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neonatal INTENSIVE CARE

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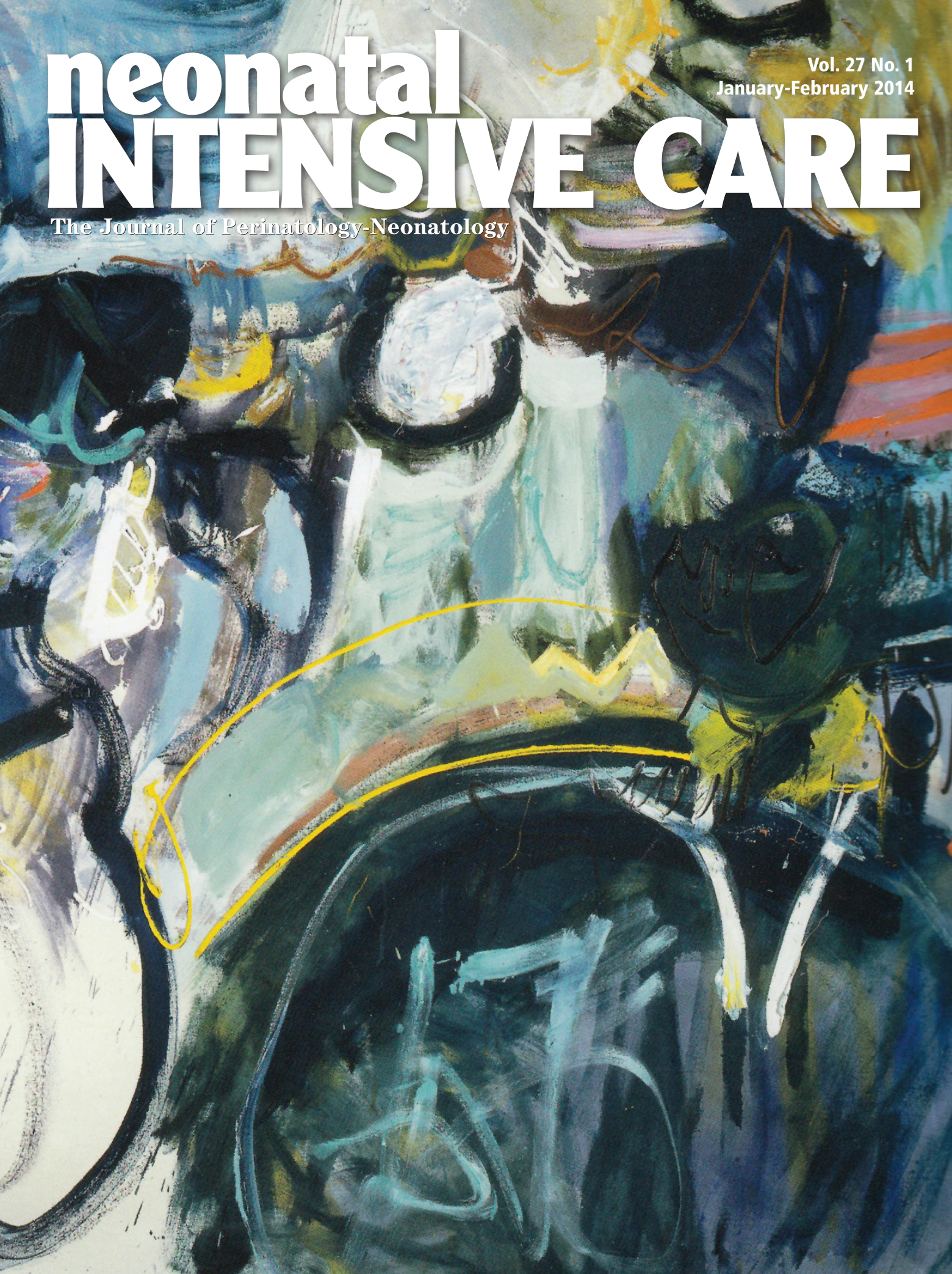

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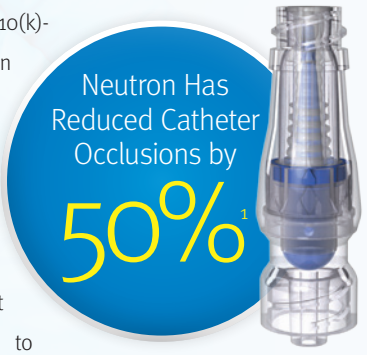

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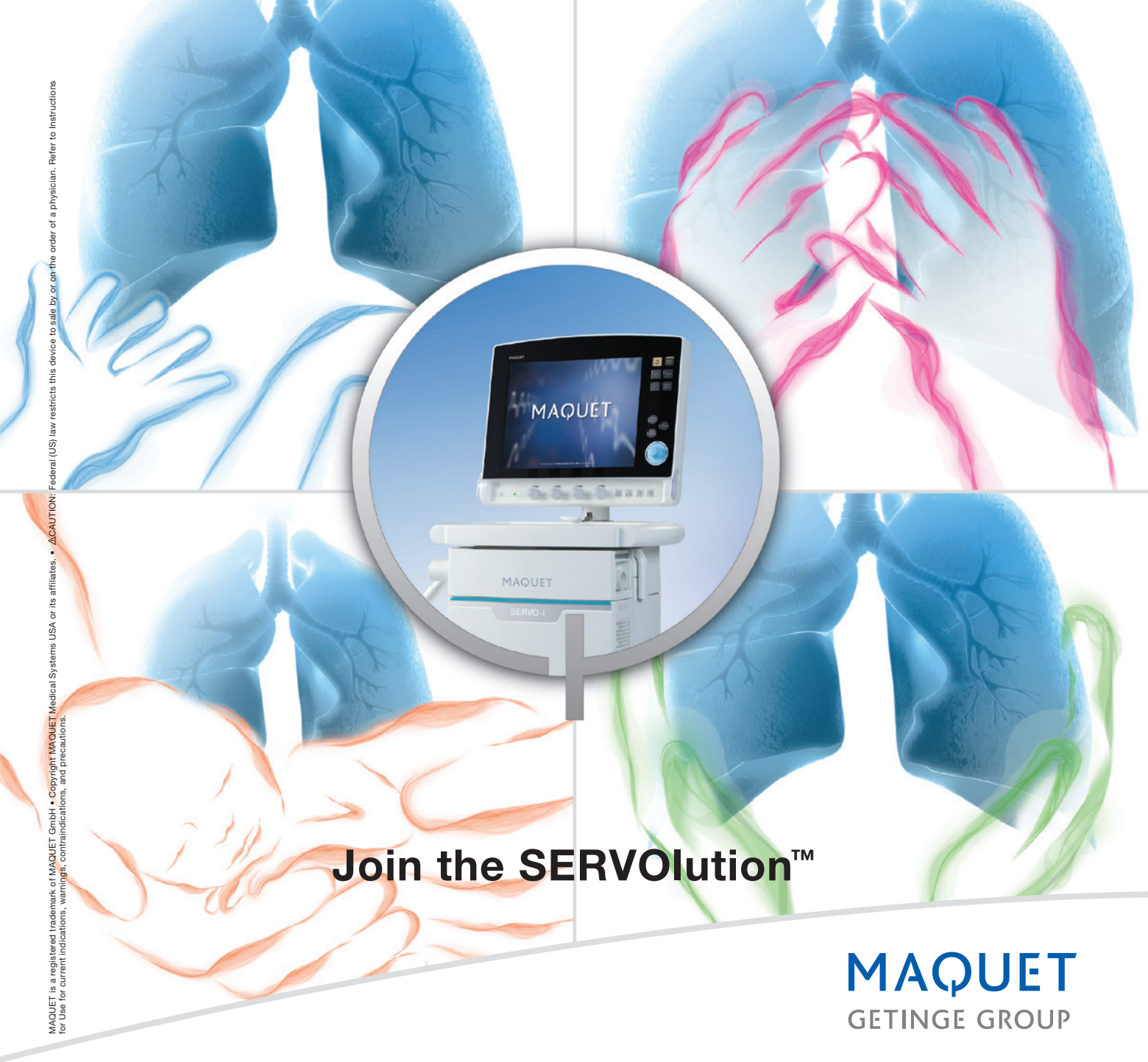

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Evolution vs Extinction

Dave Swift, RRT

Is the rapid growth of surfactant use and NIPPV leading to the extinction of neonatal mechanical ventilation skill sets?

As surfactant use became more mainstream and a first-line intervention, non-invasive ventilation quickly evolved in its delivery systems and interfaces. These two changes created a tipping point in neonatal ventilation, instead of a prolonged intubation and ventilated state, the neonate is intubated, given surfactant and rapidly extubated to NIPPV. The duration of NIPPV is actually reduced as the effects of the surfactant administered improves compliance. This is repeated right across neonatal ICUs across North America.

At the Ottawa Hospital's Civic Campus Rich Little Special Care Nursery (an enhanced level 2 NICU), in the last two years, there has been a 60% reduction of mechanical ventilation and the average time on NIPPV is down to 36-48 hours with a large number <12 hours. The ability to maintain intubation skills and mechanical ventilation skills is in doubt. The effects are being repeated across North America and being noticed by leaders in the neonatal world and efforts to ensure these skills are maintained are mixed. Therapists are expressing concerns as they see their skills erode over time and their ability to safely deliver the mandated patient care is not seen as sustainable. The government ministry (Ontario Ministry of Health and Long Term Care) responsible for health care has closely monitored the situation and is considering implementation of mandatory transfer guidelines to ensure that intubated neonates, after 48 hours and not being actively weaned, are transferred to level 3 centers to ensure that the skill sets required are maintained and level of care provided appropriate to the needs of the patient.

Such rapid evolution in patient care has rarely been seen in the Respiratory Therapy profession and many have not noticed or acknowledged the rapid changes occurring. As technologic advances improve the delivery of NIPPV, the interfaces available reduce risks of damage and patient response capabilities improve, the utilization of mechanical ventilation will drastically drop further. Evolution or extinction, either way the changes are accelerating and show no sign of slowing. Our understanding of the role of NIPPV in the neonates needs to keep pace with this evolution. We must embrace the changes or be left behind as other clinicians rise to meet the needs.

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Wireless Capabilities Key in Choosing Blood Analysis System

Chris Campbell

When Children's Hospital Central California (CHCC), a specialty pediatric medical center, was looking to upgrade its POCT system, an extensive investigation was launched to study everything from patient needs to technology to how much it would cost per test.

Kevin Kitzmiller, POCT Coordinator Department of Pathology and Laboratory Medicine, for the CHCC, said this "complex process" was necessary to take advantage of the latest advances in blood analysis technology.

It turns out that the CHCC began investigating POCT way back in the late 1980s.

"As more and more patient-care providers began requesting bedside testing," Kitzmiller said, "it became clear that easy-to-perform tests that could provide timely test results along with immediate clinician access to these results would likely play a significant role in the delivery of health care in the future."

According to Kitzmiller's findings, by the mid-1990s, technologic advances and the availability of the first generation of POCT devices paved the way for CHCC to incorporate point-of-care blood gas, and electrolyte testing into its health-care system.

Kitzmiller said CHCC derived similar process improvements with POCT as those found by Theodore Bailey and colleagues in a four-year study at Methodist Clinical Laboratory Services, which was published in 1997. "In addition, we realized multiple patient-care benefits associated with time-sensitive testing throughout the health-care system."

Requested tests from patient-care providers were actually performed in a timely manner at the patient's bedside, and gained immediate access to critical test results, he said, and testing of freshly collected blood samples at the point of care eliminated the errors often introduced to tests for pH, blood gases, glucose, lactate, and ionized calcium by metabolic activity within the blood sample and exposure of the sample to ambient air that is inherent to performing tests at a remote laboratory location.

Patient throughput has also improved through the use of POCT in the emergency department and busy outpatient sites.

"By eliminating the need for patients to make trips to the laboratory for blood draws and care providers having to wait for the laboratory to receive a sample and return a test result, patient visits were shortened," Kitzmiller said. "More than just convenience, this efficient patient throughput improved patient care and business efficiency while increasing patient access to CHCC's very specialized and busy outpatient clinics."

The center's study found that more patients were seen each day and patients were able to schedule appointments at earlier dates.

So with the CHCC needing to upgrade its POCT system, the process was heavily influenced by the needs of the patient population it served, Kitzmiller said.

"Children with medical problems require specialized care that enables a rapid recognition of their immediate medical needs," Kitzmiller said. "In a pediatric population, rapid turnaround times are required for emergent situations with minimal blood loss to the patient."

The system would be required to accommodate a large demand for results, including more than 1,000 operators, as it would be placed in all NICUs, including satellite NICUs located within 3 general hospitals in 3 other central California cities, the pediatric intensive care unit, surgery, cardiac catheterization, transport, and emergency departments, and all inpatient acute care units.

"After examining several options, we chose the epoc blood analysis system," Kitzmiller said. "Its wireless capabilities and low cost per test were deciding factors in our purchasing decision."

News

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DESIGNER BABIES A STEP CLOSER

A personal-genomics company in California has been awarded a broad US patent for a technique that could be used in a fertility clinic to create babies with selected traits. The patented process from 23andMe, whose main business is collecting DNA from customers and analyzing it to provide information about health and ancestry, could be employed to match the genetic profile of a would-be parent to that of donor sperm or eggs. In theory, this could lead to the advent of "designer babies," a controversial idea where genes would be selected to boost the chances of a child having certain physical attributes, such as a particular eye or hair color. The technique potentially could also be used to create healthier babies, by screening out donors with genes that are predisposed to disease, either on their own, or in combination with the recipient's genes. The awarding of the patent "is a massive addition to what is currently being done" in fertility clinics, said Sigrid Sterckx of the Bioethics Institute Ghent in Belgium, who co-wrote a commentary on the 23andMe patent in the journal Genetics in Medicine. "It indicates a different attitude, not just about disease-related traits, but non-disease traits." 23andMe, based in Mountain View, Calif., says that while its new patent encompasses trait selection in babies, through a tool called the Family Traits Inheritance Calculator, it has no plans to apply it to that end. Instead, 23andMe said, the tool offers customers "a fun way to look at such things as what eye color their child might have or if their child will be able to perceive bitter taste or be lactose tolerant." A spokeswoman for 23andMe, Catherine Afarian, said in an emailed response: "When the patent was first filed nearly five years ago, there was some thinking that this feature could have potential applications for fertility clinics where the donor selection process was typically based on photos, family history, and some limited genetic testing of donors—much of this has evolved in the past five years." But 23andMe "never pursued the idea and has no plans to do so," she said. 23andMe's patent explains how a patient would first specify certain traits that he or she wants in a child. Based on the patient's own genetic profile, a computerized system then "performs inheritance calculations pertaining to the [traits] of interest and identifies one or more preferred donors for the recipient," the patent states. A chart accompanying the patent describes the outlines of such a system, whereby the recipient can choose a child with a low risk of colorectal cancer, say, along with a high probability of green eyes. For this to work, the genetic profiles of both recipient and donor (the provider of sperm or eggs) would have to be known. "Test tube babies were seen as an abomination [initially] but today they are routine and boring," said Jacob Sherkow, an expert on biotechnology patents at Stanford University's law school. In the same way, he added, 23andMe's patent "is a shot across the bow—a signal to the world that this is what the future is going to look like." Information is from an article that appeared in the US edition of the Wall Street Journal written by Gautam Naik. Copyright Wall Street Journal.

AUTISM AND A BABY'S GAZE

Scientists are reporting the earliest behavioral sign to date that a child is likely to develop autism: when and how long a baby looks at other people's eyes. In a study published in November, researchers using eye-tracking technology found that 3-year-olds diagnosed with autism looked less at people's eyes when they were babies than children who did not develop autism. But contrary to what the researchers expected, the difference was not apparent at birth. It emerged when babies were two to six months old, and autism experts said that may suggest a window during which the progression toward autism can be halted or slowed. The study, published online in the journal Nature, found that infants later diagnosed with autism began spending less time looking at people's eyes between two and six months of age, and paid less and less attention to eyes as they grew older. By contrast, babies who did not develop autism looked increasingly at people's eyes until about nine months old, and then kept their attention to eyes fairly constant into toddlerhood. "This paper is a major leap forward," said Dr Lonnie Zwaigenbaum, a pediatrician and autism researcher at the University of Alberta, who was not involved in the study. "Documenting that there's a developmental difference between two and six months is a major, major finding." The authors, Warren R. Jones and Ami Klin, both of the Marcus Autism Center at Children's Healthcare of Atlanta and Emory University, also found that babies who showed the steepest decline in looking at people's eyes over time developed the most severe autism. "Kids whose eye fixation falls off most rapidly are the ones who later on are the most socially disabled and show the most symptoms," said Dr Jones, director of research at the autism center. "These are the earliest known signs of social disability, and they are associated with outcome and with symptom severity. Our ultimate goal is to translate this discovery into a tool for early identification" of children with autism. Dr Jones and Dr Klin, who directs the autism center, studied two groups of babies. One group was at high risk for autism, with a 20 times greater likelihood of developing it because they had siblings with the disorder. The other group was at low risk, with no relatives with autism. The researchers assessed 110 children, from two months to two years of age, ten times while watching videos of friendly women acting like playful caregivers. Eye-tracking technology traced when the babies looked at the women's eyes, mouths and bodies, as well as toys or other objects in the background. At age three, the children were evaluated for autism. Ultimately, researchers used data from 36 boys, 11 of whom developed autism. (They excluded data from girls because only two developed autism.) While the number of children studied was small—and the researchers are now studying more children—experts not involved in the study said the results were significant because of the careful and repeated measurements that were not just snapshots, but showed change over time. "It's well done and very important," said Dr Geraldine Dawson, director of the Center for Autism Diagnosis and Treatment at Duke University. She said it was notable that "early on these babies look quite normal; this really gives us a clue to brain development." Still, the authors and other experts cautioned that the results required confirmation in many more children. And without the technology

and expertise of an autism clinic, subtle eye-tracking differences cannot be identified by parents or pediatricians, Dr Jones said, adding: "We don't want to create concern in parents that if a child isn't looking them in the eyes all the time, it's a problem. It's not. Children are looking all over the place." Information is from an article that appeared in the New York Times Well blog written by Pam Belluck. Copyright New York Times.

DANCE PARTY IN THE WOMB

New research suggests babies can learn a melody they hear while still in the womb, and recognize it after they are born. For the study, published online in October by PLOS One, Finnish researchers divided 24 pregnant women into two groups. Five times a week, the "learning group" played a CD that included a one-minute rendition of Twinkle Twinkle Little Star, which the unborn children heard an average of 170 times before birth. The control group did not hear the recording. Then the scientists did EEG tests on the children at birth and again at 4 months as they listened to the original tune and a version in which several notes were altered. The learning group had a larger response to the melody than the control group did, and the difference was still apparent at 4 months. And the amplitude of response to the changed melody correlated with the number of times the infants were exposed to the original melody in utero. The lead author, Eino Partanen, a researcher at the University of Helsinki, urged parents not to make too much of the finding. "A baby can be relaxed and soothed by melodies it hears before birth," he said. "But there is no evidence that it will get your baby into Harvard." Information is from an article written by Nicholas Bakalar that appeared on the New York Times Well blog. Copyright New York Times.

BIG DATA HELPS BABIES

Canadian researcher Carolyn McGregor believes medical monitors that gather information about patient's heart rates, pulse, breathing and other bodily functions have untapped data that can assist neonatal units. Since 2009, McGregor, the research chair of health informatics at the University of Ontario's Institute of Technology, has looked for patterns in the data the monitors collect. McGregor and her team turned to the monitors that were keeping track of some of Canada's smallest patients: premature infants held in the neonatal intensive care unit at the Hospital for Sick Children in Toronto. Those babies are at high risk for infection, according to Dr Andrew James, associate clinical director of the hospital's neonatal intensive care unit. "Infection is a constant worry," Dr James explains. "About 20 percent of low-birth-weight babies develop an infection, and of those babies about 18 per cent actually pass away. So it's very serious—and very common." Enter the Artemis Project. Named after the Greek goddess who protected babies and childbearing women, the project sought to synthesize the millions of data samples coming from the neonatal monitors to see if there were any notable patterns. "We looked at the heart rate for trends; when babies become infected, the baseline heart rate tends to increase," Dr James says. "What I've learned is that when you look at more data and you look at it in a more granular sense, not only is there more to be seen, but you actually see more. We're beginning to see abrupt changes in heart rate variability and that really makes us think of infection." These changes in heart rate are usually a telltale sign of infection. "With inflammatory response, there are chemical signals to the brain that affect heart rate," Dr James explains. "And—when there's an infection, heart rate variability decreases." Today, Artemis allows doctors to see

early warning signs of infection upward of 24 hours before the baby would have otherwise shown any other symptoms. "So we have a means potentially to intervene earlier," McGregor says, "so these babies aren't suffering the same impact of infection." Information is from an article written by Michael Beyman of CNBC. Copyright CNBC.

PRENATAL SCREENING BREAKTHROUGHS

Prenatal diagnosis is on the cusp of revolutionary developments. The newest screening test, highly accurate and noninvasive, relies on fetal genetic fragments found in the mother's blood. Available commercially from four companies, this test is so accurate in detecting Down syndrome that few, if any, affected fetuses are missed, and far fewer women need an invasive procedure to confirm or refute the presence of Down, according to studies in several countries. The new test, done late in the first trimester of pregnancy, can also detect other genetic diseases, like extra copies of chromosomes 13 and 18, and a missing sex chromosome. It is not yet approved by the US Food and Drug Administration, however, and the American College of Obstetrics and Gynecology currently recommends it only for women at high risk for having a baby with a chromosomal abnormality. But any woman can get the new screening test if her doctor orders it and she is willing to pay for it herself, according to Dr Diana W. Bianchi, a neonatologist and geneticist at Tufts University School of Medicine. Dr Bianchi, who serves on the advisory board of a company selling fetal DNA tests, said she expects these tests will soon become routine for all pregnant women because, in addition to their "extraordinary accuracy" in detecting a Down syndrome pregnancy, they can be done earlier than other tests, and reduce costs and the risk of complications. In the past, the decision to undergo an amniocentesis or chorionic villus sampling (CVS) was based on a woman's age or genetic history. It is now standard practice to offer all pregnant women a series of noninvasive screening tests in the first and second trimesters of pregnancy to assess the chances that a fetus has the extra copy of chromosome 21, which causes Down syndrome. Taken together, these older screening tests pick up about 92 per cent of cases of Down syndrome but miss 8 per cent. And they yield false-positive results incorrectly indicating the presence of Down in about 5 per cent of fetuses. "This means a lot of women are needlessly worried and a lot have amnios that are not medically necessary," Dr Bianchi said. The new tests of fetal DNA from the mother's blood detect all or nearly all cases of Down syndrome, and they return false-positive results in fewer than 1 per cent of cases. Only those with a positive result need a CVS or amniocentesis to confirm a Down syndrome pregnancy, and only about one woman in 1,000 who are tested requires such an invasive procedure to learn that her fetus does not have Down syndrome. In a July article in the New England Journal of Medicine, however, Stephanie Morain, a doctoral candidate at Harvard who studies medical ethics, and her co-authors said the fetal DNA tests miss some chromosomal abnormalities detected by standard screening techniques, and they are "not widely covered by insurance." Prices for the tests range from about $800 to more than $2,000, although some companies offer "introductory pricing" specials at about $200. The new tests are also not required to meet the strict standards of safety and effectiveness established by the FDA, and they are valid only in singleton pregnancies. The new test requires just a small sample of a pregnant woman's blood. On average, Dr Bianchi said in an interview, at around 10 weeks of gestation, about 10 to 12 per cent of the DNA in a woman's blood will be fetal DNA from the placenta. Using modern genetic sequencing techniques, the fetal DNA can be rapidly analyzed at a relatively low cost, in part because multiple samples from different women can be examined simultaneously. Information is from an article written by Jane E. Brody for the New York Times Well blog. Copyright New York Times.

RDS IN PREMATURE INFANTS

Specialty biotechnology company Discovery Laboratories, Inc. announced the US Food and Drug Administration (FDA) has agreed to the company's updated product specifications for Surfaxin Intratracheal Suspension. Surfaxin was approved for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS. With this approval in place, the company has now started the process of manufacturing Surfaxin for its planned commercial introduction in the fourth quarter of 2013. "We are pleased that the FDA has agreed with our updated product specifications and are appreciative of the process that has lead to this decision," said John G. Cooper, chief executive officer of Discovery Labs. "Surfaxin represents the first milestone in our goal of transforming the treatment of RDS and is an important medical advancement for the neonatology community and parents of preterm infants who will soon have an effective alternative to animal-derived surfactants for the prevention of RDS." Surfaxin is the first FDA-approved synthetic, peptide-containing surfactant available for the prevention of RDS in premature infants and the only approved alternative to animal-derived surfactants currently used today. Discovery said infants receiving Surfaxin should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status. More details at surfaxin.com.

SURFACTANT DELIVERY SYSTEM

Specialty biotechnology company Discovery Laboratories, Inc. announced the US Food and Drug Administration (FDA) had received its submission of an investigational new drug (IND) application initiate its Aerosurf phase 2 clinical program. The FDA has indicated that, unless otherwise notified during its review, the company may initiate the phase 2 clinical program after a 30-day period. Discovery Labs anticipates patient enrollment could begin in the fourth quarter of 2013. Aerosurf is a novel investigational drug-device combination product being developed to deliver Discovery Labs' KL4 surfactant in aerosolized form to premature infants with respiratory distress syndrome (RDS). The company thinks Aerosurf could potentially allow for the administration of KL4 surfactant to premature infants without invasive endotracheal intubation, and may enable the treatment of a significantly greater number of premature infants who could benefit from surfactant therapy, but are currently not treated.

PROTEIN TRIAL BEGINS

Biotechnology company Edimer Pharmaceuticals announced the enrollment and completed dosing of the first X-linked Hypohidrotic Ectodermal Dysplasia-affected neonate in a phase 2 trial of EDI200, the company's novel, proprietary, recombinant protein. XLHED is an ultra-rare orphan disease of ectoderm development associated with a lack of sweat glands, poor temperature control, respiratory problems, and hair and tooth malformations. Affected individuals are at risk for serious and potentially life-threatening hyperthermia and respiratory infections. EDI200 replaces EDA-A1, the protein missing in XLHED and a key regulator of skin and tooth development. If fully developed and approved, EDI200 will be the first protein

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

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culture of "mommy one-upsmanship" that fetishizes everything natural. (MacDorman said that planned home births might be somewhat riskier than hospital births, but that "the absolute risks of home birth are very low, no matter how you slice it.") The debate about safety aside, the demand for out-of-hospital births is going up. Yet in New York, the number of supportive facilities—free-standing birthing centers and hospitals that grant privileges to homebirth midwives—is dwindling due to high malpractice premiums caused by perceived risks of out-of-hospital births, experts say. Birthing centers provide a home-like environment for laboring mothers, and eschew interventions such as epidural pain medication. New York City, home to a handful of birthing centers about a decade ago, is down to just one: the Brooklyn Birthing Center in Midwood. There is also one in-hospital birthing center, at St. Luke's Roosevelt on Manhattan's West Side. "In New York City, we like to think of ourselves at the forefront of everything, but in terms of birth, we're not," said Ellen Chuse, who teaches a childbirth education course for home birth families. "There are so few options other than hospitals, and the medical-legal environment makes it difficult to have a natural birth there." Melissa Bijur, who is planning a Brooklyn home birth, said it isn't only a natural childbirth that she is seeking, but also a more intimate birthing experience. "I'm not comfortable with the hospital environment: the light, the white walls, not having interaction with your OB/GYN," Bijur, 30, said. "It's one of those experiences that I look back on when things get difficult," said Diana Kane English, a 41-year-old boutique owner who delivered her two sons in her family's Park Slope apartment. "I say to myself, 'I gave birth at home, I know that I can get through this.'" Information in this article was written by Gabrielle Birkner and first appeared in the Wall Street Journal. Copyright Wall Street Journal.

'DOC' STEPS DOWN

Medical device manufacturer ICU Medical has announced that due to health reasons Dr George Lopez—affectionately known as 'Doc'—was stepping down as president and CEO. ICU said he will continue in his role as chairman of the board and will remain an employee in the research and development department. The company also announced that its board had appointed Steven Riggs, current vice president of operations, as acting CEO. "Doc is the founder of the company and has served as its chairman of the board, president and CEO since 1989," said Dr Michael Kovalchik, lead director of ICU Medical. "He is one of the rare individuals who has been able to transition from entrepreneur to business leader and will now have the opportunity to focus his efforts on the development of new and innovative products for the company. Doc's extraordinary vision and leadership turned ICU Medical into a world-class provider of innovative medical devices and has our company positioned for long-term growth and profitability." The company has begun the search for a full-time CEO and is considering both internal and external candidates.

CART CUSTOMIZED

Creche Innovations, which makes the Penguin Nutritional Warmer, has added the Penguin Custom Cart to its roster of products. The cart is a medical-grade solution that's ideal for use in tight spaces. It is customizable and can maneuver in any medical environment. As an example, Creche said the cart, when paired with a mounted Penguin Refrigerator will assist in both streamlining the flow of refrigerated medication, breast milk or formula from the pharmacy or your nutritional preparation rooms to the patient's bedside, while keeping all items properly cooled to within the ADA and JCAHO guidelines. "Fewer trips to the preparation room and pharmacy means fewer errors for nurses to worry about while increasing productivity, work flow, and most importantly, time at the bedside," said a news release. Digital temperature readouts and optional temperature tracking options, including remote wireless monitoring and alarming, are available when refrigerators added to the cart. The cart can run on battery for up to 24-plus hours. In addition to the on-board refrigeration units it can also power additional pieces of equipment.

MODEL PREDICTS PREEMIE OUTCOMES

New research suggests a statistical prediction model comprising eight characteristics can be used to determine the severity of neonatal outcomes for infants born at 23 to 30 weeks of gestation. According to a study published online Sept. 23 in Pediatrics, Wen J. Ge, from Mount Sinai Hospital in Toronto, and colleagues developed and validated a model to predict the severity of neonatal outcomes in infants born at 23-30 weeks of gestation. A national cohort of infants admitted to level III neonatal intensive care units (NICUs) in Canada in 2010 and 2011 were identified from the Canadian Neonatal Network database. The researchers found that 37% of the 6,106 eligible infants survived without morbidity; 32% survived with mild morbidity; and 21% survived with severe morbidity. Ten per cent of infants died. The model predictors included gestational age, small for gestational age (less than 10th percentile), gender, Score for Neonatal Acute Physiology version II >20, outborn status, antenatal corticosteroid use, receipt of surfactant, and mechanical ventilation on the first day of admission. Internal bootstrap validation confirmed high model discrimination. The probabilities predicted were consistent with the outcomes observed. "Neonatal outcomes ranging from mortality to survival without morbidity in extremely preterm infants can be predicted on their first day in the NICU by using a multinomial model with good discrimination and calibration," the authors write.

LOOKING BEYOND 'HEEL STICK'

The National Institutes of Health is studying whether sequencing an infant's DNA can improve on the well-established "heel-stick" blood test to screen newborns for potentially life-threatening diseases. The five-year, $25-million project reflects the declining costs of mapping an individual's genetic code and anticipates the day when a baby's DNA could be routinely sequenced and stored in a medical record. Currently, nearly all 4 million infants born in the US each year are tested for up to 31 life-threatening or debilitating conditions through heel-stick programs, in which a drop of blood is taken via a pin-prick in the heel. The programs, administered in each state, detect potentially treatable problems in about 12,500 cases, enabling interventions that can save lives or prevent millions of dollars in lifetime health-care costs, said Alan Guttmacher, director of the National Institute of Child Health and Human Development, which along with the National Human Genome Research Institute is funding the initiative. One of the big successes of such screening, Dr Guttmacher said, is for a condition called phenylketonuria, or PKU, an enzyme disorder that leads to the buildup of an amino acid. If the condition is detected before symptoms arise, changes in diet can prevent it, but once symptoms emerge, the disease, marked by serious neurological problems, is irreversible. But the 31 conditions make up a fraction of as many as 8,000 inheritable disorders that can affect children. States vary in the maladies they test. The hope is the new effort can "shed light on other disorders and see how genomic data might inform care for newborns

therapeutic to provide a sustained correction of the symptoms of this disorder. "The first research project the NFED funded was in 1989 for the gene identification of X-Linked Hypohidrotic Ectodermal Dysplasia, XLHED," said Anil Vora, president of the board of directors at the National Foundation for Ectodermal Dysplasias (NFED). "On that day, we started an amazing journey that lead to the development of EDI200. Along the way, NFED families stepped up to volunteer for every research project in the battle to find a cure. We are thrilled to have witnessed and supported the ongoing development of EDI200 and look forward to learning the outcomes of this clinical study." The Phase 2 clinical trial is designed to evaluate the safety, pharmacokinetics, pharmacodynamics and efficacy of EDI200 in XLHED-affected male newborns in the first two weeks of life. EDI200 dosing will be initiated between the second and 14th days of life, with each study subject receiving two doses per week for a total of five doses.

WEBCAMS FOR ANXIOUS PARENTS

A high-tech scheme called BabySam aims to help the parents of sick and premature babies bond with their newborn infants while they are in intensive care. The system, being tested at Victoria Hospital in Scotland, allows parents to view their infants on a tablet computer when they cannot be beside them in hospital. It will be installed in the hospital's neonatal intensive care unit, and will use wireless cameras to transmit live video of the baby's cot to a tablet. Health Secretary Alex Neil said: "Having a baby in an intensive care unit can be an extremely stressful and worrying time for any new parent. Through this innovative new technology parents will be able to view their baby and feel connected to them while they receive the vital treatment they need to get better." Dr Sean Ainsworth, a consultant paediatrician and neonatologist with NHS Fife, said, "the bonding between a mother and her baby is an important process, and has implications for the child's future development. Sometimes babies are admitted to a special care baby unit because they are either premature or just too poorly to remain with their mothers. We hope that BabySam will help overcome any sense of geographical isolation by allowing mothers to see real-time images of their babies, providing reassurance to parents and improving the bonding between the mother and her baby even when they cannot physically be together." Samsung and NHS Fife will work with the DHI and Dr Rhona Hogg from Edinburgh Napier University to understand how the BabySam system can help improve bonding between babies and their parents. It is hoped the system could potentially reduce separation anxiety for premature infants who are not with their mothers. Information is from an article that originally appeared on the BBC.

TELEMEDICINE ARRIVES IN TEXAS

Children's Medical Center Dallas has launched the state's first dedicated neonatal telemedicine program—known as TeleNICU. The new service will provide physicians at other hospital neonatal intensive care units with 24-hour access to the highly trained, board-certified UT Southwestern neonatologists on staff in order to consult on care for the region's tiniest and most fragile patients. The TeleNICU program utilizes specialized equipment and secure broadband transmission to allow two-way, real-time interactive communication between hospitals and enable expert neonatologists at Children's to virtually examine newborns at distant-site NICUs. Participating hospitals will connect through a mobile equipment cart that includes medical-quality videoconferencing, data transfer and digital scoping equipment. "The TeleNICU will enable us to work collaboratively with our hospital and physician colleagues to deliver the right care, at the right time, in the right place," said Christopher J. Durovich, president and chief executive officer of Children's. According to Durovich, the NICU at Children's is designated a Level-IV—the highest standard set by the American Academy of Pediatrics—and staffed 24/7 by expert UT Southwestern neonatologists. Although the total number of hospital NICUs in Texas and nationally has increased over the past decade, many are Level-I and Level-II NICUs that are not staffed or equipped for complex care. The hope is that TeleNICU consultation will minimize or even eliminate the need for transport in many cases, so newborns can remain at their home hospitals longer. The Children's Medical Center TeleNICU also is expected to play an important regional role in ongoing provider education and quality care by facilitating greater flow of information and expertise among health care providers, and accomplishing it more efficiently. "As a Level-IV NICU and a major academic and research center, we have a responsibility to import and export best practices and share established protocols with other hospitals—and telemedicine enables us to be available without the constraints of physical travel," said Dr Rashmin Savani, division director of neonatal-perinatal medicine at UT Southwestern and Children's, and professor of pediatrics at UT Southwestern Medical Center. Savani also pointed out that North Texas has a growing population with a climbing birthrate, in contrast to other parts of the country, and the demand for NICUs remains high due to premature deliveries and multiple births, among other factors.

BIRTHS FIND A HOME IN BIG APPLE

A growing number of New York residents are choosing to give birth at home. Home birthrates nationally, while still less than 1% of total deliveries, have climbed quickly—rising 50% between 2004 and 2011, according to US Centers for Disease Control and Prevention data. And the increase has been even more dramatic in New York state, where home births have grown 71% since 2004. Statewide, there were 2,130 home births in 2011. But a home birth in New York City—where neighbors live cheek-by-jowl, often in small walk-up apartments—poses unique challenges not faced in, say, rural Tennessee, where home-birth maven Ina May Gaskin started her practice. Will neighbors hear screaming through labor pains? Will creaky floorboards give way under the weight of the birthing pool? How does a laboring mother get down four flights of stairs, in case of a hospital transfer? The city does, though, offer advantages. New Yorkers are likely to live close to at least one medical center, should a transfer become necessary. And New York state law requires state-regulated insurance providers to pay some expenses associated with a home birth, regardless of whether the midwife is in their network. Marian F. MacDorman, a statistician who studies birth trends, said that more families are choosing home birth to avoid what they perceive as unnecessary hospital interventions. "Another theme that comes out is wanting control over the birth process, and to share the experience with friends and family—not having five [medical] residents looking at their bottom," said MacDorman, who works for the CDC's National Center for Health Statistics. As much as some home-birth advocates reject common interventions at American hospitals, opponents of the practice assert—in no uncertain terms—that home birth is dangerous. They cite a 2010 study linking planned home births to a neonatal death rate up to three times that of babies born in hospitals. One of home birth's fiercest critics is Amy Tuteur, a Boston-based OB-GYN who runs the Skeptical OB website. She said the trend is a particularly risky aspect of the

generally," Dr Guttmacher said. Under the program, the DNA of some 2,000 newborns will be sequenced at five institutions: Brigham and Women's Hospital and Boston Children's Hospital in Boston, which are working jointly; Children's Mercy Hospital in Kansas City, Mo.; University of California, San Francisco; and University of North Carolina at Chapel Hill. Each will look at different aspects of sequencing. Mercy Hospital, for instance, will study the value of genomic screening for newborns requiring treatment in a neonatal intensive-care unit. The centers will also examine ethical questions about how results are presented to parents and clinicians, and how to protect a baby's privacy. "We really want to know about what types of situations does this work best in, when would the information be most useful and what information parents would find most useful," said Anastasia Wise, NHGRI's program director for the initiative. Cost-effectiveness is another issue. Eric Green, director of the NHGRI, said heel-stick tests cost about $100 per infant, including some follow-up care. Some partial sequencing is available for under $1,000 and whole-genome analyses cost about $5,000. If sequencing yields false positives requiring expensive follow-up, that could undermine its value, he said. But if it expands the number of disorders that can be identified and prevented, the health-cost savings "may be worth it," he said. Information in this article was written by Ron Winslow and first appeared in the Wall Street Journal. Copyright Wall Street Journal.

HEPATOCYTES AND NEONATAL LIVERS

With livers available for transplants in short supply, a Spanish research team has found that neonatal hepatocytes show better thawing recovery than those isolated from adult livers. The team has developed high-yield preparations of viable hepatocytes (liver cells) isolated for transplantation from cryopreserved (frozen), banked neonatal livers that ranged in age from one day to 23 days. "There are challenges in keeping a supply of good quality livers for hepatocyte isolation," said study co-author Dr M.J. Gomez-Lechon of the Center for Hepatological Investigation in Valencia, Spain. "Once more, hepatocyte transplantation competes with organ transplantation. The source for hepatocyte isolation for transplantation is mainly adult livers that have been found unsuitable for organ transplantation. Accordingly, neonatal livers have emerged as an alternative source for hepatocytes because they are too small for organ transplantation, yet have good quality cells." According to Dr Gomez-Lechon, the purpose of their current work was to explore various aspects of livers derived from neonates as alternative sources for isolating human hepatic cells. This required assessing the suitability of neonatal livers that did not fill the organ transplant requirements; assessing cell viability, the preservation of cell membrane integrity; assessing the functionality of thawed neonatal hepatocytes and; analyzing the percentage of progenitor cells in cryopreserved hepatocyte preparations. Knowing that cryopreservation can have a detrimental impact on adult hepatocytes upon thawing, including the diminishment of cell attachment efficiency, their research suggests that neonatal hepatocytes can be cryopreserved with "no significant loss of viability after thawing", an important factor for cell transplantation. Another benefit of hepatocytes derived from neonatal livers, said the researchers, is that their greater viability provided greater cell attachment efficiency and expression of adhesion molecules. They also suggested that there are good indications of hepatocyte mitochondria preservation. "The larger number of progenitor cells in thawed hepatocyte suspensions suggests that they may have an advantage for being engrafted into the host liver and better long-term survival," they wrote. "Thus, the characteristics of thawed neonatal hepatic cells may confer important advantages for transplantation when compared to adult cells."

INFANTS FIT TO A 'T'

Providing consistent pressure and sparing clinicians from hand fatigue were just two of the points Mercury Medical made when it showcased the Neo-Tee Infant T-Piece Resuscitator and the Flow-Safe II CPAP system at the Novation Innovative Technology Expo in October at the Irving Convention Center, Las Colinas, Texas. The event provides medical technology suppliers the opportunity to gain direct feedback from onsite clinical experts and health-care providers on the impact their products have on improving patient care and reducing the risk of harm to patients and caregivers. Neo-Tee is a disposable infant T-piece resuscitator with color-coded manometer on the tee for immediate viewing of airway pressures. Neo-Tee is flow-controlled, pressure-limited and offers the ability to measure Peak Inspiratory Pressure (PIP) and Positive End-Expiratory Pressure (PEEP). Mercury says the Neo-Tee provides more consistent pressure than either the self-inflating or flow-inflating bag and the clinician is not subject to hand fatigue. The Neo-Tee can attach to a face mask, endotracheal tube or Laryngeal Mask Airway. For the Flow-Safe II CPAP system, Mercury said it is the only disposable CPAP system on the market that provides over 50% less oxygen consumption while delivering high FiO_2. Similar to the Neo-Tee, Flow-Safe II also has a color-coded manometer for verifying and documenting delivered airway pressure to patients. Flow-Safe II has easy set-up, as it is ready to use out of the bag and includes a comfortable mask with head harness. Clinicians can also add an in-line nebulizer, capnography and filter. Flow-Safe II can be used in the pre-hospital setting as well as in-hospital areas such as the PACU, ED or any other areas where a patient needs immediate CPAP treatment. Mercury said both items offer low-cost solutions for health facilities. Since 2003, more than 1,500 new and innovative technologies have been submitted through the Novation Innovative Technology program. Novation works with member-led councils and task forces to identify and review potentially innovative technology. Once these teams have evaluated the technology and determined that it provides an incremental clinical benefit over existing products, a contract for the innovative technology may be awarded outside of Novation's competitive bid cycle.

DISTANCE AFFECTS NEONATAL OUTCOMES

Infants with hypoplastic left heart syndrome (HLHS) who are born far from a hospital providing neonatal cardiac surgery for the condition have increased neonatal mortality, with most deaths occurring before surgery, according to new research. Results of a study by the Texas Children's Hospital and Baylor College of Medicine were published online in October in the journal Circulation. The study concluded that efforts to improve prenatal diagnosis of HLHS and subsequent delivery near a large volume cardiac surgical center may significantly improve neonatal HLHS survival. HLHS occurs when the fetus' left side of the heart does not develop normally, and is present in approximately one in 6,000 live births. HLHS is one of the most complex heart defects to treat because most of the structures on the left side of the heart are too small and underdeveloped—or hypoplastic—and it is difficult for the heart to provide enough red blood flow for the body's needs. The rate of mortality is high in HLHS, and optimal outcomes depend on aggressive cardiology and surgical management. All children with HLHS will have to undergo at least three surgeries within the first three years

of life to survive, but many die in the first few months of life. "Babies can be diagnosed with HLHS in-utero or after they are born," explained Dr Daniel J. Penny, chief of cardiology at Texas Children's, professor and head of the section of cardiology in the department of pediatrics at BCM and contributing author on the study. "This study sheds light on delivery distance in addition to prenatal and postnatal diagnosis. If an infant is diagnosed after they are born, it is crucial that they are cared for at a center with expertise and high HLHS volumes." The research used the Texas Department of State Health Services' Texas Birth Defects Registry data from 1999-2007 to retrospectively examine the associations between distance from birth center to a cardiac surgical center, number of newborns cared for with HLHS at each hospital, and neonatal mortality in infants with HLHS. Of the more than 3.4 million births during the study period, 463 infants with HLHS were assessed. Mothers delivering farther from a cardiac surgical center were less educated and more often lived in a poverty-stricken area. Additionally, 39 per cent of newborns studied were prenatally diagnosed with HLHS and delivered significantly closer to a cardiac surgical center. Forty per cent of newborns with HLHS died that were born more than 90 minutes from a cardiac surgical center, compared to 21 per cent of those born within 10 minutes of a surgical center. The percentage of patients who died after the first surgery for HLHS was two to four times higher in low volume surgical centers than in the highest volume centers. Overall, in the latest years of the study, newborns with a prenatal diagnosis, born less than 10 minutes from a cardiac surgical center, and cared for at a large volume cardiac surgical center, had a neonatal mortality of 6 per cent. For those born in the same era without a prenatal diagnosis, more than 10 miles from a cardiac surgical center, and cared for at a low volume cardiac surgical center, 28-day mortality was 29 per cent.

DATA ON RDS ADDED

International data provider Research and Markets has added the Neonatal Respiratory Distress Syndrome Global Clinical Trials Review, H2, 2013 to its offering. The review provides data on the Neonatal Respiratory Distress Syndrome clinical trial scenario, including an overview of the trial numbers and their recruitment status as per the site of trial conduction across the globe. The databook offers a preliminary coverage of disease clinical trials by their phase, trial status, prominence of the sponsors and also provides briefing pertaining to the number of trials for the key drugs for treating Neonatal Respiratory Distress Syndrome. For more information, visit researchandmarkets.com/research/cm277f/neonatal.

INFANT PAIN HAS LONG-TERM IMPACT

New research says early life pain alters neural circuits in the brain that regulate stress, suggesting pain experienced by infants who often do not receive analgesics while undergoing tests and treatment in neonatal intensive care may permanently alter future responses to anxiety, stress and pain in adulthood. According to a research team led by Dr Anne Murphy, associate director of the Neuroscience Institute at Georgia State University, about 12 per cent of live births in the US are considered premature. These infants often spend an average of 25 days in neonatal intensive care, where they endure 10-to-18 painful and inflammatory procedures each day, including insertion of feeding tubes and intravenous lines, intubation and repeated heel lance. Despite evidence that pain and stress circuitry in the brain are established and functional in preterm infants, about 65 per cent of these procedures are performed without benefit of analgesia. Some clinical studies suggest early life pain has an immediate and long-term impact on responses to stress- and anxiety-provoking events. The Georgia State study examined whether a single painful inflammatory procedure performed on male and female rat pups on the day of birth alters specific brain receptors that affect behavioral sensitivity to stress, anxiety and pain in adulthood. The findings demonstrated that such an experience is associated with site-specific changes in the brain that regulate how the pups responded to stressful situations. Alterations in how these receptors function have also been associated with mood disorders. The study findings mirror what is now being reported clinically. Children who experienced unresolved pain following birth show reduced responsiveness to pain and stress. "While a dampened response to painful and stressful situations may seem advantageous at first, the ability to respond appropriately to a potentially harmful stimulus is necessary in the long term," Dr Murphy said. "The fact that less than 35 per cent of infants undergoing painful and invasive procedures receive any sort of pre- or post-operative pain relief needs to be re-evaluated in order to reduce physical and mental health complications associated with preterm birth." The research team included scientists at Georgia State's Center for Behavioral Neuroscience and Yerkes National Primate Center. Results of the study were published in the most recent edition of the journal Psychoneuroendocrinology.

EARLY-TERM RISKS HIGHER

According to a new study, early-term births are associated with higher neonatal morbidity and with more neonatal intensive care unit or neonatology service admissions than term births. The study by Dr Shaon Sengupta, now of the Children's Hospital of Philadelphia and formerly of the University at Buffalo, N.Y., and colleagues examined data over a three-year period from medical records of 33,488 live births at major hospitals in Erie County, N.Y.—29,741 at a gestational age between 37 to 41 weeks. According to study results, 27 per cent of all live births were early-term (birth at 37 to 38 weeks). In comparison with term newborns (birth at 39 to 41 weeks), early-term newborns had higher risks for birth complications, including: hypoglycemia (low blood sugar, 4.9 per cent vs. 2.5 per cent), NICU or neonatology service admission (8.8 per cent vs. 5.3 per cent), need for respiratory support (2 per cent vs. 1.1 per cent), and requirement for intravenous fluids (7.5 per cent vs. 4.4 per cent). Cesarean deliveries, common among early-term births (38.4 per cent), posed a higher risk for NICU or neonatology admissions and morbidity compared with term births; NICU or neonatology admission was also more common in vaginal early-term births compared with term newborns. "We conclude that early-term delivery is associated with greater morbidity and with increased admission to the NICU or neonatology service in a geographic area-based setting," a study report said. "This increased risk is more profound with cesarean section deliveries but exists for vaginal deliveries as well."

SIMPLE TEST A LIFESAVER

The patchy adoption of heart screening known as the pulse oximetry test highlights larger questions about public health and why good ideas in medicine take so long to spread and when we should legislate clinical practice. Connecticut passed a new state law that requires all newborns to be screened for congenital heart defects, but not all states have this law. The Centers for Disease Control and Prevention estimate that about one in 555 newborns have a critical congenital heart defect that usually requires surgery in the first year of life. Many cases

are caught in prenatal ultrasounds or routine newborn exams. But as many as 1,500 babies leave American hospitals each year with undetected critical congenital heart defects, the CDC has estimated. Typically, these babies turn blue and struggle to breathe within the first few weeks of life. They are taken to hospitals, often in poor condition, making it harder to operate on them. By then, they may have suffered significant damage to the heart or brain. Researchers estimate that dozens of babies die each year because of undiagnosed heart problems. The new screening is recommended by the US Department of Health and Human Services, the American Heart Association and the American Academy of Pediatrics. Yet more than a dozen states—including populous ones like Massachusetts, Pennsylvania, Florida, Georgia, Wisconsin and Washington—do not yet require it. Newborns are already screened for hearing loss and dozens of disorders using blood drawn from the heel. The heart test is even less invasive: light sensors attached to the hand and foot measure oxygen levels in the baby's blood. This can cost as little as 52 cents per child. Depending on the heart defect, the onset of symptoms can be sudden. This is what happened to Samantha Lyn Stone, who was born in Suffern, NY, in 2002. A photograph taken the day before she died shows a wide-eyed baby girl lying next to a stuffed giraffe. The next morning, her mother, Patti, said that she was wiping Samantha's face when she heard a gurgle from the baby's chest. Before her eyes, Samantha was turning blue. Blood began to spill from her mouth. Stone dialed 911, and minutes later, a doctor who heard the call over a radio was there performing CPR. Samantha went to one hospital and was flown to another. But the damage was irreparable. Samantha had gone 45 minutes without oxygen—she lapsed into a coma and died six days later. It wasn't until several years later that Stone learned about the pulse oximetry test. "This could have saved my daughter," she said. "There is no parent that should ever have to go through what I went through." Pulse oximetry is not a costly, exotic procedure. Most hospitals already have oximeters and use them to monitor infants who suffer complications. You can buy one at Walmart for $29.88. A recent study in New Jersey, the first state to implement the screening, estimated that the test cost $13.50 in equipment costs and nursing time. If hospitals use reusable sensors similar to those found on blood-pressure cuffs, the test could cost roughly 50 cents. With pulse oximetry, the false positive rate is less than 0.2 per cent. The follow-up test is usually a noninvasive echocardiogram, or an ultrasound of the heart. A federal advisory committee came down in favor—three years ago. Opposition has taken two forms. One is from doctors who believe policy makers shouldn't interfere with how medical professionals do their jobs. The other is from smaller hospitals, which worry about access to echocardiograms and the costs of unnecessary transfers. "There's really no question, scientifically, this is a good idea," said Darshak Sanghavi, a pediatric cardiologist and a fellow at the Brookings Institution. "The issue is, how do we change culture?" Information in this article was written by Michael Grabell and first published in the New York Times. Copyright, New York Times.

BABIES NEED THIS TEST

Screening of newborns for inherited and congenital disorders is a revolution that needs continuing. Every US state tests babies at birth for phenylketonuria (PKU) and more than 50 other disorders that can be picked up through screening, including 31 of which comprise the "core conditions" of the government's Recommended Uniform Screening Panel. Other conditions are likely to be added to the panel in the future. All but two of them—heairng loss and critical congenital heart disease—can be detected by automated analysis of a few drops of dried blood from a heel stick done within a few days of birth. In 2008, the Newborn Screening Saves Lives Act was adopted, establishing national screening guidelines and financial help for every state to create a comprehensive screening program. The law, which also provides professional education, parental support and a check on laboratory reliability, is up for renewal. Conditions that can be detected through newborn screening include hormonal disorders like thyroid and adrenal abnormalities, blood disorders like sickle-cell anemia, severe immunodeficiencies, and dozens of enzyme disorders that result in a wide range of serious and sometimes fatal conditions. Each of these disorders is relatively rare, but the effect of widespread screening has proved to be economical as well as lifesaving, sparing countless children years of costly medical and educational services and institutional care. Each state decides which conditions to test for; most now screen for at least 20 disorders. But with more babies now born outside hospitals, it often becomes the parents' responsibility to get newborns screened before they are a week old. An abnormal result on a screening test does not necessarily mean the baby has a problem; additional diagnostic testing is required. If a diagnosis is confirmed, parents are told how best to care for the baby. If a newborn is found to have hearing loss, for example, a treatable cause may be responsible. If the condition cannot be corrected, speech therapy, sign language or cochlear implants may minimize its severity. Dr Edward R. B. McCabe, a pediatric geneticist and medical director for the March of Dimes, envisions an exciting future for early detection and treatment of inherited and congenital disorders. In an interview, he said the National Institutes of Health awarded several research grants for DNA sequencing of newborn blood, which could facilitate the earliest possible diagnosis of health-threatening problems. Information in this article was written by Jane E. Brody and first published on the Well blog of the New York Times. Copyright, New York Times.

TB DEATH RAISES ALARM

More than 200 people were tested in October for tuberculosis as the Southern Nevada Health District staged an investigation into a case of the infectious disease that killed a mother and her child at a Las Vegas hospital. Local health officials said they were contacting parents of 140 infants who could have been exposed while in Summerlin Hospital Medical Center's Level III neonatal intensive care unit from May 11 to Aug. 8. The Health District got notice of the mother's July death and informed Summerlin Hospital about the tuberculosis risk, said Dr Joseph Iser, the district's chief health officer. The mother gave the baby TB, Iser said, either while in the womb or while giving birth. As of Aug. 22, the date of the Health District's report, 155 Summerlin Hospital staffers and at least 69 friends and family members of the mother had been tested for TB. By Monday, Iser said the Health District, with assistance from the Centers for Disease Control and Prevention, was pushing for additional testing out of "an abundance of caution." "I don't believe that we'll have many—if any—exposures that turn out to be positive for tuberculosis," Iser said. Someone who visited Summerlin Hospital a few times while the infected baby was there probably is not at risk, Iser said. At least one NICU staffer was infected, Iser said, but has since recovered. About 400 babies a year enter Summerlin Hospital's Level III NICU, according to the Valley Health System, which operates five medical centers in the Las Vegas Valley. The hospital stressed Monday that it takes multiple levels of precautions against spreading germs, including washing

hands, wearing protective gowns, gloves and masks and rigorous cleaning and disinfecting. "People with infectious diseases may visit many places until they are diagnosed and hospitalized," said Robert Freymuller, CEO and managing director of Summerlin Hospital, in a prepared statement. Tuberculosis spreads with prolonged contact in close quarters, such as classrooms, homeless shelters or jails. Allison Newlon Moser, executive director of the American Lung Association in Nevada, said many people carry a latent, or dormant, case of tuberculosis. It's similar to people who break out with chickenpox—they may never show symptoms again but still carry the virus that causes it. Information in this report was written by Adam Kealoha and first appeared in the Las Vegas Review-Jounral. Copyright the Review-Journal.

VANCOMYCIN MISUSED

More than 85% of the instances of vancomycin administration in a neonatal ICU were inappropriate, according to prospective study results presented at ID Week 2013. The study included children aged at least 3 days admitted to the neonatal ICU at Children's Memorial Hermann Hospital in Houston during a five-month period from 2012 to 2013. Appropriate use of vancomycin included treatment for methicillin-resistant Staphylococcus aureus, coagulase-negativestaphylococci or ampicillin-resistant enterococci. Researchers observed 137 administrations of antibiotics to 91 patients. Of them, 82 (90%) received vancomycin, for a total of 115 cases. Of the 82 patients who received vancomycin, 45 (55%) received it for more than 2 days, accounting for 59 (51%) of the cases. Vancomycin was administered for a total of 557 days, equating to 0.6 days/1,000 patient-days. However, only eight (14%) of these 59 cases were positive for MRSA (n=3), coagulase-negative staphylococcus (n=4) or an infection related to coagulase-negative staphylococci (n=1). Vancomycin was frequently used in the treatment of clinical sepsis and necrotizing enterocolitis as empiric therapy, the researchers noted. "Vancomycin is inappropriately utilized in more than 85% of antibiotic administration episodes in our neonatal ICU," researchers wrote. "Despite culture data demonstrating low prevalence of MRSA and coagulase-negativestaphylococcal infections, it is still utilized as the first-line agent for suspicion of sepsis as well as necrotizing enterocolitis. Interventions to decrease empiric, unnecessary vancomycin usage in the neonatal ICU should be developed."

FAMILY GRILLS UP DONATION

The family of Weber kettle grill creator George Stephen Sr has pledged a $10-million gift to the neonatal intensive care unit at the University of Chicago Medicine Comer Children's Hospital. The gift will allow for the recruitment of a neonatologist, who will be named the Stephen Family Professor of Pediatrics, and funding of research to better understand early childhood illness and to improve treatments for critically ill and premature newborns, the Chicago-area family and hospital officials said. "There are a lot of babies out there who need help, so there's no time to waste," said Jim Stephen, who, along with nine siblings, mother Margaret and one niece, made equal contributions to form the gift. The donation builds on about a decade of the family's philanthropy toward the neonatal ICU, which admits about 1,000 babies per year. The gift's purpose, Stephen said, is to help advance the neonatal field so that babies can be assured of a healthy adult life. David Gozal, a doctor and physician-in-chief at Comer, said the money will fund research aimed at providing custom treatments for ailing babies. "The idea of this gift is really to transform the way that we develop new therapies for babies that are born prematurely," Gozal said. "We want to be so precise that every child will have treatment uniquely designed for them." In honor of the family's contribution, the ICU will be named for Margaret Stephen and her late husband, George. Information in this article was written by Kim Greiger and was first published in the Chicago Tribune. Copyright, Chicago Tribune.

EXECUTIVE ROUNDTABLE ON OXIMETRY

Covidien

Describe the oximetry products your company offers.
Covidien offers Nellcor monitors, sensors and alarm management systems, designed to enhance clinician efficiency and effectiveness. Recently, Covidien became the first company to receive FDA clearance for a motion-tolerant bedside pulse oximeter portfolio that is also compliant with ISO 80601-2-61 (International Organization for Standardization) standards for pulse oximetry. The Nellcor Bedside Respiratory Patient Monitoring System incorporates the latest Nellcor digital signal processing technology for accurate, reliable readings even during low perfusion and other forms of signal interference, providing clinicians with access to the most critical information regarding their patients' respiratory status. With continuous SpO_2 and pulse rate monitoring capabilities, plus trending data and SatSeconds alarm management, the technology offers clinicians the ability to detect respiratory complications earlier and intervene sooner. SatSeconds alarm management technology, built into the Nellcor bedside respiratory patient monitoring system offers a safe, practical way to reduce clinically insignificant alarms. The SatSeconds alarm management function analyzes desaturation events by multiplying the duration (seconds) by the number of percentage points the patient exceeds the alarm limit. Clinicians can set SatSeconds alarm management technology limit to 10, 25, 50 or 100. Once the limit is set, only events that equal or surpass the set limit cause the alarm to sound. The LoSat expanded accuracy feature of Nellcor SpO_2 adhesive sensors with OxiMax technology assures clinicians of the industry's widest accuracy range (60% to 100% SpO_2) when used with the Nellcor bedside respiratory patient monitoring system.[1] This allows improved patient assessment at challenging lower saturation levels. The low saturation feature in Nellcor adhesive sensors offers clinicians the ability to monitor patients accurately and non-invasively in lower SpO_2 ranges. Covidien also offers the Nellcor N-65 Portable Pulse Oximetry Monitor, an economical, easy-to-use handheld device, as well as the Nellcor N-85 Portable Pulse Oximetry Monitor with Microstream technology, a convenient, handheld device that accurately provides both SpO_2 and $etCO_2$ values.

Tell us about your company's R&D pertinent to oximetry.
Covidien is proud of the funds it allocates to research and development activities that have made it a market leader in innovation of medical products, including pulse oximetry. Our commitment to innovation in pulse oximetry monitoring is evident with the expansion of our R&D center in Boulder, Colorado. Nellcor brand R&D efforts are well supported, and Covidien currently has numerous research and development projects in process.

The Covidien commitment to R&D efforts is evident in meeting technology recommendations for CCHD screenings with pulse oximetry, established by the United States Department of Health and Human Services: Screening should be performed with pulse oximeters that are motion tolerant, report functional oxygen saturation, have been validated in low perfusion conditions, have been cleared by the FDA for use in newborns and have an accuracy of ±2 digits.[1]

1. Kemper AR, Mahle WT, Martin GR et al. Strategies for implementing screening for critical congenital heart disease. Pediatrics. 2011;128(5):e1259-1267.

What type of training and user support programs do you offer?
Through the Professional Affairs and Clinical Education (PACE) Online Platform, (www.covidien.com/PACE), Covidien offers a variety of free, clinical and non-clinical education modules online, including courses intended to develop clinician understanding of pulse oximetry technology, CCHD screening, and initiatives in patient care. Covidien is committed to promoting CCHD awareness activities to ensure clinicians understand how to use pulse oximeters to generate reliable readings. In fact, Covidien offers specific education about recommendations for early screening and monitoring for congenital heart disease in infants. Additionally, Covidien offers complimentary in-servicing and on-site clinical support for customers.

Discuss the cost of your oximetry products.
Pricing is generally structured with multiple pricing tiers based on a customer's commitment/compliance levels within their Group Purchasing Organization or Integrated Delivery Network contract arrangements.

Other good information.
Monitoring a wide range of critical respiratory parameters, the Sensing Systems of Covidien help caregivers provide faster, more informed interventions for their patients.

Masimo

Since its inception, pulse oximetry was plagued by unreliability when it was needed most—during patient motion and low perfusion. The industry had given up and considered the problem "unsolvable." Clinicians were forced to live with the results—excessive false alarms, delayed notification due to long averaging times, inaccurate data, and an inability to obtain data on the most critical patients. Conventional pulse oximetry works under the assumption that by looking at only the pulse and normalizing the pulsating signal over the non-pulsating signal, oxygen saturation (SpO_2) can be measured without calibration. Although this was a big step forward in the evolution of pulse oximetry, it has one major flaw—it assumes the only pulsating component is arterial blood. Unfortunately for conventional pulse oximetry, venous blood moves every time the patient moves or breathes.

Masimo SET (Signal Extraction Technology) overcame the technological limitations of conventional pulse oximeters, making it more accurate during the challenging conditions of patient motion and low perfusion. Masimo SET has made pulse oximetry a clinically useful tool and, for the first time since pulse oximetry was introduced in the 1970s, it has been shown in clinical studies to improve patient outcomes. To date, more than 100 independent and objective studies have shown that Masimo SET outperforms all other pulse oximetry technologies, providing clinicians with the sensitivity and specificity to make critical patient-care decisions. Masimo SET Measure-through Motion and Low Perfusion technology is at the core of Masimo noninvasive monitoring instruments, such as the:

- Radical-7—Three-in-one monitor (bedside, handheld, transport), designed to automate the process of care and enable clinicians to instantly adapt to changing monitoring needs in individual patients and care areas. Features the full suite of Masimo SET and rainbow measurements including oxygenation (SpO_2), pleth variability index (PVI), perfusion index (PI), noninvasive and continuous hemoglobin (SpHb), and acoustic respiration rate (RRa).
- Rad-87—Offers Masimo SET pulse oximetry and upgradable rainbow technology in a versatile, easy-to-use bedside monitor.
- Rad-57- The world's most versatile, portable handheld oximeter features Masimo SET pulse oximetry and upgradable rainbow technology.
- Pronto-7—Offers noninvasive and quick spot-check testing of total hemoglobin (SpHb), SpO_2, pulse rate, and perfusion index.

The breakthrough performance of Masimo SET is often most appreciated by the clinicians caring for fragile newborns. Up to 30% of all congenital heart disease (CHD) deaths occurring in the first year of life are unrecognized at the time of hospital discharge after birth. Masimo SET pulse oximetry has been shown to reliably assist clinicians in the screening for critical congenital heart disease (CCHD),[1,2] spurring the US Secretary of Health and Human Services to add Measure-through Motion and Low Perfusion pulse oximetry to the recommended Uniform Screening Panel for newborns.[3] Masimo SET pulse oximeters and sensors meet the recommended criteria for newborn screening, were exclusively used in the two studies that were the basis for the CCHD workgroup decision to recommend newborn screening, and were the first to receive FDA 510(k) clearance with labeling for CCHD screening.

Table 1. CCHD Detection Screening with Masimo SET

N = 39,821 babies	Physical exam alone	Physical exam + Masimo SET Pulse Oxymetry Screening
Sensitivity for CCHD detection	63%	83%
Specificity for CCHD detection	98%	99.8%

SpO_2 screening was conducted on 39,821 newborn babies, preductally (palm of right hand) and postductally (either foot) before routine physical examination. The baby was considered to be screening positive if; 1) either preductal or postductal Sp)2 measurement was ≤90%; 2) if in three repeat measurements, both preductal and postductal Sp02 were <95%, or the difference between the two measurement was >3%.

Premature infants requiring neonatal intensive care need enough oxygen to preserve vital organ function, but too much oxygen can cause severe eye damage from retinopathy of prematurity (ROP). Masimo SET is the only pulse oximetry proven to help clinicians dramatically reduce ROP.[4] In cyanotic infants, Masimo SET with the Blue Sensor is the only pulse oximeter proven accurate—enabling accurate maintenance of targeted oxygen saturation levels.[5] And for very low birth weight babies, only the Masimo NeoPt-500 Sensors are designed for both size and performance in infants as small as 500 grams.

Table 2. Reduction of ROP with Masimo SET

Centre	Severe Retinopathy of Prematurity (ROP) Rate		
	Period 1 (pre-policy change)	Period 2 (post-policy change)	Period 3 (post-policy change)
A	12% with Nellcor	5% with Masimo	4% with Masimo
B	13% with Nellcor	13% with Nellcor	6% with Masimo

In period one the baseline rate for severe ROP in two center, both using Nellcor pulse oximetry, is established. In period two, the oxygen targeting policies, caregivers, and patient characterisrics were the same at both centers, but only Center A switched to Masimo SET, which led to a significant reduction in ROP (from 12% to 5%). In period three, Center B switched to Masimo SET and experienced a reduction in ROP from period two (from 13% to 5%).

When each second matters during newborn resuscitation, the Masimo Newborn Sensor ensures the fastest response time at the highest sensitivity—allowing clinicians to focus on real-time patient management instead of the device. In addition, Masimo SET is increasingly being used to supplement the standard APGAR score to more reliably assess general newborn health. From the very beginning, infants and children have been the focus of our research development. As a result, Masimo leads the industry in solutions designed exclusively for these most vulnerable patients.

Tell us about your company's R&D pertinent to oximetry.

Masimo's innovation engine has fueled many industry firsts, which have significantly improved patient care and reduced costs. As one example, Masimo's noninvasive and continuous total hemoglobin (SpHb) monitoring has been shown to help clinicians reduce the number of risky and costly blood transfusions in surgical patients, speed up blood transfusion for those who need it, and in multiple cases has demonstrated its lifesaving potential to help clinicians detect occult bleeding. Masimo rainbow technology has also been shown to help clinicians assess fluid responsiveness, improve fluid management, identify changes in breathing, and assess carbon monoxide levels for faster therapy for those with CO poisoning.

In 2013, Masimo re-wrote the rules for monitoring and connectivity with the launch of Root. Now available in the US, Root is a powerful new patient monitoring and connectivity platform that integrates Masimo's full suite of rainbow measurements with multiple additional parameters in an integrated, clinician-centric platform. Masimo's approach is designed to unleash innovation in patient monitoring via third-party development of new measurements. With a dock for the Radical-7, an instantly interpretable display, and a networking/connectivity gateway, Root integrates multiple streams of data and simplifies patient-care workflows, empowering caregivers to make quicker patient assessments, earlier interventions, and better clinical decisions throughout the continuum of care.

What type of training and user support programs do you offer?

Masimo offers interactive e-Learning courses on our learning website, Masimo U. These courses consist of review material, demonstration videos, and assessment. Masimo also has a large Clinical Specialist team that offers follow-up to e-Learning with return demonstration verification as well as live classroom training as needed. Additionally, Masimo Clinical Specialists can provide Super User training to designated personnel if desired. Masimo Clinical Specialist and Project Management teams handle everything from the initial order of equipment, to device check-in documentation, to education, placement, and return of decommissioned equipment if applicable.

Discuss the cost of your oximetry products.

Pricing is based on the individual needs and requirements for our customers. Masimo works closely with purchasing departments, clinicians, and other hospital staff to meet their goals.

Hospitals around the world continue to see significant advantages provided by SET Measure-through Motion and Low Perfusion pulse oximetry. It is estimated that over 100 million people around the world each year are better cared for with Masimo break through, lifesaving, and life-improving technologies. The improvements in the process of care have resulted in real cost savings as clinicians use Masimo technologies to their fullest potential.

There have been multiple publications that demonstrate the proven accuracy and reliability of Masimo SET pulse oximetry to allow for better clinical decision-making, leading to improved patient care.

Table 3. Potential annual savings in critical care environment using Masimo SET Technology

Adhesive Sensor Reduction[6,10]	49% - 56%
Reduction in Arterial Blood Gases[7]	34%
Reduction in O_2 Requirements[7,8]	40% - 49%
Length of Stay Reducation[8]	42%
Reduction in False Alarms[9]	93%

In one case for improved patient care, a dyspneic child with left heart hypoplasia was profoundly pale with circumoral cyanosis as his clinical status worsened.[11] During ongoing resuscitative efforts, several conventional pulse oximeters failed to read. A Masimo SET pulse oximeter displayed true saturation and pulse rates that correlated with the ECG during the next two hours of resuscitation and stabilization. The child was placed on mechanical ventilation and stabilized. Eight days later he received a cardiac transplant and is healthy today.

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Career Longevity for Neonatologists

Leonard Eisenfeld, MD

It has been 42 years since I graduated from Yale Medical School and currently I am the oldest Connecticut full-time neonatologist. Since I have been on the editorial advisory board of neonatal Intensive Care, Steve Goldstein asked if I would write an editorial on a subject of my choosing.

We are faced with changes in medical practice, house officer hour restrictions, continued prominence of midlevel practioners, research interests and funding, third-party reimbursement and compensation to our institutions and ourselves. I recently lead a one-hour conference for our attendings and fellows about longevity and believe the subject of career longevity is worthy of continued study, discussion and improvement. The issues are important since my questions are as follows:

1. How do we encourage and/or dissuade medical students and pediatric house officers to consider neonatology as a career choice?
2. How do we best nourish our fellows and neonatology colleagues in their career paths?
3. How do we address the benefits and limitations of the aging neonatologist?

Like all medical topics, these issues remain ripe for research utilizing input from multiple sources such as the behavioral sciences and health-care administration.

I began my recent conference with brief presentations of 8 publications. Their selection was only a sampling of other important work. I started with my own study[1] published 14 years ago. The manuscript was entitled Neonatologist Attrition to General Pediatrics. I had noted at that time that of 24 local neonatologists, 9 were no longer practicing neonatology. Of those nine, 8 had returned to general pediatric practice and one was our department chairman. We developed an open-ended questionnaire for an audio-recorded interview conducted by a college student, which was transcribed to maintain confidentiality. We explored issues related to the origin of neonatology as a career choice, positive and negative aspects of practice, the uniqueness of the newborn as a patient, ethical conflicts, themes related to death, job composition, finances, co-worker and family relations and coping mechanisms. In addition a written questionnaire graded the positive and negative aspects of practice. By comparison the remain neonatologists were more likely to have neonatal board certification, be in an academic practice, and practiced full-time rather than part-time neonatology. We learned that only 38% of the entire group said they would do it over again. Given reasons for attrition were lack of intention to practice full-time neonatology, personality mismatches, depression with poor outcomes, missing well child care and longitudinal care, repetitive rounds, enclosed environment, less personal family time and inability to find a job without research requirements.

Bellieni, et al[2] reported on burnout and risk factors on a cohort of Italian Neontaologists. Factors for relative success were being a parent, more work experience, belief that living with a physical disability was worthy, less death ideation, belief in a deity and willingness to resuscitate at borderline viability.

Moshe et al[3] reported on work satisfaction, quality of life and leisure time of neonatology fellows and senior neonatologists in Israel. Satisfaction levels were high for self-reward, work relations, quality of life, but a major concern is the lack of leisure time. Most would encourage medical students to pursue neonatology, however only 65% would encourage their children to pursue medicine as a career choice.

Mercurio et al[4] warns about the strain of work hour restrictions on the remaining attending neonatologist who does not have a work hour limit. He refers to that attending as the last man standing.

Marshall et al[5] in their excellent monograph outline the impact of the various services providing for the care of critically ill newborn patients. Of note they comment on the importance of leadership, staffing, ongoing education, support between and within groups, regular meetings, nursery design and personal relations.

Using data from other specialty areas may be useful to our colleagues. Fields et al report on a group of pediatric intensivists and emphasize the importance of regular exercise, a sense of value, peer appreciation of their work and the need to maintain outside interests. Shanafelt et al. comment on avoiding burnout for US surgeons. They suggest regular preventive medical care, life-work balance, maintaining meaning in work, a positive outlook and focusing on what is important in life.

The author is an Attending Neonatologist at the Connecticut Children's Medical Center, Harftord, CT. He is an Associate Professor of Pediatrics and Adjunct Professor of Biomedical Engineering at the University of Connecticut, Farmington and Storrs, CT. He is an Editorial Advisory Board Member of neonatal Intensive Care.

My colleagues at Connecticut Children's Medical Center (Sanders et al) have published a report on our task force charged with responding to the needs of an aging workforce. They encourage planners to recognize the strengths of senior faculty in teaching, mentoring, professional development, administration, fund raising and advocacy.

To enhance longevity they suggested enhanced vacation time and block vacations, support from fellows, postdoctoral physicians, and midlevel practioners during clinical time, enhancements in continued medical education and preferred parking.

In summary the issues of career longevity and success in neonatology practice are important for continuing study and discussion. Awareness and sensitivity to the experience of others is an opportunity to learn how best to proceed with our careers.

I have been fortunate to be able to build on the shoulders of my colleagues, mentors and students. Most of all I have been privileged to work with numerous individuals who have complimented and/or compensated for my skill-set or lack thereof.

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Experiences using the Neutron catheter patency device

In this feature, Neonatal Intensive Care interviews clinicians and health-care providers about the actual application of specific products and therapies. This interview is with Dayna Holt, MSN, RN, CRNI, CPN, VA-BC of Rady Children's Hospital Vascular Access Service Team In San Diego, CA.

Laszlo: How long has your facility been using the Neutron Catheter Patency Device?
Dayna: We started the trial in 2011 with hematology oncology. We implemented the device hospital wide in December of 2012. Although our NICU did not implement fully until May/June of 2013.

Laszlo: I understand that you were one of the first facilities to trial and implement the Neutron. Has the functionality and performance of the device met your expectations?
Dayna: Yes, but I have not finished evaluating our hospital-wide occlusion rate after implementation in December.

Laszlo: Implementing a new technology such as Neutron often requires extensive clinical and business review. How did you make the clinical and business case for implementing this new technology in your facility?
Dayna: We tracked our occlusion rate on all of our Hickman/Broviac catheters prior to implementation of the valve. We estimated the costs of t-PA utilization and catheter replacement. We then projected the cost of the valve with the anticipated reduction of occlusion events. this resulted in an overall cost savings to the hospital. We hoped for a 40-50% reduction in occlusions. We realized a 60% reduction in complete occlusions in that patient population.

Laszlo: Did implementing Neutron require any changes to your care protocols?
Dayna: No.

Laszlo: Can you comment on Neutron's impact on the rate of occluded IV catheters and other IV-related complications?
Dayna: As noted above we initially experienced a reduction of 60%. The housewide outcome report is pending but looks promising.

Laszlo: How do you feel that Neutron has improved your practice in terms of patient care?
Dayna: Fewer complete occlusions results in improved consistency of care and fewer delays in care. Using less t-PA is less expensive as well.

Laszlo: How do you feel that Neutron has improved your practice in terms of cost of care?
Dayna: Fewer occlusions to manage allows for timely administration of medications, fewer additional needle sticks for patients, and frees the nurse to provide other important care instead of troubleshooting a malfunctioning central venous catheter.

Laszlo Sandor is assistant editor of Neonatal Intensive Care. Input on questions was provided by Jason Woodbury, Director of IV Therapy Marketing at ICU Medical. If you would like to participate in this feature, as a company or healthcare provider, please contact Christopher Hiscox or Steve Goldstien at s.gold4@verizon.net.

The benefits of hypo-hyperthermia systems in the care of infants

In this feature, Neonatal Intensive Care interviews clinicians and health-care providers about the actual application of specific products and therapies. This interview is with Susan Peloquin, RN, MS, CNIV, Clinical Coordinator, NICN Intensive Care Nursery UCSF Benioff, Children's Hospital of San Francisco, CA.

NIC: What type of treatments are you using hypo-hyperthermia systems for (HIE, neonatal neuro, etc)?
Susan: Currently, hypothermia is indicated for full-term infants with hypoxic ischemic encephalopathy (HIE). Infants who meet clinical and laboratory criteria for hypoxic ischemic encephalopathy (HIE) are cooled according to standard guidelines for 72 hours. We use whole body cooling and cool to a core temperature of 33.5 degrees C. In addition, all cooled newborns are evaluated by a child neurologist at the time of admission and through cooling, are monitored using continuous video-EEG and amplitude integrated EEG, and are imaged using 3T MRI.

NIC: What drove UCSF to start a cooling program 5 years ago?
Susan: Five years ago, the Chiefs of Neonatology and Pediatric Neurology understood that the evidence for cooling was very strong, and made the decision to implement cooling in the context of our Neuro-Intensive Care Nursery interdisciplinary program. The core of the interdisciplinary program is a team of neonatologists, child neurologists, and specialized nurses, who evaluate neonates together on a daily basis during co-management rounds. The core team is backed by pediatric neurophysiologists and neuroradiologists. This model relies on individual expertise and team collaboration to promote brain-focused care throughout the infant's hospitalization. Upon discharge, infants who are cooled receive close neurodevelopmental follow up through the Infant High Risk Follow Up Program (HRIF) and Neonatal Neurology Follow Up Clinic.

NIC: What was the most difficult hurdle to overcome?
Susan: Our most difficult hurdle has had to do with developing the co-management model, which is an interdisciplinary team approach between Neonatology and Neurology that also prioritizes nursing expertise at the bedside. Because we pushed the group to interact in new ways, development of standardized protocols required extensive discussions across departments.

NIC: What does the team feel about cooling today versus 5 years ago?
Susan: We are convinced of the benefits of cooling, having now evaluated over 200 at risk infants for cooling therapy. We are also convinced that intensive neuromonitoring, sophisticated MR imaging, and the interdisciplinary team approach to care of such infants delivers an optimized standard. We are publishing papers to validate these impressions for the medical community so they may adopt similar practices.

NIC: What would you say to an NICU that is thinking about starting a cooling program?
Susan: While therapeutic hypothermia can be technically straightforward to apply, it is important for centers to be adequately prepared for the complications that neonates with HIE may experience. Severe PPHN requiring ECMO, subclinical seizures detected only through advanced monitoring, and devastating brain injuries are common; access to Pediatric Neurology and Epilepsy services, as well as Palliative Care, social work and a bedside nursing team that is familiar with the procedures is incredibly important for optimizing care. The treatment of HIE requires expertise that a neonatologist is unable to provide solo. We believe that regionalized centers, with high volumes and access to an experienced, multidisciplinary team that can provide brain-focused care through therapeutic hypothermia and other neuroprotective interventions are best suited to caring for neonates with brain injury including HIE. It is reasonable for a level 3 NICU to consider starting a cooling program, as this becomes a standard of care in the field. However, an important consideration is whether hypothermia should be performed in regional centers rather than community level 3 NICUs. The interdisciplinary intervention of Pediatric Neurology and Epileptology, as well as the management of complex conditions such as PPHN plus HIE requires expertise that a neonatologist is unable to provide solo. It is likely that as the regionalized centers develop more sophisticated protocols that hypothermia will increasingly be moved to these centers for delivery of hypothermia and other neuroprotective interventions.

Input on questions was provided by Allison Doviak, Communications Manager at Cincinnati Sub-Zero Products, Inc. If you would like to participate in this feature, as a company or health-care provider, please contact Christopher Hiscox or Steve Goldstien at s.gold4@verizon.net.

Addition of SNAP to perinatal risk factors improves the prediction of bronchopulmonary dysplasia or death in critically ill preterm infants

Yanhong Li, Jie Yan, Mengxia Li, Zhihui Xiao, Xueping Zhu, Jian Pan, Xiaozhong Li and Xing Feng

Abstract

Background: Bronchopulmonary dysplasia (BPD) is the most common serious pulmonary morbidity in premature infants. The score for neonatal acute physiology (SNAP) is a physiologic severity index for neonatal intensive care and correlates well with neonatal mortality and clinical outcomes. The prognostic value of the SNAP score for BPD in preterm infants remains to be clarified. The aim of the study was to determine whether SNAP can predict the development of BPD or death, and to investigate the contribution of SNAP to the predictive accuracy of other potential perinatal risk factors for the adverse outcome in critically ill preterm infants.

Methods: We conducted a study in 160 critically ill preterm infants with less than 33 gestational weeks. The original SNAP score was prospectively calculated based on 28 items collected during the first 24 hours of admission. The potential perinatal risk factors were assessed during the first 72 hours of life. Major outcome measures were BPD and mortality before the time of BPD screening.

Results: Of the 160 infants, 17 died and 41 developed BPD. The SNAP score was significantly associated with BPD or death (odds ratio [OR] =1.28; 95% confidence interval [CI], 1.16-1.41; p<0.001), even after adjustment for gestational age (OR =1.27; 95% CI, 1.13-1.41; p<0.001). High SNAP score was an independent predictor of BPD or death (area under the curve [AUC] =0.78; 95% CI, 0.70-0.85; p<0.001), with additional predictive value when combined with other perinatal risk factors. Multivariate regression analysis resulted in a final model, including SNAP, gestational age, apnea of prematurity, patent ductus arteriosus, and surfactant use as independent risk factors, with a higher predictive accuracy compared with individual components (AUC =0.92; 95% CI, 0.87-0.96; p<0.001).

Conclusions: SNAP is associated with adverse outcome of BPD or death. High SNAP scores are predictive of BPD or death in critically ill preterm infants, and add prognostic value to other perinatal risk factors.

The authors are with Institute of Pediatric Research, Children's Hospital affiliated to Soochow University, Department of Nephrology, Children's Hospital affiliated to Soochow University, Department of Neonatology, Children's Hospital affiliated to Soochow University.

Background: Bronchopulmonary dysplasia (BPD) is the most common serious pulmonary morbidity in premature infants.[1-4] Although there was a lack of universally acceptable accurate predictive models of BPD in clinical practice and research, it is widely acknowledged that BPD is a multi-factorial disorder, with low gestational age, low birth weight, lower Apgar scores, longer duration of oxygen exposure and assisted mechanical ventilation, and the presence of sepsis and patent ductus arteriosus (PDA) being important risk factors[5-10]

Illness severity scores have been widely used to adjust outcomes between populations for quality improvement and research purposes.[11-15] The score for neonatal acute physiology (SNAP) is a physiologic severity index for neonatal intensive care. SNAP is based on 28 items collected over the first 24 hours of life, and applicable to any infant admitted to a neonatal unit.[11]

Previous studies have demonstrated that SNAP is a valid measure of illness severity at admission and important predictor of neonatal mortality and clinical outcomes.[12,16-19] However, to the best of our knowledge, no study has investigated the association between SNAP and the development of BPD. The predictive value of SNAP in critically ill preterm infants in relationship to BPD is currently unknown. In addition, mortality is a competing outcome for BPD. When identifying risk factors, the outcome of BPD/death should be used rather than BPD alone.[9,20,21] We hypothesized that in neonates SNAP could predict the development of BPD or death. The goal of this study was to investigate the contribution of SNAP to the predictive accuracy of other perinatal risk factors for the adverse outcome in critically ill preterm infants. It is clinically significant to evaluate additional predictive value by combining SNAP with other perinatal risk factors. Clinicians might be able to accurately predict BPD or death when taking account of the full and changing clinical picture of an infant.

Methods

This study included preterm infants with less than 33 gestational weeks admitted to the neonatal intensive care unit (NICU) during the period from July 2010 to May 2012. Infants greater than 33 weeks of gestational age were not included because less than 1% of them developed BPD. The exclusion criteria were as follows: infants admitted to NICU after 24 hours of life, infants unexpectedly discharged or transferred to other departments or hospitals, and infants with severe congenital anomalies. The Institutional Ethics Review Board of the Children's Hospital

Table 1 Patient characteristics and bivariate analysis of perinatal risk factors for BPD or death*

	Survival without BPD (n = 102)	BPD or Death (n = 58)	Odds ratio (95%)[#]	*P* value
Gestational age, weeks	31.86 [28.29-32.86]	29.29 [25.86-32.29]	0.41 (0.31-0.55)	<0.001
Birth weight, g	1570 [900–2320]	1330 [670–2100]	0.81 (0.72-0.90)[a]	<0.001[b]
Gender, male/female	67/35	37/21	1.09 (0.55-2.13)	0.809
Small for gestational age (<10%), n (%)	12 (11.8)	9 (15.5)	1.38 (0.54-3.50)	0.500
Apgar score, 1 min	8 [1-10]	7 [1-10]	0.90 (0.77-1.04)	0.139
Apgar score, 5 min	9 [3-10]	8.5 [2-10]	0.76 (0.63-0.93)	0.007[c]
SNAP	8 [3-26]	13 [4-27]	1.28 (1.16-1.41)[d]	<0.001[c]
Apnea of prematurity, n (%)	12 (11.8)	18 (31.0)	3.23 (1.42-7.33)	0.005[b]
Patent ductus arteriosus, n (%)	1 (1.0)	8 (13.8)	16.33 (1.99-134.2)	<0.001[c]
Respiratory distress syndrome, n (%)	45 (44.1)	50 (86.2)	8.89 (3.68-21.49)	<0.001[c]
Hypoxic-ischemic brain damage, n (%)	7 (6.9)	2 (3.4)	0.49 (0.10-2.43)	0.382
Intraventricular hemorrhage, n (%)	0 (0)	3 (5.2)	3E + 009	0.999
Early-onset sepsis, n (%)	4 (3.9)	2 (3.4)	0.88 (0.16-4.97)	0.887
Respiratory support[e]			2.95 (1.89-4.61)	<0.001[c]
Oxygen therapy, n (%)	85 (83.3)	57 (98.3)	9.39 (1.20-73.39)	0.033[b]
CPAP, n (%)	45 (44.1)	30 (51.7)	1.16 (0.60-2.25)	0.659
Mechanical ventilation, n (%)	21 (20.6)	33 (56.9)	4.97 (2.45-10.08)	<0.001[c]
Surfactant, n (%)	35 (34.3)	46 (79.3)	7.12 (3.34-15.17)	<0.001[c]
Postnatal steroid, n (%)	23 (22.5)	20 (34.5)	1.81 (0.89-3.69)	0.104
Antenatal steroid, n (%)	11 (10.8)	5 (8.6)	0.78 (0.26-2.36)	0.658
Pre-eclampsia, n (%)	14 (13.7)	7 (12.1)	0.86 (0.33-2.28)	0.766
Premature rupture of the membranes (>24 h), n (%)	14 (13.7)	10 (17.2)	1.31 (0.54-3.17)	0.550

Values are median [min-max range]; *BPD* bronchopulmonary dysplasia, *CI* confidence interval, *CPAP* continuous positive airway pressure, SNAP the score for neonatal acute physiology.
*Potential perinatal risk factors obtained during the first 72 hours of life were studied. [#]Data from all preterm infants (n =160) were analyzed to predict BPD or death (n =58). Preterm infants who died or developed mild, moderate, or severe BPD were combined into one group.
[a]Odds ratio represents the increase in risk per 100 g increase in birth weight. [b]The association did not remain significant after controlling for gestational age.
[c]The association remained significant after controlling for gestational age. [d]Odds ratio per 1-point increase in SNAP. [e]Respiratory support was assigned as none, nasal cannula, nasal CPAP, or invasive mechanical ventilation.

affiliated to Soochow University approved the study. Informed consent was obtained from the parents of the infants.

Potential perinatal risk factors

To investigate the early prediction of BPD or death, the potential perinatal risk factors obtained during the first 72 hours of life were studied. Maternal data including chorioamnionitis, premature rupture of the membranes (PROM) >24 hours, gestational diabetes mellitus (GDM), pre-GDM, hypertension, pre-eclampsia, antenatal steroids, and mode of delivery, as well as neonatal data including gestational age, birth weight, gender, the Apgar scores, and delivery room resuscitation course were collected. Antenatal steroids were considered to have been administered if at least one dexamethasone injection was given 12 hours before delivery. Gestational age was calculated from the mother's menstrual history and was confirmed by ultrasonography.

Clinical status, medication, and therapeutic interventions of the infants were recorded daily during the first 72 hours of life. We evaluated all infants for the presence of perinatal asphyxia, respiratory distress syndrome (RDS), transient tachypnea of the newborn, apnea of prematurity, pneumothorax, pulmonary hemorrhage, PDA, early onset sepsis, necrotizing enterocolitis (NEC), hypoxic-ischemic brain damage, intraventricular hemorrhage (IVH), and acute kidney injury.

In addition, we examined the use of postnatal steroids and surfactants at any time during the first 72 hours of life.

Respiratory support, including oxygen, continuous positive airway pressure (CPAP), invasive mechanical ventilation, and the duration of therapies, were recorded. We assigned the respiratory support as none, nasal cannula, nasal CPAP, or invasive mechanical ventilation.

The SNAP score

The original SNAP score was prospectively calculated for each infant based on 28 items collected during the first 24 hours of admission, including blood pressure, heart rate, respiratory rate, temperature, partial pressure arterial oxygen/fractional inspired oxygen (PaO_2/FiO_2) ratio, PaO_2, partial pressure of carbon dioxide ($PaCO_2$) in arterial blood, oxygenation index, hematocrit, white blood cell count, immature total ratio, absolute neutrophil count, platelet count, blood urea nitrogen, serum creatinine (Cr), urine output, serum indirect bilirubin, serum direct bilirubin, serum sodium, serum potassium, serum ionized calcium, serum total calcium, serum glucose, serum bicarbonate, arterial pH, seizure, apnea, and stool guaiac.[11] All the data were prospectively collected by trained graduate students under the supervision of the attending neonatologists and the chief of neonatology.

Clinical outcomes

The outcome measures included the development of BPD or death before the time of BPD screening.[20]

Definition of BPD

Infants were categorized as having mild, moderate, or severe BPD, according to the National Institutes of Health consensus

Table 2 Multivariate logistic regression final model predicting BPD or death[a]

	Odds ratio[b]	95% CI	*P* value
Gestational age	0.38	0.25-0.57	<0.001
SNAP	1.19[c]	1.04-1.32	0.010
Apnea of prematurity	4.89	1.18-20.36	0.029
Patent ductus arteriosus	16.51	1.08-252.49	0.044
Surfactant use	7.99	2.33-27.47	0.001
Apgar score, 5 min	0.77	0.59-1.02	0.071

BPD bronchopulmonary dysplasia, *CI* confidence interval, *SNAP* the score for neonatal acute physiology.
[a]Variables with *P* <0.2 in the unadjusted analysis (Table 1) were entered into a backward stepwise multivariate logistic regression analysis. [b]Data from all preterm infants (n =160) were analyzed to predict BPD or death (n =58).
[c]Odds ratio per 1-point increase in SNAP.
The *p* value of the Hosmer-Lemeshow goodness-of-fit test for the final model was 0.333.

definition of BPD.[5,22] Mild BPD was defined as receiving supplemental oxygen for ≥28 days but not at a postmenstrual age (PMA) of 36 weeks or at discharge; moderate BPD as receiving oxygen for ≥28 days plus treatment with <30% oxygen at 36 weeks' PMA; and severe BPD as receiving oxygen for ≥28 days plus ≥30% oxygen and/or positive pressure at 36 weeks' PMA.

Diagnostic criteria and clinical indications

Apnea of prematurity was defined as cessation of breathing that lasts more than 15 seconds and is accompanied by bradycardia or hypoxia.[23] Diagnosis of PDA was based on echocardiogram and color Doppler test. PDA was considered as significant when the following criteria were met, as described previously: (a) a ductal diameter > 1.5 mm; (b) a left ventricular output index of more than 300 ml/kg/min; (c) left atrium to aortic root ratio greater than 1.5; (d) retrograde or absent diastolic flow in the cerebral anterior artery or in the descending thoracic aorta.[24] The criteria for the diagnosis of RDS were in accordance with the European consensus on the management of neonatal RDS in preterm infants. The diagnosis was confirmed on chest x-ray with a classical 'ground glass' appearance and air bronchograms. Infants with or at high risk of RDS were given a natural surfactant preparation.[25,26] Perinatal asphyxia was defined according to the following criteria: (1) pH ≤ 7.0 or base deficit ≥ 16 mmol/l in cord blood or during the first 1 hour after birth; or (2) If the pH was between 7.01 and 7.15, or the base deficit was between 10 and 15.9 mmol/L, or an arterial blood gas value was not available, either a 10 min-Apgar score ≤ 5 or assisted ventilation for ≥ 10 minutes from birth was required.[27] Once these criteria were met, all neonates underwent a standardized neurologic examination performed by neonatologists. Encephalopathy was defined as the presence of one or more signs in at least three of the following six categories (1) level of consciousness; (2) spontaneous activity; (3) posture; (4) tone; (5) primitive reflexes; and (6) autonomic nervous system signs.[28] Preterm infants who met the criteria for diagnosis of encephalopathy were considered as having hypoxic-ischemic brain damage, and diagnosis was confirmed by MRI examination. Diagnosis of IVH was based on the findings on head ultrasound and/or MRI according to the criteria of Papile et al.[29] A head ultrasound was routinely performed in all preterm infants and in infants diagnosed with perinatal asphyxia. A brain MRI was conducted only in preterm infants who presented with signs and symptoms suggestive of encephalopathy or brain damage during the hospitalization, as described in our previous study.[30] The NEC diagnosis was made according to the modified Bell's staging criteria. Infants with stage II or greater were defined as having NEC.[31,32] The diagnostic criteria of sepsis were in accordance with our previous study. Infants with positive clinical and/or laboratory screen and positive culture were defined as having sepsis.[33] EOS refers to sepsis presenting in the first 72 hours of life.[34] The diagnosis of AKI was based on serum Cr >1.5 mg/dl (132.6 µmol/l) and/or a ≥150% increase in serum Cr from baseline.[33,35,36]

The indication for oxygen therapy in the newborn was PaO_2 <50 mm Hg (6.6 kPa) or transcutaneous oxygen saturation <85% in room air, except in the presence of cyanotic congenital heart

Table 3 Predicting performance of SNAP and other risk factors for development of BPD or death

	AUC	95% CI	*P* value
Low gestational age	0.83	0.76-0.89	<0.001
SNAP	0.78	0.70-0.85	<0.001
Surfactant use	0.72	0.64-0.80	<0.001
Apnea of prematurity	0.59	0.50-0.69	0.050
Patent ductus arteriosus	0.57	0.47-0.66	0.174
SNAP, combined with gestational age	0.88	0.84-0.94	<0.001
SNAP, combined with surfactant use	0.81	0.75-0.88	<0.001
SNAP, combined with gestational age and surfactant use	0.90	0.85-0.95	<0.001
Combination of 5 risk factors[a]	0.92	0.87-0.96	<0.001
P value (comparison of the difference between AUCs)			
p = 0.352 (between SNAP and gestational age)			
p = 0.178 (between SNAP combined with gestational age and gestational age alone)			
p = 0.023 (between SNAP combined with gestational age and SNAP alone)			
p = 0.026 (between combination of 5 risk factors and gestational age alone)			
P = 0.002 (between combination of 5 risk factors and SNAP alone)			
p = 0.362 (between combination of 5 risk factors and SNAP combined with gestational age)			

AUC area under the receiver-operating-characteristic curve, *BPD* bronchopulmonary dysplasia, *CI* confidence interval, *SNAP* the score for neonatal acute physiology.
[a]Five risk factors: gestational age, SNAP, surfactant use, apnea of prematurity, and patent ductus arteriosus.

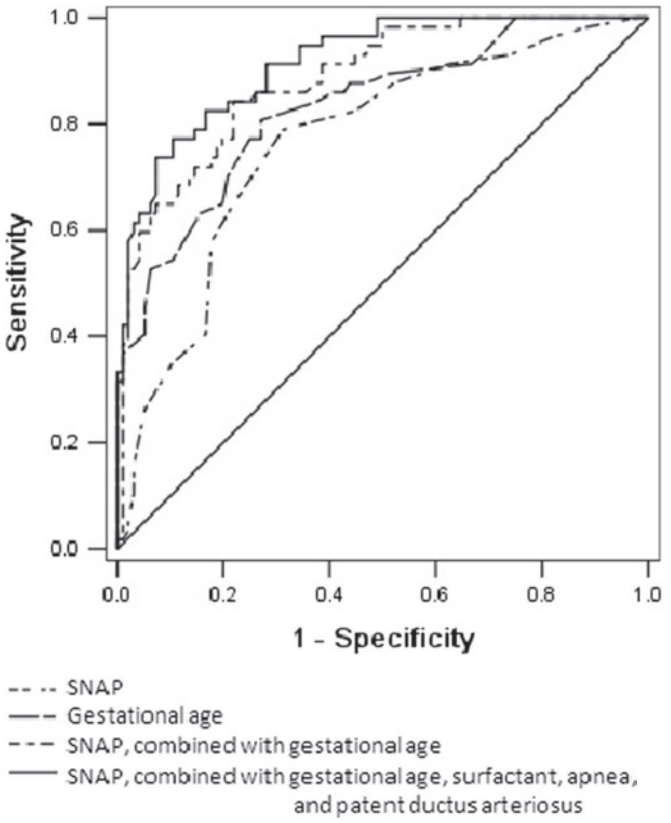

Figure 1. Receiver operating characteristic curves for the ability of the score for neonatal acute physiology (SNAP), gestational age and the models to predict the development of bronchopulmonary dysplasia or death in critically ill preterm infants with less than 33 gestational weeks (n =160). The area under the receiver operating characteristic curve for gestational age, SNAP, SNAP combined with gestational age, and SNAP combined with gestational age, apnea of prematurity, patent ductus arteriosus, and surfactant use were 0.83, 0.78, 0.88 and 0.92, respectively, withThe sensitivity and specificity of risk factors for the development of BPD or death are shown in Table 4. SNAP displayed sensitivity of 79% and specificity of 71% to predict BPD or death at the optimal cut-off score of 10.5, and the positive and negative likelihood ratios were 2.7 and 0.29, respectively. Gestational age displayed sensitivity 81% and specificity 73% at the optimal cut-off value of 31 weeks for predicting the development of BPD or death, with the positive and negative likelihood ratios of 3.0 and 0.26, respectively. When combining the variables of SNAP and gestational age, the sensitivity and specificity increased to 84% and 77%, with the positive and negative likelihood ratios of 3.8 and 0.20, respectively. Meanwhile, when we combined the variables of SNAP, gestational age, apnea of prematurity, PDA, and surfactant use in the final model, specificity increased to 90%, and positive likelihood ratio increased to 7.4.

disease. Inability to maintain oxygenation with nasal cannula (FiO_2 >60% to maintain PaO_2 >50 mm Hg or arterial blood pH <7.25) or apnea unresponsive to stimulation is an indication for CPAP. The indications for mechanical ventilation were respiratory failure in newborns: PaO_2 <50 mm Hg on FiO_2 >60%, $PaCO_2$ >60 mm Hg (8.0 kPa), arterial pH <7.20 or prolonged or repetitive unresponsive apnea associated with bradycardia or cyanosis.

Statistical analysis

Statistical analyses were performed with SPSS 13.0. Bivariate and multivariate logistic regression was performed to identify potential perinatal risk factors associated with adverse outcome. Variables with p<0.2 in the bivariate analysis were entered into a backward stepwise multivariate regression model. Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test. A non-significant value for the Hosmer-Lemeshow Chi-square test suggests an absence of biased fit. Analysis of the area under the curve (AUC) of the Receiver Operating Characteristic (ROC) curve was constructed to assess the prognostic performance. The nonparametric method of Delong was used to compare significant difference between AUCs (Sigmaplot 10.0 software). Sensitivity and specificity were also determined. All probability values are two-sided. Differences with p values <0.05 were considered to be statistically significant.

Results

A total of 160 infants were included in this study. During the time period of the study, 207 preterm infants with less than 33 gestational weeks were admitted to NICU during the first day of life. Forty-seven infants were excluded: 2 were diagnosed with severe congenital anomalies, 1 was transferred to another department, and 44 were unexpectedly discharged because of economic reasons.

Of the total 160 preterm infants, 17 died before the time of BPD screening. Among the 143 survived infants, 41 fulfilled the criteria for the diagnosis of BPD, including 25 with mild, 9 with moderate, and 7 with severe BPD. Patient characteristics of survivors without BPD and infants who died or developed BPD are shown in Table 1. In addition, there was no significant difference between included and excluded preterm infants with regards to gestational age (31.00 [25.86-32.86] vs 30.86 [24.00-32.86] weeks, p=0.797), birth weight (1460 [670-2320] vs 1550 [850-2300] g, p=0.285), gender (male/female: 104/56 vs 30/14, p=0.724), SNAP (10 [3-27] vs 9 [3-16], p=0.146), 1 min-Apgar score (8 [1-10] vs 8 [5-10], p=0.841), 5 min-Apgar score (9 [2-10] vs 8.5 [6-10], p=0.476), and oxygen therapy during the first 72 hours (p >0.05).

Bivariate analysis of risk factors for the development of BPD or death

Data from all preterm infants were analyzed to predict BPD or death. Preterm infants with mild BPD were included into the group of BPD or death. There was no association between the severity of BPD and BPD or death (p=0.996).

Preterm infants with adverse outcome of BPD or death were more likely than controls to have a lower gestational age at delivery, lower birth weight, lower 5 min-Apgar score, and higher SNAP score (Table 1). The impact of SNAP (Odds ratio [OR] per 1-point increase = 1.27, 95% confidence interval [CI] 1.13-1.41, p<0.001) and 5 min- Apgar score (OR 0.72, 95% CI 0.57-0.91, p=0.005) persisted when controlling for gestational age. Birth weight, however, did not remain associated with BPD or death when adjusted for gestational age. Gender and 1 min- Apgar score were not associated with BPD or death at the unadjusted bivariate level. Furthermore, SNAP (OR 1.21, 95% CI 1.07-1.39, p=0.004), 5 min-Apgar score (OR 0.59, 95% CI 0.43-0.81, p=0.001) and gestational age (OR 0.37, 95% CI 0.23-0.58, p<0.001) remained associated with BPD or death after controlling for the severity of BPD.

Among infants with BPD or death, apnea of prematurity, RDS, and PDA were observed more frequently than in the control group. The association of RDS and PDA with BPD or death remained significant after controlling for gestational age. In contrast, the presence of early onset sepsis, hypoxic-ischemic brain damage, IVH, NEC or pneumothorax was not associated with BPD or death.

Table 4 Predictive characteristics of SNAP and other risk factors for BPD or death

	Cut-off value	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Gestational age	31 weeks	81%	73%	75%	79%	3.0	0.26
SNAP score	10.5	79%	71%	73%	77%	2.7	0.29
SNAP, combined with gestational age		84%	77%	79%	83%	3.8	0.20
Combination of 5 risk factors[a]		77%	90%	88%	80%	7.4	0.25

BPD bronchopulmonary dysplasia, *LR* + likelihood ratio positive, *LR-* likelihood ratio negative, *NPV* negative predictive value, *PPV* positive predictive value, *SNAP* the score for neonatal acute physiology.
[a]Five risk factors: gestational age, SNAP, surfactant use, apnea of prematurity, and patent ductus arteriosus.

Preterm infants with BPD or death were much more likely than controls to have received oxygen therapy and to be exposed to mechanical ventilation. Although we did not find an association between nasal CPAP and BPD or death, there was a significant association of respiratory support included nasal cannula, nasal CPAP, and invasive mechanical ventilation with BPD or death.

Moreover, BPD or death cases had more surfactant treatment than controls. After adjustment for gestational age, surfactant use was associated with a seven-fold increased risk of BPD or death (OR 6.71, 95% CI 2.70-16.63, p<0.001). There was no association between pre-eclampsia, PROM, caesarean section or antenatal steroid use and BPD or death.

Multivariate analysis of risk factors for the development of BPD or death

Variables with p<0.2 in the bivariate analysis were entered into a backward stepwise multivariate logistic regression analysis to identify the factors independently associated with increased risk of BPD or death in critically ill preterm infants. The final model retained gestational age, SNAP, the presence of apnea of prematurity and PDA, and surfactant use as significant predictors, with 5 min- Apgar score as a confounder (p=0.071) (Table 2). The Hosmer-Lemeshow goodness-of-fit test for the final model was not significant (p=0.333), indicating that the model fits the data adequately.

SNAP as predictor for BPD or death

Based on the above-mentioned association between SNAP and adverse outcome of BPD or death, SNAP could be a useful prognostic predictor in critically ill preterm infants. To assess the potential to predict BPD or death, we compared the predictive value of SNAP with other prognostic predictors demonstrated by multivariate regression analysis (Table 3). Gestational age and SNAP appeared to be significant predictors, and achieved AUC of 0.83 (95% CI 0.76-0.89, p<0.001) and 0.78 (95% CI 0.70-0.85, p<0.001) respectively, for predicting the development BPD or death. When combining SNAP and gestational age, the predictive performance improved (AUC 0.88, 95% CI 0.84 to 0.94, p<0.001) over that of gestational age alone, but not reaching statistical significance (p=0.178).

Multivariate logistic regression analysis resulted in a superior final model containing variables of SNAP, gestational age, the presence of apnea of prematurity and PDA, and surfactant use as independent risk factors. With an AUC of 0.92 (95% CI 0.87-0.96, p<0.001), the prognostic accuracy of the final model was superior to the accuracy of the other predictors. By using the nonparametric method of Delong, the prognostic performance of the final model was significantly better than gestational age (p=0.026) or SNAP (p=0.002) alone. Figure 1 shows the ROC curves and AUC for the final model and for SNAP and gestational age.

Discussion

Our data demonstrate that the SNAP score based on 28 items collected during the first 24 hours of admission to NICU is significantly associated with the development of BPD or death in critically ill preterm infants with less than 33 gestational weeks. High SNAP score is predictive of BPD or death, and adds predictive value to other potential perinatal risk factors in this population.

The present study first confirmed the known strong association between low gestational age and BPD.[6,7,9] Infants with lower gestational age have worse outcomes. The gestational age displayed the best predictive performance, when compared with other perinatal risk factors determined by bivariate analysis. Our study is the first to compare the predictive value of candidate perinatal risk factors obtained during the first 72 hours of life, for the early prediction of BPD or death. Our findings are in agreement with a large multicenter study, which has reported that the gestational age was the most predictive information for BPD risk on postnatal days 1 and 3 in infants of 23-30 weeks' gestational age.[9]

The major finding in the study was that the SNAP score was significantly associated with adverse outcome of BPD or death. For each point increment in the SNAP score, the odds ratio for predicting BPD or death was 1.28. The SNAP score, based on 28 items from a variety of sources including every body system and selected blood test results, reflects the full clinical picture of an infant during the early postnatal period. Previous studies suggest that considering the full clinical picture of an infant is likely beneficial in the prediction of neonatal mortality and morbidity.[12,16-19] One study evaluated the usefulness of SNAP version II (SNAP-II) to predict BPD,[37] suggesting SNAP-II predicts chronic lung disease in the NICU. SNAP-II is a simpler version of SNAP and reduces the number of variables to six.[12] This previous study, however, excluded infants who died, which is a competing outcome for BPD.

The SNAP score and gestational age contributed independently to the risk of BPD or death. Although the predictive accuracy of SNAP for BPD or death (AUC of 0.78) was not better than that of gestational age (AUC of 0.83), the addition of SNAP improved BPD or death prediction of gestational age (AUC of 0.88), increasing the contribution of gestational age to BPD or death. This suggests that SNAP was not a confounder here, but was probably an effect modifier. In addition, the combination of gestational age, apnea of prematurity, PDA, surfactant use and SNAP appeared to be the best predictive model for BPD or death in critically ill preterm infants, with an AUC of 0.92. Our data indicate that SNAP, as a measure of newborn illness severity, could add predictive value to other previously described perinatal risk factors for BPD or death.

Previously identified risk factors for BPD, including gestational age, apnea of prematurity, PDA, and surfactant use, were included in our final model.[5,7,9,38] Surfactant therapy is a standard of care for infants at risk of RDS. Although current evidence is insufficient to support surfactant treatment strategies for the prevention of BPD,[4,39] the surfactant with brief ventilation as part of the intubation surfactant extubation approach was found to reduce the rates of BPD.[40] Surfactant use included in the model is likely not causal for BPD or death, but reflective of respiratory illness or management. Previously described risk factors, including birth weight, male gender, sepsis, oxygen therapy, and mechanical ventilation, were not included in the model.[5,7,9,21,41] None of these factors improved prediction of the risk of BPD or death after adjustment for the five critical risk factors. The comparison of the prognostic value of SNAP to the predictive ability of known risk factors on the adverse outcome of critically ill preterm infants is a novel aspect of this work. Our findings suggest that the additional predictive value of combining SNAP with known perinatal risk factors improves the quantification of the risk for prediction of neonatal mortality and morbidity.

Neonatal care has changed dramatically over the past decades, and the improvement in antenatal corticosteroid treatment, surfactant replacement therapy and ventilator support greatly reduced the severity of long-term respiratory morbidity and mortality. Despite that, the risk of developing BPD remains high.[42] The overall aim of the clinical research is to identify novel preventive and therapeutic strategies for BPD. It has been documented that vitamin A supplementation in extremely low birth weight infants and caffeine therapy for apnea of prematurity are effective in reducing the incidence of BPD.[39] Our findings will contribute to identifying preterm infants at high risk of BPD who could benefit the most from the prophylactic administration of vitamin A and caffeine during the early period of life. In addition, our study focused on the early postnatal period, which is clinically relevant. Previous studies suggested that the benefits of postnatal treatment strategies might be dependent on the baseline risk of BPD or death.[9,43]

There were several limitations to our study. First, this was a single-center study. Our results might be biased due to the small sample size. There was a wide confidence interval for odds ratio of apnea of prematurity, PDA and surfactant use for BPD or death in the final model, which might be in part attributed to a low incidence related to the small sample size. Second, we excluded 44 infants who were unexpectedly discharged before the time of BPD screening because of economic reasons, although demographic and clinical characteristics of infants included in the analyses were comparable with those being excluded, as shown in the results. Furthermore, the ratio of male to female in the study population was 1.9:1 (104/56). During the study period, the gender ratio of male to female in neonates admitted to our unit of neonatology was 1.5:1. We were not able to determine the effects of gender differences. These factors may lead to the potential of selection bias and limit the generalizability of our results to similar patient populations in other NICUs. The results of the study should be confirmed in a multicenter study. Third, SNAP, unlike SNAP-II and the clinical risk for babies score (CRIB), is cumbersome to use in clinical practice. SNAP-II is scored within the first 12 hours of admission, and thus limited in practical use. The CRIB score is only created to predict mortality for infants born at less than 32 weeks gestation at birth.[12]

Conclusions

In the study, high SNAP scores were significantly associated with increased risk for BPD or death in critically ill preterm infants with less than 33 gestational weeks. SNAP is predictive of BPD or death, with additional prognostic value when used in conjunction with other perinatal risk factors. The combination of SNAP score with gestational age, apnea of prematurity, PDA, and surfactant use appears to be the best predictive model for BPD or death during the early postnatal period in this population. Large studies are needed to further explore the role of the SNAP score for prediction of BPD or death in neonates.

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Adherence to oxygenation and ventilation targets in mechanically ventilated premature and sick newborns: a retrospective study

Marianne Trygg Solberg, Ida Torunn Bjørk and Thor Willy R Hansen

Abstract

Background: Ventilator treatment exposes newborns to both hyperoxemia and hyperventilation. It is not known how common hyperoxemia and hyperventilation are in neonatal intensive care units in Norway. The purpose of this study was to assess the quality of current care by studying deviations from the target range of charted oxygenation and ventilation parameters in newborns receiving mechanical ventilation.

Methods: Single centre, retrospective chart review that focused on oxygen and ventilator treatment practices.

Results: The bedside intensive care charts of 138 newborns reflected 4978 hours of ventilator time. Arterial blood gases were charted in 1170 samples. In oxygen-supplemented newborns, high arterial pressure of oxygen (PaO_2) values were observed in 87/609 (14%) samples. In extremely premature newborns only 5% of the recorded PaO_2 values were high. Low arterial pressure of CO_2 ($PaCO_2$) values were recorded in 187/1170 (16%) samples, and 64 (34%) of these were <4 kPa. Half of all low values were measured in extremely premature newborns. Tidal volumes above the target range were noted in 22% of premature and 20% of full-term newborns.

Conclusions: There was a low prevalence of high PaO_2 values in premature newborns, which increased significantly with gestational age (GA). The prevalence of low $PaCO_2$ values was highest among extremely premature newborns and decreased with increasing GA. Further studies are needed to identify whether adherence to oxygenation and ventilation targets can be improved by clearer communication and allocation of responsibilities between nurses and physicians.

Background

Clinical practice with respect to ventilator management, administration of oxygen, and assessment of oxygenation differs greatly among neonatal intensive care units (NICUs).[1,2] Ventilator treatment exposes newborns to both hyperoxemia and hyperventilation. The goal of ventilator treatment is to balance gas exchange while minimising trauma to the lung tissue.[3] Adjusting oxygenation and ventilator therapy is challenging, and improved strategies are needed to minimize hyperoxemia[4] and hyperventilation with hypocarbia[5,6] in preterm and full-term newborns. Appropriate oxygenation is achieved by titrating the fraction of inspired oxygen (FiO_2) and the mean airway pressure (MAP). The aim of appropriate ventilation is to maintain an arterial pressure of carbon dioxide ($PaCO_2$) of ~5.3 kPa (40 mm Hg).[7]

Nurses need a target range for oxygen saturation (SpO_2) in order to titrate FiO_2 appropriately. SpO_2 in the 85-95% range excludes hyperoxia,[8] but there is no consensus for the optimal saturation target ranges in premature newborns.[9] A collaborative prospective meta-analysis of five ongoing trials in the US, Australia, United Kingdom, New Zealand and Canada (NeOProM) aimed to establish the optimal SpO_2 target ranges for extremely preterm newborns.[9-11] Interim results recommend SpO_2 levels >90% to avoid mortality.[9] Previous recommendations suggested SpO_2 levels <85%.[12,13] There is no evidence or consensus to guide the administration of oxygen in full-term newborns.[14]

The Neovent study group found that time-cycled, pressure-limited ventilation was the most common mode currently used for neonatal ventilation. The tidal volume (TV) was usually targeted to 4-7 ml/kg.[15] The same study group found that hypocarbia was relatively uncommon during neonatal ventilation, and they speculated that hypercarbia was more common because of the practice of permissive hypercarbia.[15]

Few studies relate arterial oxygen tension values to SpO_2 targets.[8] It is not known how often the problem of hyperoxemia and hyperventilation occurs in NICUs in Norway. The present retrospective study is the first part of a larger study that aims to discover areas for quality improvement regarding oxygen and ventilator treatment of preterm and sick newborns. The purpose of this study was to investigate the documentation of oxygenation and ventilation among newborns receiving mechanical ventilation in a Norwegian NICU, to report on the following: (1) use of oxygen during ventilator treatment; (2) extent of charted deviations from oxygenation and ventilation targets; and (3) data associated with variations in MAP.

Methods

Patients and study design

The setting of this study was a level 4 NICU at Rikshospitalet, Oslo University Hospital, Norway. We retrospectively studied

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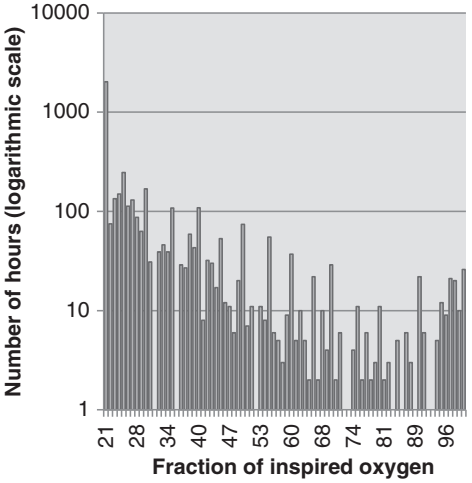

Figure 1. Distribution of FiO2. n = 4428 hours (138 patients).

the documentation of oxygen and ventilator treatment practices between July 2010 and November 2011using intensive care charts. Patients who satisfied the inclusion criteria were identified through the NICU proprietary quality control database. Infants were eligible for inclusion if they had been mechanically ventilated for a minimum of 3 hours, and we chose to limit data collection to a maximum of 48 hours for each patient. The sample was grouped by gestational age (GA) into extremely premature (23-28 weeks GA), moderately premature (29-37 weeks GA), full-term (38-41 weeks GA), and newborns >41 weeks post-conceptual age (defined as GA plus chronological age).[10] The principal diagnoses were categorized using ICD 10 (KITH-Health Affairs) and were: immature lungs, other lung/ respiratory problems, circulatory problems, and infection.

Relevant variables for oxygenation and ventilator treatment were defined according to the literature, clinical practice, and discussion with experts in the field. Variables collected and reported in this study were GA, sex, birthweight, diagnoses (infection, lung problems, immature lungs and circulatory problems), peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), inspiratory time (TI), FiO_2, TV, MAP, highest preductal SpO_2 value, arterial pressure of oxygen (PaO_2), and $PaCO_2$. Data were collected on expiratory TV measured from the ventilator, because this measures the effectiveness of mechanical ventilation.[16] Blood gas analysis was carried out on arterial samples only, because capillary blood gases were deemed to have insufficient reliability for our purposes. This reliability problem relates to newborn infants crying as a reaction to vasopuncture, which frequently presents as rapid changes in PaO_2 and $PaCO_2$.[17] Capillary blood gases were therefore analyzed solely for comparison with arterial gases.

The limit of acceptable $PaCO_2$ was set at 4.7-5.9 kPa.[18] Normal limits for PaO_2 were 6-10 kPa for premature newborns [19]and 8-10.7 kPa for full-term infants.[18] Appropriate limits for SpO_2 for newborns receiving supplemental oxygen were set at 88-93% in premature infants and not above 95% in full-term newborns, according to existing practice guidelines in our unit. The normal limits of TV were considered to be 4-6 ml/kg for premature and 5-8 ml/kg for full-term newborns.[20]

Statistical analyses

Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, US). A research assistant checked data for accuracy. A power analysis resulted in the inclusion of charts from 138 premature and full-term newborns. This was based on the assumption that the proportion of newborns with SpO_2 outside the recommended limit, was approximately 10%, estimated with an accuracy of ±5% and calculated with a 95% confidence interval (CI).

Descriptive statistics and frequencies were calculated for GA, weight, number of newborns with measurements of arterial blood gases, 1-hour periods with and without arterial and capillary blood gas measurements (based on 24 1-hour periods per day), PaO_2, $PaCO_2$, and TV. The recorded values for TV were summarized with respect to the two limits that were applicable to premature and full-term newborns in the NICU. Preductal SpO_2 values were analyzed for the trend in mean values over time. The cutoff point for defining hypocarbia was $PaCO_2$ <4.7 kPa, and extreme hypocarbia was defined as $PaCO_2$ <4.0 kPa. When analyzing the distribution of arterial blood gases, and comparing the prevalence of high versus low PaO_2 and $PaCO_2$ between the GA groups, we controlled for possible interdependence due to repeated measurements in each individual by using a generalized linear model and Wald's analysis.[21] We used partial correlation to analyze the correlation between $PaCO_2$ and TV.[22] A mixed linear model with repeated measures was used to analyze variations in MAP. Any p value < 0.05 was considered significant.

Ethical approval

Approval by the Regional Committee for Medical Research Ethics in Norway was not required for this study because data collection was anonymous. Permission for the study was obtained from the Data Protection Officer at Oslo University Hospital and from the director of the NICU.

Results

Sample description

The documentation included 4978 hours of ventilator time for 138 newborns. Ventilator support consisted of 4702 hours of conventional mechanical ventilation and 276 hours of oscillation. The minimum duration of ventilator treatment was 5 hours and our predetermined maximum period of study was 48 hours. There were 85 male (62%) and 53 female (38%) infants. GA ranged from 23 to 52 weeks and weight at the time of study entry was 426-5345 g. There were 42 (30%) extremely premature, 42 (30%) moderately premature, 34 (25%) full-term and 20 (15%) newborns aged >41 weeks. The leading diagnoses were lung immaturity [57 (41%)], other lung problems [43 (31%)], circulatory problems (including congenital heart disease) [32 (23%)] and infection [6 (5%)].

Use of oxygen during ventilator treatment

Figure 1 summarizes the distribution of oxygen concentrations received by the newborns. In total, newborns received 2020 hours of ventilator support with FiO_2=21%. Oxygen was given at a median FiO_2 of 24% in premature newborns and a median of 21% in full-term newborns. The mean values were respectively 30% (CI 95%=29.4-30.6) and 32% (CI 95%=31.1-32.9).

Charting of deviations from oxygenation and ventilation targets

Blood samples were taken for arterial blood gas analysis from once an hour, to every 3 to 4 h. Table 1 shows the number of newborns with measurements of arterial blood gases.

Table 1 Number of newborns with measurements of arterial blood gases

	GA 23 - 28	GA 29 - 37	GA 38 - 41	GA > 41	Total count
Total number of newborns with recorded arterial blood gases	41	35	29	16	121
Total number of newborns with recorded arterial blood gases who received FiO_2 >21%	33	27	19	14	93
Number of newborns with at least one low PaO_2 (Prem. < 6, full term < 8 kPa)	23	15	15	9	62
Number of newborns with at least one high PaO_2 (Prem. > 10, full term >10.7 kPa)	8	9	7	9	33
Number of newborns with at least one $PaCO_2$ < 4.7 kPa	26	18	18	8	70
Number of newborns with at least one $PaCO_2$ < 4 kPa	15	10	7	3	35

Prem. = premature.

Monitoring and assessment of oxygenation

Table 2 shows the arterial blood gas measurements in 1-hour periods obtained during ventilator treatment.

Capillary blood gas measurements were obtained in 47 patients. There were 226/4978 (5%) 1-hour periods with recorded capillary blood gases: with 39 (17%) in extremely premature, 94 (42%) in moderately premature, 56 (25%) in full-term, and 37 (16%) in newborns >41 weeks old. Analysis comparing the frequency of capillary and arterial blood gas sampling showed that arterial blood gas sampling was most common. Wald's analysis indicated significant differences between the GA groups in the frequency of using arterial blood gases (p=0.02). Further analysis showed that samples for arterial blood gas analysis were withdrawn significantly more often from the extremely premature versus moderately premature infants (p=0.004).

Table 3 shows the distribution of low, normal and high PaO_2 values according to GA in newborns who received oxygen supplementation.

Although extremely premature infants had relatively few high PaO_2 values, the percentage of high-value samples increased with GA. There was a significant difference between GA groups with regard to the risk of low versus normal PaO_2 values (p<0.001) and normal versus high values (p<0.001). Further calculations showed that the odds ratio (OR) of normal PaO_2 (compared to high PaO_2) in newborns of GA 23-28 weeks was 16 (95% CI=6.5-40) times greater than that in newborns of GA >41 weeks.

The mean SpO_2 trends over time are shown in Figure 2.

Monitoring and assessment of ventilation

Low PaCO2 values were recorded in 187/1170 (16%) samples (70 patients). When the cutoff for low PaCO2 was set at 4-4.7 kPa, there were 42 (34%) low PaCO2 values in extremely premature, 30 (24%) in moderately premature, and 35 (28%) in full-term newborns, and 16 (13%) in newborns aged >41 weeks. The analysis showed no significant difference in the occurrence of low PaCO2 between GA groups (p=0.639). However, when the cutoff value was reduced to <4 kPa (n=64), there was a significant difference (p=0.015) between the groups. The OR of PaCO2 <4 kPa in newborns of GA 23-28 weeks was 5 (95% CI=1.6-15) times greater than that in newborns of GA >41 weeks.

For premature infants of GA 23-37 weeks, there were 2374 recorded TV measurements in 1-hour periods, with a median TV of 4.7 ml/kg. Less than half of the measurements (n=1058) were within the normal reference range of 4-6 ml/kg, and 520 (22%) were >6 ml/kg. There was no significant correlation between PaCO2 and TV (r=0.007, p=0.87). Full-term newborns had a total of 1535 TV measurements in 1-hour periods, with a median TV of 6.1 ml/kg. More than half of all measurements (n=883) were in the normal range, while 301 (20%) were >8 ml/kg. There was a significant weak negative correlation between PaCO2 and TV (r=–0.12, p=0.03).

Data associated with variations in MAP

A linear mixed-effects model was used to estimate variations in MAP using the independent variables PEEP, TI and PIP (Table 4).

Table 4 shows that there was a significant correlation between MAP variability, TI and PIP, which decreased with the passage of time. There was no significant correlation between MAP variability and PEEP. This suggests that changing PEEP was not used as a strategy to adjust MAP and thereby affect oxygenation. The two groups of premature infants received PEEP with a mean pressure of 4.7 cm H_2O (CI 95%=4.67-4.73), and full-term newborns received PEEP with a mean pressure of 4.9 cm H_2O (CI 95%=4.85-4.95).

Discussion

The purpose of oxygen administration in the NICU is to prevent free radical damage.[23] In the present study, the median FiO_2 in premature newborns was lower (24%) than in the study by van Kaam et al., who found a median FiO_2 value of 28% during conventional mechanical ventilation.[24] Furthermore, we found that newborns achieved acceptable mean SpO_2 during the observation period (Figure 2). Targeting saturation to 88-93% in premature newborns and not more than 95% in full-term newborns has been a goal for several years.[25,26] However, these

Table 2 Arterial blood gas measurements in 1-hour periods

Hours of observation	GA 23 – 28	GA 29 – 37	GA 38 – 41	GA > 41	Total hours observation
	n (%)	n (%)	n (%)	n (%)	n (%)
Total hours of observation	1624 (100)	1480 (100)	1112 (100)	762 (100)	4978 (100)
1-hour blocks with listed arterial blood gases	442 (27)	297 (20)	262 (24)	169 (22)	1170 (24)
1-hour blocks without listed arterial blood gases	182 (73)	183 (80)	850 (76)	593 (78)	3808 (76)

Obtained in 121 patients.

Table 3 PaO_2 values in 1-hour periods when FiO_2 was >21%

	GA 23 – 28	GA 29 – 37	GA 38 – 41	GA > 41	Total count
	n (%)	n (%)	n (%)	n (%)	N (%)
No. of low PaO_2 values (Prem. < 6, full term < 8 kPa)	57 (24)	50 (31)	71 (60)	30 (33)	208 (34)[a]
No. of normal PaO_2 values (Prem. 6–10, full term 8–10.7 kPa)	170 (71)	91 (57)	24 (20)	29 (32)	314 (52)
No. of high PaO_2 values (Prem. > 10, full term >10.7 kPa)	12 (5)	19 (12)	24 (20)	32 (35)	87 (14)[b]
Total count	239 (100)	160 (100)	119 (100)	91 (100)	609 (100)

Obtained in 93 patients.
[a]Data from newborns with circulatory problems were included in the count of low PaO_2 values.
[b]Of the high PaO_2 values, 28 (32%) were >14.6 kPa.

targets have not yet been fully agreed upon, because the results of ongoing randomized trials testing high versus low SpO_2 targets are still pending.[9,10,27] Our calculation of mean SpO_2 may have masked episodes of hypoxemia or hyperoxia when nurses titrated FiO_2. Nevertheless, it suggests that the goal for saturation targets was met to a large extent. Using SpO_2 alone to guide decisions concerning oxygen administration is not evidence-based practice. Thus, nurses also have to assess skin color, heart rate, and values from blood gases as well transcutaneous O_2 measurements.[28]

Although it has been suggested that entrenched clinical practices and cultures make it difficult to change the use of oxygen,[29] our results showed that extremely premature newborns did not receive excessive amounts of oxygen (Tables 1 and 3). The incidence of hyperoxemia increased with GA. Because of the haemoglobin oxygen dissociation curve,[12] sick newborns with pulmonary hypertension are at higher risk of developing high levels of hyperoxemia when they are treated with an oxygen saturation of ~95%. It is common practice in NICUs that nurses wait until an infant is stable before withdrawing arterial blood for gas analysis, and this practice will affect the results. In addition nurses' workload is an important factor in the achievement of SpO_2 goals and appropriate oxygen management in the NICU. There is evidence that compliance with saturation targets is improved with higher nurse/patient ratios.[30] The good results for oxygen management in the NICU in the present study may in part have been due to the practice of having a 1:1 nurse/patient ratio for all infants on mechanical ventilation.

Our study revealed that low $PaCO_2$ values occurred most commonly in extremely premature infants. Hypocarbia may cause cerebral vasoconstriction, resulting in decreased oxygen delivery to the brain.[7,10] Moreover, in extremely preterm infants, $PaCO_2$ in the normal range seems to yield the best electroencephalography activity.[31] $PaCO_2$ can be regulated by controlling the minute ventilation with TV, or the ventilator rate.[3] It is therefore noteworthy that we found high TVs in 22% of preterm infants and 23% of newborns aged >37 weeks. Nevertheless, the median TV of 4.7 ml was lower than the 5.3 ml recorded in the study of van Kaam et al.[24] Mechanical ventilation using high TVs is known to cause lung damage.[32] We did not find any significant correlation between $PaCO_2$ and TV in the premature infants, and only a weak negative correlation in full-term infants. This suggests that the relationship between lung physiology and what happens during respirator treatment may not be simple.

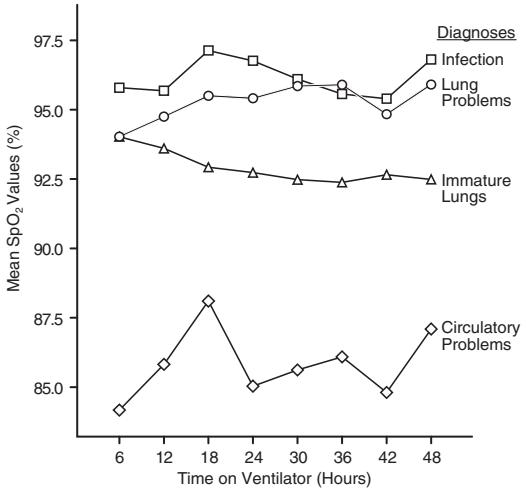

Figure 2 Mean SpO_2 trends by diagnosis.

Our results showed that variations in PEEP had no significant effect on MAP variability (Table 4). Changing PEEP is often an effective way to adjust oxygenation[33] and to regulate MAP for experienced clinicians who can accurately assess changes in measured data and calculate the impact of any adjustments.[34] The premature newborns in our study had a PEEP mean value of 4.7 cm H_2O which was similar to that observed in the study of van Kaam et al., although they suggested that PEEP values >7 cm H_2O might be protective for the lungs.[24]

It is suggested that maintaining appropriate oxygenation is hindered by insufficient communication of unit policies as well as personal bias about the best practice.[35] Control of oxygenation and ventilation is crucial during mechanical ventilation. Therefore, further studies should identify how communication and allocation of responsibilities between nurses and physicians can reduce the incidence of hypocarbia and hyperoxemia.

One limitation of this study was that we had no record of fluctuations in oxygenation levels, nor observations of how soon after blood gas analyses adjustments were made. Regarding

Table 4 Mixed-model repeated-measures analyses for variations in MAP

	Estimate	95% confidence interval		Sig (p)
		Lower	Upper	
Change over time	6.7	1.87	11.54	0.007
PEEP	- 4.43	- 11.76	2.91	0.237
Hours×PEEP	0.12	- 0.26	0.50	0.546
TI	27.77	12.01	43.52	0.001
Hours×TI	- 0.67	- 1.27	- 0.08	0.026
PIP	23.81	17.68	29.94	0.000
Hours×PIP	- 0.55	- 0.79	- 0.31	0.000

Dependent variable: MAP.

the analysis of the mean SaO_2, it would have been helpful to include an analysis that indicated the uncertainty in the results. However, because of the volume of repeated measurements for each individual, a standard box plot could not be used. Another weakness of the study was related to the high TV values, which were presented as a general occurrence regardless of how many high values there were from each individual patient.

Conclusions

We showed that, in general, premature newborns were treated within the desired limits of SpO_2, and few high PaO_2 values were noted. The occurrence of high PaO_2 values increased significantly with GA. Many recorded TVs were too high and hypocarbia during ventilation was more common in the extremely premature infants.

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Breastfeeding and pain relief in full-term neonates during immunization injections: a clinical randomized trial

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Abstract

Background: The aim of this study was to examine the effect of breastfeeding on pain relief in full-term neonates during injection of hepatitis B vaccine.

Methods: This was a randomized clinical trial. A sample of full-term neonates was randomly allocated into two groups: the experimental group and the control group. Neonates in the experimental group were breastfed two minutes before, during, and after the hepatitis B immunization and the control group were held in mothers' arms but not fed. Pain was assessed using the Douleur Aiguë du Nouveau-né (DAN) scale measuring facial expressions, limb movements and vocal expressions. The assessments were carried out after hepatitis B immunization.

Results: One hundred thirty healthy full-term neonates were studied (65 in the experimental group and 65 in the control group). Gestational age, birth weight, Apgar score and gender did not differ between the two groups. The mean total pain score as measured by the DAN scale was 3.52 (SD=1.37) for the experimental group and it was 6.78 (SD=1.69) for the controls indicating a significant lower pain score for the experimental group (P<0.001). Also, there were significant differences for the three measures of DAN scale that are facial expressions, limb movements and vocal expression, between the two study groups (P<0.001).

Conclusion: The findings confirm that breastfeeding reduces pain and is an effective way for pain relief during hepatitis B vaccine injection.

Background

Healthy neonates usually experience pain during the first week of life due to several medical procedures such as intramuscular injections and heal lancing.[6] Immunization injections are the most common source of pain in childhood.[2] Untreated pain early in life may cause harmful effects on the developing central nervous system[3] and also, it might exaggerate affective and behavioral responses during subsequent painful events.[4,5] The American Academy of Pediatrics recommended that:

'Every health-care facility caring for neonates should implement an effective pain-prevention program, which includes strategies for routinely assessing pain, minimizing the number of painful procedures performed, effectively using pharmacologic and nonpharmacologic therapies for the prevention of pain associated with routine minor procedures, and eliminating pain associated with surgery and other major procedures'.[6,7]

It was suggested that pain management could be based on a "3-P" approach involving pharmacologic, physical and psychological strategies.[8] Thus, studies of pain relief in neonates still are a topic of interest in pediatrics. As such, breastfeeding was found to be a safe and an effective method of pain relief in newborn babies.[9-13]

Several reasons were suggested to explain why breastfeeding during painful procedures might reduce pain in neonates. These could be summarized as: maternal odor,[14] antinociceptive effect[15] skin-to-skin contact,[16] the sweet tasting of milk and the act of sucking.[8]

The pain reduction methods that are used in painful procedures, including the use of oral sucrose, and pacifiers have been demonstrated.[17,18] However, these methods may interfere with a correct beginning of breastfeeding.[19] Therefore it is important to assess the analgesic effect of breastfeeding as a non-pharmacological and useful approach.

In the present study, we report the results from a randomized clinical trial that assessed the efficacy of breastfeeding for pain relief during injection of hepatitis B vaccination in term neonates.

Methods

Trial design

This was a randomized, controlled trial. The study was carried out in Mirza Kochak Khan Hospital, Tehran, Iran. The painful procedure used for this study was the hepatitis B vaccination.

Participants

A sample of breastfeeding neonates was entered into the trial. Criteria for inclusion were: full-term neonate; had Apgar score of

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Table 1 The Douleur Aigüe du Nouveau-né (DAN) scale [10,20]

Pain estimation	Score
Facial expressions	
Calm	0
Snivels and alternates gentle eye opening and closing	1
Intensity of eye squeeze, brow bulge, nasolabial furrow:	
- Mild, intermittent with return to calm*	2
- Moderate†	3
- Very pronounced, continuous‡	4
Limb movements	
Calm or gentle movements	0
Intensity of pedalling, toes spread, legs tensed and pulled up, agitation of arms, withdrawal reaction:	
- Mild, intermittent with return to calm*	1
- Moderate†	2
- Very pronounced, continuous‡	3
Vocal expression	
No complaints	0
Moans briefly (for intubated child, looks anxious or uneasy)	1
Intermittent crying (for intubated child, expression of intermittent crying)	2
Long lasting crying, continuous howl (for intubated child, expression of continuous crying)	3

* Present during <1/3 of observation periods.
† Present during 1/3 to 2/3 of observation periods.
‡ Present during >2/3 of observation periods.

7 and higher at five minutes after birth; delivered by spontaneous and vaginal delivery; were exclusively breastfed; postnatal age not more than 24 hours. We excluded infants with any evidence of congenital abnormalities, medical complications, or drug exposure.

Study setting

This study was conducted in Mirza Kochak Khan Hospital, Tehran, Iran.

Intervention

The study did not start until the infant was observed to be sucking at the breast. Neonates in the experimental group were breastfed during two minutes before, during, and after hepatitis B vaccination. At the end of the second minute of breastfeeding, while the infants were still sucking, an experienced nurse performed the immunization injections.

A dose of the vaccine (0.5 ml) was drawn into an Auto-disable (AD) syringe under the aseptic technique and then administered intramuscularly to the anterior thigh at a 90 angle to the skin with a 23-G, 1-inch needle. The Hepatitis B vaccine was manufactured by the Pasteur Institute of Iran and it preserved with Thimerosal. In order to minimize variability one experienced nurse performed immunizations. For the controls the same procedure was applied while they were held in mothers' arms but not fed. None of the infants had been breastfed for at least 30 minutes before the study procedures commenced. A trained research assistant using an electronic timer was responsible for timing of breastfeeding or holding. To standardize the procedure a pilot trial with five neonates was performed.

Table 2 Perinatal characteristics of the study samples

	Control group (n = 65)	Experimental group (n = 65)	
	Mean (SD)	Mean (SD)	P
Gestational age (weeks)	39.4 (1.2)	39.1 (1.3)	0.08
Birth weight (1000 gr.)	3.59 (0.40)	3.55 (0.38)	0.50
Apgar score	8.8 (1.2)	7.0 (1.3)	0.20
Boys/girls (numbers)	30/35	29/36	0.80

Outcome measure

The Douleur Aiguë du Nouveau-né (DAN) scale was used to assess pain. The scale was developed by Carbajal et al. in order to measure acute pain in newborn infants.[10,20] Scores on the scale range from 0 (no pain) to 10 (maximum pain) and measures three items: facial expressions, limb movements, and vocal expression (Table 1). We asked permission from Ricardo Carbajal to use the DAN in this study. Since several studies reported different timing for the assessment of pain,[9-11] we performed a pilot study and found that behavioural changes were the most important measurements for assessing pain. Also we found that the best time for assessing pain would be 45 seconds from needle injection. Scoring was performed in real time. There was an observer (outcome assessor) to complete the outcome measure.

Sample size

Based on a previous study,[21] a minimum sample size of 60 infants per group (at least) was estimated. A study with such a sample size would have a power of 90% at a 0.05 significance level. However, we recruited 65 infants for each group, giving a total sample of 130 neonates.

Randomization

Neonates were randomly assigned to the study groups. A system of sealed envelopes was used for assignment of the eligible neonates (Figure 1).

Allocation concealment

The randomization code was available only to a research fellow who was not connected to the study. The code was disclosed to the researchers when the statistical analysis was completed.

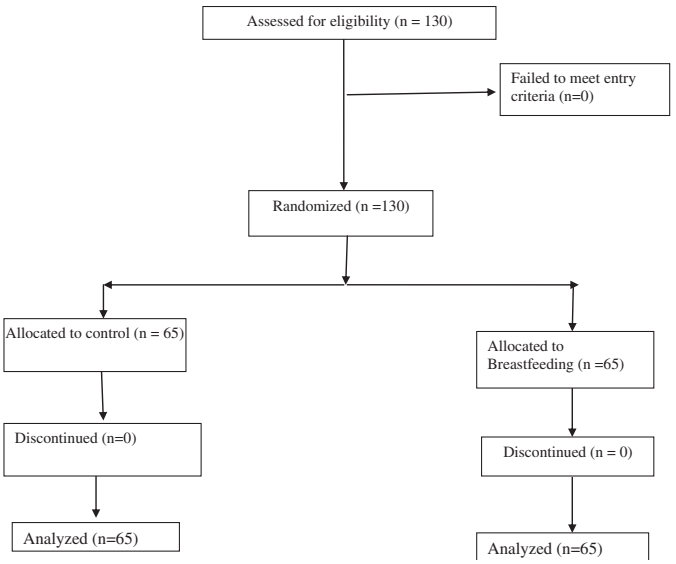

Figure 1. The trial flowchart.

Blinding

The mothers and nurses were not blind to the group assignments. However, outcome assessor (observer) did not know the purpose and hypothesis of the study and the main investigator was blind to when the statistical analysis had been completed.

Analysis

The SPSS version 16.0 was used to analyze the data. Descriptive analyses were carried out to explore the data. The chi square test used to compare categorical variables. The t test was used to compare pain scores between two groups. A significance level of alpha 0.05 or lower was adopted for all main analysis.

Ethics

Approval for the study was obtained from the Office for Protection of Research Subjects in Tehran University of Medical Sciences. We obtained written informed consent from the mother of each neonate included in the study.

Results

Neonate characteristics

In all, 130 neonates were studied (65 in the experimental group and 65 in the control group). There were no significant differences between the two groups concerning perinatal characteristics including Apgar scores (P=0. 20), gestational age (P=0. 08), neonates' weight (P=0. 08), and gender (P=0.86) (Table 2). The mean time since birth when the neonates actually received their injection was 12.0 (SD=4.03) hours.

Effect of the intervention

There was significant difference in mean of facial expressions of neonates between the control and experimental groups (2.58 (SD=0.72), 1.39 (SD=0.65) respectively). (P<0.001, Table 3).

The results also showed that there was significant difference between the two groups in mean of limb movements 1.92 (SD=0.69) and experimental groups 0.83 (SD=0.51). (P<0.001, Table 3).

The results of this study showed that there were significant differences in mean of vocal expression between control 2.28 (SD=0.57) and experimental groups 1.31 (SD=0.68). (P<0.001, Table 3). In addition as shown in Table 3 the difference of the DAN total score between two groups was significant.

Finally to have a better insight the DAN scores for each subscales that are facial expression, limb movements and vocal expressions are presented in Table 4.

Table 4 Pain evaluation with the DAN (0–10) in details (facial expression, limb movements and vocal expressions)

		Control group (n = 65)		Experimental group (n = 65)	
Facial expressions	**Scores**	**Frequency**	**%**	**Frequency**	**%**
	0	0	0	0	0
	1	3	4.6	4	6.2
	2	27	41.5	34	52.3
	3	29	44.6	25	38.5
	4	6	9.2	2	3.1
Limb movements					
	0	0	0	15	23.1
	1	18	27.7	36	70.8
	2	34	52.3	4	6.2
	3	13	20	0	0
Vocal expression					
	0	0	0	7	10.8
	1	4	6.2	32	49.2
	2	39	60	25	38.5
	3	22	33.8	1	1.5

Discussion

Fortunately, women usually do breastfed their neonates in Iran. We thought this would be a good opportunity to assess whether we could confirm previous findings on the effectiveness of breastfeeding for pain relief during a hurting medical procedure such as immunization injections. The findings from this study revealed that breastfeeding was effective for pain relief in neonates during injection of hepatitis B vaccination. This study was a step forward among similar studies for two reasons. Firstly, we assured if breastfeeding was real by observing sucking movement. Secondly, breastfeeding was begun two minutes before and continued during and after hepatitis B vaccination.

The finding from this study was very similar to the findings from other investigations.[22] For example, studies have shown that the breastfeeding effectively reduced response to pain during minor invasive procedure in term neonates[10] and significantly decreased crying in infants receiving immunization.[12]

The role of facial expressions in measuring pain has been questioned by a recent study.[23]. Therefore we reported the DAN subscales in addition to the total score to evaluate the role of each separately. However, the results showed that the three measures of DAN scale (facial expressions, limb movements, and vocal expression) were lower in the experimental group as compared to the controls.

It is argued that reactions to pain by nenonates are both physiological and psychological. Consistent with our study, a study revealed that the newborns who received breastfeeding demonstrated less physiologic and behavioral responses to pain in comparison with newborns held in their mother's arms and not breastfed.[1]. In addition studies have shown that breastfeeding, maternal holding, and skin-to-skin contact reduced crying in infants receiving an immunization injection.[11]

The vaccine we used in this study was preserved with Thimerosal. In general it is argued that infant pain would be higher when using different physicochemical properties.[24,25] However, since we used the same vaccine for all the participants, thereby the possibility of bias could be ruled out.

As indicated it is interesting to know that most women (90%) do breastfeed their neonates in Iran.[26] Despite such advantage, unfortunately health centers do not use breastfeeding as a non-pharmacological intervention for pain relief for immunizations or other practices.[27]

Limitations

This study had some limitations. For instance selection of a single center and un-blinded nature of the study might influence the results. In addition we did not assess intra-rater reliability. Thus one should be cautious in generalizing the findings from

Table 3 Pain evaluation with the DAN scale (0–10) according to the facial expressions, limb movements and vocal expression

	Control group (n = 65)	Experimental group (n = 65)	
	Mean (SD)	Mean (SD)	P*
Facial expressions			
	2.58 (0.72)	1.39 (0.65)	<0.001
Limb movements			
	1.92 (0.69)	0.83 (0.51)	<0.001
Vocal expression			
	2.28 (0.57)	1.31 (0.68)	<0.001
Total DAN Score			
	6.78 (1.69)	3.52 (1.37)	<0.001

* Derived from t-test.

this study. However, we were fortunate that all participants met the study criteria for the inclusion. One explanation for such compliance might be attributed to the pure chance. In addition one might question, for instance, how was it that all women in this study had Apgar score of 7 or higher? The reason for this was due to the fact that all women in this study had vaginal delivery and we did not include any women who underwent caesarean section and therefore we did not consider this as failure or refusal.

Conclusion

The findings from this study suggest that breastfeeding is effective in pain reduction in immunization procedure in neonates. It may replace practices with procedures.

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Comparison of the T-piece resuscitator with other neonatal manual ventilation devices: a qualitative review

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Aim

To review published literature regarding the use of a T-piece resuscitator (TPR) for neonatal resuscitation, with a focus on data comparing TPR with other manual ventilation devices (self-inflating bag [SIB] and flow-inflating bag [FIB]).

Details

The proportion of infants requiring resuscitation at birth is approximately 5-10%. Three devices are currently recommended by neonatal resuscitation guidelines: SIB, FIB and TPR. TPR provides pressure-controlled, flow-delivered positive pressure ventilation, and modification of positive end-expiratory pressure (PEEP) is possible by rotating the PEEP valve. A number of different TPR devices are available, but data suggests that the most popular of these is Neopuff™ (Fisher & Paykel Healthcare); other options are Tom Thumb (Viamed) and Neotee (Mercury Medical).

A literature search was conducted using Medline (1966-2011), EMBASE (1986-2011) and the Cochrane Clinical Trial Register and fifty studies were identified. Thirty studies were included in the review, two studies were conducted in infants, 14 were simulated, one was an observational study and the 13 remaining used TPR without comparison. A number of primary and secondary endpoints were defined *a priori* including: mortality before discharge home, need for endotracheal intubation in the delivery room, incidence of bronchopulmonary dysplasia (primary determinants of efficacy), provision of predetermined positive inspiratory pressure (PIP), ability to provide predetermined PEEP, ability to alter both pressures during resuscitation, inspiratory time provided, ability to provide a prolonged inflation breath, ability to provide consistent targeted tidal volumes, mask leak and the effect of training on device use (secondary determinants of efficacy).

***Primary determinants of efficacy*:** Data from two studies were available. The first did not report any significant difference between TPR and SIB with respect to mortality, need for endotracheal intubation, need for respiratory support at 28 days and oxygen saturation at 5 minutes. The second study reported a 26% reduction in the incidence of chronic lung disease over a 3-year period following the introduction of Neopuff™ for delivery room management of infants with a birthweight of <1500g. However, the contribution of TPR to this decrease cannot be definitively determined because of the presence of too many confounding variables.

***Provision of predetermined PIP (15 studies)*:** Comparative collated data reported from 11 studies suggested that Neopuff™ provided less variation in pressures than both SIB and FIB. In another comparative trial the percentage of pressures within the target range was substantially higher for Tom Thumb (89%) versus SIB (5%) and FIB (17%). At a target PIP of 20 cmH_2O, percentage of breaths with a PIP <21 cmH_2O and percentage of breaths with PIP >30 cmH_2O were all significantly lower with Neopuff™ compared with SIB and FIB. PIP was shown to be flow dependent in a number of studies, while use of a commercially available gas flow restrictor (Flowtec Model HBD2) allowed the Neopuff™ to provide appropriate levels of PIP and PEEP without inadvertently delivering excessive pressures.

***Provision of predetermined PEEP (12 studies)*:** The comparison between Neopuff™ and both SIB (with and without a PEEP valve) and/or FIB in the 7 manikin studies was favorable. In the one study conducted in infants, PEEP was closer to the target with Neopuff™ than with SIB without a PEEP valve. PEEP was shown to increase as gas flow increased, although use of the PEEP valve could reduce the change in PEEP for the same increase in gas flow. In one study, the results suggested that the PEEP valve may be inadvertently turned during resuscitation. When the PEEP valve is fully occluded and the mask loosely at the infant's fact, Neopuff™ can provide nearly 100% free flow oxygen.

***Ability to alter pressures during resuscitation (two studies)*:** The time taken to change pressure from 20 to 40 cmH_2O during resuscitation was longer with Neopuff™ compared with SIB and FIB (5.7 sec vs. 2.2 and 1.8 sec, respectively). In a manikin study, Neopuff™ users did not respond to change in compliance during resuscitation whereas those using SIB increased PIP in response to reduced compliance.

***Inspiratory time (three studies)*:** Inspiratory time during Neopuff™ use has been reported to be decreased when the operator is distracted, to be significantly affected by operator experience, and to be slightly longer than that with SIB and FIB when the target was 60 inflations per minute.

***Prolonged inflation breaths (three studies)*:** The Neopuff™ provided more consistent prolonged inflation than SIB (in all

three studies reporting this endpoint), and than FIB in two of the three studies. There was no difference reported between Neopuff™ and FIB in one study.

***Tidal volumes (eight studies)*:** The results of all eight comparative manikin studies reported that tidal volumes were lower and more stable during use of Neopuff™ versus SIB. In one infant study, TPR tended to provide a lower tidal volume than SIB in preterm infants born at <29 weeks' gestation. Delivery of tidal volume with Neopuff™ did not vary according to operator experience, but SIB inexperienced operators tended to provide a greater tidal volume than those who had more resuscitation experience.

***Mask leak (six studies)*:** Five studies comparing mask leak with TPR versus SIB reported lower mask leak during use of SIB; there was no difference between devices in one manikin study. During use of Neopuff™, mask leak was greater with one operator than with two, availability of a manometer decreased mask leak, training in mask handling reduced mask leak, and mask leak increased at higher gas flow rates. One manikin study reported no difference in mouth leak between Neopuff™, SIB and FIB.

***Training (six studies)*:** Data from three studies reported that operator experience had no effect on the PIP or tidal volume provided during Neopuff™ use. Operators who had used Neopuff™ infrequently had difficulty setting up the device, but could provide ventilation with an SIB without assistance. The level of operator experience had no effect on mean airway pressures or tidal volumes during Neopuff™ use, but inexperienced operators provided a longer inspiratory time while mean airway pressures and tidal volumes remained constant.

***Ongoing clinical trials (five studies)*:** Use of Neopuff™ in the delivery room is being investigated in three ongoing randomized controlled trials. Main outcome measures include the incidence of transient tachypnea of the newborn, need for mechanical ventilation and surfactant in very low birthweight infants, and establishment of functional residual capacity. Comparative studies are investigating Neopuff™ versus SIB, with and without a PEEP valve, in infants born at >26 weeks' gestation, and Neopuff™ then continuous positive airway pressure versus intermittent positive pressure ventilation in infants born at 27-33 weeks' gestation.

Conclusion

Overall, there was insufficient data to allow accurate determination of the optimal manual resuscitation device for use in infants at birth. In general, though, TPR is good at providing PIPs close to the target with little variation and PEEP closer to predetermined targets compared with SIB and FIB. In addition, volutrauma appears to be less likely with TPR and inspiratory times are more consistent. However, it is more difficult for users to detect changes in compliance when using TPR for resuscitation, mask leak is higher for TPR versus SIB or FIB, and changes to gas flow during TPR have marked effects on PIP, PEEP and mask leak. In addition, the TPR is more difficult to set up and requires a higher level of operator training. The results of ongoing randomized clinical trials will help to determine whether TPR improves resuscitation outcomes and reduces morbidity compared with SIB, and whether TPR-associated sustained lung inflation is superior to SIB ventilation. Until these data become available it is recommended that health-care providers are well trained to use the device of choice for their clinical practice, and have a good knowledge of its limitations.

Key points

- Neonatal resuscitation guidelines recommend three different devices: SIB, FIB and TPR.
- A number of different TPR devices are available, but the most popular of these is Neopuff™ (Fisher & Paykel Healthcare).
- TPR provides PIPs close to the target with little variation and PEEP closer to predetermined targets compared with SIB and FIB.
- PEEP is likely to be closer to predetermined values when TPR is used compared with SIB and FIB.
- Volutrauma appears to be less likely with TPR versus SIB and FIB.
- Inspiratory times are more consistent during TPR than during SIB or FIB.
- Changes in compliance are more difficult to detect when TPR is being used for resuscitation compared with SIB or FIB.
- Mask leak is higher for TPR versus SIB or FIB.
- Changes to gas flow during TPR have marked effects on PIP, PEEP and mask leak.
- TPR is more difficult to set up than SIB or FIB and requires a higher level of operator training.

Definitions

- Flow-inflating bag (FIB) — A hand-held resuscitation device that fills with gas from a compressed flow source.
- Inspiratory time—The time over which the tidal volume is delivered or inspiratory pressure is maintained.
- Positive end-expiratory pressure (PEEP) — The amount of pressure above atmospheric pressure present in the airway at the end of the expiratory cycle during mechanical ventilation.
- Positive inspiratory pressure (PIP) — The highest pressure applied to the lungs during inspiration.
- Self-inflating bag (SIB) — A hand-held resuscitation device that fills spontaneously with gas after it has been squeezed.
- Tidal volume — The volume inspired or expired per breath.
- T-piece resuscitator (TPR) — A resuscitation device that provides flow-controlled and pressure limited breaths, using gas from a compressed flow source.

Volume Ventilation in the Neonatal Population

Edwin Coombs, MA RRT-NPS, ACCS, FAARC

Mechanical ventilation has improved to the point where few newborns die because of acute respiratory failure. Mortality now is predominantly from other complications of extreme prematurity, such as infection, necrotizing enterocolitis, and intracranial hemorrhage or congenital anomalies. As a result, much focus has shifted from reducing mortality to reducing the incidence of chronic lung disease. As a result of improved survival of extremely premature infants, chronic lung disease has increased in recent years. One focal point has been the improvements in neonatal respiratory support. Volume-targeted modalities of conventional ventilation allows for the effective control of delivered tidal volume for neonates.

Exceedingly high inspiratory pressures have been thought to be a chief contributing factor of lung injury. Pressure-limited, time-cycled, continuous flow ventilation has been the standard of care in neonatal ventilation for more than 30 years. One of the advantages cited for the preference for pressure-limited over volume-controlled ventilation has been the ability to directly control the inspiratory pressure. Over the past eight to ten years, a wealth of accumulating evidence shows that volume, rather than pressure, is the critical determinant of ventilator induced lung injury.[1]

Dreyfuss and colleagues demonstrated as early as 1988 that severe acute lung injury occurred in animals ventilated with large tidal volume, regardless of whether that volume was generated by positive or negative inspiratory pressure. However, animals whose chest walls and diaphragmatic excursions were limited by external binding, but who were exposed to the same high inspiratory pressure, experienced much less lung damage. Results from this and other experiments clearly show that excessive tidal volume, not pressure per se, is chiefly responsible for lung injury.[2,3]

A second rationale for volume-targeted ventilation is the extensive body of evidence demonstrating hypocarbia is as a potential contributor of neonatal brain injury. Despite clinicians' awareness of the dangers of hypocarbia, inadvertent hyperventilation remains a common problem with pressure-limited ventilation, especially early in a patient's clinical course where lung compliance can be changing rapidly in response to clearing of lung fluid, surfactant administration, and optimization of lung volume.[4,5,6]

Volume Guarantee (VG) is a volume-targeted, time-cycled, pressure-limited form of ventilation that can be combined with any of the standard ventilator modes (assist control, synchronized intermittent mandatory ventilation, or pressure support ventilation). The operator chooses a target tidal volume and selects a pressure limit up to which the ventilator operating pressure (the working pressure) may be adjusted. The microprocessor compares the tidal volume of the previous breath, using exhaled tidal volume to minimize possible artifact due to air leak, and adjusts the working pressure up or down to try to achieve the set tidal volume. The algorithm limits the amount of pressure increase from one breath to the next to avoid overcorrection leading to excessive tidal volume.

This, and use of the exhaled tidal volume of the prior breath, means that very rapid changes in compliance or patient inspiratory effort requires several breaths to reach target tidal volume. To minimize the risk of excessively large tidal volume, the microprocessor opens the expiratory valve, terminating any additional pressure delivery if the delivered tidal volume exceeds 130% of the previous breath. By design, the Draeger algorithm is geared toward slower adjustment for low tidal volume and more rapid adjustment for excessive, potentially dangerous tidal volume.

As a result of the overwhelming evidence that excessive tidal volume, rather than high inspiratory pressure, is the primary determinant of lung injury, most clinicians now monitor the delivered tidal volume when using pressure-limited ventilation or volume-targeted ventilation. The critical importance of distributing the tidal volume evenly into an optimally aerated lung has not been as widely appreciated and requires attention at the bedside. If extensive atelectasis is allowed to persist, the normal physiologic tidal volume entering the small proportion of open alveoli inevitably leads to overexpansion of the relatively healthy portion of the lung, with subsequent volutrauma and/or biotrauma. The collapsed portion of the lung is also damaged known as atelectotrauma.[7]

The benefits of volume-targeted ventilation cannot be realized without ensuring that the tidal volume is distributed evenly

Continued on page 51…

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Long-term health-care costs of infants who survived neonatal necrotizing enterocolitis: a retrospective longitudinal study among infants enrolled in Texas Medicaid

Vaidyanathan Ganapathy, Joel W Hay, Jae H Kim, Martin L Lee and David J Rechtman

Abstract

Background: Infants who survive advanced necrotizing enterocolitis (NEC) at the time of birth are at increased risk of having poor long-term physiological and neurodevelopmental growth. The economic implications of the long-term morbidity in these children have not been studied to date. This paper compares the long-term health-care costs beyond the initial hospitalization period incurred by medical and surgical NEC survivors with that of matched controls without a diagnosis of NEC during birth hospitalization.

Methods: The longitudinal health-care utilization claim files of infants born between January 2002 and December 2003 and enrolled in the Texas Medicaid fee-for-service program were used for this research. Propensity scoring was used to match infants diagnosed with NEC during birth hospitalization to infants without a diagnosis of NEC on the basis of gender, race, prematurity, extremely low birth weight status and presence of any major birth defects. The Medicaid paid all-inclusive health-care costs for the period from 6 months to 3 years of age among children in the medical NEC, surgical NEC and matched control groups were evaluated descriptively, and in a generalized linear regression framework in order to model the impact of NEC over time and by birth weight.

Results: Two hundred fifty NEC survivors (73 with surgical NEC) and 2,909 matched controls were available for follow-up. Medical NEC infants incurred significantly higher health-care costs than matched controls between 6-12 months of age (mean incremental cost = US$ 5,112 per infant). No significant difference in health-care costs between medical NEC infants and matched controls was seen after 12 months. Surgical NEC survivors incurred health-care costs that were consistently higher than that of matched controls through 36 months of age. The mean incremental health-care costs of surgical NEC infants compared to matched controls between 6-12, 12-24 and 24-36 months of age were US$ 18,274, 14,067 ($p<0.01$) and 8,501 ($p=0.06$) per infant per six month period, respectively. These incremental costs were found to vary between sub-groups of infants born with birth weight <1,000g versus ≥1,000g ($p<0.05$).

Conclusions: The all-inclusive health-care costs of surgical NEC survivors continued to be substantially higher than that of matched controls through the early childhood development period. These results can have important treatment and policy implications. Further research in this topic is needed.

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Background

Neonatal necrotizing enterocolitis (NEC) is a gastrointestinal inflammatory condition in neonates that has a detrimental effect on the survival and long-term development of affected infants. The disease is most commonly seen in premature infants, although up to 25% of NEC cases have been observed among full-term babies.[1,2] The overall incidence of necrotizing enterocolitis in the United States among infants born with birth weights <1500 grams is estimated to be 7-12%.[1,3-7] The etiology of NEC is understood to be multi-factorial; ischemic injury and aberrant microbial colonization, among other factors, have been found to play a very important role in the disease process.[1]

Initial management of NEC is often highly complicated and resource intensive. About 44-70% of neonates diagnosed with NEC show signs of advanced disease (commonly categorized as Bell's stage III) that requires surgical management.[3,8,9] The economic burden of NEC has been estimated to be approximately 500 million to 1 billion US dollars annually.[1,10] These estimates are probably conservative given the strong evidence to support the many adverse consequences of surgical NEC beyond the initial hospitalization period. In particular, the outcomes of bowel resection among survivors of the procedure has been well studied and has been found to be associated

Table 1 Procedures and ICD-9-CM codes used to define infants with surgical NEC

Surgical procedures	ICD-9-CM Codes
Intestinal resection procedures	45.02-3, 45.1, 45.29, 45.3-4, 45.41, 45.49, 45.50-2, 45.60-3, 45.70-9, 45.8, 46.99
Procedures related to stoma creation	46.0 – 46.64
Intestinal anastomosis	45.9 – 94, 46.73-79, 46.93-4
Exploratory laparotomy	45.0, 45.00, 54.11
Percutaneous abdominal drainage	54.91

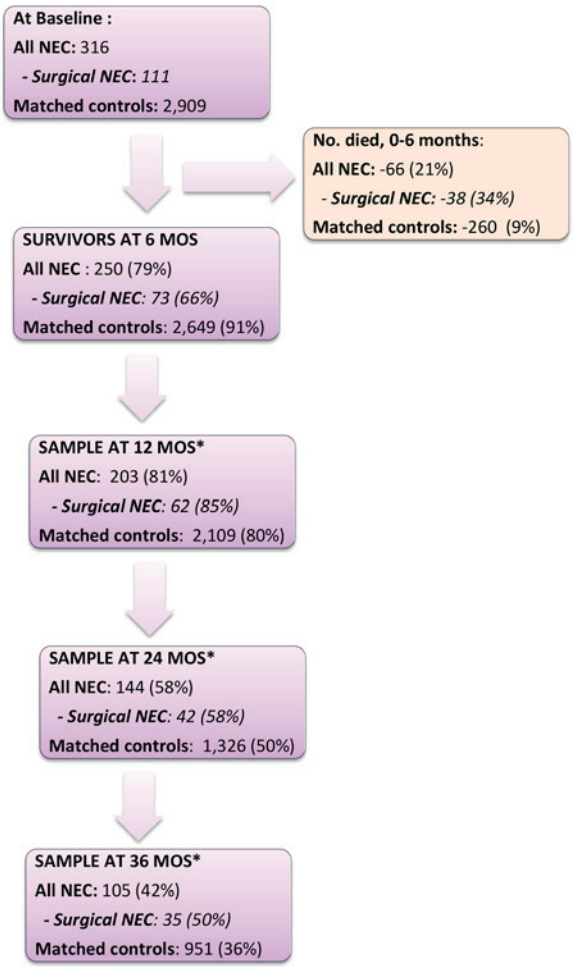

Figure 1. NEC and control group sample sizes (after matching) from 6 months to 3 years of age.

with complications such as short gut syndrome and prolonged administration of parenteral nutrition.[9,11,12] There also is growing evidence for a possible link between surgical NEC and growth and neurodevelopmental impairment, leading to poor health outcomes in the long-term.[9,13,17] The long-term economic outcomes, such as health-care or special education costs, of NEC survivors have not been well studied and there are very few published studies on this topic. There is a clear need for research on this topic to understand the full spectrum of disease burden, and also to evaluate the cost-effectiveness of novel therapeutic strategies that can mitigate the risk of developing NEC or reduce its impact on infant growth and development in the long-term.

The primary goal of this study is to compare the health-care costs between 6 and 36 months of chronological age, among survivors of medical and surgical NEC to that of matched infants without a diagnosis of NEC during birth hospitalization. This study was driven by the hypothesis that NEC survivors on average will continue to have greater demand for health-care services throughout the early developmental period due to the increased risk of long-term complications in these children as compared to similar infants without a diagnosis of NEC. Furthermore, the incremental demand for health-care services will vary depending on the type of NEC (medical or surgical).

Methods

This is a retrospective cohort study using claims database analyses. Infants enrolled in the Texas Medicaid fee-for-service program, born between January 2002 and December 2003, were selected for this study. Greater than 50% of live births in Texas were covered by Medicaid.[18] Also, unlike in other large states such as California, Illinois or New York, a significant proportion of Texas Medicaid clients were managed under traditional fee-for-service arrangements during the study period (2002 to 2006), making this data source ideal for our research.[19]

Infants with NEC diagnoses were identified using a primary or secondary ICD-9-CM code of 777.50-53 in the hospital or physician claims at the time of initial hospitalization. NEC infants who had undergone procedures such as exploratory laparotomy involving bowel resection, peritoneal drainage, enterostomy with creation of stoma, etc. were defined as having "surgical NEC" (Table 1). NEC infants without claims for any of these surgical procedures were defined as having "medical NEC". Based on the theoretical work of Rosenbaum & Rubin (1985) [20] and Imbens & Rubin [21] on the role of propensity score matching in the design of observational studies, each NEC infant was matched to infants without NEC diagnoses at a 1:10 ratio without replacement. Propensity scores were obtained from a stepwise logistic regression of NEC on infant demographic and birth characteristics at baseline including black race, gender, prematurity, born with extremely low birth weight (ELBW; defined as birth weight <1,000 g using the 5th digit of ICD-9 codes: 765.0x-765.1x), and presence of any major birth defects, which was defined as having one or more of the following conditions: congenital heart disease (CHD) including patent ductus arteriosus (PDA), neural tube defects (NTD), hereditary CNS conditions and cleft lip or palate. The matching technique was implemented using the PSMatching algorithm in SAS 9.2. [22]

The longitudinal inpatient, outpatient, physician and prescription claim files of all infants were followed from 6 months up to 3 years after birth. Follow-up beyond this period was restricted by the extremely small sample size (< 30 children) in the surgical NEC cohort. Descriptive tests for attrition were performed by comparing the sample characteristics of children retained in each group at the end of 36 months to the characteristics at baseline. The prevalence of chronic developmental health conditions in the NEC and control groups were studied over the follow-up period. The combined Mantel-Haenszel odds ratios [23] adjusted for ELBW status were reported for these conditions for the NEC and matched control groups. The hospital utilization, inpatient, ambulatory care including home health-care, and the all-inclusive (grand total) health-care costs in the NEC and matched control groups were evaluated descriptively. The total all-inclusive health-care costs represent the inflation-adjusted amounts paid by Medicaid for inpatient, ambulatory care including home health-care, prescription and professional services (all in 2009 US$).

Generalized linear regressions with a log link function and gamma distribution assumption were used to model the incremental costs for medical and surgical NEC over matched controls between 6-36 months of age.[24] Cluster robust standard errors were used to account for correlation within subject. Three different models were explored to estimate the total health-care costs per six months: 1) allowing the impact of NEC to vary over time by fitting an interaction term between NEC type (no NEC, medical NEC and surgical NEC) and age-period (6-12, 12-24 and 24-36 months of age); 2) allowing both NEC and ELBW effects to vary over time; and 3) adding an interaction term

Table 2 Comparison of baseline characteristics between the NEC and control samples before and after propensity score matching

Characteristics	NEC (n = 316)	No NEC	
		Before matching (n = 122,929)	After matching (n = 2,909)
Prematurity	212 (67%)	15,451 (13%)**	1869 (64%)
ELBW status	101 (32%)	921 (0.8%)**	759 (26%)*
Race			
African-American	36 (11%)	7,777 (6%)**	350 (12%)
White	35 (11%)	13,964 (11%)	257 (9%)
Hispanic	111 (35%)	68,361 (56%)	1,407 (48%)
Other / Unknown	134 (43%)	32,827 (27%)	895 (31%)
Male	173 (55%)	62,252 (51%)	1,480 (51%)
Birth defects			
Any major birth defects‡	153 (48%)	8874 (7%)**	1,279 (44%)
Patent ductus arteriosus	95 (30%)	2284 (2%)**	501 (17%)**
Neural tube defects	33 (10%)	1101 (1%)**	200 (7%)*

ELBW extremely low birth-weight (BW <1000g), *NEC* necrotizing enterocolitis.
**p<0.01 and *p<0.05.
‡Includes congenital heart disease (CHD), neural tube defects, hereditary degenerative CNS conditions and cleft lip or palate.

between NEC type and ELBW status in addition to specifying the time-varying slope terms for NEC and ELBW status. Race, gender and hospitalization status in the previous period (Yes/No) were included as covariates in all 3 specifications. The three model specifications were tested for over-fitting using standard goodness-of-fit criteria such as the deviance and the AIC (Akaike information criteria). The average incremental costs of medical and surgical NEC over matched controls at each age-period were estimated using the margins command in STATA 11.0 (College Station, TX) and predicted costs were estimated.[25] Statistical significance of all descriptive between-group comparisons and model-based coefficients was determined using an alpha level of 0.05.

This study was approved by the Health Sciences Review Board at University of Southern California.

Results

Three hundred and sixteen infants in the 2002-2003 fee-for-service Medicaid sample had NEC diagnoses, 111 of which had surgical NEC (Figure 1). Propensity matching at baseline resulted in 2,909 controls well-matched on all baseline characteristics except ELBW status, PDA and presence of neural tube defects (Table 2). There were 101 (32%) and 759 (26%) ELBW infants in the NEC and matched control groups, respectively (p<0.05). PDA was the most common birth defect observed among NEC infants (30%) followed by neural tube defects (10%). The proportions of infants with PDA and neural tube defects among matched controls were 17% and 7%, respectively (p<0.05). However, the two groups were comparable in the proportion of infants with any major birth defects as defined in the methods section (48% and 44% among NEC and matched controls, respectively, p=0.13).

Thirty-eight infants in the surgical NEC (34%), 28 in the medical NEC (14%) and 260 infants in the control groups (9%) died before 6 months of age (Figure 1). This left 250 NEC survivors (73 among them with surgical NEC) and 2,649 survivors among matched controls for follow-up beyond 6 months of age.

Attrition was high among survivors in both NEC and control groups, mainly due to drop-out from the Medicaid program. Comparison of the characteristics of infants who were retained in the NEC and control groups at 36 months showed that there was no significant change within and between groups for the characteristics that were matched at baseline.

Table 3 lists the proportion of survivors in the medical NEC, surgical NEC and matched control groups with diagnoses of various chronic conditions observed during 6-12 and 24-36 months of age. Adjusting for ELBW status, the risk of developing bronchopulmonary dysplasia (BPD) was significantly higher in the medical and surgical NEC groups through 36 months of age (p<0.01); the risk of malabsorption syndrome, metabolic disorders, failure to thrive (FTT) and neurodevelopmental delay (NDD) were significantly higher in the surgical NEC group than matched controls through 36 months of age (p<0.05). Also, a significant difference was observed in the proportion of children receiving care for feeding difficulties and gastrointestinal ostomies between the surgical NEC and matched control groups through 36 months (p<0.05). Medical NEC infants faced a significantly higher risk of FTT, feeding difficulties, NDD and open gastrointestinal ostomies between 6-12 months of age, but not in the subsequent periods of evaluation.

The univariate distributions of health-care utilization and costs in the NEC and matched control groups are presented in Table 4. Health-care utilization and cost estimates were highly skewed and the bulk of utilization and health-care costs were concentrated in the upper right tails in all 3 groups. Medical NEC infants on average had 3 additional hospital days than matched controls between 6-12 months of age (p<0.01) but the corresponding inpatient costs did not reach significance between the two groups (p=0.056). The total ambulatory care cost, including home health-care costs, was significantly higher in the medical NEC group compared to matched controls for the 6-12 months of age period (p<0.01). The difference in health-care utilization and costs between medical NEC and control groups after 12 months of age was not statistically significant.

Table 3 Prevalence of chronic developmental health conditions in the NEC and matched control groups between 6–12 and 24–36 months of follow-up

Age: 6–12 Months					
Chronic Conditions	**Controls (N = 2,109) n (%)**	**Medical NEC (N = 141) n (%)**	**Surgical NEC (N = 62) n (%)**	**Adjusted odds ratio‡ (95% CI) Medical NEC vs. Controls**	**Adjusted odds ratio‡ (95% CI) Surgical NEC vs. Controls**
BPD	98 (5%)	19 (14%)	16 (26%)	3 (1.8 – 5.6)**	4 (2–7)**
Malabsorption syndrome†	13 (1%)	2 (1%)	13 (21%)	2.3 (0.5 – 10)	47 (19–116)**
Failure to thrive	132 (6%)	22 (16%)	18 (29%)	3 (1.7 – 5)**	4 (2–6)**
NDD	168 (8%)	21 (15%)	16 (26%)	1.9 (1.2 – 3.2)**	2.4 (1.4 – 4.5)**
Cerebral palsy	17 (1%)	3 (2%)	2 (3%)	2.6 (0.7 – 9)	2.3 (0.5 – 10.8)
GI artificial openings present	42 (2%)	9 (6%)	15 (24%)	3.2 (1.5 – 6.9)**	9 (5–21)**
Metabolic disturbances§	58 (3%)	5 (4%)	8 (13%)	1.2 (0.5 – 3)	4.8 (2.1 – 10.7)**
Feeding difficulties	33 (2%)	8 (6%)	14 (23%)	4 (1.7 – 8.4)**	11 (5.2 – 21.8)**
Age: 24–36 Months					
Chronic Conditions	**Controls (N = 951) n (%)**	**Medical NEC (N= 70) n (%)**	**Surgical NEC (N = 35) n (%)**	**Adjusted odds ratio‡ (95% CI) Medical NEC vs. Controls**	**Adjusted odds ratio‡ (95% CI) Surgical NEC vs. Controls**
BPD	14 (1%)	4 (6%)	5 (14%)	4.6 (1.4 – 15)**	5.5 (2–16)**
Malabsorption syndrome†	4 (0.4 %)	0 (0%)	7 (20%)	-	62 (15–249)**
Failure to thrive	97 (10%)	6 (9%)	11 (31%)	0.8 (0.3 – 2)	3 (1.3 - 6)*
NDD	133 (14%)	13 (19%)	13 (37%)	1.5 (0.8 – 2.9)	2.6 (1.2 – 5.6)*
Cerebral palsy	35 (4%)	1 (1%)	4 (11%)	0.4 (0.05 – 3)	2.1 (0.7 – 6.4)
GI artificial openings present	35 (4%)	4 (6%)	10 (29%)	1.8 (0.6 – 5.3)	6 (3–14)**
Metabolic disturbances§	29 (3%)	3 (4%)	4 (11%)	1.4 (0.4 – 5)	3.4 (1.1 -10)*
Feeding difficulties	19 (2%)	3 (4%)	4 (11%)	2.4 (0.7 – 9)	4 (1.2 - 13)*

BPD Bronchopulmonary dysplasia, *ELBW* extremely low birth weight, *GI* gastrointestinal, *NDD* Neurodevelopmental delay.
**p<0.01 and *p<0.05.
‡Odds ratios were obtained after adjusting for extremely low birth weight status using Mantel-Haenszel chi-squared tests.
†Malabsorption syndrome includes post-surgical non-absorption (ICD-9 579.3 commonly used to code for short bowel syndrome) and other unspecified intestinal malabsorption (ICD-9 579.9).
§Metabolic disturbances include disorders of amino acid, carbohydrate, lipid and mineral metabolism, etc. (ICD-9 codes 270–279).

Surgical NEC survivors had significantly higher inpatient utilization and inpatient costs than matched controls during all time periods (Table 4). The difference in the mean unadjusted inpatient costs between surgical NEC and control groups was US$ 32,945, 21,160 and 6,796 per child corresponding to the difference in mean hospital days of 15, 9 and 1.5 days for the periods 6-12, 12-24 and 24-36 months of age, respectively (p<0.01). The mean unadjusted ambulatory care cost among surgical NEC survivors was US$ 6,432, 15,754 and 12,115 more than that for matched controls, between 6-12, 12-24 and 24-36 months of age, respectively (p<0.01). Home health-care costs

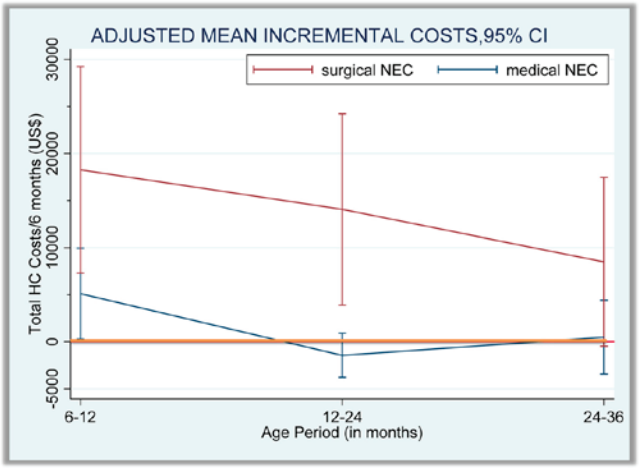

Figure 2. Adjusted incremental total healthcare costs per 6-months incurred by medical and surgical NEC survivors over matched controls from 6 months to 3 years of age.

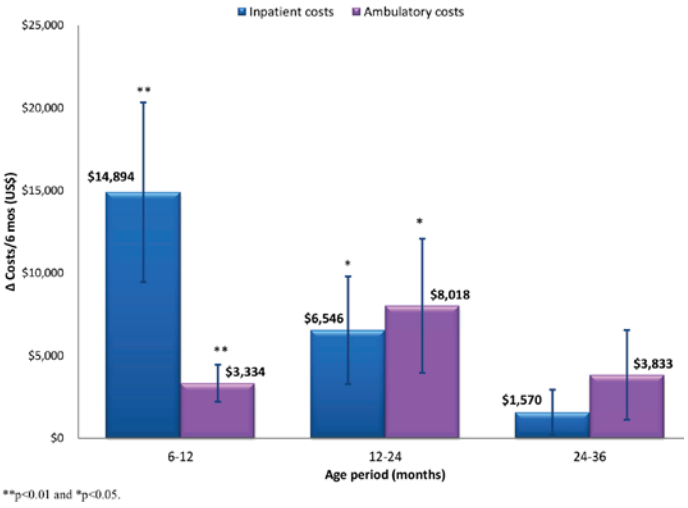

Figure 3. Adjusted incremental inpatient and ambulatory care costs per 6-months (± SE) incurred by surgical NEC children over matched controls, 6 months to 3 years of age.

Table 4 Comparison of healthcare utilization and cost estimates (unadjusted) for medical, surgical NEC and matched control groups from 6 months to 3 years of age

Age ->	6-12 months			12-24 months			24-36 months		
	Controls	Medical NEC	Surgical NEC	Controls	Medical NEC	Surgical NEC	Controls	Medical NEC	Surgical NEC
N ->	2109	141	62	1326	102	42	951	70	35
Mean Hospital admissions [a] (SD)	0.1 (0.4)	0.2 (1)**	1 (1)**	0 (1)	0 (0.5)	1 (2)**	0 (1)	0 (0.3)	1 (1)**
IQR	0	0	1	0	0	1	0	0	1
90th percentile	0	1	2	1	1	3	0	0	1
Mean Hospital days [b] (SD)	1 (9)	4 (17)**	16 (33)**	1 (4)	1 (4)	10 (33)**	0.5 (3)	0.5 (3)	2 (6)**
IQR	0	0	10	0	0	4	0	0	2
90th percentile	2	6	59	2	3	13	0	0	3
Inpatient costs (SD) [b]	2,922 (28,056)	8,068 (33,452)	35,867 (79,511)**	1,942 (12,319)	2,557 (9,823)	23,102 (71,101)**	1,046 (8,737)	1,039 (6,395)	7,842 (29,930)**
IQR	0	0	24,150	0	0	7,589	0	0	2,615
90th percentile	2,167	8,769	126,901	3,435	6,296	26,085	0	0	11,786
Total home healthcare [b] costs (SD)	741 (5,575)	2,882 (14,251)**	3,564 (9,895)**	2,539 (17,372)	3,102 (16,412)	11,364 (34,901)**	2,237 (14,806)	2,380 (13,167)	9,485 (23,184)**
IQR	0	0	1,741	0	0	3,533	0	0	4,947
90th percentile	160	1,536	7,761	184	386	36,309	199	128	31,976
Total ambulatory care costs[b,c] (SD)	2,332 (7,388)	5,129 (16,391)**	8,764 (14,920)**	5,961 (21,091)	6,392 (18,719)	21,715 (38,769)**	4,346 (19,294)	3,946 (14,009)	16,461 (34,291)**
IQR	1,247	3,414	10,572	2,154	4,144	21,573	1,372	1,874	11,320
90th percentile	5,958	10,846	20,126	14,984	17,382	61,962	5,691	4,357	61,559
Overall healthcare	5,598(30,654)	13,610 (38,264)**	45,213 (87,497)**	8,726 (28,039)	9,856 (23,111)	46,378 (91,535)**	6,279 (24,018)	5,809 (16,966)	26,055 (52,637)**
IQR	2,238	7,157	41,957	3,987	8,921	32,077	2,466	1,706	17,753
90th percentile	8,661	25,432	143,132	18,075	22,827	106,997	8,779	10,290	84,338

SD standard deviation, *IQR* interquartile range (difference between the 75th and 25th percentile estimates).
*p<0.05 and **p<0.01.
a) Outcome was assumed to be negative binomial distributed while evaluating statistical significance of difference estimates between NEC versus control groups. b) Outcome was assumed to be t-distributed while evaluating statistical significance of difference estimates between NEC versus control groups. c) Total ambulatory care costs included costs of laboratory, medical consultation, preventive care, ambulatory surgery, home health services and professional payments. Overall healthcare costs include inpatient, ambulatory as well as prescription medication costs.

accounted for 44 to 60% of the difference in ambulatory care costs observed over the follow-up period between surgical NEC and control groups. The difference in the mean unadjusted all-inclusive health-care costs between surgical NEC and control groups was US$ 39,615, 37,652 and 19,776 for the period 6-12, 12-24 and 24-36 months of age, respectively (p<0.01).

Multivariate modeling demonstrated that the incremental effect of the two NEC types and ELBW status on the all-inclusive health-care cost decreased over time (p<0.01 for the slope terms NEC type and ELBW status by age-period). The health-care cost models also predicted a decrease in the incremental effect of NEC on health-care costs in ELBW infants (p=0.09 and 0.02 for the interaction effect of medical and surgical NEC, respectively, with ELBW status). The specification that included all three interaction terms in the model (as shown below) had a superior fit over the other models tested, and, therefore, was used to obtain the adjusted incremental health-care cost estimates of each NEC type over matched controls.

The model-adjusted difference in all-inclusive health-care cost between each NEC type and matched controls is shown in Figure 2. The adjusted mean incremental cost of medical NEC survivors was $5,112 between 6-12 months of age (95% confidence interval (CI): $274-$9,950; p<0.05). The adjusted health-care cost difference between medical NEC and matched control groups was not statistically significant after 12 months of age. The adjusted mean incremental health-care cost per six months in the surgical NEC group over matched controls was US$ 18,274 (95% CI: 7,315-29,234; p<0.01), 14,067 (95% CI: 3,906-24,228; p<0.01) and 8,501 (95% CI: -475-17,448; p=0.06) for the periods 6-12, 12-24 and 24-36 months of age, respectively. Ambulatory care cost was the main driver of the health-care cost differences between surgical NEC and control groups beyond 12 months of age as shown in Figure 3. The predicted mean health-care costs of surgical NEC survivors and matched controls among sub-groups of children born with birth-weights <1,000g and ≥ 1,000g are reported in Table 5.

Discussion

Neonatal necrotizing enterocolitis has a high fatality rate among infants affected by the condition. The morbidity and long-term health outcomes among NEC survivors are highly influenced by the pathological stage of NEC and the extent of damage to the intestines.[11,26-28] Surgical intervention is an important surrogate for severity of NEC and the associated high risk of mortality and poor developmental outcomes, regardless of the surgical procedure used. [9-16,29-32] Previous studies of health-care costs associated with NEC have shown that both medically and surgically treated NEC infants incur significantly higher inpatient hospital expenditures than similar infants without NEC due to longer length of stay in neonatal intensive care units.[10,33-35] However, the health-care costs of NEC survivors over the long term have not been studied to date despite increasing evidence of poor health outcomes among these children.

In this study we compared the health-care utilization of 250 NEC survivors in the Medicaid population to that of controls matched on prematurity and ELBW status, black race and presence of birth defects, from 6 months to 3 years of age. When matching NEC infants to controls, we found that patent ductus arteriosus was more frequently observed in the NEC group. The association of PDA and NEC is well known and is thought to be due to excessive left to right shunting leading to systemic hypoperfusion, a known risk factor for NEC.[36] We found that 28 infants in the NEC group (9%) and 119 infants in

Table 5 Predicted costs per 6-months for surgicalNEC children versus matched controls over time across birth-weights

	Birth-weight <1000g			Birth-weight ≥ 1000g		
Age	**6-12**	**12-24**	**24-36**	**6-12**	**12-24**	**24-36**
Control gp.						
Predicted costs	8,540	15,559	10,347	1,526	3,795	3,356
95% CI (low)	6,210	11,830	7,287	1,086	3,026	2,156
95% CI (high)	$10,869	19,289	13,407	1,966	4,565	4,554
Surgical NEC gp.						
Predicted costs	34,020	27,013	14,476	17,311	18,764	13,367
95% CI (low)	12,597	9,329	2,945	5,603	7,158	3,143
95% CI (high)	55,443	44,696	26,006	29,020	30,371	23,590

the matched control group (4%) had undergone surgical PDA ligation or division procedures. While additional costs due to PDA surgery can be incurred during the initial hospitalization period, the cost of PDA over the long term should be no different in infants with or without NEC. In other words, a PDA-NEC association that was observed in the daWe found that medical NEC survivors incurred $5000 more in health-care costs on average than matched controls between 6 to 12 months of age. These incremental costs were mainly driven by ambulatory care expenses, possibly attributable to management of artificial GI openings and follow-up care received for other developmental problems observed during this period. These included failure to thrive, feeding difficulties, BPD and NDD. However, the health-care costs of medical NEC survivors did not differ from matched controls after 12 months of age. These results indicate that the likelihood of experiencing developmental complications leading to increased utilization of health-care resources over the long term (>1 year of age) is not significant in comparing medical NEC survivors to matched controls.

On the other hand, the all-inclusive health-care costs among surgical NEC survivors continued to be higher than matched controls beyond 6 months with the adjusted incremental costs being statistically significant up to 2 years of age. The incremental costs of surgical NEC between 2 to 3 years were still substantial and the lack of statistical significance could be due to the very small number of surgical NEC infants remaining in this time period (n=35). Our findings show that surgical NEC survivors incurred an average $60,000 more in health-care costs than matched controls over the period from 6 months to 3 years of age.

The high costs among surgical NEC survivors were initially driven by inpatient expenditures. However, the frequency of hospital admissions and level of inpatient expenditures decreased over time. Home health-care and other ambulatory care expenditures were the main drivers of costs among surgical NEC children from 1 to 3 years of age. The net difference in costs between surgical NEC children and matched controls was smaller in the extremely low birth weight group (BW <1,000g) compared to the cost difference found in children born with BW ≥1,000g. A similar trend was noted in the risk of chronic health conditions wherein the odds ratios for the association of surgical NEC with developmental health conditions were smaller for infants with BW <1,000g compared to BW ≥1,000g (though only the combined odds ratios were reported due to the very small number of NEC infants with BW <1,000g). These results are to be expected given the already higher rate of complications in extremely low birth weight status and the consequent decrease in the marginal effect of surgical NEC on health-care costs in these children. Nevertheless, the results clearly show that children born with extremely low birth weight and who survive severe NEC incurred higher health-care costs than children with only one of these risk factors.

The intensity of health-care use and costs among surgical NEC survivors could be driven by one or more factors such as: treatment for post-surgical complications (eg, short bowel syndrome (SBS) / intestinal malabsorption which was seen more often in the surgical NEC group), costs associated with nutrition (eg, length of total parenteral nutrition (TPN) support required by survivors and the complications associated with TPN), treatment of infections associated with ostomies (a significantly higher proportion of surgical NEC survivors lived with open ostomies for a significant period of time), and costs of care for very frequently reported conditions such as failure to thrive, NDD and nutritional and metabolic disturbances.

In a study among infants with short bowel syndrome, Spencer, et al. reported the average costs of SBS between year 1 to year 5 to be US$ 250,000-300,000 per year and that parenteral nutrition alone contributed to roughly $200,000 each year.[37] These costs appear to be much higher than the 90th percentile of costs among surgical NEC infants that we observed in the Medicaid cohort. The higher costs in the Spencer, et al. study are partly due to the use of billable Medicaid charges for home health-care services, whereas we used the actual Medicaid paid amounts which typically represent very low reimbursement rates for these services. Also, children with SBS represent those who have the most severe health status among surgical NEC survivors. Our surgical NEC sample had 13 out of 62 patients (21%) between 6-12 months and 7 out of 35 patients (20%) between 24-36 months receiving care for intestinal malabsorption and the average costs in this sub-group would have been much higher. Also, it could not be ascertained from the claims data how many patients had severe SBS as defined in the Spencer, et al. study (i.e. loss of ≥70% of small intestinal length, ≥2 months of parenteral nutrition dependence, etc.)

Regardless of the data source, the health-care costs reported in this paper are to be treated as highly conservative, since very expensive treatments such as small bowel transplantation were not accounted for in the analyses (because these procedures were not covered under Texas Medicaid during the study period). Transplant procedures may be required for long-term survival in a small proportion of surgical NEC survivors with failure of intestinal function.[38] Also, a significant proportion of surgical NEC infants in the Medicaid sample were found to have NDD and the odds ratios were comparable to those reported in other studies.[15-17] The extent to which NDD influences direct health-care costs is not very clear, although NDD can have a significant impact on diagnostic screening tests, physical and occupational therapy, and special education costs. More research using multiple data sources is needed to specifically understand the economic impact of neurodevelopmental delay among survivors of surgical NEC.

While the health-care costs discussed above are highly relevant from a payer perspective, it should be remembered that the long-term costs from a societal perspective would also account for the value of lives lost due to mortality attributed to NEC during

the first 6 months of life. The value of a statistical life (VSL) is estimated at $7.4 million according to the 2002 Environmental Protection Agency (EPA) estimates.[39] Medicaid covers 40% of live births in the US. If the NEC mortality rate observed in the current study were to be applied to the overall Medicaid population in the US, approximately 700-900 Medicaid infants would be expected to die because of NEC annually and the total economic value of lives lost to NEC would be 5.2-6.6 billion US$.

This paper investigates the real world utilization of a longitudinal cohort of NEC survivors. Unfortunately, attrition in the sample resulted in smaller cohorts over time. However, the extent of attrition in the NEC and control groups was comparable and the balance in the baseline characteristics between the NEC and control cohorts was maintained over time. Additionally, a set of exploratory analyses (not shown in this paper) that was conducted to evaluate the probability of attrition over time showed that demographics and health outcomes in the previous time periods (eg, health-care costs, disability status and hospitalizations) together explained less than 10% of total variation in attrition in the Medicaid cohort. This suggests that attrition in the Medicaid cohort is predominantly caused by extrinsic factors that do not impact health outcomes (eg, loss of Medicaid eligibility due to income changes, availability of employer insurance, migration to a different state, etc.)

A significant limitation of this study could be that our findings may not be generalizable to the universe of NEC survivors. This is because the study's findings were derived from a sample of children who belonged to low-income families with a higher proportion of Hispanic children and, possibly, with a higher baseline risk for poor health status than NEC survivors in the commercially insured population. Additional research using health-care utilization data obtained from a representative sample of commercially insured NEC survivors is needed in order to improve the generalizability of our findings. Nevertheless, given the fact that Medicaid is one of the largest payers of health-care for children in the US, the estimates from this population are very useful in understanding the overall economic burden of surgical NEC from a US public payer perspective. Besides generalizability, the study also suffers from some of the classical limitations of using claims data that are not collected for research purposes. Most importantly, these data do not contain specific information that may be of potential research interest, such as gestational age of infants at birth, birth order, maternal characteristics such as education, income and breastfeeding practices. Considering that data on the NEC population may be significantly hard to find in practice or simply too expensive to collect prospectively, we consider that the benefit of finding easy to collect longitudinal economic data outweighs the significant challenges of using retrospective claims data. Further research is needed on long-term costs that are not captured by medical claims, such as special education costs and caregiver productivity costs.

Conclusions

The health-care costs of children who survived surgical necrotizing enterocolitis during birth hospitalization are substantial over the early childhood development period. Understanding the economic burden of NEC in the long-term would aid health-care providers, policy makers and payers to make informed decisions in providing care for infants at high risk for NEC. Further research on this topic is needed.

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Volume Ventilation…continued from page 43
throughout the lungs. In practical terms, optimization of lung inflation, referred to as the "open lung concept," is achieved by applying adequate positive end-expiratory pressure (PEEP). It is important to understand that there is no single "safe" PEEP level.[8]

Optimal end-expiratory pressure must be tailored to the degree of lung injury. For example, infants who have no lung disease and, thus, normal lung compliance, a PEEP of 3 cm H2O is probably appropriate, and a PEEP of 5 cm H2O may result in overexpansion of the lungs, with impairment of venous return, elevated cerebral venous and systemic venous pressures, and decreased cardiac output.[8]

Conversely, severely atelectatic, poorly compliant lungs may require PEEP levels as high as 8 to 10 cm H2O or more to achieve adequate lung volume and improve the ventilation/perfusion ratio.[8]

Volume Guarantee ventilation has led to more stable tidal volumes, with a lower incidence of hypocarbia and excessively large tidal volumes. When combined with other lung-protective strategies aimed at optimizing lung volume and ensuring even distribution of tidal volume, VG appears to offer a significant impact to minimize ventilator-induced lung injury. However, the development of chronic lung disease in extremely preterm infants is multi-factorial. The degree of prematurity and presence of intrauterine inflammation have a very significant effect that may minimize the impact of a protective ventilation strategy. Thus, it will be difficult to demonstrate substantial differences in various ventilation strategies specific to long term outcomes.

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Clinical experience with the Ram cannula and other novel interfaces wth neonatal NIV

Dave Lockwood, RRT

Historically, non-invasive ventilation of the neonate has mostly been defined as nasal CPAP in some form, such as bubble CPAP where the exhalation limb is placed in a water column to create higher than atmospheric pressure during the expiratory phase or with commercially available flow generators and fluidic valve breathing circuits. It has only been within the last 8 years or so that there have been ventilators offering any form of positive inspiratory pressure to allow the use of biphasic non-invasive ventilation of infants. Depending on the brand of ventilator or flow generator one either had a pretty good bi-phasic capability but poor interface or vice versa. A good interface that could be used with almost any apparatus had not yet been developed.

At Renown Regional Medical Center, Reno, NV, where I was a clinical practitioner up until January 31 of this year, we started NICU units to use the Ram cannula (NeoTech, Valencia, CA) immediately after its debut in November 2011. Prior to the introduction of the Ram cannula, we had been using a commercial system that, while it had a pretty good interface circuit using fluidic a fluidic valve, the flow generator itself was poorly thought out. Peak inspiratory pressure was limited to 11cmH20 and only non-synchronized machine breaths were pressure supported. Any spontaneous breathes by the infant were merely CPAP supported. While I did like the fluidic breathing circuit, it could not be incorporated into a ventilator.

The Ram cannula was used with a new NIV mode on our Hamilton G5 ventilators called nCPAP-PS. (Hamilton Medical, Inc., Reno, NV) Prior to the Ram cannula we had considered other commercial nasal prong interfaces but those required that the infant stay relatively supine which our neonatal group (M.D.s, RCP's, RN's) did not care for. Using the Ram cannula allowed us to perform our usual rotation of the infant and with good leak minimization and leak compensation on the G5, we were able to progress in our desire to minimize intubation of the infant. Another of our Neonatal Respiratory Practitioners came up with the brilliant idea of taking the tracheal tube adapter from a 6.0mm adult tracheal tube and placing it on the end of a Fisher & Payakel (Fisher & Paykel, New Zealand) neonatal Optiflow cannula which turned it into a Ram cannula equivalent. For reasons that I won't go into in this article, within a year of its debut NeoTech Products pulled all reference of the use of the Ram cannula as a NIV interface off of its website. But the "cat was out of the bag". The Ram cannula was effective for NIV and so was the modified F & P Optiflow cannula. At the 2012 AARC Congress in New Orleans there were Open Forum abstracts displayed from 3 different facilities documenting and comparing the Ram and modified Optiflow for NIV use.

My use of both systems is limited to use with the Hamilton G5 ventilator. When the Ram cannula debuted the company stated in a handout that for proper use the cannula should create a 60%-80% occlusion of the nares. Somehow that fact was misconstrued and many practitioners believed that the Ram was supposed to be able to function with a 60%-80% leak! Dr Ramanathan also stated that, "And one of the other things I really don't like is a tight fit nasal cannula because how is the baby going to exhale" (Teleconference with Dr Ramanathan, Jan 12, 2012). But his statement has not been tested clinically. Our group decided to go with the concept of the largest fitting cannula that did not cause any pressure on the nares or septum. With NIV in pediatric or adult patients, you want a machine with good leak compensation but for the most effective NIV, you also want to minimize the leak as much as possible. We felt it should be the same with infants. We also used a skin barrier to protect the septum. Using this set up with either cannula we were having good success using nCPAP on the G5. When I left Renown we had successfully used nCPAP-PS on infants in the low 600gm range using the preemie size Optiflow cannula.

nCPAP-Ps on the G5 ventilator allows for pressure supported spontaneous breaths in addition to machine generated mandatory pressurized breathes. A unique feature of nCPAP-PS on the G5 is that with good leak minimization (leak ≤50%) the infant can usually sync well with the vent and no mandatory machine breaths will be delivered as long as spontaneous breaths are detected. The mandatory breaths are only generated if no spontaneous breath is detected (mouth breathing/leak or large leak around the nasal interface) or the infant is apneic. The key here is to minimize the leak. This is important for effective NIV no matter what brand of patient interface or ventilator. I have heard anecdotally from other practitioners using ventilators that superimpose the mandatory machine breaths in addition to spontaneous breaths that the infants seem to have more gastric bloating. While this could happen with the G5 nCPAP, due to the breath detection feature mentioned above it doesn't seem to happen as much.

The other discussions that NICU practitioners need to have when progressing down the path of NIV is, at what peak

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The associations of birth intervals with small-for-gestational-age, preterm, and neonatal and infant mortality: a meta-analysis

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Abstract

Background: Short and long birth intervals have previously been linked to adverse neonatal outcomes. However, much of the existing literature uses cross-sectional studies, from which deriving causal inference is complex. We examine the association between short/long birth intervals and adverse neonatal outcomes by calculating and meta-analyzing associations using original data from cohort studies conducted in low-and middle-income countries (LMIC).

Methods: We identified five cohort studies. Adjusted odds ratios (aOR) were calculated for each study, with birth interval as the exposure and small-for-gestational-age (SGA) and/or preterm birth, and neonatal and infant mortality as outcomes. The associations were controlled for potential confounders and meta-analyzed.

Results: Birth interval of shorter than 18 months had statistically significant increased odds of SGA (pooled aOR: 1.51, 95% CI: 1.31-1.75), preterm (pooled aOR: 1.58, 95% CI: 1.19-2.10) and infant mortality (pooled aOR: 1.83, 95% CI: 1.19-2.81) after controlling for potential confounding factors (reference 36-<60 months). It was also significantly associated with term-SGA, preterm-appropriate-for-gestational-age, and preterm-SGA. Birth interval over 60 months had increased risk of SGA (pooled aOR: 1.22, 95% CI: 1.07-1.39) and term-SGA (pooled aOR: 1.14, 95% CI: 1.03-1.27), but was not associated with other outcomes.

Conclusions: Birth intervals shorter than 18 months are significantly associated with SGA, preterm birth and death in the first year of life. Lack of access to family planning interventions thus contributes to the burden of adverse birth outcomes and infant mortality in LMICs. Programs and policies must assess ways to provide equitable access to reproductive health interventions to mothers before or soon after delivering a child, but also address underlying socioeconomic factors that may modify and worsen the effect of short intervals.

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Introduction

Providing access to family planning in low- and middle-income countries (LMIC) has social and economic benefits, but is also a critical public health intervention that may increase survival and improve health of mothers and newborns. Short and long birth intervals, or the time between previous and index live births, have been linked to adverse neonatal outcomes, including child mortality, low birth weight, preterm birth, and intrauterine growth restriction (IUGR).[1-3] Studies have reported J-shaped risk associations, with the highest risk occurring for children born after the shortest birth intervals, then dropping to a plateau roughly around 36 months, then a gradual increase beginning around 60 months.[1-3] Better quantifying the magnitude of these associations may provide invaluable information to estimate the possible impact of family planning interventions in reducing adverse birth outcomes, and the potential for saving newborn lives and reducing stillbirths.

Several mechanisms have been proposed linking short birth intervals with adverse pregnancy outcomes, which were recently systematically reviewed by Conde-Agudelo et al.[4] The maternal depletion syndrome (MDS) postulates that a mother may not be physiologically recovered from the previous birth if she conceives the next child shortly thereafter, leading to adverse outcomes.[5-6] Alternately, short birth intervals may simply be an indicator of non-biological mechanisms. The sibling competition theory hypothesizes that too many children shortly spaced may place resource pressures on families. Short intervals may also be a result of the mother suboptimally breastfeeding the previous child, as proper breastfeeding delays the mother regaining fecundity. Finally, a mother may have a history of preterm births, making the short interval its product rather than preterm birth a product of the short interval.

Long birth intervals, whether intended or unintended, may also have negative outcomes, and thus important to understand the associations. A woman's physiologic and anatomic capacity to accommodate fetal growth may revert to a nulliparous state if she has undergone a long period since her last birth, and that the infant subsequent to a long interval may experience the same risks as a first birth.[7]. The long interval may also be correlated with negative outcomes if it is not a result of conscious family planning; for instance, mothers may be struggling with secondary infertility.

There are limitations to the current literature on this topic. Much of the literature on this subject utilizes cross-sectional studies

Table 1 Description of studies included in the analysis

				Data from full original cohort, including those not retained in the birth interval analysis*							
Study Name	**Setting**	**Primary Study design**	**Population represented**	**N**	**Neonatal mortality rate****	**Infant mortality rate****	**% LBW**	**% preterm**	**% SGA**	**% facility delivery**	**N* (analyzed cohort for this study)**
Brazil (1982) [11]	Urban Pelotas city, Rio Grande do Sul, Southern BRAZIL	Longitudinal Birth Cohort Survey	Population based, all births in Pelotas hospitals	5,914	11	28	7	5	17	100	3,526
Brazil (1993) [12]	Urban Pelotas city, Rio Grande do Sul, Southern BRAZIL	Longitudinal Birth Cohort Survey	Population based, all births in Pelotas hospitals	5,279	7	14	9	10	19	100	3,057
Brazil (2004) [13]	Urban Pelotas city, Rio Grande do Sul, Southern BRAZIL	Longitudinal Birth Cohort Survey	Population based, all births in Pelotas hospitals	4,287	10	17	11	16	15	100	2,326
Philippines (1983) [15]	Urban Cebu, PHILLIPINES	Longitudinal Health-nutritional survey of infant feeding patterns	Population based, random cluster sample of census	3,080	14	36	11	18	25	34	2,423
Zimbabwe (1997) [14]	Urban Harare, ZIMBABWE	RCT of maternal-neonatal Vitamin A supplementation	Facility based recruitment, 14 maternity clinics and hospitals	14,110	12***	93	14	8	33	100	7,908

*Primparous babies were excluded from the analysis.

**Per 1000 live births

***Enrollment of newborns occurred up to 96 hours after birth, and the study may have missed neonatal deaths prior to enrollment.

such as Demographic and Health Surveys (DHS), especially with long recall periods.[1-3,8] Causal inference is difficult to draw from cross-sectional studies, and the quality of both exposure and outcome measures may be poor in datasets that heavily depend on maternal recall. Another major drawback to synthesizing the current evidence is the substantial heterogeneity in definitions of exposures and outcomes across studies.

Thus, the aim of this work is to address some of these limitations by examining the association between birth intervals and poor neonatal outcomes (small-for-gestational-age (SGA), preterm, neonatal and infant mortality), using original data from prospective birth cohort studies conducted in LMIC, and conducting analyses using standardized categorizations and definitions of risk exposure and outcome variables. We controlled for available socioeconomic, nutritional, and reproductive health confounders in each dataset. The ultimate objective is to generate estimates to feed into the Lives Saved Tool (LiST). LiST is a computer-based tool that estimates the impact of scaling up various health interventions, such as family planning, on maternal and child mortality.[9]. This work was conducted to make recommendations regarding the link connecting contraceptive use to adverse neonatal outcomes.

Methods

Identification and description of studies included in the analysis

For this analysis, we identified individual prospective birth cohorts from LMICs, conducted a standardized set of primary analyses to answer the study objectives, and performed meta-analyses to derive pooled effect sizes. The birth cohorts were identified from a separate activity assessing the association between SGA/preterm and neonatal and infant mortality.[10]

Briefly, we conducted a literature review in February 2009 to identify prospective birth cohorts from LMICs that had data available on gestational age, birthweight, and vital status systematically collected through at least the neonatal period (28 days). Medline, WHO regional database, and bibliographies of key articles were searched, and additionally, Child Health Epidemiology Reference Group investigators were also consulted to identify potential datasets by word-of-mouth. Investigators with birth cohorts containing the minimum required data were contacted to conduct a standard set of analyses or to contribute their data to the analyses. More details on the search strategy are available elsewhere.[10] For inclusion in the present analysis, datasets also had to include data on birth interval, and parity and maternal age information as control variables.

In total, five birth cohort datasets from three countries (Brazil, Philippines, Zimbabwe) were included,[11-15] totaling 32,670 singleton live births, of which 19,240 had relevant information. Initial year of data collection in these studies ranged from 1982 to 2004. All studies were conducted in urban locations, and four of the five studies were facility-based. One study was a randomized controlled trial, while the rest were longitudinal surveys. Gestational age was collected using different methodologies: the Brazil studies used date of last menstrual period (LMP) (1982), LMP and the Dubowitz method[16] (1993), and LMP, the Dubowitz method, and ultrasound (2004), the Philippines study used LMP and Ballard method,[17] and the Zimbabwe study used the Cappuro method.[18] In the Zimbabwe study, mother-child pairs were enrolled within 96 hours of delivery, while the other studies enrolled prior to or at birth. See Table 1 for further descriptions of the original cohorts.

Exposure/independent variable

The independent variable was birth interval (the time between the previous and index live birth). Birth interval was categorized as <18 vs. 18-<24 vs. 24-<36 vs. 36-<60 (reference) vs. ≥60

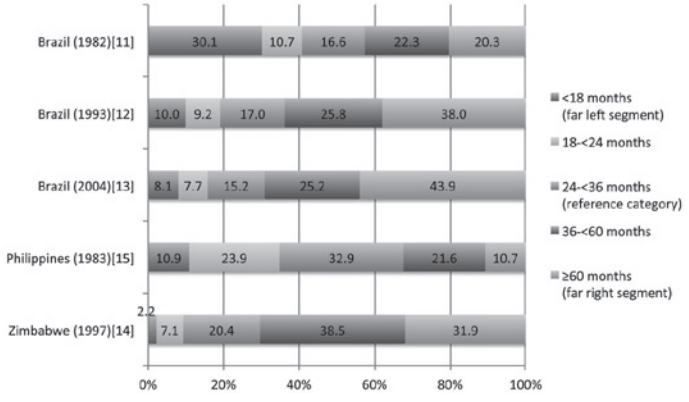

Figure 1. Percent of pregnancies within each birth interval exposure category.

Table 2 Prevalence of adverse newborn outcomes in each study, among newborns included in the analysis

Study	SGA <10%	Preterm	Term-SGA	Preterm-AGA	Preterm-SGA	Neonatal Mortality Rate*	Infant mortality Rate*
Brazil (1982) [11]	21.1	5.0	12.4	3.9	1.0	21	40
Brazil (1993) [12]	20.3	10.2	15.4	9.3	1.0	16	24
Brazil (2004) [13]	16.7	16.1	11.8	14.3	1.7	11	19
Philippines (1983) [15]	25.3	17.0	22.7	14.4	2.6	13	33
Zimbabwe (1997) [14]	32.8	7.6	29.9	4.7	2.9	9**	78

*per 1000 live births

**Enrollment of newborns occurred up to 96 hours after birth, and the study may have missed neonatal deaths prior to enrollment.

SGA = small-for-gestational-age, AGA = appropriate-for-gestational-age. Preterm = below 37 completed weeks of gestation.

months. The reference category was chosen in light of previous literature reporting a plateau in risk between roughly 36 and 60 months,[2] and also to have a long interval category with high enough prevalence to account for its possible adverse effects. Cut-offs lower than 18 months could not be used because there were too few pregnancies with such short intervals.

Outcomes/dependent variables

SGA was defined as below the 10th percentile of a gender-specific reference distribution at each completed gestational week, using births in the US in 1991.[19] We selected this reference population for comparability of our results to existing literature, as a large number of publications have used this reference population. Preterm was defined as below 37 completed weeks of gestation. We also created gestational age-SGA combination categories: term-SGA, preterm-appropriate-for-gestational-age (AGA), preterm-SGA, and term-AGA (reference). Neonatal mortality was defined as death within 28 days of life and infant mortality as death within the first 365 days of life.

Analysis

For each birth cohort, logistic regression was performed with the birth outcome as the dependent variable and birth interval, parity, age, and other potential confounders included as independent variables. In each dataset, the available socioeconomic and maternal nutrition variables were placed in the multivariate model to calculate adjusted odds ratios (aOR). The covariates are listed in Supplemental Table 1 in Additional file 1. The aORs of birth interval with adverse neonatal outcomes were pooled across studies using meta-analysis techniques. We used the random effects DerSimonian-Laird pooled ORs and 95% CIs to address heterogeneity across studies. Nulliparous women were excluded, as they had no preceding birth interval. We used Stata 12.0 (Stata Corp.) for analysis.

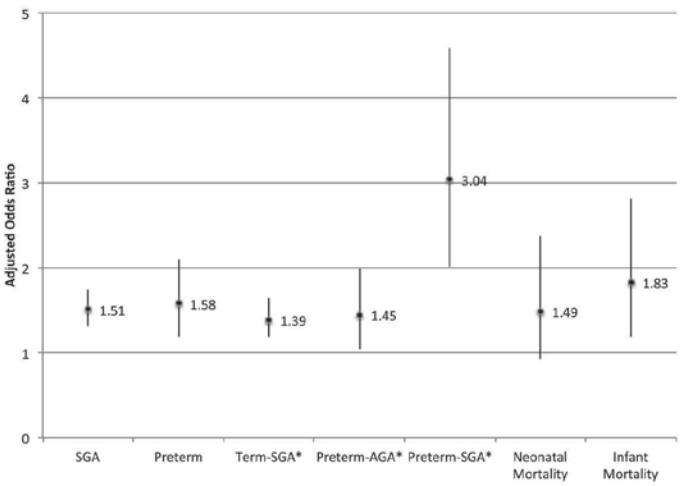

Figure 2. Associations between birth interval <18 months (reference: 36-<60 months) and adverse neonatal and infant outcomes. SGA = Small-for-gestational-age, below the 10th percentile of a gender-specific reference distribution at each completed gestational week, using births in the US in 1991. 19 AGA = Appropriate-for-gestational-age. Preterm = below 37 completed weeks of gestation. *Reference: term-AGA

Results

Distribution of exposure/outcomes: individual birth cohorts

The percentage of births in each birth interval category are shown in Figure 1. The 1982 Brazil study had the highest percentage of women in the <18 month birth interval category. The Philippines data was the most evenly distributed in terms of the percentage of women in the short versus reference versus long interval categories, and finally, the 1993 and 2004 Brazil and Zimbabwe studies had the highest percentage of mothers in the longer birth interval categories.

Table 2 shows the prevalence of the adverse neonatal outcomes for each study. The SGA prevalence ranged from 16.7-32.8% and preterm from 5.0-17.0%. NMR ranged from 9 to 21. The low NMR of 9 in Zimbabwe is most likely due to lower risk associated with facility deliveries in Harare and also enrollment into the study extending up to 96 hours after delivery; we expect the study missed some neonatal deaths by enrolling beyond time of delivery. IMR ranged from 19 to 78.

Association of birth intervals and adverse outcomes

Supplemental Tables 2a-2c in Additional file 1 present the unadjusted and adjusted associations of birth interval length and adverse outcomes from each individual birth cohort and Table 3 presents the meta-analyzed pooled associations from the five studies.

Short birth interval

Birth interval <18 months was statistically significantly associated with almost all adverse neonatal outcomes. It had a pooled aOR of 1.51 (95% CI: 1.31, 1.75) for SGA and 1.58 (95% CI: 1.19, 2.10) for preterm. Examining the SGA and preterm combination outcomes, the short interval increased the odds of term-SGA (pooled aOR: 1.39, 95% CI: 1.18, 1.64) and preterm-AGA (pooled aOR: 1.45, 95% CI: 1.05, 1.99), and had a 3-fold increase in odds of preterm-SGA (pooled aOR: 3.04, 95% CI: 2.02, 4.58). See Figure 2 and Table 3.

Birth interval <18 months did not increase the risk of neonatal mortality to a level of statistical significance (aOR: 1.49, 95% CI: 0.93-2.37), however we observed an 83% increase in odds of infant mortality (1.83, 95% CI: 1.19, 2.81). See Figure 2 and Table 3. The 18-<24 month category was significantly associated with SGA (pooled aOR: 1.23, 95% CI: 1.03, 1.48), and although it had no significant association with preterm alone, the risk of the combined outcome of preterm-SGA was significantly increased

Table 3 Meta-analyzed adjusted odds ratios of the association between short and long birth intervals and adverse neonatal and infant outcomes (36-<60 months as reference)

	<18 months aOR (95% CI)	18-<24 months aOR (95% CI)	24-<36 months aOR (95% CI)	36-<60 months	≥60 months aOR (95% CI)
SGA	1.51 (1.31, 1.75)	1.23 (1.03, 1.48)	1.05 (0.87, 1.27)	Ref	1.22 (1.07, 1.39)
Preterm	1.58 (1.19, 2.10)	1.16 (0.94, 1.42)	1.02 (0.87, 1.19)	Ref	1.05 (0.88, 1.26)
Term-SGA*	1.39 (1.18, 1.64)	1.15 (0.98, 1.35)	1.01 (0.83, 1.22)	Ref	1.14 (1.03, 1.27)
Preterm-AGA*	1.45 (1.05, 1.99)	1.09 (0.86, 1.37)	1.01 (0.85, 1.21)	Ref	1.06 (0.87, 1.29)
Preterm-SGA*	3.04 (2.02, 4.58)	1.58 (1.01, 2.49)	0.92 (0.65, 1.31)	Ref	1.19 (0.87, 1.63)
Neonatal mortality	1.49 (0.93, 2.37)	1.07 (0.52, 2.22)	0.95 (0.62, 1.47)	Ref	1.01 (0.68, 1.49)
Infant mortality	1.83 (1.19, 2.81)	1.08 (0.66, 1.78)	1.17 (0.96, 1.43)	Ref	1.01 (0.84, 1.22)

*Reference: Term-AGA

by 58% (95% CI: 1.01, 2.49). None of the associations for the 24<36 month category were statistically significant, and were all close to 1. The increased risk of adverse outcomes associated with short birth interval appears to have a dose response relationship, as the magnitudes of the association are higher in the shorter birth interval categories.

Long birth interval

Birth interval of ≥60 months was associated with a slight increase in odds of SGA (pooled aOR: 1.14, 95% CI 1.07-1.39) and term-SGA (pooled aOR: 1.14, 95% CI: 1.03, 1.27). The risks for other outcomes were small and non-significant.

Discussion

In our meta-analysis, short birth interval (<18 months) was significantly associated with SGA (aOR 1.51), preterm (aOR 1.58), and infant mortality (aOR 1.83). We observed a dose response relationship, with the magnitude of risk increasing as the birth intervals got shorter from the reference 36-<60 month category. Birth interval <18 months carried a substantially higher (three-fold) risk of delivering an infant who is both preterm and SGA compared to those who had a reference birth interval; preterm-SGA babies carry substantially higher risk of mortality than those born term-AGA.[10]

Our findings produced a similar magnitude of associations as previous literature for short intervals with SGA and preterm outcomes, although the results cannot be directly compared due to different birth interval cut-offs and definitions. Conde-Agudelo et al.'s meta-analysis found an adjusted odds ratio of 1.26 (95% CI: 1.18-1.33) for SGA and 1.40 (95% CI 1.24, 1.58) for preterm, examining an interpregnancy interval (IPI) (period between birth and conception) of <6 months, against a reference of 18 to 23 months.[1] However, the definition of SGA accepted for inclusion in the meta-analysis was not clearly defined. In Wendt et al.'s meta-analysis,[20] preterm associations had similar magnitudes also looking at an IPI of six months with a range of reference intervals, but they did not examine SGA or IUGR because of the inconsistencies in definitions across studies. Using IPI <6 month exposure and 18-<24 month reference, a study examining 173,205 children from Utah birth records (1989-1996) saw an SGA aOR of 1.3 (95% CI: 1.2-1.4) and a preterm aOR of 1.4 (95% CI: 1.3-1.5).[7] A separate study used Michigan birth records and linked births by mother to create longitudinal cohorts; that study noted statically significant aORs with low birthweight, ranging from 1.2 to 1.5 depending on birth order of the children.[21] However, the low birthweight outcome is not directly comparable to SGA or preterm.

In our meta-analysis, short birth interval was significantly associated with increased infant mortality risk, however had no significant association with neonatal mortality risk. This finding may be driven by the smaller number of neonatal deaths, compared to infant deaths; we noticed increased risk in all datasets, but confidence intervals were wide and crossed unity in the pooled association. Incomplete neonatal mortality information in the Zimbabwe dataset may also have affected the association. Another possible explanation may be the confounding effect of breastfeeding. Those who fail to breastfeed will regain their fecundity sooner than those who do, leading to shorter birth intervals. We also expect mothers to repeat negative breastfeeding patterns for the subsequent child,[22] which impacts the child's survival in the infant period. Therefore it may not be the physiological effect of short birth intervals, but breastfeeding practices correlated with short intervals that lead to adverse infant outcomes. We did not have relevant information available to explore this hypothesis. A meta-analysis using 17 DHS datasets found neonatal and infant mortality associations with birth interval <18 months stronger than what we found in our data (neonatal: aOR 2.72, 95% CI 2.3-3.2, infant: aOR 2.84, 95% CI 2.5-3.2); however the study used cross-sectional data and a reference category of 36-47 months.[2]

Long intervals do not appear to have a strong adverse association with neonatal outcomes; we only observed a statistically significant 12% increase in odds in SGA but no association with any other adverse outcomes. A meta-analysis of DHS data showed no adverse association for long birth intervals as well.[2] In contrast, Conde-Agudelo et al's meta-analysis found 36% increased odds of SGA (95% CI: 1.20, 1.54) and 27% increased odds of preterm (95% CI: 1.17, 1.39) for IPI over 60 months (birth interval of approximately 69 months), but had a different reference category.[1]

Some researchers have hypothesized that maternal depletion drives the association between short birth intervals and adverse neonatal outcomes; a mother may not have nutritionally and physiologically recovered enough before conceiving the next child. Upon controlling for available maternal nutritional variables, we witnessed no significant change in the magnitude of the associations. This may imply that nutritional depletion either plays no or a small role. A systematic review also found weak evidence to support the maternal depletion hypothesis,[4] examining 15 studies that used anthropometric outcomes, maternal anemia or iron deficiency, and micronutrient deficiency as indicators of depletion. However, a separate study noted that only short birth interval children of higher birth order had a high risk of death.[23] It may be that nutritional depletion only plays a role following a cumulative effect of having multiple children or multiple short interval children. The same study also revealed

fundamental background differences between mothers who completed their reproductive period with high fertility versus low fertility, and that low birth orders of high fertility mothers are worse off after a short interval than low birth orders of low fertility mothers after a short interval. Mothers who have low completed fertility may have background characteristics (i.e. better socioeconomic status) that allow them to tolerate nutritional and economic demands of short interval births, while high completed fertility mothers, who start worse off than low completed fertility mothers, may not have the capacity to handle those demands. Parity may be modifying the effect of birth intervals only when certain socioeconomic and/or nutritional conditions are present. The prospective cohort studies presented in our meta-analyses do not have information like mother's final fertility that may serve as a proxy for effect modifiers or residual confounders that are not captured by available variables; the findings in the aforementioned study[23] suggests that we may have failed to address either some Numerous other hypotheses on mechanisms linking birth intervals to adverse health outcomes have been identified.[4] Mechanisms with more evidence base include folate deficiency. While there is substantial evidence reporting folate deficiency following pregnancy, very few report on likelihood of folate deficiency among short birth interval mothers, and on the association between short birth interval and birth outcome among mothers who were not supplemented with folic acid. Regarding sibling competition theory, evidence implied that competition was not a major factor linking short birth intervals to neonatal mortality, but possibly for post-neonatal mortality. Other hypotheses include cervical inefficiency and vertical transmission of infections, but there is no clear evidence that supports these hypotheses.

The strength of our analysis is the use of high quality exposure, outcome, and confounder data from prospective birth cohorts. Unlike some cross-sectional survey data, the outcome information is collected soon before or around the time of birth. Also, by standardizing the categorization of birth intervals and outcomes, we were able to meta-analyze five studies with the same exposure and outcome definitions. One of the largest methodological issues with other meta-analyses is the heterogeneity of birth interval categorization, definition of SGA, use of birth-to-birth intervals versus birth-to-conception intervals (or IPI), and other exposure and/or outcome definitions.

The main weakness of this study and of almost all other studies reporting on birth interval is the inability to examine the associations taking into account the length of each component of a birth interval (birth to fecundity, fecundity to conception, and conception to birth.) Non-live birth outcomes (abortion, miscarriage, stillbirth) in between two live births may attenuate the association between short intervals and adverse outcomes by attributing more adverse outcomes to the reference or long birth interval. A study conducted in Bangladesh[24] noted differences in associations between an IPI <6 months with induced abortion, miscarriage, and stillbirth, depending on what outcome the IPI began with. The magnitude of association was highest among IPIs starting with live births for outcomes of induced abortion and miscarriage, but with stillbirths for outcome of stillbirth, although not all associations were statistically significantly different from each other. Furthermore, the first live births that we excluded from our analysis may contribute more information, as these children may have followed a pregnancy that ended in a non-live birth. The length of gestation would also affect the conception-to-birth period, and preterm outcomes could have a variety of etiologies that may not be captured through available confounding variables. We did not have complete pregnancy histories that would help us better explore these issues. Future research on birth intervals would benefit greatly from collecting appropriate data to distinguish these birth interval components and their predictors. Finally, there may have been residual confounders that were not fully captured in the available data, such as the mother's history of preterm births and breastfeeding practices, as we only controlled for available nutritional and socioeconomic variables.

The associations we see between short birth intervals and adverse outcomes emphasize the importance of family planning interventions and the timing of the interventions. As Conde-Agudelo et al. have also stated,[1] unmet need for family planning is not only a socioeconomic issue, but a public health issue for both the mother and the child. Assuming a 10% prevalence of short birth interval (<18 months) and infant mortality aOR of 1.83, lengthening the birth intervals of those individuals to ≥18 months could reduce infant mortality by 7.7%, a magnitude that is of public health significance. Furthermore, if a differential impact of short birth intervals exists by mothers' background characteristics, unmet need poses a major health equity problem. While modern contraceptive use among women of reproductive age is ~70% in North America and Western Europe, it is only ~15% in Sub-Saharan Africa, with many countries reporting single digit figures.[25] Within countries also, there are huge equity gaps; taking Burkina Faso and Mozambique as examples, they have a close to a 30 percentage point difference in modern contraceptive use between the lowest wealth quintile (6.3% in Burkina Faso,[26] 3.9% in Mozambique)[27] and the highest wealth quintile (35.5%, 34.8%). Equitable access to family planning interventions need to consciously target the most vulnerable women, as they may carry the highest health risks associated with short intervals and are also the least likely to have access to health education, contraceptives, and medical care.

Conclusion

Our results suggest that birth intervals under 18 months are associated with adverse neonatal outcomes, with as high as an 83% increase in odds of infant mortality. Policymakers have the responsibility to secure family planning access to all women, which would benefit the health and the economy of the population. Programs and policies also need to focus on vulnerable mothers, as they may have higher risks associated with short intervals and are least likely to have interventions reach them. Finally, more operations research needs to be conducted to determine the most effective ways to delay subsequent births in LMICs.

In LiST, we recommend the inclusion of the associations between short birth intervals and adverse outcomes, with the understanding that birth intervals may have differential impact on neonatal and infant outcomes, depending on the baseline condition of the mother.

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Ram cannula…continued from page 52

inspiratory pressure and or ventilator rate does it make sense to place a tracheal tube for airway protection. This discussion was occurring but was not settled when I left Renown but my observations were this; when PiP started to exceed 18-20 cmH2O and the infant needed a backup rate greater than 30 or was riding that rate, there tended to be other issues going on such as sepsis or fatigue. When PIP's exceeded 18-20 it was difficult to control oral leaks and with the infant requiring rates higher than 30 what was the calorie expenditure vs. work of breathing. Should infants be fed while on NIV? Should infants be held or "kangarooed" whileon NIV. What frequency should lab work or cxr's be with NIV? Should it be more or less than with invasive ventilation? What criteria should be used and what thresholds established to define failure/fatigue on NIV?

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