer] instead of some other answer on the list.

After the first three interviews, we assessed each nurse's feedback and revised items and response options in the scale that respondents had thought were unclear. We then conducted three more interviews and made minor changes to the scale after each one.

Phase 5: Final scale revision: We used the results of the focus groups and cognitive interviews to develop a prototype PRPOS and prepare it for field testing in five geographically dispersed academic centers with varying rates of BPD.

Results

Phase 1: Identification of domains, items, and responses: During the brainstorming phase, 15 experienced clinicians identified an initial item pool of nine activity domains and nine assessments (Table 5). The national expert panel included two neonatologists, two pediatric pulmonologists, two infant feeding experts, and two neurodevelopmental specialists (seven from the United States and one from Canada). They confirmed that these domains and assessments were comprehensive, observable, and related to CLD at age 36 weeks adjusted gestational age. However, the expert panel raised a potential concern about assessing feeding behaviors because of the interaction of immaturity, respiratory disease, and feeder skill. Based on this input, we modified the feeding assessment to include only the initial period of feeding. Using input from the face-to-face interviews and expert panel, we arrived at a set of 15 activity domains and assessments, or "qualities and conditions," to be included in the next phase of the development process.

Phase 2: Item classification and selection (modified Delphi and workgroups): We received 38 responses to the first survey (response rate=64%) and 43 responses to the second survey (response rate=64%). Seventeen people took part in the working groups: ten from UNC, including nurses and a feeding specialist, and seven from Duke, including developmental/family specialists, researchers, and a nurse.

First Survey: The open-ended responses to the first survey provided us with user-generated, specific terms and phrases with which respondents could describe an infant's appearance at the four levels of BPD severity. Nurses and neonatal nurse practitioners provided more detailed descriptions than did neonatologists, and the feeding and developmental specialists provided more nuanced responses about feeding and development.

Table 7 Response option rewording after cognitive interviews

Question	Original Response Options	Revised Response Options
How would you describe the infant's general state?	Mainly calm or quiet	Active or quiet sleep
	Restless	Drowsy - eyes open and closed
	Agitated or irritable	Awake
	Distressed	
	Frantic	
How would you describe the infant's general status?*	n/a	Mainly calm or quiet
	n/a	Tired
	n/a	Restless
	n/a	Agitated or irritable
	n/a	Distressed
	n/a	Frantic
How would you describe the infant's tone?	Soft flexion	Soft or neutral flexion
	Some increased extensor tone, fingers splayed	Arms extended
	Increased extensor tone with arching and/or shoulders elevated or retracted	Arms extended with arching and/or shoulders elevated or retracted
		Limp (wiped out)
How do the infant's eyes appear?	Asleep - can't observe	Asleep or closed - can't observe
	Engaged/alert/bright-eyed	Crying
	Easily distracted	Tired
	Panicked/wide-eyed	Engaged or alert
		Easily distracted
		Panicked
How would you describe the infant's endurance during care time? ("Endurance" revised to "stamina")	No fatigue (tolerates care time well	Sufficient stamina - tolerated care time well
	Minimal fatigue (shows some signs of fatigue with care but recovers quickly)	Tired some with care but recovered quickly
	Moderate fatigue (frequent signs of fatigue with care but recovers with pause)	Tired easily with care but recovered with pause
	Easily fatigued ('wiped out' 3-5 minutes into normal care time)	Tired easily without recovery ('wiped out' 3-5 minutes into normal care time)

* new question broken out of "general state" question as a result of discussion, thus, original response not applicable (n/a)

Table 6 shows that, on average, registered nurses, nurse practitioners, neonatologists, and developmental and feeding specialists scored alertness, tone, eyes, eyebrows, and feeding cues mid-range (4-6) on the scale. Desaturation, tachypnea over baseline, time to recover from tachypnea, retractions received high scores (8 or 9). Nurses and specialists were more likely than were physicians to rate aspects of tone and feeding as valuable discriminators of levels of CLD severity.

Respondents reported that pre-assessment data should include information on the clinical environment (eg, parent visits, room noise), administration and timing of medications (eg, timing of last steroid course, dose of caffeine/aminophylline), procedures and tests (eg, laboratory tests, immunizations, radiology visit), and respiratory support (eg, type and magnitude of support).

Workgroup Feedback: The workgroup participants assisted in narrowing multiple terms to a single, best term for 12 items. For example, eyebrow descriptors "furrowed," "scrunched," "contracted," and "tense" were narrowed to "furrowed." In addition, participants clarified, defined, or distinguished similar descriptions for eight items. For instance, participants helped discriminate between eyes closed due to stress, described by the term "eyes tightly closed," and eye closure that does not indicate distress, denoted by "closed and sleepy" eyes. In three cases, workgroup participants simplified terms; for example, we reduced descriptions of musculoskeletal tone from four to three because of clinicians' inability to discriminate accurately between four different levels.

Participants also highlighted areas of uncertainty, expressing concern that some of our feeding items (mouth/tongue position; rooting/feeding cues) might be influenced by the feeder's technique and level of experience or the infant's development and feeding skills, rather than by the infant's level of CLD severity. The groups also noted that it is difficult to decipher whether "raised" and "furrowed" eyebrows signal distress related to the infant's CLD.

When we asked workgroup members to rescore after discussion, their responses did not change significantly from what they reported before discussion. Overall, most items scored as "moderately" or "pretty closely" reflecting severity of CLD in infants.

Table 8 Examples of question and response option wording changes to the PRPOS

Original	Revision
Question: Does this infant's care plan or orders require or allow an increase in oxygen support during care time? *Response options:* No, Yes	Split "yes" response option into "yes - required" and "yes - allowed"
Question: How would you describe the infant's general state? *Response options:* Asleep, Drowsy - eyes open and closed, Awake	Changed "asleep" response option to "asleep (active sleep or quiet sleep)"
Question: How would you describe the infant's color?	Added instruction to ignore jaundice.
Question: How would you describe the infant's breathing?	Reworded question to "How would you describe the greatest degree of retractions you observe?"
Question: How would you describe the infant's tone? *Response options:* Soft flexion; some increased extensor tone, fingers splayed; increased extensor tone with arching and/or shoulders elevated and retracted	Revised response options to "soft or neutral flexion," "arms extended," "arms extended with arching and/or shoulders elevated or retracted," lip (wiped out)
Question: How do the infant's eyes appear as you begin care? *Response options:* asleep- can't observe, engaged/alert/bright-eyed, easily distracted, panicked/wide-eyed	Revised response options to "asleep or closed - can't observe," "crying," "tired," "engaged or alert," "easily distracted," and "panicked"

Second Survey: Results from the second survey of the modified Delphi process suggested that we had a range of behaviors and actions that would indicate different levels of CLD severity for each domain. For five of the domains (tone and desaturations during the first five minutes of feeding, respiratory rate with feeding, and calming and desaturations during care time), we did not have a descriptive behavior or action that would reflect the absence of disease, or "no CLD." Thus, we added a descriptor that reflected no CLD more clearly. For five domains (sleep, arousal/transition, general state during care time, color change, and feeding cues), we had descriptive behaviors or actions that showed overlap between moderate and severe disease. Most respondents (81%) reported that intercostal, subcostal, and substernal retractions, head bobbing, and nasal flaring were familiar and/or useful terms to describe breathing. A few respondents (16%) noted other degrees to consider between "barely visible" and "pronounced," and a few others (9%) did not find the term "head bob" familiar or useful.

We chose eleven areas for further discussion, expansion, and clarification using focus groups. We eliminated four potential assessment domains (sleep, rooting/feeding cues, mouth/tongue position, and tone during first five minutes of feeding) because of difficulty in defining an appropriate scale (sleep) or low scores on the CLD discrimination question. We also added two areas–retractions and nasal flaring– for inclusion on the tool, but we determined that we did not need to explore these further during the focus groups.

Phase 3: Focus Groups: Eighteen beside nurses and specialists participated in the two focus groups, with nine participants in each group. All participants had at least three years of experience in the neonatal intensive care unit. The focus group discussions helped us to confirm response options for our items and determine the scale endpoints from no disease to severe CLD. Focus groups also helped us discover which terms should not be used as response options (eg, "mottled" to describe the infant's color, and "floppy" or "hypotonic" to describe the infant's tone). As we note above, we began by presenting the focus groups with eleven areas, arousal, general state during care time, calming, eyes, eyebrows, color, tone, desaturations during feeding, respiratory rate during feeding, desaturations, and tachypnea, and asked group members to discuss transition/arousal, calming, agitation and energy/activity level, eye appearance, color change, tone, desaturations, and respiratory rate. We also asked focus group members to think about descriptors of general state–mainly calm or quiet, restless, agitated or irritable, distressed, and frantic–and of the ability to calm-self-calms, calms with containment, voice soothing, irritable, not easily calmed, frantic/inconsolable. In the course of listening to focus group discussion, we chose to eliminate the questions about color and tone, and also to eliminate questions about eyebrows, but retain questions on eyes, and add questions about respiratory rate and desaturation during both care time and feeding.

Phase 4: Cognitive Interviews: Six bedside nurses from three academic medical centers, UNC (n=3), Stanford University (n=2), and the University of Iowa (n=1) participated in one-hour cognitive interviews.

Overall, the nurses reported that the questions were easy to answer. Interview respondents found that the tool's instructions were understandable for the overall assessment and the care time portion of it, but they found the instructions less clear for the feeding portion of the assessment. At least one respondent suggested wording changes to the response options of 12 of 20 questions, but half or more of the respondents suggested changes to the response options for only these four questions: (1) How would you describe the infant's general state?; (2) How would you describe the infant's tone?; (3) How do the infant's eyes appear as you begin care?; and (4) How would you describe the infant's endurance during care time?

In response to these cognitive interview results, we changed the response options in four cases about which at least half the respondents had suggestions. The old and new responses to the questions are presented in Table 7. To illustrate the evolving refinement of responses, we initially included two additional response options to the general state question: "sleeping" and "tired." After testing this twice, we realized that the question should actually be divided into two questions– one on "general state" and one on "general status."

Phase 5: Final item revision: We refined the directions for using the scale, particularly for the feeding assessment section. We defined "desaturation" as an oxygen saturation of less than 80%, and we defined "increased respiratory rate" as a respiratory rate above 60 or, if the infant's baseline respiratory rate was already above 60, an "increase" is defined as a respiratory rate above the baseline. We provided instructions for how to calculate the baseline respiratory rate–count for 30 seconds, then multiply by 2–and we revised other question wording and response options, examples of which can be seen in Table 8.

Discussion

The use of the PROMIS methodology in PRPOS's development assures us that the creation of the instrument has been both transparent and replicable expert clinical judgment from registered nurses, neonatal nurse practitioners, neonatologists, and developmental and feeding specialists has informed all the phases of the development process. We continually refined the scale's potential set of items and response options with the goal of achieving a parsimonious set of items going into the cognitive interviews. We did not have to remove any items during the final scale revision. The prototype scale includes 26 questions about the infant that a nurse assesses before, during, and after a routine care time and feeding, and takes less than 2 minutes to complete.

Our scale development process was similar to, but more broadly inclusive and iterative than, the development of the Premature Infant Pain Profile[23,24] because of our use of modified Delphi surveys, workgroups, focus groups, and cognitive interviews. We used the more extensive and rigorous modified PROMIS methodology in an attempt to overcome some of the inherent limitations of proxy measures and to accomplish much of the work of establishing valid and reliable items prospectively, rather than depending entirely on retrospective testing of measures. Each phase of the development process produced uniquely valuable information. The initial consultation with expert providers helped us explore and define the domains we needed to measure. The modified Delphi Process, including the two surveys interrupted by workgroup discussion, gave us enormous insight into shared–and unshared–conceptual underpinnings to common terms. The focus groups of end-users–the bedside neonatal intensive care unit nurses who care for infants with BPD–reassured us that we had succeeded in narrowing the domains to the minimum number that adequately describes BPD infants' disease state, to decrease the burden of administration. Finally, the cognitive interviewing gave us an exceptional opportunity to query users' experience with the instrument itself: "Was it understandable? Easy to complete? Effective? Did response categories mean to users what we intended them to mean?" We expect that completion of all these steps will enhance the usefulness of each individual item and enhance the usability of these assessment items across different clinical settings.

Each instrument development phase could not alone lead to a successful product, but no phase was dispensable, and, taken together, they have generated a set of items ready for quantitative assessment. Our development process is limited by the fact that it is performed only in academic medical centers, although it is reasonable to assume that most non-academic center neonatal intensive care units would share many features of the academic medical center environment. Our focus groups were conducted at only two neonatal intensive care units both located in a single state, opening the possibility of limitations by region, or practice culture. Our more geographically dispersed cognitive interviewing and field testing should help us identify any such problems.

The PRPOS is currently undergoing field testing at five academic medical centers, where bedside nurses are applying the assessment tool to a cohort of 150-200 neonates (25-40 per institution) between 23 and 30-6 weeks gestational age at birth (excluding infants with chromosomal abnormalities) and between 36-0 and 36-6 weeks postmenstrual age. At the conclusion of field testing, we will perform psychometric analyses of the data to test item validity and reliability, for the purpose of further scale refinement.

Conclusions

We expect that use of the PRPOS to assess observable, functional domains will greatly enhance the current unidimensional assessment of BPD severity based on oxygen use alone. For example, the PRPOS might allow clinicians and researchers to test therapies for BPD more effectively by accurately identifying subtle effects on lung function. In addition, refinement in the definition of BPD may allow more accurate prediction of important outcomes such as hospital length of stay and re-hospitalization after discharge, and further refine the relationship between BPD and neurodevelopmental outcome.

Use of a structured approach modeled on the rigorous PROMIS methodology helped us develop and refine a proxy-reported measurement instrument over a short period of time, while maintaining precision, clarity, discrimination, and comprehensiveness balanced with parsimony. This approach will serve as a useful model for others interested in developing proxy-reported outcomes measures.

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Development and Validation of Serum Bilirubin Nomogram to Predict the Absence of Risk for Severe Hyperbilirubinemia Before Discharge

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Abstract

Background: Early discharge of healthy late preterm and full term newborn infants has become common practice because of the current social and economic necessities. Severe jaundice, and even kernicterus, has developed in some term infants discharged early. This study was designed to elaborate a percentile-based hour specific total serum bilirubin (TSB) nomogram and to assess its ability to predict the absence of risk for subsequent non physiologic severe hyperbilirubinemia before discharge. Methods: A percentile-based hour-specific nomogram for TSB values was performed using TSB data of 1708 healthy full term neonates. The nomogram's predictive ability was then prospectively assessed in five different first level neonatal units, using a single TSB value determined before discharge. Results: The 75th percentile of hour specific TSB nomogram allows to predict newborn babies without significant hyperbilirubinemia only after the first 72 hours of life. In the first 48 hours of life the observation of false negative results did not permit a safe discharge from the hospital. Conclusion. The hour-specific TSB nomogram is able to predict all neonates without risk of non physiologic hyperbilirubinemia only after 48 to 72 hours of life. The combination of TSB determination and risk factors for hyperbilirubinemia could facilitate a safe discharge from the hospital and a targeted intervention and follow-up.

Background

Early discharge of healthy late preterm and full term newborn infants has become common practice because of the current social and economic necessities. The association between early discharge and the need for readmission has been frequently reported, mainly because of unexpected severe hyperbilirubinemia. In fact, severe jaundice and even kernicterus has developed in some term infants discharged early. For these reasons the detection of infants without risk of severe hyperbilirubinemia has become one of the most intriguing challenges for neonatologists. However, the ability of physicians and other health care providers to recognize clinically significant jaundice and predict bilirubin levels based on the cephalocaudal progression of jaundice is limited. Total serum bilirubin (TSB) or Transcutaneous bilirubin (TcB) determination is often the only way to avoid such difficulty but the reliability of a single TSB/TcB value to identify newborn infants at risk of significant hyperbilirubinemia is not univocally accepted. Moreover, some authors suggested caution in applying hour-specific nomograms elaborated on different newborn population. In this study, we aimed to design a percentile-based hour-specific TSB nomogram in healthy full term neonates in the first four days of life and to verify its clinical reliability in a prospective multicenter study involving five neonatal units of our region in order to identify infants without risk for subsequent severe hyperbilirubinemia and to achieve a safe neonatal discharge.

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Materials and Methods

The study was conducted in 2 phases. In phase one 1708 healthy full term infants were studied to assess the normal neonatal trend of TSB with the aim to elaborate the percentile-based hour specific nomogram. In phase two, the predictive ability of the nomogram was assessed in a large study population from five different neonatal units of our region.

Phase one – Elaboration of the predictive model

During a seven months period ended on December 2008 a total of 2147 live births took place in our institution but only 1708 healthy newborn infants were considered for the study because 439 did not meet criteria for enrolment. Exclusion criteria were prematurity, congenital anomalies, Rh or major ABO isoimmunization indexed by a positive direct antiglobulin test, or the need of intensive care. Infants presenting with delayed meconium emission (>24 hours), hypoglycemia, hypothermia, cephalohematoma, cutaneous bruising, hemorrhagic disease of the newborn (vitamin K deficiency), urinary tract infection, and suspected clinical sepsis were also excluded. All included babies were full term (gestational age ≥37 weeks), appropriate for gestational age (birth weight >10th centile), delivered by vaginal birth or caesarean section after uneventful pregnancy, without asphyxia (Apgar score ≥7 at 1 and 5 minutes). No drugs were administered to the infants, except for 1 mg vitamin K (Konakion, Roche Laboratories, Nutley, NJ) intramuscularly soon after birth. Feeding was started at 1 hour of life, followed by breast-feeding or bottle-feeding every 3 hours in case of low breast milk intake. No prophylactic intervention for hyperbilirubinemia was employed. Environmental lighting was constant during the study period. The infants were eligible for discharge 72 hours after birth in case of vaginal delivery and 96 hours in case of caesarean section. After obtaining parental informed consent, TSB was measured on capillary blood (OHC Photo-Ictometer, model IV, O'Hare & Co, Ltd., Tokyo, Japan) at

Table 1 Clinical characteristics of newborn infants studied to perform hour-specific nomogram.

Variables	Neonates (1708)
Gestational age (wks)	
37	234 (13.7)
38	325 (19.0)
39	364 (21.3)
40	453 (26.5)
41	284 (16.6)
42	48 (2.8)
Birth weight (g)	
≤3000	350 (20.5)
3001-3499	697 (40.8)
3501-3999	521 (30.5)
≥ 4000	140 (8.2)
Male/Female	943/765 (55.2/44.8)
Mode of delivery	
Vaginal	1085 (63.5)
Cesarean section	542 (31.7)
Vacuum extractor	81 (4.8)
Feeding	
Exclusive breast feeding	1304 (76.3)
Breast + bottle feeding	143 (8.4)
Bottle feeding	261 (15.3)

Values expressed as number (%)

Table 2 Values of TSB corresponding at the 50th, 75th and 90th percentile of the hour-specific nomogram elaborated in our population.

Hrs	50th	75th	90th	Hrs	50th	75th	90th	Hrs	50th	75th	90th
24	**6.1**	**7.5**	**8.9**	49	9.0	10.3	11.9	73	10.0	11.7	13.2
25	6.2	7.7	9.1	50	9.1	10.4	12.0	74	10.0	11.8	13.3
26	6.4	7.8	9.2	51	9.1	10.4	12.1	75	10.1	11.8	13.3
27	6.5	8.0	9.3	52	9.2	10.5	12.2	76	10.1	11.8	13.4
28	6.7	8.2	9.5	53	9.2	10.6	12.3	77	10.2	11.9	13.4
29	6.8	8.3	9.6	**54**	**9.3**	**10.7**	**12.4**	**78**	**10.2**	**11.9**	**13.5**
30	**7.0**	**8.5**	**9.7**	55	9.3	10.8	12.5	79	10.3	12.0	13.5
31	7.2	8.6	9.9	56	9.3	10.8	12.5	80	10.3	12.1	13.6
32	7.3	8.7	10.1	57	9.3	10.9	12.6	81	10.4	12.1	13.7
33	7.5	8.9	10.2	58	9.4	10.9	12.7	82	10.5	12.2	13.7
34	7.7	9.0	10.5	59	9.4	11.0	12.8	83	10.6	12.3	13.8
35	7.9	9.1	10.6	**60**	**9.5**	**11.0**	**12.9**	**84**	**10.6**	**12.4**	**13.8**
36	**8.0**	**9.2**	**10.8**	61	9.5	11.1	12.9	85	10.6	12.4	13.9
37	8.1	9.3	10.8	62	9.5	11.1	12.9	86	10.7	12.5	14.0
38	8.2	9.4	10.9	63	9.5	11.2	12.9	87	10.7	12.5	14.1
39	8.3	9.5	10.9	64	9.6	11.2	13.0	88	10.7	12.5	14.2
40	8.4	9.6	11.0	65	9.6	11.3	13.0	89	10.8	12.6	14.3
41	8.5	9.7	11.1	**66**	**9.6**	**11.3**	**13.0**	**90**	**10.8**	**12.6**	**14.4**
42	**8.6**	**9.8**	**11.1**	67	9.6	11.4	13.0	91	10.9	12.7	14.5
43	8.7	9.9	11.2	68	9.6	11.4	13.1	92	11.0	12.9	14.6
44	8.7	9.9	11.3	69	9.7	11.5	13.1	93	11.2	13.0	14.7
45	8.8	10.0	11.5	70	9.8	11.6	13.1	94	11.3	13.2	14.8
46	8.9	10.1	11.6	71	9.8	11.7	13.2	95	11.4	13.4	14.9
47	8.9	10.2	11.7	**72**	**9.9**	**11.7**	**13.2**	**96**	**11.5**	**13.5**	**15.0**
48	**9.0**	**10.2**	**11.8**								

Table 3 Baseline characteristics of the study population included in phase 2.

Variables	Neonates (2167)
Gestational age (wks)	38.9 ± 1.5
> 37 wks	1983 (91.5)
35 - 36 wks	184 (8.5)
Birth weight (g)	3237 ± 471
Small for gestational age	115 (5.3)
Male	1137 (52.5)
Race	
White	1952 (90.1)
Asian	106 (4.9)
Black African	55 (2.5)
Hispanic	54 (2.5)
Mode of delivery	
Vaginal	1159 (53.5)
Cesarean section	953 (44)
Vacuum extractor	55 (2.5)
Apgar score	
< 7 at 1'	53 (2.4)
< 7 at 5'	0
Feeding	
Exclusive breast feeding	1267 (58.5)
Breast + bottle feeding	848 (39.1)
Bottle feeding	52 (2.4)
Weight loss > 10%	127 (5.9)
Age at TSB (h.)	63 ± 21
TSB value (mg/dL)	9.4 ± 0.6
Significant hyperbilirubinemia	55 (2.5)
Required phototherapy	46 (2.1)
TSB > 17 mg/dL	9 (0.4)

Values expressed as mean ± SD or number (%)

12 hours of life and then every 12-24 hours during the first three day of life or when clinically indicated. Newborn babies with TSB values >15 mg/dl were discharged after a TSB decrease at two consecutive samples. In these infants direct acting bilirubin measurement was also performed. Table 1 shows the clinical characteristics of the infants considered to perform hour-specific nomogram. Mean gestational age was 39.3 ± 1.3 weeks (range: 37-42) and mean birth weight was 3.302 ± 432 grams (range: 2580-4720); the male to female ratio was close to one; two thirds of the infants had been vaginally delivered and the majority was totally breastfed. Eighty-nine neonates (5.2%) had TSB value > 15 mg/dl, while only 51 (3.0%) exceeded the value of 17 mg/dl. For newborn infants treated with phototherapy according to the American Academy of Pediatrics we considered only pretreatment values. The highest TSB values showed a Gaussian distribution. Three hundred fifty (20.5%) infants reached their highest value between 24 and 48 hours of life, 837 (49.0%) had the highest TSB value between 49 and 72 hours, while 364 (21.3%) and 157 (9.2%) newborn infants reached their highest value from 73 to 96 hours and from 97 to 120 hours of life, respectively. The correlation between the TSB value obtained at single hourly determination during the first 96 hours of life and the highest absolute value was calculated using the linear regression analysis. No significant correlation between the TSB value in the first 12-24 hours of life and the highest TSB level was observed. On the contrary, there was a significant correlation between TSB values measured from 25 hours onwards and highest TSB levels ($p < 0.001$). Data were analyzed by using

Table 4 Ability of TSB measurements over the 50th, the 75th and the 90th percentile of TSB nomogram to predict significant hyperbilirubinaemia, for designated time periods.

Hours of age	TP (n)	FN (n)	TN (n)	FP (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
24 to 48 hours								
< 50th percentile	24	1	357	263	96.0	57.6	8.4	99.7
< 75th percentile	22	3	479	141	88.0	77.3	13.5	99.4
< 90th percentile	12	13	576	44	48.0	92.9	21.4	97.8
49 to 72 hours								
< 50th percentile	23	0	657	368	100	64.1	5.9	100
< 75th percentile	22	1	860	165	95.7	83.9	11.8	99.9
< 90th percentile	17	6	975	50	73.9	95.1	25.4	99.4
73 to 96 hours								
< 50th percentile	7	0	322	145	100	69.0	4.6	100
< 75th percentile	7	0	409	58	100	87.6	10.8	100
< 90th percentile	6	1	446	21	85.7	95.5	22.2	99.8

TP True Positive; FN False Negative; TN True negative; FP False Positive; PPV Positive Predictive Value; NPV Negative Predictive Value

SPSS 15.0 for Windows (SPSS, Chicago, IL). TSB percentiles for each designated time were calculated, and these data were used for the design of an hour specific nomogram (Table 2) with Microsoft Excel (Microsoft, Redmond, WA).

Phase two – Prospective application of the predictive model

In phase two the predictive ability of an hourly TSB value measured between 24 to 96 hours was assessed using percentile-based hour-specific nomogram and based on the frequency of any subsequent significant severe hyperbilirubinemia defined as TSB value >17 mg/dL, or as need for phototherapy treatment according to AAP guidelines.

During a 10-month period, ending in December 2009, a multicenter prospective study was conducted in five neonatal units of Rome. The study involved 2167 neonates with gestational age >34 weeks, based on postmenstrual date confirmed by clinical assessment. Infants with congenital anomalies and those requiring neonatal intensive care were excluded from the study. All infants received 0.5 – 1 mg of vitamin K intramuscularly or orally soon after their birth. No prophylactic intervention for hyperbilirubinaemia was employed. The measurement of TSB was performed in jaundiced newborn infants and/or just before the discharge from the hospital. In all newborn babies blood samples (75 µl) for the measurements of TSB were collected by heel stick puncture. Capillary tubes were protected from light exposure and after centrifugation they were assayed with the direct spectrophotometer (Microbilimeter Dual Beam Plus model 11144A73G, Ginevri, Rome, Italy) within 30 minutes. Studied infants were never discharged before 72 hours of age independently from the mode of delivery. All newborn babies with a predischarge TSB value >75th percentile of our nomogram were discharged only after two consecutive decreasing TSB values, 12 hours apart, making us able to identify the maximum TSB level. Newborn infants with pre-discharge TcB level between the 50th and the 75th percentile were discharged and controlled 48 hours later for hyperbilirubinemia. Parents of infants with TSB <50th percentile were counseled to return to the hospital within 5 days after discharge, or even earlier if persistent jaundice was observed. The decision to use phototherapy was made by the attending neonatologist according to AAP guidelines. For babies exposed to phototherapy we considered only pre-treatment measurements. All perinatal data were recorded in a single database for each site with a selected log of any event occurring during the study period. Care was taken that the same clinical protocol study, method for sample collection and strategies for patient recruitment were prospectively maintained, so that the data from each unit could be pooled.

In our percentile-based hour-specific nomogram the TSB measurements were plotted on our nomogram separately by two researchers (CR and GB) after completion of the study. Statistical analysis was performed using Student's t-test for continuous predictors and Fisher's test for categorical data. We calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) plotting TSB data in the 50th, 75th and 90th percentile of our TSB nomogram. Special care was given to evaluate the ability of our nomogram in predicting infants without risk for subsequent severe hyperbilirubinemia. Receiver operating characteristic (ROC) curve analysis was performed with SPSS software, which was used to assess the predictive ability of our TSB nomogram.

Results

Table 3 shows the baseline characteristics of the study population. 184 neonates (8.5%) were late preterm and there was a slight prevalence of males. The mean + SD value for birth weight was 3237 + 471 g (range 2000-5090) and for gestational age 38.9 + 1.5 weeks (range 35-42). Babies were predominantly Caucasian (90.1%) and uniformly coming from caesarean section or vaginal delivery. Exclusive breastfeeding was prevalent, but 39.1% of babies received also bottle-feeding during their hospital stay. The mean age for TSB sampling was 63 + 21 SD hours and the mean TSB value was 9.4 + 0.6 mg/dL. Significant hyperbilirubinemia, defined as TSB value >17 mg/dL or as need for phototherapy was diagnosed in 55 newborns (2.5%): 46 neonates required phototherapy while 9 newborn babies reached a TSB value greater than 17 mg/dL but were not treated. Direct acting bilirubin was normal in all infants with TSB > 15 mg/dL. No exchange transfusion was performed and no case of significant hyperbilirubinemia was documented after discharge.

Sensitivity, specificity, PPV and NPV of percentiles of our TSB nomogram in predicting significant hypebilirubinemia are listed in table 4. Using the 75th percentile 100% of sensitivity was reached only after 72 hours, while three false negative results were obtained between 24-48 hours and one false negative result has been observed between 49-72 hours. The use of the 50th percentile predicted all newborn without subsequent significant hyperbilirubinemia after 48 hours while there was only one false negative result between 24-48 hours.

Figure 1 depicts the ROC curves during different hours of age.

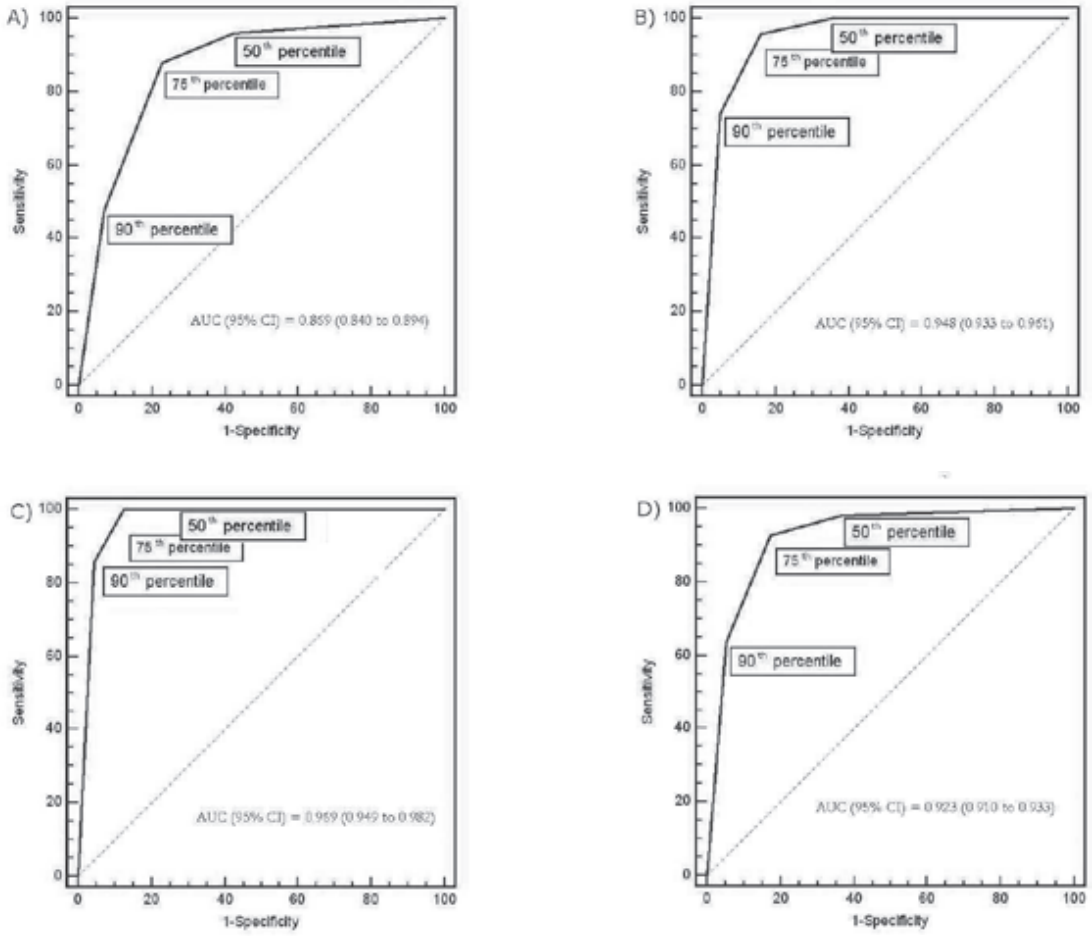

Figure 1 ROC curves during different hours of age: A) 24-48 h; B) 49-72 h; C) 73-96 h; D) 24-96 h. (AUC area under the curve).

The AUC measures the accuracy of the 50th, the 75th and the 90th percentile in predicting significant hyperbilirubinemia. AUC increased gradually with hours of age (0.869 for 24-48 h; 0.948 for 49-72 h; 0.969 for 73-96 h). Figure 2 shows the comparison of the ROC curves during different hours of age.

Bhutani hour specific nomogram was applied in our study population (table 5). We found no difference between the predictive ability of our 50th percentile and that of the 40th percentile of Bhutani (table 6). The sensitivity of our 75th percentile was greater than the one obtained with the 75th percentile of Bhutani, and this difference was more evident between 49 and 72 hours (1 vs. 6 false negative results).

Discussion

Early discharge is making the jaundice management quite difficult, since hyperbilirubinemia is one of the main reasons for hospital readmission. Recent reports suggest an increased occurrence of kernicterus in otherwise healthy newborns in North America, Western Europe and less developed part of the world. In its 2004 guidelines, the AAP recommended every newborn be assessed for risk of severe hyperbilirubinemia before hospital discharge. Two methods have been validated: the hour specific bilirubin measurements (using serum or transcutaneous determinations) and the jaundice clinical risk factor assessment. These methods can be used individually or jointly for a pre-discharge risk assessment for subsequent severe hyperbilirubinemia. The evaluation of jaundice is now facilitated by the availability of different nomogram for both serum and transcutaneous bilirubin. Although there is good evidence that TcB provides excellent estimates of the TSB level, TcB should be used more as a screening tool in order to reduce the number of TSB measurements needed in the nursery than as a substitute of TSB. Bhutani and colleagues demonstrated a strong relationship between the hour specific TSB level and the risk of subsequent hyperbilirubinemia, but concerns regarding the use of pre-discharge TSB values were expressed as a consequence of false negative results. Such false negative results have been described but their exact frequency is unknown. Two studies of infants readmitted for hyperbilirubinemia showed that 2.7% to 3.6% of babies had a pre-discharge bilirubin level in the low-risk zone (<40th percentile) while 13.5% to 43% of babies were in the low-intermediate risk zone (40-75th percentile) so showing a significant risk of false negative results. The rate of false negative and the different performances of Bhutani nomogram as a predictive tool can be explained by racial, genetic and environmental factors that affected the course of neonatal hyperbilirubinemia. A nomogram cannot perform well in every setting if the background between the published and the tested population is too much different. Moreover, predictive tools should be developed in one sample and validated in another one. The use of Bhutani nomogram as a screening tool has been questioned because of concerns regarding its reliability on different population and some methodological flaw of the study from which it was developed (i.e. follow-up bilirubin levels not performed in more than 75% of study participants, and the lack of validation in an independent patient sample). Bhutani's nomogram was generated in a retrospective study including infants from a single urban Pennsylvania hospital, so the demographic, racial, genetic and environmental features of

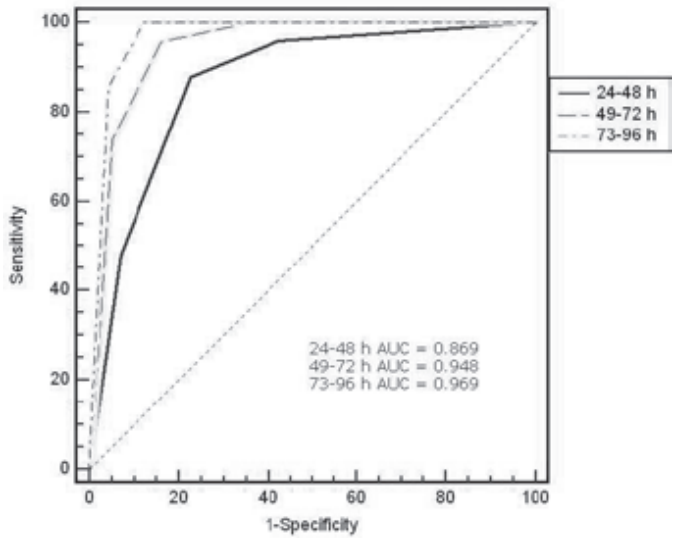

Figure 2. Comparison of the ROC curves during different hours of age.

that population may not adequately represent other newborn populations.

To reach the aim of our study we previously developed our hour-specific percentile based nomogram using serial measurements of TSB in a cohort of healthy full term neonates. In the second phase we verified prospectively its predictive ability to identify newborn at risk for significant hyperbilirubinemia (defined as TSB> 17 mg/dL or need for phototherapy) in a multicenter study involving a large neonatal population. The sensitivity of the 50th percentile was 100% between 49 and 96 hours, while it was affected by one false negative result before 48 hours of age. Using the 75th percentile as risk discriminator we obtained 88% of sensitivity between 24 and 48 hours (3 false negative results) and 95.7% of sensitivity between 49 and 72 hours (one false negative result). The false negative between 49 and 72 hours was a preterm infant who had his TSB measurement at 70 hours of age and subsequently needed phototherapy because he reached a TSB value of 16 mg/dL. This observation suggests that a risk assessment strategy combining the pre-discharge bilirubin risk zone and some clinical factor (such as gestational age) could have a better overall predictive accuracy than a strategy using pre-discharge bilirubin risk zone by itself.

In a subsequent analysis we plotted TSB measurements of our study population on Bhutani hour specific nomogram and we found that the sensitivity and the specificity of our 50th percentile were the same as the 40th percentile of Bhutani. Instead our 75th percentile performed better than the 75th percentile of Bhutani (sensitivity 92.7% vs. 80%) especially between 49 and 72 hours of age (sensitivity 95.7% vs. 73.9%).

Table 5 Ability of TSB measurements over the 40th and 75th percentile of Buthani nomogram to predict significant hyperbilirubinaemia, for designated time periods.

Hours of age	TP (n)	FN (n)	TN (n)	FP (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
24 to 48 hours								
< 40th percentile	25	0	238	382	100.0	38.4	6.1	100.0
< 75th percentile	21	4	447	173	84.0	72.1	10.8	99.1
49 to 72 hours								
< 40th percentile	22	1	732	293	95.7	71.4	7.0	99.9
< 75th percentile	17	6	963	62	73.9	94.0	21.5	99.4
73 to 96 hours								
< 40th percentile	7	0	374	93	100	80.1	7.0	100
< 75th percentile	6	1	451	16	85.7	96.6	27.3	99.8

The strengths of our study are the large sample size, well representing the demographic characteristics of Italian neonatal population, the high follow-up rate, and its robust design. It is also noteworthy that it is a prospective observational study in which enrolled babies were studied during their hospital stay, thus avoiding sampling bias. All newborns referred to their birth hospital for clinical follow up after discharge, and no readmissions because of hyperbilirubinemia were noticed. Our study has some limitations: firstly, the incidence of significant hyperbilirubinemia is low; secondly it is not a population based study but the newborns were enrolled according to the clinical practice of each neonatal unit.

Conclusion

Our percentile based TSB nomogram is a useful tool for predicting infants without subsequent severe hyperbilirubinemia before discharge. There is a notable difference in the false positive rate with the Bhutani's nomogram, especially between 49 and 72 hours of age. It has to be emphasized that the use of pre-discharge bilirubin screening alone may falsely reassure physicians about a safe early discharge of the mother-neonate pair. Bilirubin level should be assessed together with clinical risk factors (such as gestational age, exclusive breastfeeding, east asian race, cephalhematoma, significant bruising or previous sibling with jaundice) to determine infant risk for subsequent severe hyperbilirubinemia, thus ensuring an appropriate follow up.

Table 6 Comparison between the predictive ability of our percentiles and those of Buthani.

Hours of age	TP (n)	FN (n)	TN (n)	FP (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
24 to 96 hours								
< 40th percentile of Buthani nomogran	54	1	1344	768	98.2	63.6	6.6	99.9
< 50th percentile of our nomogram	54	1	1336	776	98.2	63.3	6.5	99.9
< 75th percentile of Buthani nomogram	44	11	1861	251	80.0	88.1	14.9	99.4
< 75th percentile of our nomogram	51	4	1748	364	92.7	82.8	12.3	99.8

TP True Positive; FN False Negative; TN True negative; FP False Positive; PPV Positive Predictive Value; NPV Negative Predictive Value

Incubators

Susan Goldstein

In the mid-nineteenth century, the infant incubator was first developed, based on the incubators used for chicken eggs.

Dr Stephane Tarnier is considered to be the father of the incubator (or isolette), having developed it to attempt to warn premature infants in a Paris maternity. Other methods had been used before, but this was the first closed model. Additionally, he helped convince other physicians that the treatment helped premature infants. France became a forerunner in assisting these infants, in part due to concerns about a falling birth rate.

Dr Pierre Budin, followed in Tarnier's footsteps after the latter retired, noting the limitations of infants in incubators and the importance of breastmilk and the mother's attachment to the child. Budin is known as the father of modern perinatology, and his seminal work The Nursling (Le Nourisson) became the first major publication to deal with the care of the neonate.

Another factor that contributed to the development of modern neonatology was thanks to Dr Martin Couney and his permanent installment of premature babies in incubators at the Coney Island amusement park. A controversial figure, he studied under Dr Budin and brought attention to premature babies and their plight through his display of infants as sideshow attractions at Coney Island and the World's Fair in New York and Chicago in 1933 and 1939, respectively. These sideshow attraction were often shown with babies inside.

Dr A. Robert Bauer MD at Henry Ford Hospital in Detroit, successfully combined oxygen, heat, humidity, ease of accessibility, and ease of nursing care in his incubators as early as 1931, but it was not until after the Second World War that special care baby units (SCBUs) were established in many hospitals. In Britain, early SCBUs opened in Birmingham and Bristol. At Southmead Hospital, Bristol, initial opposition from obstetricians lessened after quadruplets born there in 1948 were successfully cared for in the new unit. More resources became available: the first unit had been set up with £100. Most early units had little equipment and relied on careful nursing and observation.

1 Incubator exhibit interior, Alaska-Yukon-Pacific-Exposition, Seattle, Washington, 1909. Photographer unknown.

2 From the baby incubator exhibit Pay Streak, Alaska-Yukon Pacific Exposition, 1909, photo by Frank H. Nowell.

3 The photo file says: "Miss Haxby is holding a newborn baby that is in an incubator at the Toronto Western Hospital in Toronto, Ontario." 1955.

4 October 1929, Deutsches Bundesarchiv (German Federal Archive).

Still, incubators were expensive so the whole room where preemies were cared for was often kept warm instead. Cross-infection between babies was greatly feared. Strict nursing routines involved staff wearing gowns and masks, constant hand washing and minimal handling of babies was the norm. Parents were sometimes allowed to watch through the windows of the unit. (The photographs are from Wikimedia, and are open access.)

Susan Goldstein is news editor of Neonatal Intensive Care.

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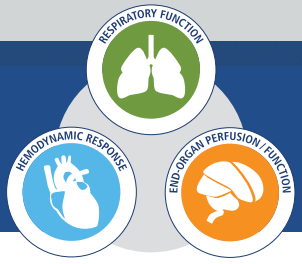

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1. Centers for Disease Control and Prevention. (2003) Guidelines for Environmental Infection Control in Health-Care Facilities. Recommendations of CDC and Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR, 52(RR10):1-42.

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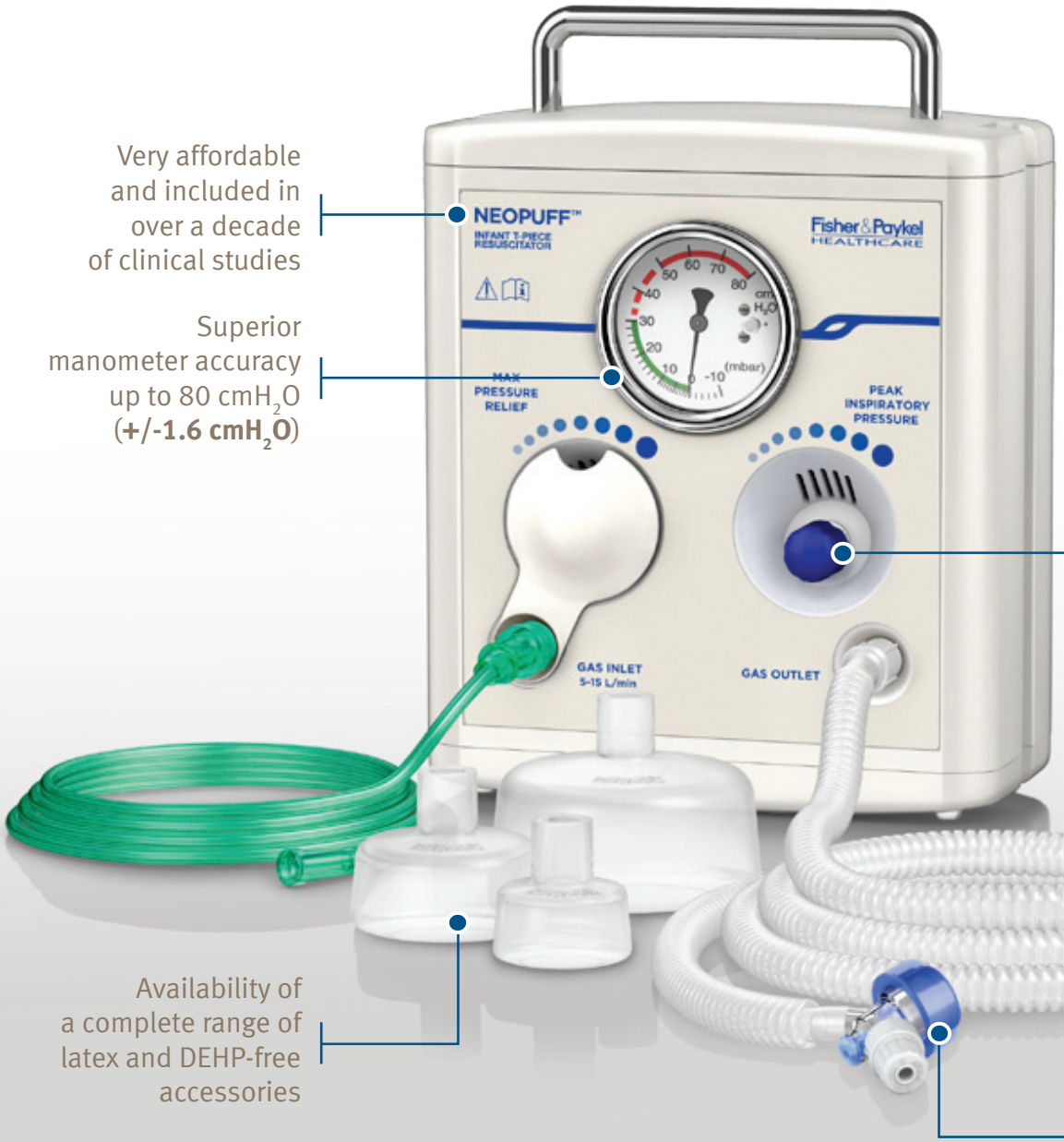

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