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Neonatal Transport: Are We Heading in the Right Direction?

Sergei Roumiantsev, MD, PhD; Muhammad Aslam, MD

Specialized neonatal interfacility transport program was first introduced in the late 60s as a better way to transport premature infants to the tertiary care centers (Segal 1966). This program became well established in the United States (US) in the early 70s as an extension of service provided by Neonatal Intensive Care Units (NICUs). The initial goal of this service was to deliver expertise in the treatment of critically ill infants born outside of large neonatal-perinatal centers. Benefits of regionalized perinatal care were recognized in the late 70s and neonatal interfacility transport programs have become an important aspect of neonatal health care delivery in the US.

Over the last four decades technological advances in perinatal and neonatal care such as the use of antenatal corticosteroids, improvements in mechanical ventilation, the use of exogenous surfactant, extracorporeal membrane oxygenation, and iNO have resulted in dramatic changes. Neonatal outcomes have significantly improved with an overall decrease in infant mortality along with an increase in survival of premature infants and improvement of their outcomes including the ever-moving gestational threshold of viability (Luke and Brown 2006; Eichenwald and Stark 2008).

Regionalization of the health care system in the US, as well as other developed countries, has resulted in significant changes in health care delivery systems. Between 1987 and 2008 the number of Neonatal Special Care Beds in the US almost doubled while the birth rate remained almost unchanged resulting in even further concentration of expertise in large perinatal centers (American Hospital Association 2010). Multiple studies have demonstrated increased morbidity and mortality associated with neonatal transport, especially in the cohort of very low birth weight infants (Warner, Musial et al 2004). Over the years the American Academy of Pediatrics (AAP), American College of Obstetrics and Gynecology and March of Dimes concentrated their efforts on promoting perinatal transports (in-utero transports) as a way to improve outcomes of high-risk neonates and secure their delivery in the highly expert perinatal centers. This approach has effectively reduced the number of very low birth weight infants born outside of the tertiary care centers (Binder, Hill et al 2011). Despite that, it is estimated that every year there are almost 200,000 neonatal transports in the US including retro transfers (Robert Insoft, personal communications).

Over the last decade multiple organizations, including the AAP, developed the goals and guidelines for neonatal transport. Current understanding of the goals for neonatal transport include stabilization and initiation of advanced care at a referring institution with continuation of critical care therapies and monitoring during transport to a tertiary care center. Published guidelines detail specifics of regional organization and team structure, training of personnel, quality improvement and safety, ethical and legal considerations, mode of transportation and equipment (Woodward, Insoft et al 2007). Despite the long history of neonatal transport service and body of literature explaining systematic approaches to establish and manage a neonatal transport team, there are significant differences in how the neonatal transport teams are run. Recently Karlsen et al have published a study that illustrated the problem exceptionally well (Karlsen, Trautman et al 2011). This survey-based study provided a detailed outlook on the state of neonatal interfacility transport programs in the US.

Over the years many neonatal transport teams have evolved from the unit-based teams, where the members utilize the NICU staff for transport, to the dedicated and/or free standing transport teams with staff solely responsible for transports. Some teams provide combined pediatric and neonatal transports. Composition of the transport team is also changing. Traditional use of physician-in-training (such as fellows and Continued on page 26…
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NO FREE SAMPLES
Hospitals should stop including industry-provided samples of infant formula in new mothers’ discharge bags because the distribution is unethical and violates good public health policy, according to the organization Public Citizen. It set forth its demand in letters co-signed by more than 100 other organizations, sent to the administrators of 147 California hospitals. The organization is sending letters to more than 2,600 hospitals across the country. Public Citizen also is launching an online petition calling on the three major formula makers to stop marketing their products in healthcare facilities. At least two-thirds of hospitals in the US distribute samples of infant formula. Formula feeding costs between $800 and $2,800 per year. A 2009 study by the CDC found that 34.2% of hospitals nationwide have stopped the practice, and in November 2011, Rhode Island became the first state in which all hospitals with maternity wards stopped distributing formula samples to new mothers. Public Citizen is a national, nonprofit consumer advocacy organization.

TOO EARLY/TOO LATE
A factor for severity of autism is to be born several weeks early or late, according to a report by Nurse.com. Researchers at Michigan State University also said their study revealed a variety in manifestations of autism spectrum disorder. The study also found that babies born outside of normal gestational age and very preterm babies showed an increase in stereotypical autistic mannerisms. The researchers analyzed a 2006-10 online database of 4,200 mothers with autistic children ages 4 to 21 and divided the data on births into four categories: very preterm (born before 34 weeks), preterm (34 to 37 weeks), standard (37 to 42 weeks) and post-term (born after 42 weeks).

ALERT FATIGUE
From Douglas Farrago, MD, authenticmedicine.com: “There is a new term going around in medicine. It is called “alert fatigue.” I had blogged before about nurses having alarm alert fatigue in Boston. With so many monitors on so many patients the nurses were constantly dashing to see patients for overly sensitive warnings. This led them to start missing or ignoring some of those warnings. Now physicians are having the same alert fatigue with their EMRs. The damn things are so sensitive to any drug interaction that it seems that they have pop up warnings any time you touch the damn thing. As an article in the American Medical News states, ‘The alerts are designed to inform physicians of possible patient safety issues, but their frequency and often lack of necessity make them the electronic equivalent of the boy who cried wolf.’ It looks like research is ongoing to cut these alerts down so that we doctors can actually pay attention to the ones that matter. The problem with the current system is that everyone is covering their asses and no one wants to get sued. The only way for the EMR companies to protect themselves is to warn about everything. Once again, litigation wags the dog.”

DRUG WITHDRAWAL
Nearly half of the newborn babies at the East Tennessee Children’s Hospital NICU are suffering from prescription drug withdrawal, according to a report by CNN. The hospital has been dealing with a dramatic increase in the number of newborns with neonatal abstinence syndrome, the withdrawal process a newborn goes through after in utero exposure to certain medications. Opioids like oxycodone are said to be the worst. Between 55% and 94% of babies exposed to opioids prior to birth exhibit signs of withdrawal, according to the AAP. Symptoms are agitation, constant crying, and an aversion to sound and light, as well as a high-pitched cry, tightening of the muscles, and seizures. The Tennessee health department said a third of the pregnant women in state treatment programs are addicted to prescription pain meds, and that the number of babies born with NAS at the hospital doubled between 2010 and 2011. The CNN article also noted that there is no national protocol on how to treat NAS. The hospital has trained volunteers, called cuddlers, to hold and comfort the babies. The babies are treated with morphine in small doses every three hours, then weaned. Since this protocol, the average hospital stay for NAS infants is 24 days. Information is from CNN’s website.
NO TO iNO

Newsmedicalnet reports: Many premature infants throughout the United States continue to receive inhaled nitric oxide during their NICU stay, despite the lack of evidence to support its use. Whether or not a preemie will receive iNO treatment, when and for how long, varies greatly throughout the country, as its use in premature infants appears to be unstandardized. These are the findings of a Nationwide Children’s Hospital study that appeared in the journal Pediatrics. The National Institutes of Health (NIH) and the Agency for Healthcare Research and Quality (AHRQ) have concluded that there is no evidence to support the routine use of iNO in preterm infants who require respiratory support. Nationwide Children’s faculty and members of the Ohio Perinatal Research Network (OPRN) performed a retrospective study using the Child Health Corporation of America’s Pediatric Health Information Database. The study cohort included 22,699 premature infants born less than 34 weeks gestation admitted to NICUs in 37 children’s hospitals during a three-and-a-half-year period. The use of inhaled nitric oxide in premature infants was variable, even when controlling for demographic characteristics and disease. There was substantial variation in the age of initiation of iNO treatment and the average number of days of use. Hospitals that used iNO in more patients also used iNO for a longer duration. Higher volume NICUs used less iNO and had lower mortality rates. Northeastern hospitals reported less use of iNO. Infants who received iNO were less likely to survive, suggesting that iNO is used in infants already at high risk of death. The researchers reported that there is a pervasive lack of standardization in iNO use across NICUs. The findings suggest that the use of iNO in extremely low birth weight infants with the most severe forms of respiratory failure did not improve mortality rates.

COME ON, REALLY?
The Huffington Post reported that “Hospitals in Minnesota, and possibly elsewhere in the country have sunk to a new low in their debt-collection practices by employing collectors in emergency rooms, as well as labor and delivery rooms to pressure patients into paying up. The Minnesota attorney general revealed that Accretive Health, one of the nation’s largest collectors of medical debt, regularly embedded debt collectors among hospital employees. The collectors, who looked like regular employees and sometimes had access to patients’ medical files, would demand payment before patients received treatment and sometimes discouraged them from getting emergency care at all. Employees at Accretive’s client hospitals ask patients to make ‘point of service’ payments before they receive treatment.” HuffPost quoted a hospital worker as saying, “Patients are harassed mercilessly.” The report went on to say, “Patients with outstanding balances were closely tracked by Accretive staff members, who listed them on ‘stop lists,’ internal documents show... Doctors complained that such strong-arm tactics were discouraging patients from seeking lifesaving treatments... The Minnesota attorney general said such practices are in violation of the Emergency Medical Treatment and Active Labor Act and the Health Insurance Portability and Accountability Act... [Another] state law is broken when Accretive employees fail to identify themselves as debt collectors.”

JUST WAIT
During the past 20 years, elective inductions of labor have increased from as few as 1 in 10 to as many as 1 in 3 births. Some women and their obstetric providers opt for an elective induction because it’s thought to be more convenient. Now, many hospitals and healthcare systems are implementing new policies that encourage spontaneous labor since there are no research studies that show that elective inductions are as safe for mothers and babies as spontaneous labor. A recent article in the Journal of Obstetric, Gynecologic & Neonatal Nursing, published by AWHONN discusses the effect of implementing policies aimed at reducing elective inductions and increasing rates of spontaneous labor. In “A Systematic Review of Implementing an Elective Labor Induction Policy,” D. Claudia Akinsipe, et al, examines the benefits of induction policies. The authors say women experiencing labor by medical and/or elective induction have a significantly greater risk for cesarean women going into spontaneous labor. In the studies featured in the article, researchers found that by implementing an elective labor induction policy, overall induction rates declined and spontaneous labor rates increased. Furthermore, positive health outcomes for infants were attributed to the implementation of elective labor induction policies, including...
lower rates of NICU admissions, decreased still births, reduced meconium and amniotic fluid aspiration, increase in one-minute APGAR scores, decrease Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores; decrease in infants with one or more neonatal complications, and decline in prematurity rates. Information provided by JOGNN and AWHONN.

HOUSE ARREST
A prominent Hungarian home-birth expert has spent a year and a half under house arrest and constantly faces imprisonment for practicing as a midwife. According to the Guardian newspaper, “Géreb's crime is to have spent the past 17 years quietly resisting Hungary's attempts to criminalize home births. Against a background of escalating police harassment and abuse, Géreb helped deliver 3,500 babies at home, one of whom died some 14 months after a difficult labor; another as a result of shoulder dystocia. A third infant died seven months after suffering a lack of oxygen at birth. According to the WHO, Hungary's early neonatal mortality rate (babies aged 0-6 days) is five deaths in every 1,000 live births. By this measure, Géreb could have expected to see 17 or 18 babies – not three – die during her almost two decades as an independent midwife. But because the government refuses to regulate independent midwives in Hungary, these cases triggered a criminal investigation and Géreb was found guilty of manslaughter, negligent malpractice and two other charges involving common obstetric occurrences. Géreb's supporters petitioned against the rulings but [an] appeal court increased her sentence... Géreb's supporters – including the Royal College of Midwives, the International Confederation of Midwives, and the International Federation of Gynaecology and Obstetrics – say she has been singled out for punishment because of her dedication to the home-birthing cause. They are going to the European court of human rights on Géreb's behalf, but the process is expected to take years. In the meantime, there are serious concerns about whether the increasingly fragile mother of four can survive more time in a prison system criticized in a 2010 UNHCR report as inhumane and degrading.” There is an organization fighting for her, at freeregereb.org. From The Guardian.

NANN NEWS
NANN’S new aggregator web news service, Smartbrief (smartbrief.com) reports the following: Empiric antifungal therapy should be considered before blood culture results are available for extremely low birth weight babies at high risk of invasive Candida to help prevent death or neurodevelopmental impairment, researchers reported in The Journal of Pediatrics. Duke University researchers said Candida species are a leading cause of death in NICUs and waiting for blood culture results could take days and have fatal consequences [Medscape via Reuters]... In the past 15 years, more than a third of hospitalizations for Trisomy 18 and Trisomy 13 involved children older than 1 year of age, according to a study in the journal Pediatrics. Researchers also found that more than 10% of these hospitalizations involved children older than age 8 [ABC News]... The American Academy of Pediatrics' committees on Fetuses and Newborns and on Infectious Diseases issued a joint statement highlighting the importance of good hand hygiene in preventing nosocomial infections in neonatal intensive care units. Committee members also suggested strategies for preventing central line-associated bloodstream infection as well as health care-associated pneumonia [PediatricSuperSite.com]... Mississippi's recorded teen birth rate was more than 60% above the national average in 2010, with 55 births per 1,000 teens aged 15 to 19 years, according to the CDC. New Hampshire recorded 15.7 births for the same age group. Since 2007, teen birth rates fell at least 8% in 47 states and Washington, DC [Reuters]... The Louisiana Department of Health and Hospitals launched an initiative to discourage elective deliveries before 39 weeks; NICU admissions at East Jefferson General Hospital have fallen by 20%. East Jefferson was the state's first hospital to adopt the initiative [Gambit Weekly (New Orleans)]... Early cycling of parenteral nutrition to reduce the metabolic load to the liver does not delay or prevent cholestasis in very low birth weight babies, according to researchers from Albert Einstein Medical Center in Philadelphia. The study in the Journal of Pediatrics said risk factors for cholestasis included bronchopulmonary dysplasia, duration of parenteral nutrition and days to full enteral nutrition [MedPage Today/RWJ]... More hospitals are using webcam systems that allow parents of infants in a NICU to watch over them. Since January 2011, about 30 hospitals nationwide have begun to use or are considering systems called NICVIEW, but some experts worry about privacy issues, security breaches and liability risks with the webcams [American Medical News]... NANN's new 2012 online product catalog offers a variety of educational and professional development programs and resources to enhance your knowledge and provide you with valuable networking opportunities in neonatal nursing. NANN members receive a significant discount on products and many are available for free. To purchase NANN products, visit NANNstore.org... NANN's Policies, Procedures, and Competencies for Neonatal Nursing Care is a helpful, up-to-date resource that will serve and advance your organization's commitment to evidence-based nursing and support your efforts to give the highest quality of care to your patients. This book, with a companion flash drive, features forms that can easily be revised and customized to align with your internal institutional policies and federal, state and local regulations... Mortality rates for very low birth weight babies in NICUs of hospitals that have achieved recognition for nursing excellence were slightly lower than for those in hospitals without the designation, University of Pennsylvania researchers reported. The study included 558 hospitals in the Vermont Oxford Network, and the recognized facilities also had lower rates of nosocomial infection and severe intraventricular hemorrhage. The study was funded by the Robert Wood Johnson Foundation Interdisciplinary Nursing Quality Research Initiative and the National Institute of Nursing Research [MedPage Today/RWJ]... Florida reported a 500% increase in the past five years in the number of babies born with neonatal withdrawal syndrome... UK researchers analyzed 13 studies involving 229,421 newborns and found that pulse oximetry was able to detect 76.6% of congenital heart defects and had a false positive rate of only 0.14% [Google]... St Luke’s Hospital in Kansas City opened a breast milk bank to meet the needs of all hospital NICUs in the area [The Kansas City Star]... The NICU at All Children’s Hospital in St Petersburg, FL is using immobilization bags to make MRIs easier on newborns and to ensure they remain still. Before using the bag, infants had to be sedated and many ended up with breathing tubes during the procedure. [WTVT-TV]... NANN is offering a portable neonatal reference guide. Neo-Care Cards provide valuable information for bedside care in a concise, accessible format. These 26 cards contain conversion and calculation charts along with diagrams summarizing crucial guidance for care in the NICU.

HEART SURGERY
In the largest multicenter clinical trial of children undergoing
early-stage surgery for single-ventricle heart defects, differences in intraoperative management did not significantly affect neurodevelopmental outcomes at 14 months of age. Instead, the strongest influences were innate patient characteristics and general medical morbidity during the child's first year of life. Researchers suspected that variations in heart shunts and in cardiopulmonary bypass might affect outcomes. However, the study leaders concluded that substantial improvements in neurodevelopmental outcomes are likely to require interventions that occur outside the operating room. For example, because infants delivered closer to term had better neurodevelopmental outcomes, the researchers suggest postponing elective delivery from 37 weeks to 39 or 40 weeks might benefit patients.

Researchers from 15 hospitals in the National Heart, Lung, and Blood Institute’s Pediatric Heart Network published these results from the Single-Ventricle Reconstruction (SVR) trial online March 28 in the journal Circulation (Newburger, et al). The SVR trial, sponsored by the National Heart, Lung and Blood Institute, is the largest prospective study of children undergoing the Norwood procedure, the first in a series of three staged surgeries. The trial compared outcomes after the Norwood procedure for the Blalock-Taussig shunt and the right-ventricular-to-pulmonary artery (RV-to-PA) shunt. The current study reported on an important secondary trial outcome, neurodevelopment assessed at 14 months of age. The study leaders hypothesized that children in the RV-to-PA shunt group would fare better in neurodevelopmental tests, reasoning that cerebral blood flow was improved compared to that provided by the Blalock-Taussig shunt. However, neurodevelopmental delay remained common in both groups, a finding that was similar to results from earlier studies. Factors such as the presence of genetic syndromes, lower maternal education and lower birth weight led to lower development scores. The study included infants from 15 participating centers, recruited between May 2005 and July 2008. The researchers evaluated 321 infants at 14 months of age. MDI scores for the infants who had the Norwood procedure were significantly lower than in the general population, and PDI scores for the cohort were profoundly lower—greater than 2 standard deviations lower in 44% of the patients. Infants with both shunt types had similar developmental scores. No characteristics such as center volume or surgeon volume had an effect on PDI or MDI scores, nor did the type of perfusion. The subgroup of patients with the highest PDI and MDI scores, as well as a shorter post-operative hospital stay, were children with no genetic syndrome and birth weights higher than 2.5 kg (5.5 lbs). The authors suggested that birth weight might be improved by postponing the time of elective delivery to 39 to 40 weeks. Recent studies have shown that babies with critical congenital heart disease were delivered electively as early as 37 weeks. The study team found that infants with more post-operative complications tended to have worse neurodevelopmental outcomes.

CONSEQUENCES
Children conceived with the aid of fertility treatments are more likely to be born with serious physical defects, according to a study at the University of Adelaide. Agence France Presse via Raw Story reported that conception using treatments like ovulation induction, in-vitro fertilization or the injection of sperm directly into an egg, resulted in serious defects in 8.3% of cases studied. The corresponding ratio in spontaneous conceptions was 5.8%. The scientists noted birth defects in 7.2% of children born from in-vitro fertilization and 9.9% from intracytoplasmic sperm injection (ICSI). For IVF, the percentage dropped significantly when taking into consideration factors like parental age, smoking and other factors, but for ICSI it remained high. The researchers also found a tripling of risk in women using clomiphene citrate, a drug for ovulation induction.

NURSING LEADERS
AWHONN recently announced this year’s class of emerging leaders. The association’s Emerging Leaders Program engages nurses in a formal, year-long leadership training program. Activities include guidance from mentors, networking events, meetings with members of Congress and their staff, multiple continuing education opportunities, AWHONN committee assignments, and other experiential training to build confidence and leadership skills among participants. Participant selection was based on the applicants’ skills, experience and enthusiasm for women’s health and perinatal nursing. The 2012 emerging leaders are: Anne Daniele, BSN, RNC, a Captain in the Army Nurse Corp, assigned to the labor and delivery unit at the Carl R. Darnall Army Medical Center in Ft Hood, TX; Mesha Farrington, AD, BSN, RN, a nurse educator in the maternal-child unit at Henry Ford Hospital in Detroit; Anne Faust, RNC, MSN, IBCLC, LCCE, a registered nurse working in labor and delivery at Mission Hospital in Mission Viejo, CA; Lori Folkens, RNC, a registered nurse in the obstetrics department at Illinois Valley Community Hospital; Erica Gillesby, BSN, RNC, the labor and delivery shift specialty coordinator at Exempla Lutheran Medical Center in Colorado; Elizabeth Kester, RN, CLC, CCE, a registered nurse, clinical resource nurse, certified lactation counselor and certified childbirth educator at The Mom's Place at Catholic Medical Center in Manchester, NH; Cheryl Larry-Osman, MS, CNM, CNS, RNC, a clinical nurse specialist in labor and delivery at Henry Ford Hospital in Detroit; Kumi Mogensen, BSN, RNC, a registered nurse in labor and delivery at Exempla Lutheran Medical Center in Colorado; Mary Paterno, PhD(c), MSN, CNM, RN, a certified nurse midwife at Mercy Medical Center in Baltimore; and Terry Smith, MS, RNC-OB, a nurse educator in perinatal services at Flagstaff Medical Center in Arizona.

TWO AWARDS
AWHONN has awarded Fort Worth-area perinatal nurse Karen P. Langston, MSN, RNC-OB, C-EFM, as one of the first recipients of the Fetal Heart Monitoring Instructor Recognition and Incentive Award. The quarterly awards program was launched in 2012. Langston has been an AWHONN fetal heart monitoring instructor since 2003 and an instructor trainer since 2007. In addition to volunteering as a fetal heart monitoring teacher, Langston has been a perinatal nurse and educator for more than 27 years. She is currently the Perinatal Outreach Coordinator at Texas Health Harris Methodist Hospital Fort Worth, where she has worked since 1994. Another recipient of the award was Michelle S. Flanagan, RNC, BSN. Flanagan has been an AWHONN fetal heart monitoring instructor since 2008 and a designated instructor, teaching both the advanced and intermediate courses, since 2010. She is the Obstetrical Outreach Educator for Palmetto Health Richland, Perinatal Systems in Columbia, SC. Contact awhonn.org.

PREVENTABLE
The Journal of Obstetric, Gynecologic and Neonatal Nursing reported: Obstetric remains the leading cause of maternal death in the United States, yet 54% to 93% of these deaths may be preventable according to the latest research. Mortality is only the tip of the iceberg since in 2006, approximately 2.9% of the women who gave birth, or 124,708 women, suffered
a postpartum hemorrhage. There was a 92% increase in the
number of obstetric-related blood transfusions in 2004 to 2005
compared to 1998 to 1999. A series of five articles in the journal
address specific strategies and tactics nurses can use to lead
efforts in eliminating preventable hemorrhage-related maternal
morbidity and mortality.

ACCESS TO RESEARCH
In our last issue, we wrote about protests about the high cost
of medical journals. Below is a copy of a correspondence
we received from Harvard, titled, "Faculty Advisory
Council Memorandum on Journal Pricing – Major Periodical
Subscriptions Cannot Be Sustained." It said: "To: Faculty
Members in all Schools, Faculties, and Units: We write to
communicate an untenable situation facing the Harvard
Library. Many large journal publishers have made the scholarly
communication environment fiscally unsustainable and
academically restrictive. This situation is exacerbated by efforts
of certain publishers (called "providers") to acquire, bundle,
and increase the pricing on journals. Harvard's annual cost for
journals from these providers now approaches $3.75M. In 2010,
the comparable amount accounted for more than 20% of all
periodical subscription costs and just under 10% of all collection
costs for everything the Library acquires. Some journals cost
as much as $40,000 per year, others in the tens of thousands.
Prices for online content from two providers have increased
by about 145% over the past six years, which far exceeds not
only the consumer price index, but also the higher education
and the library price indices. These journals therefore claim
an ever-increasing share of our overall collection budget. Even
though scholarly output continues to grow and publishing can be
expensive, profit margins of 35% and more suggest that the prices
we must pay do not solely result from an increasing supply of
new articles... The Faculty Advisory Council to the Library,
representing university faculty in all schools and in consultation
with the Harvard Library leadership, reached this conclusion:
major periodical subscriptions, especially to electronic journals
published by historically key providers, cannot be sustained:
continuing these subscriptions on their current footing is
financially untenable. Doing so would seriously erode collection
efforts in many other areas, already compromised. It is untenable
for contracts with at least two major providers to continue
on the basis identical with past agreements. Costs are now
prohibitive. Moreover, some providers bundle many journals
as one subscription, with major, high-use journals bundled in
with journals consulted far less frequently." Harvard suggested
that its researchers: "Consider submitting articles to open-
access journals, or to ones that have reasonable, sustainable
subscription costs; move prestige to open access. If on the
editorial board of a journal involved, determine if it can be
published as open access material, or independently from
publishers that practice pricing described above. If not, consider
resigning..."

RESEARCH REDUX
In related news, Alok Jha wrote in The Guardian that The
Wellcome Trust, which spends more than $600m on scientific
research a year, said it planned to adopt a more robust approach
with the scientists it funds, to ensure scientific results are freely
available within six months of first publication. As we went to
press, more than 9,000 researchers had signed up to a boycott of
journals that restrict free sharing as part of a campaign dubbed
the “academic spring” by supporters. Research Councils UK
(RCUK), the coordinating body for the distribution of public
money for scientific research, is also reviewing its policy on open
access.

OK WHILE PREGNANT
Infants born to women who used the anti-HIV drug tenofovir
during pregnancy do not weigh less at birth and are not of
shorter length than infants born to women who used anti-HIV
drug regimens that don’t include it, according to the NIH. But by
their first birthday, kids born to these moms were a bit shorter
and had a slightly smaller head circumference. Over the seven
years of the study, the number of participants being treated with
tenofovir increased from 14% to 43%. The study included 2,000

HOW MANY PREAMIES?
One in ten babies worldwide are born prematurely according to
of Dimes, and Newborn & Child Health. The US is among the
10 countries with the highest number of preterm births (ranked
6th). In the US, 12% of all babies are born premature, that is
more than 1 in every nine births - twice as many in the majority
of European countries. Leading in number of preterm births are
India, China, Nigeria, Pakistan and Indonesia. The highest rates
of preterm babies to births are in Africa. The lowest are Belarus,
Ecuador, Latvia, Finland, Croatia, Samoa, Lithuania, Estonia,
Antigua, Japan and Sweden. How come the rate is so high?
According to the report, more older women are giving birth,
more women are using fertility drugs, more have diabetes, and
more are obese. There are also more inductions and C-sections
before full term. In the US, the African-American preterm birth
rate in 2009 was 17.5%; Caucasian, 10.9%; between age 25 and
35, 11-12%; under 17 and over 40, 15%. In poor countries, the
increase was due to HIV, teen pregnancy, infections and malaria.
In poor countries, 90+ of babies born three months prematurely
die. In high-income countries, less than 10%. Information is from
Medical News Today, from an article by Christian Nordqvist,
copyright Medical News Today.

GUT FEELING
Early colonization of the gut by microbes in infants is critical
for development of their intestinal tract and in immune
development. A study at Texas A&M University showed
that differences in bacterial colonization of formula-fed and
breast-fed babies leads to changes in the infant’s expression of
genes involved in the immune system, and in defense against
pathogens. The researchers used transcriptome analysis
to compare the intestines of three month old exclusively
breast-fed or formula-fed infants, and related this to their gut
microbes. Transcriptome analysis looks at the small percentage
of the genetic code that is transcribed into RNA molecules
and is a measure of what genes are actively making proteins.
Concurrently the microbes (microbiome) were identified by
genetic analysis. The results showed that the breast-fed babies
had a wider range of microbes in their gut than the formula-fed
infants but that their immune systems had developed to cope.

IRON AND STRESS
Newborns whose mothers are under stress during the first
trimester of pregnancy may be at risk for low iron status,
which could lead to physical and mental delays down the road,
according to a study in Israel and by the University of Michigan.
Other risk factors for poor iron status in infants are maternal
iron deficiency, maternal diabetes, smoking during pregnancy,
preterm birth, low birthweight and multiple pregnancy.
Researchers recruited pregnant women who were about to give birth at Barzilai Medical Center in Israel. The stress group lived in an area where there were more than 600 rocket attacks during their first trimester of pregnancy. The control group lived in the same area and became pregnant three to four months after the rocket attacks ended. Cord blood was collected from newborns, and serum ferritin (iron) concentrations were measured. Results showed that the 63 babies whose mothers were in the stress group had significantly lower cord-blood ferritin concentrations than the 77 infants in the control group.

IN YOUR FACE
In a first, developmental biologists at Tufts University have identified a self-correcting mechanism by which developing organisms recognize and repair head and facial abnormalities. Researchers used a tadpole model to show that developing organisms are not genetically hard-wired with a set of predetermined cell movements that result in normal facial features. Instead, the process of development is more adaptive and robust. Cell groups are able to measure their shape and position relative to other organs and perform the movements and remodeling needed to compensate for significant patterning abnormalities, the study shows. The researchers found that when they created defects in the face, facial structures moved around and mostly ended up in their correct positions. This means that what the genome encodes ultimately is a set of dynamic, flexible behaviors by which the cells are able to make adjustments to build specific complex structures. Previous research had found self-correcting mechanisms in other embryonic processes, but not in the face. Images of tadpoles showed that as they aged, the craniofacial abnormalities, or perturbations, became less apparent. This was particularly true for the jaws and branchial arches. Eye and nose tissue became more normal over time but varied in ability to achieve a completely expected shape and position. In tadpoles with severe malformations, the facial structures shifted dramatically in order to repair those malformations.

PRODUCTS

GO WITH THE FLO
Maxtec, Salt Lake City UT is pleased to announce our new MaxFLO. The MaxFLO provides an affordable method for mixing and monitoring air and oxygen in both high flow (0-50 liters per minute) and low flow (0-10 liters per minute) applications. Each unit comes equipped with dual flow meters and a mixed gas analysis port for intermittent or continuous monitoring of FiO2. When used in conjunction with our MaxO2 handheld oxygen analyzer, users can mix and measure accurate oxygen concentrations with added confidence. Gas ratios are also visibly identified on the face of the unit to allow for fast, accurate flow settings. Every unit also includes a built-in pole mount and is backed by a Maxtec 24 month warranty. Contact (800) 748.5355, www.maxtecinc.com.

WEATHERED IT
Yamile Jackson’s son Zachary, the impetus for her company, Nurtured by Design, was the featured Weekend Weather Kid recently on Fox 26 in Houston, giving a brief weather update (including “It’s going to be nice.”) Nurtured by Design specializes in the research and development of innovative and evidence-based solutions that facilitate the best possible neurological, physical, physiological, and psychological developmental support to the neonate. Its main product is The Zaky. After Ms. Jackson developed preeclampsia, Zachary was born prematurely weighing less than two pounds. Three weeks after his birth, a tropical storm knocked out all power at his hospital, and his parents and the NICU staff kept him alive by hand for nine hours. Yamile kept him on kangaroo care. Zachary was in the hospital for 155 days. Contact nurturedbydesign.com.

ARTFUL
Having received clearance under Section 510(k) from the US Food and Drug Administration, Spacelabs Healthcare is adding the qube patient monitor to its Art of Monitoring portfolio. Inspired by the revolutionary style of the company’s XPREZZON patient monitor, qube breaks with tradition to offer a fresh, new perspective in compact monitoring. Small and lightweight – with a battery life that goes the distance – qube offers portability, accessibility and heightened connectivity – perfect for emergency, general/step-down, and post-anesthesia care units. qube is mountable anywhere – wall, bedrail, anesthesia system – and can be detached via a quick-release feature for immediate mobility. Caregivers can access current, critical patient information, from bedside throughout transport, to provide the ultimate level of patient care. Contact spacelabshealthcare.com.

COLLABORATION
Covidien and GE Healthcare announced a five-year, global collaboration to incorporate Covidien measurement technologies into GE Healthcare patient monitors. The Nellcor Respiratory Function portfolio, which includes Nellcor pulse oximetry with OxiMAX Technology, and the BIS Brain Monitoring system, are now available on many GE Healthcare patient monitors. This includes the CARESCAPE Monitor B850 and CARESCAPE Monitor B650. The Covidien collaboration reflects GE Healthcare’s commitment to maintain an open monitoring architecture, bringing together streams of patient data and making it usable for clinicians at the point of care. The collaboration leverages the Covidien portfolio of patient monitoring technologies, including: Nellcor pulse oximetry with OxiMAX Technology, a cardiac-based pulse oximetry platform, which accurately monitors patients at all acuity levels and in challenging conditions. The Nellcor pulse oximetry solution from Covidien offers SpO2, Pulse Rate and Respiration Rate in a single sensor design. INVOS Cerebral/Somatic Oximetry monitors site-specific oxygen levels to optimize end-organ perfusion and help protect against devastating major organ morbidity and neurological injury. BIS Brain Monitoring measures the effects of anesthetics and sedatives on the brain. Contact covidien.com or gehealthcare.com.

COMMUNICATE
AirStrip OB enables physicians to effectively communicate with the L&D staff in a more timely and accurate manner, minimizing unnecessary trips to the hospital and more importantly, responding quickly to situations that need clinical attention. This technology enhances the health and safety of expectant mothers and their unborn child by allowing physicians the ability to closely monitor patients 24/7 when they cannot be bedside, allowing “anywhere, anytime” access to critical patient information on a variety of mobile devices (including iPhone, Android, BlackBerry and several of Windows Mobile devices). AirStrip OB from AirStrip Technologies, works in tandem with existing in-hospital patient monitoring systems to pull data and securely send it to the doctor’s mobile device. It provides access to live, vital patient waveform data, including fetal heartbeat and maternal contraction patterns and access to nursing notes,
vital signs and the fetal strip and maternal contraction pattern information for an individual patient. AirStrip OB is FDA-cleared and HIPAA compliant. A free demo version can be downloaded by iPhone users from the Apple App Store. Contact airstriptech.com.

HIGH RISK RESULTS
MedImmune, the global biologics arm of AstraZeneca, announced results from a new retrospective database cohort study of 8,443 high-risk infants receiving palivizumab in Medicaid programs across 12 states. Approximately 67% of infants were non-compliant with palivizumab. Non-compliance with the FDA-approved dosing of Synagis (palivizumab), defined as not receiving at least 5 doses or having dosing gaps, significantly increased likelihood of hospitalization from RSV among high-risk infants in a Medicaid population. The percentage of RSV-related hospitalization was significantly higher among non-compliant vs compliant infants (12.0% vs 7.4%) respectively. These results suggest that inconsistent dosing or dosing less than approved in the FDA label for Synagis is correlated to the risk of RSV hospitalization for high-risk infants. Compliance with Synagis dosing was evaluated across six RSV seasons (2003-2009), with RSV season typically running from November through March. Babies were required to have been discharged between May 1 and September 30 and to have received one or more doses of Synagis during their first RSV season (October through April) with no gaps of > 35 days between any dose. Inclusion criteria were defined as infants born with prematurity (34 weeks gestational age or less), congenital heart disease (CHD), or chronic lung disease of prematurity (CLDP). Contact medimmune.com.

CERTIFICATION
Inspire Health Solutions, Inc, the technology subsidiary of Sheridan Healthcare, Inc, has achieved 2011/2012 EHR Modular ONC-ATCB Certification for its PremiEHR 5 neonatal intensive care unit (NICU) electronic health record software. Sheridan is the second largest neonatology services provider in the nation. With 26 features certified, PremiEHR 5 is one of the most comprehensive modular programs available to NICUs. PremiEHR 5 now carries the designation that the software is capable of supporting providers with Stage 1 Meaningful Use measures required to qualify for funding under the American Recovery and Reinvestment Act. PremiEHR 5 is Inspire Health Solutions' fifth generation neonatal intensive care unit electronic health record and incorporates years of insight from practicing neonatologists. After nearly a decade of success, PremiEHR 5 has processed more than half-a-million patient days at more than 29 NICUs. Its customized web-based interface can be delivered to providers over a full-service cloud or as a licensed software product with secure access for providers, both at the facilities and remotely. PremiEHR 5 and the suite of companion products were designed and built as an integration-friendly platform using a service-oriented architecture that is highly scalable and offers smooth integration with core hospital or independent physician group electronic medical record systems. Contact inspirehealthsolutions.com.

DELIVERY
Smiths Medical introduces its new paraPAC plus Oxygen delivery platform. The paraPAC plus gives you the versatility to deliver oxygen therapy, CPAP, demand oxygen and mechanical ventilation all from one compact, lightweight unit. The paraPAC plus is designed for the most demanding environments.
Reduction Morbidity and Necrotizing Enterocolitis: The Interface of Human Milk with the Preterm Infant Gastrointestinal System

Jean Rhodes, PhD, CNM, IBCLC

Introduction

Breast milk is very important if your baby is born early or is sick. Breast milk can help your baby get better faster and develop properly. The nurses or lactation consultant can help you learn how to pump your milk if your baby cannot breastfeed.

– The Joint Commission – Speak up: What you need to know about breastfeeding.1

Recently, the Joint Commission joined medical, nursing and other professional organizations, the CDC and the US Surgeon General in publically promoting the benefits of human milk for all infants. The evidence supporting the use of human milk in the NICU is both extensive and compelling: laboratory and clinical research demonstrate the value of human milk in reducing multiple disease states of the preterm infant including necrotizing enterocolitis (NEC), chronic lung disease, retinopathy of prematurity, and infections.2-10 Against this backdrop of information and data, it is easy to lose sight of the most critical and consistent element in all of these diseases: the interface of human milk with the infant gastrointestinal system.

Protective Function of Human Milk in the Preterm Infant GI System

At the time of birth, the preterm infant’s gastrointestinal system is anatomically and physiologically immature. As the infant develops, tight junctions between the cells of the intestinal mucosa close, reducing the risk of invasion by pathogens in the environment.

In a 2009 study, Taylor, Basile, Ebeling, and Wagner11 investigated the effects of human milk feeds on preterm infants’ gut permeability in the first month of life. Intestinal permeability can be accurately measured by the ratio of lactulose to mannitol in infants’ urine. In this study, infants who received mother’s milk were found to have better tight junction closure with less gut permeability when compared to infants who received little or no human milk. Conversely, exclusively formula-fed infants demonstrated a 2.8-fold higher composite median lactulose/ mannitol ratio when compared with those who received any mother’s milk. These results suggest formula feedings may be associated with delayed closing of tight junctions, predisposing preterm infants to gastrointestinal morbidities including NEC.

The gastrointestinal tract has a dual purpose of absorbing nutrients and protecting the organism from invasion of environmental pathogens. This protection begins in the lumen of the GI tract with functional barriers like mucus and commensal (or protective) bacteria and continues into deeper layers of the mucosa with cells specific to immune response and regulation of inflammation.

The human gastrointestinal tract is comprised of several layers of functional substances overlying the intestinal epithelial absorptive cells, commonly referred to as enterocytes. At the apical end of the enterocyte, several layers of coatings protect the epithelial cells from harmful microbes. The glycocalyx is a thick, mucin-rich glycoprotein matrix lining the entire gastrointestinal system. Together with the mucus layer, it forms a sticky gel-like barrier that lubricates and protects the intestine.12,13 Embedded within the mucus layer are antimicrobial inhibitors that help regulate gut colonization.13 Lastly, a biofilm of symbiotic bacteria develops at the interface with the intestinal lumen. All three layers work in concert to protect the infant from pathogenic bacteria.13

Gut permeability is one of multiple developmental limitations of the preterm infant’s immature gastrointestinal system, all of which can contribute to an increased risk of feeding intolerance as well as short and long-term morbidities. Other aspects of the preterm gastrointestinal system related to immaturity include a need for rapid cellular growth and turnover14 decreased peristalsis,10,15,16 decreased gastric acid,15 decreased proteolytic enzymatic activity,15,16 altered intestinal mucus,14-16 and an immature inflammatory response.13

According to Wagner et al,14 amniotic fluid and human milk are sources of multiple growth factors important to the continuum of fetal-infant gut development and maturation. Like amniotic fluid, human milk promotes gut maturation by supplying epidermal growth factor as well as other trophic factors. After birth, human milk assumes the role of exogenous source of bioactive substances stimulating cell growth and repair through the synergistic actions of cytokines, insulin-like growth factors, transforming growth factors a and b, insulin, erythropoietin and vasoactive endothelial growth factor. Wagner et al hypothesize trophic factors in human milk also enhance the development and function of the intestinal mucus barrier.14 By promoting growth
of enterocytes, tight junctions and the mucus barrier, human milk contributes to the overall functioning and integrity of the infant gastrointestinal system. Human milk provides other benefits related to immaturity of the neonatal gastrointestinal tract. Human milk increases peristalsis, thereby decreasing the build up of toxins and pathogens in the intestinal lumen.\textsuperscript{16,17} Additionally, milk lipases breakdown triglycerides into anti-microbial free fatty acids promoting an acidic gastric environment essential for nutrient degradation.\textsuperscript{13} These are just a few of the numerous protective functions of human milk in the preterm gastrointestinal tract.

The Role of Human Milk in Reducing the Risk of NEC and Other Morbidities

Several studies have demonstrated the protective effects of human milk for preterm infants against the risk of sepsis and NEC.\textsuperscript{4,5,8,9,18,19} Research by Meinzen-Derr and colleagues\textsuperscript{20} evaluated the impact of the dose and total percent of human milk over a short period of time in a large population of infants. Their findings suggested an inverse relationship between human milk feedings during the first 14 days of life and the risk of NEC or death over hospital stay. Increasing cumulative and proportional amounts of human milk in the first 2 weeks was associated with increased survival time in which the infant was free of NEC. Infants who developed NEC or died after the first 2 weeks were fed less human milk and had a lower mean daily volume of human milk than infants who survived free of NEC.

In a separate prospective cohort clinical study, also of ELBW infants, Sisk et al\textsuperscript{21} evaluated the impact of low (<50% of total feeds) and high (>50% of total feeds) doses of human milk. Their results indicated a six-fold decrease in the risk of NEC in infants receiving at least 50% human milk feedings in the first 14 days of life. For mothers who did not plan to provide milk for their infants, this information could positively influence their decisions about initiating pumping.

Human milk is a well-known source of multiple anti-infective agents including secretory IgA, lactoferrin, lysozyme, macrophages and free fatty acids.\textsuperscript{2,11} These agents work in concert to inactivate, destroy or bind to specific microbes, preventing their attachment to mucosal surfaces.\textsuperscript{8} At the same time, human milk contains lact acid bacteria, primarily bifidobacteria (also referred to as lactobacillus bifidus). These protective commensal bacteria become part of the gut microflora and influence inflammatory and immunomodulatory processes.

The significance of a healthy gut microbiota cannot be understated. Commensal bacteria prevent the overgrowth of pathogenic bacteria, acidify the gut, ferment lactose, break down lipids and proteins, and produce vitamins K and biotin.\textsuperscript{10,15-17} Colonization of the infant’s GI tract begins at the time of birth with exposure to the mother’s vaginal flora or skin flora, depending on mode of delivery.\textsuperscript{23} Colonization continues with exposure to the environment and is heavily influenced by type of infant feeding.

Recent discoveries have clarified the symbiotic relationship of human milk oligosaccharides (HMOs) and lactic acid bacteria in the infant’s gut.\textsuperscript{22,26} HMOs are complex carbohydrate molecules abundant in human milk. However, human infants cannot digest HMOs, thus their purpose in human milk has been an enigma. In the last few years, researchers have discovered that HMOs in human milk are digestible by specific bifidobacteria in infants’ gastrointestinal tracts. In this capacity, HMOs function as prebiotics, feeding and stimulating the growth of commensal bacteria. They also act as decoys or receptor analogs to inhibit binding of pathogens - including rotaviruses - to intestinal surfaces.\textsuperscript{24-27}

Human milk reduces the risks of NEC,\textsuperscript{2,3,5,9} sepsis,\textsuperscript{4,5,8,28} and intestinal disturbances in part by promoting healthy gut microbiota and intact mucosa. Anti-infective agents in mothers’ milk (mentioned above) contribute to these layers of protection against infection. However, localized actions do not explain the ability of human milk to reduce the risk of diseases remote from the GI tract, eg, chronic lung diseases, retinopathy of prematurity and disorders which lead to neurodevelopmental delays. These diseases, like NEC, are characterized by a systemic inflammatory response triggered by overproduction and release of pro-inflammatory cytokines, such as Interleukin-8 (IL-8).\textsuperscript{10,16,29,30}

Normally, inflammation acts as a healthy defense mechanism to rally immune factors, including leukocytes, to the site of infection or tissue injury. However, preterm infants lack the regulatory mechanisms to keep inflammation in check.\textsuperscript{31} Caicedo et al\textsuperscript{10} hypothesize the release of IL-8 and other pro-inflammatory factors in the preterm gut can cause an exaggerated inflammatory response, leading to intestinal injury (NEC) as well as damage to other organs. Several human milk components interrupt or downgrade inflammatory processes in preterm infants, including interleukin-10 (an anti-inflammatory cytokine), lactoferrin, epidermal growth factor, transforming growth factor-β, HMOs, soluble CD-14 and insulin-like growth factor.\textsuperscript{10,11,13} These factors work synergistically to protect the preterm infant from over-productive inflammatory responses.

In the context of studies we have already examined – those by Taylor, Meinzen-Derr and Sisk in which the early use of human milk had a significant positive effect on preterm infant outcomes – it should be mentioned that many of these protective milk components are at their highest in colostrum.\textsuperscript{31} Furthermore, as Meier notes so concisely, it is “during this critical exposure period…that [infant] formula appears to exert an independent, pro-inflammatory effect.”\textsuperscript{31} (p.222)

The Confounding Role of Human Milk Fortifiers in Preterm Infant Morbidities

Studies evaluating the efficacy of human milk in reducing the risks of short and long term morbidities are confounded by the need for milk fortification. Once preterm infant feedings progress to volumes greater than 100 ml/kg/day, bovine-based human milk fortifiers are frequently added to human milk – mother’s own or donor milk – to enhance nutrients, including protein, calcium and phosphorous. This practice raises questions about the impact of bovine-based fortifiers on preterm infant health.

In a 2009 Cochrane Database Review, Kuschel and Harding\textsuperscript{32} analyzed research related to human milk fortification. Noting that current practice, research and clinical ethics have moved beyond the discussion of whether or not to fortify human milk, they recommended further research of fortifier components and comparisons of different fortifier preparations.

The predominant protein in bovine milk and bovine-based human milk fortifiers – casein – has been identified since the 1970s as a chemoattractant to human leukocytes.\textsuperscript{33} Leukocytes

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\textit{neonatal INTENSIVE CARE} Vol. 25 No. 4 • July-August 2012
have specific receptor sites for binding with casein. In laboratory and animal studies, casein activates movement of leukocytes to the casein molecules. Thus, casein is inherently pro-inflammatory, causing activation of mucosal defenses and the release of inflammatory mediators which can progress to NEC, particularly in the presence of pathogenic bacteria.\textsuperscript{16,34,35}

A 2010 study by Sullivan et al\textsuperscript{36} suggests a diet that includes bovine proteins – including those in human milk fortifiers – can have a significant negative impact on preterm infant morbidity and mortality. Their research examined extremely premature infants whose mothers intended to provide their expressed milk for feedings. Infants fell into two basic groups: 1) those who received mother's milk (or human donor milk if needed) plus a newly developed human milk-based human milk fortifier, or 2) those who received human milk (or preterm formula if needed) plus standard bovine-based human milk fortifier. Results indicated extremely low birth weight infants receiving only human milk products had significantly lower rates of NEC and surgical NEC when compared infants fed a mother's milk-based diet that also includes bovine milk-based products. Furthermore, all cases of surgical NEC and all study deaths related to NEC were in infants who had received bovine-based products.

Perhaps in anticipation of concerns about the cost of using human milk-based fortifiers, Ganapathy, Hay and Kim\textsuperscript{37} published a revealing cost analysis in 2011. Using Sullivan's outcomes data, these authors calculated the cost effectiveness of a 100% human milk-based diet comprised of mother's milk and human milk-base fortifier when compared to a diet of mother's milk supplemented with formula and standard fortifier. Their results supported the cost effectiveness of a human milk-based diet; the use of a 100% human milk-based diet could yield a net direct savings of $8,167 per extremely preterm infant.

**Concluding Remarks**

In this article, we have explored a wide range of topics related to the interaction of human milk, the preterm gastrointestinal system and diseases affecting preterm infants. Of particular importance in this discussion is the evidence supporting the ability of human milk to decrease the risk of many life-threatening morbidities in preterm infants, including necrotizing enterocolitis. As we look to improve practice we must make every effort, from the first day of life, to provide human milk to hospitalized infants.

**References**


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Developing a Closed, Intravenous Medication System for a Neonatal Intensive Care Unit

John “Jack” Tanner, RN

The quality of neonatal intensive care is reliant upon a blend of nursing competency, techniques, and technologies each developed specifically for a specialized and fragile patient population. The importance of intravenous medication therapy in the care of these delicate patients is especially critical to their survival. Yet complications that arise from intravenous administration of medications and nutrition are a primary source of serious iatrogenic events such as medication errors and hospital-acquired bloodstream infections. Critically ill, premature infants are especially vulnerable to bloodstream infections (BSIs), because of their immature immune systems, their poor skin integrity, repeated invasive procedures, exposure to numerous caregivers, and being in an environment conducive to bacterial colonization.1,2,3,4 Mitigating these risks, while ensuring essential care, is the challenge of all neonatal intensive care professionals.

To address issues of practice uniformity and infection in their 80-bed tertiary care facility, the neonatal intensive care unit (NICU) at Women & Infants Hospital in Providence, Rhode Island, implemented a custom designed medication administration system in February 2010. With 24,300 patient days annually, the NICU employs 210 nurses and dispenses approximately 175,000 medication doses each year. To guide neonatal medication practice, the facility established a multidisciplinary NICU Medication Task Force (MTF), which consists of representatives from Pharmacy, Nursing, Nursing Management, Risk Management, and Medicine. The group meets monthly to discuss areas to improve the medication processes within the NICU and to track reported errors on the unit. In 2006, a spike in central line infection rates as well as an increase in reported medication errors motivated the task force to evaluate discrepancies in medication administration practices.

Over the years, the nurses employed in the Women & Infants Hospital NICU had given medications via different routes and methods. In 2006, the NICU staff utilized a medication administration system that consisted of a positive flow needlefree IV connector that was attached to a tri-fuse or quad-fuse connector. The nurse would prime 0.3 mL extension tubing to administer a medication. The NICU staff also used Medex MedFusion 2001 syringe pumps when delivering intravenous medications. It was observed that nurses were giving medications differently using the various IV connectors available, thus causing potential errors with the incompatibility of medications and total parental nutrition (TPN). Likewise, nurses programed the syringe pumps differently based on inconsistent training. Some nurses elected to program infusions by a volume-over-time method, while others were trained to program only continuous infusions. The lack of a clear practice standard when administering medications created confusion and increased the potential for medication errors to occur.

The intravenous medication system employed in the NICU in 2006 was an open-ended luer design that worked with a positive pressure needlefree connector. Positive displacement designs were created to reduce the backflow of blood into the device, which can lead to clotting and requires clinicians to add an anticoagulant, such as heparin to saline flushes, as a precaution. However, the more complex mechanisms required to maintain positive displacement made the devices harder to disinfect, flush completely, and use correctly. Although it was several years before the FDA called for a formal investigation of positive displacement IV connectors, the clinical literature at the time indicated that these devices presented an increased risk of BSI.5 The Society for Hospital Epidemiologists of America (SHEA), the Association for Practitioners in Infection Control (APIC)6 and others raised the issue with the temporal relationship between a rise in central line associated bloodstream infections (CLABSIs) and a change in needlefree connection device. The task force took this information into consideration, recognized the threat to patient safety, and identified the need to change medication administration methods on the unit. The NICU began to investigate a system that would address these safety issues by enforcing consistent medication administration processes that fostered a safer environment for the patients in the unit.

New IV System Development

Advances are continually being made in the devices and materials used to infuse medications in the acute care setting. When new products with potential value are identified by Women & Infants Hospital professionals, the technology is presented to the MTF. In 2007, the MTF decided to make the switch from positive pressure needlefree valves to a neutral displacement IV connector. The replacement connector was selected based on several design features. A split-septum design, for example,
has been noted in the Centers for Disease Control (CDC) draft guidelines as a preferred design feature for connectors while a straight fluid path allows for clearing of blood and blood residual with low flush volumes. Minimal dead space (also referred to as residual volume) allows for lower flush volumes, and a flat, smooth, swappable surface facilitates more effective hub disinfection.

Rather than simplify the system for nurses, the task force felt that a stopcock system would introduce complexity to the workflow and potentially contribute to medication administration errors. To address these concerns, ICU Medical introduced a device concept that could be adapted to the NICU. The intravenous device consisted of two one-way valves with a MicroClave attached to IV tubing maintaining a closed system without the use of a stopcock.

Using a one-way valve system and existing tubing sets, a task force member created a model of the closed IV system. A tri-fuse (3-way IV tubing connector) was attached to one port via 0.3 mL extension tubing, dedicating one port for fat emulsions, one for TPN, and one for medication administration. The one-way valve system connected to the 0.3 mL tubing and standard IV tubing was added to the end of the set. The model was presented to the ICU Medical development team, which then set out to create a prototype of the custom set.

Testing
ICU Medical submitted multiple prototypes of the closed IV system to the MTF. Nursing staff members tested the manufacturer prototypes and provided feedback. Working with an IV tubing manufacturer, the team sought to achieve a balance between fluid volume and tubing length in the med-line portion of the system. It proved challenging to configure the tubing length appropriately to offer sufficient tubing while maintaining a low volume for flushing medications through the system. Volume control in the med-line is especially critical to the neonatal patient population who can be negatively affected by excessive volumes. The balance between low volume and
tubing length also affected the syringe pumps used for infusions. If the diameter of the tubing was too small, pressure in the lines increase causing the syringe pumps to alarm and potentially decreasing the effectiveness of the tubing. To avoid this complication, each closed system prototype was tested on the MedFusion 2001 syringe pumps to ensure that the pumps did not alarm when administering a sample medication on the system.

**Evaluation**

Gathering input from the NICU nursing staff was an essential element of moving forward with the closed IV system. Once a prototype was developed, ICU Medical produced sterile sample sets for trial in the NICU. The trial took place for one month between June 28th and July 25th, 2009. To prepare the nursing staff, the hospital held inservicing sessions, provided PowerPoint presentation tools, and created a poster board to introduce the new medication system. Approximately 80 percent of the nurses were trained on the trial medication system initially.

Infants who were on intermittent IV medications participated in the trial while patients who were critical and/or prescribed continuous drips were excluded. Simple four-question evaluations were provided to the nurses to give their feedback on the set. Thirty-one evaluations were completed.

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<th>YES</th>
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<td>2) Did you have any difficulty priming the system?</td>
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<td>4) Was it easy to fill the flush syringe and reset the pump for the flush?</td>
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Table 1: Medication Administration System Evaluation

The evaluation also elicited comments from the users to help further improve the closed medication system. Feedback included a request for a fourth port on the system for use with continuous infusions. Nurses expressed a concern that the tubing was too long causing it to become tangled or fall on the floor. With the feedback provided, an improved design was submitted to the manufacturer for further design refinement. As a result, the subsequent design included a fourth port and a clip to hold excess tubing and prevent it from falling on the floor or tangling.

**Implementation**

On February 16th, 2010, the closed IV system was implemented in tandem with the new MedFusion 3500 smart syringe pump. Training began in December 2009 for all NICU nurses utilizing a super user method of training to in-service the entire nursing staff on the closed system and the new smart pumps. There were 26 super users responsible for assisting in teaching classes and providing support during the “Go Live” period. The classes were scenario-based to simulate giving medications on the systems and programming the pumps. There was 100 percent attendance from nursing staff. Super users remained available as resource personnel to assist nurses with administering medications with the closed system and the new smart pumps.

**Results**

Since implementing the new closed IV system and smart infusion devices, the number of reported medication errors has decreased. In the 2009-2010 timeframe, there were 138 medication events reported as compared to only 63 events documented in the subsequent 12 months, representing a 54.3 percent reduction in reported medication errors. Much of this error reduction was ascribed to the use of the closed system, which ensures that nurses deliver intermittent IV medications via a single, consistent method.

In addition to the introduction of the closed IV system, the NICU initiated several additional measures to reduce bloodstream infection rates. A bundle line program began in 2009 introducing two-nurse sterile central line changes, the use of the MicroClave neutral displacement needlefree connector, the use of chlorhexidine gluconate (CHG) for skin antisepsis during line changes, and the implementation of the closed IV system. As a result, infection rate per 1,000 line days has steadily fallen in the past five years.

<table>
<thead>
<tr>
<th>Year</th>
<th>Infection rate per 1,000 line days</th>
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<tr>
<td>2007</td>
<td>5.6</td>
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<td>2008</td>
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Table 2: Infection Rate Trend 2007 - 2011

**Conclusion**

Women & Infants Hospital dedicated four years to the development and testing of a customized closed IV system designed to meet the needs of the NICU environment. The design focused on the creation of a standardized medication administration process that fosters a high degree of nurse compliance. The closed system incorporated the use of neutral displacement IV connector technology to reduce the incidence of infection correlated with positive pressure connectors. Feedback and input from NICU nurses was vital in every step of the process to ensure success of this initiative. The nursing staff provided confirmation that the closed system worked well with the facility’s smart infusion pump technology and offered valuable information to improve the design of the system and enhance the training experience. As a result, the hospital has documented reductions in NICU infection rates and medication errors.

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Volume-Targeted vs Pressure-Limited Ventilation in the Neonate

Karl Kaminski, RRT-NPS; Ray Braxton, RRT

There is a saying in practicing respiratory therapy that if you wait long enough, the practices of earlier decades will become the new practices of the future. During the late 1970s, I [Kaminski] remember utilizing the Bourns LS 104-150 piston-driven volume targeted ventilator for support of difficult to ventilate neonates. Generally, the practice that I experienced working with neonates at that time was to start all infants utilizing pressure-limited ventilation (PLV) on the Bear BP 200 ventilator and to convert to volume targeted ventilation (VTV) on the Bourns LS 104-150 if the infant experienced uncontrolled fluctuating PaCO2 levels. The LS 104-150 had an ancillary volume monitoring unit that the respiratory therapist used to adjust targeted tidal volume delivery. In the early 1980s, efforts at VTV were mostly abandoned with the further development in time-cycled, pressure-limited, constant-flow ventilators, which have been the primary method of ventilating infants for the past 30 years. Recent improvements in signal processing, servo-controlling and volume monitoring have made VTV a reality again for even the smallest of patients.

In 2011, a Cochrane Review was published that addressed the question of whether to ventilate a neonate with volume or with pressure modes of ventilation. The background for this review centered on evidence that points to damage caused by lung over distention (volutrauma) or under-distension (atelectrauma) leading to the development of bronchopulmonary dysplasia (BPD) in newborns requiring mechanical ventilatory support. The objective for this review was to determine whether volume-targeted ventilation compared with pressure-limited ventilation leads to reduced rates of death and development of BPD. Secondary objectives were to determine whether use of VTV affected outcomes including air leak, cranial ultrasound findings and neurodevelopment. The authors’ conclusion from this review found improvements in important outcomes that favor a VTV strategy. Compared with PLV, infants ventilated using VTV had reduced deaths/BPD, shortened duration of ventilation and less incidents of pneumothoraces, hypocarbia and periventricular leukomalacia/severe intraventricular hemorrhage.

Tracheal tube (TT) air leak related to the use of uncuffed neonatal endotracheal tubes often poses a challenge to the clinician. Accurate measurement and delivery of appropriate tidal volumes during mechanical ventilation can be problematic.

A recently released retrospective clinical study conducted by Ramadan, et al concluded that:
- Volume monitoring in mechanically ventilated neonates is a prerequisite for lung-protective mechanical ventilation.
- TT leaks of > 40% indicate that the displayed VT was underestimated by 1.2 mL/kg (about 24% of target VT). (This was specific to [one particular brand of] infant ventilator, however; the same underestimation of actual delivered volume would occur anytime expired volume was used to assess achieving the set volume target.)
- High TT leak increased with smaller TT diameter, reduced birth weight, and extended duration of mechanical ventilation, indicating that very low-birth-weight infants are at greater risk of TT leak.

There are many different ways of delivering, monitoring and adjusting tidal volumes. Targeting a set pressure demands close vigilance of delivered tidal volumes. With changes in resistance or compliance, clinicians may observe large changes in tidal volume. Maintaining appropriate ventilation (as evidenced by stable blood gas results) may prove difficult.

In the face of significant leaks, optimizing the performance of some ventilators in VTV modes can be challenging for the respiratory therapist. The characteristics of ventilators used to provide support to neonates may influence success with VTV. For instance, a ventilator that uses inspired volumes as a target reference for delivered tidal volume may tend to underventilate patients in the presence of an airleak around an uncuffed endotracheal tube. On the other hand, ventilators targeting expired volumes exclusively, need to have protective mechanisms or volume limitations imposed to avoid an excessively large volume being delivered, should the air leak go away with repositioning or changing physiologic factors.

Surfactant replacement for infants experiencing respiratory distress has become routine therapy. It is not uncommon to see dramatic changes in an infant’s lung mechanics within minutes of receiving surfactant.

Often, delivered tidal volumes in a pressure-limited mode dramatically increase leading to hypocarbia for the infant and long term neurological sequelae related to cystic brain lesions (periventricular leukomalacia). Volume targeted ventilation has the advantage of keeping tidal volumes consistent, thereby avoiding these tidal volume changes.
Another advantage of VTV is during “BPD” spells. Though much less common today, acute episodes of desaturation and bradycardia are often seen in infants with BPD. Extremely low birth weight infants breathing air months before they are physiologically prepared to do so experience abnormal alveolar, small airway, and vascular development. The resultant hyperactivity of the airway and impaired airway clearance results in acute bouts of cyanosis and bradycardia. In PLV, the patient still receives the same level of pressure but the volumes to the baby are dramatically reduced resulting in cyanosis, hypercarbia and bradycardia. During VTV, volumes are noted to decrease so the ventilator increases pressure to bring the volume to the pre-set value resulting in improved ventilation, decreasing the number of episodes experienced by the infant.

Over the past several years there has been resurgence in providing VTV to the neonatal population of patients for various reasons. Whether your practice with the neonatal population centers on PLV versus VTV depends heavily on the capabilities of the selected ventilator to provide accurate and reliable information to the respiratory therapist and is able to react to the ever-changing pulmonary dynamics of the neonate.

References
Abstract
Background: Systemic Candida infections are of major concern in neonates, especially in those with risk factors such as longer use of broad spectrum antibiotics. Recent studies showed that also term babies with underlying gastrointestinal or urinary tract abnormalities are much more prone to systemic Candida infection. We report a very rare case of candidiasis caused by Candida kefyr in a term neonate.

Case Presentation: Renal agenesis on the left side was diagnosed antenatally and anal atresia postnatally. Moreover, a vesico-ureteral-reflux (VUR) grade V was detected by cystography. The first surgical procedure, creating a protective colostoma, was uneventful. Afterwards our patient developed urosepsis caused by Enterococcus faecalis and was treated with piperacillin. The child improved initially, but deteriorated again. A further urine analysis revealed Candida kefyr in a significant number. As antibiotic resistance data about this non-albicans Candida species are limited, we started liposomal amphotericin B (AMB), but later changed to fluconazole after receiving the antibiogram. Candiduria persisted and abdominal imaging showed a Candida pyelonephritis. Since high grade reflux was prevalent we instilled AMB into the child's bladder as a therapeutic approach. While undergoing surgery (creating a neo-rectum) a recto-vesical fistula could be shown and subsequently was resected. The child recovered completely under systemic fluconazole therapy over 3 months.

Conclusions: Candidiasis is still of major concern in neonates with accompanying risk factors. As clinicians are confronted with an increasing number of non-albicans Candida species, knowledge about these pathogens and their sensitivities is of major importance.

Background
Systemic Candida infections in children are of major concern in preterm infants, neonates with risk factors and in immunocompromised children. Further risk factors such as use of central venous catheters, longer use of broad spectrum antibiotics and use of parenteral nutrition contribute as well. Over the last decade non-albicans Candida species are emerging as causative pathogens for systemic Candida infections in children. Here, we report of a candidiasis caused by Candida kefyr in a term neonate.

Case Presentation
After an uneventful birth anal atresia was observed and a vesico-ureteral-reflux (VUR) grade V was detected by cystography. Renal agenesis on the left side was already diagnosed antenatally. The first surgical procedure, creating a protective colostoma, on day 2 was uneventful. The child was treated with intravenous cefotaxime for 10 days and was put hereafter on cefixime prophylaxis. On day 21 the patient developed an urosepsis caused by Enterococcus faecalis which was treated with piperacillin according to the antibiogram. After initial improvement the child deteriorated again 10 days after initiation of antibiotic treatment. Antibiotic therapy was changed to imipenem, gentamicin and vancomycin. A lumbar puncture showed normal results, but the urine analysis revealed significant fungal growth (106 CFU/mL). Primary isolation was performed on Candida ChromTM Agar (BD) which yielded growth of large rough pink colonies, resembling Candida krusei. Therefore systemic antifungal therapy was initiated with liposomal amphotericin B (AMB). Further identification of the suspected non-albicans Candida species was performed by biochemical identification using the API 20 C AUX (BioMerieux) biochemical identification panel which yielded excellent identification (probability > 99.9%, profile number 7220300031). This biochemical result was confirmed by sequencing of the internal transcribed spacer (ITS) regions using primer pairs ITS 1 and ITS-4. Both primers span the complete ITS1, 5.8S, and ITS2 regions. A databank search of the amplified sequences revealed 99% and 100% homology with the ITS region from Kluyveromyces marxianus which represents the teleomorph form of Candida kefyr. Susceptibility testing against fluconazole, amphotericin B (AMB), and caspofungin was performed by ellipsometer test (‘E-test”) and showed a minimal inhibitory concentrations (MIC) of 0.25 μg, 0.047 μg, and 0.25 μg, respectively. All tests were repeated two times with similar results. The inoculum for susceptibility testing was generally performed by pooling of 10–20 individual colonies. No macrocolonies were observed in the inhibition zone of the E-test. Further subplating and antibiotic susceptibility testing of individual colonies in order to detect antibiotic susceptibility variants was not performed. Species-specific susceptibility breakpoints for Candida kefyr have neither been published by the clinical laboratory institute (CLSI) nor by the European committee on antimicrobial susceptibility testing.

The authors are with the University Hospital Mannheim of Heidelberg University, Mannheim, Germany. Reprinted from BioMed Central, BMC Infectious Diseases, © 2012 Weichert et al; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License. This article has been slightly edited for our readers.
(EUCAST). Therefore we used the EUCAST breakpoints for Candida albicans for the interpretation of the MICs obtained with the Candida kefyr isolate. According to these breakpoints the isolate was susceptible to all three antifungal agents tested. After the availability of susceptibility data antifungal treatment was changed to fluconazole. Although the child improved clinically, a significant candiduria persisted and renal ultrasound showed persistent signs of Candida pyelonephritis (Figure 1). Blood culture results turned out to be negative. An initial contrast enema did not show a connecting fistula between bladder and rectum. But due to the clinical course a fistula was suspected and surgical repair of the anorectal atresia was performed. While undergoing surgery (creating a neo-rectum) a recto-vesical fistula was found and subsequently was resected. Since high grade reflux was prevalent in our patient AMB (1 μg/mL) was successfully instilled into the child’s bladder twice daily over 7 days. Candida kefyr was isolated for the last time after 7 days of treatment, afterwards, all tested urine cultures remained sterile and a second blood culture remained sterile as well. The child recovered completely under systemic fluconazole therapy (8 mg/kg/day) over 3 months.

Discussion
The high burden of systemic Candida infection in children with risk factors led to a significant increase in fluconazole use over the last decades, which was accompanied by an increased incidence of non-albicans Candida species. Interestingly, susceptibility of the main causative pathogen Candida albicans to fluconazole remains stable. In contrast, a recent study showed only 82% susceptibility of all isolated non-albicans Candida species to fluconazole. Data regarding susceptibilities of antifungal agents against Candida kefyr are limited. The isolated Candida kefyr from our patient was fully sensitive to fluconazole. In a 10.5-year world-wide surveillance study resistance to fluconazole ranged from 3.3% in the first 4 study years to 1.7% for all Candida kefyr isolates in the last 3 study-years. So far, good susceptibilities of AMB against most non-albicans Candida species were shown, although country specific differences were observed. According to a study from Pfaffer et al. the susceptibility of Candida kefyr to amphotericin B appears to be quite low (4 of 10 isolates were susceptible at ≤1 μg/mL). A study conducted in Germany involving mainly adult patients showed an increased MIC of AMB for 9% of all Candida kefyr isolates, whereas a more recent study from Spain showed no increased MIC of AMB.

Although our patient had recurrent infections due to Candida kefyr and had clinical symptoms of systemic disease the pathogen Candida kefyr was only isolated from urine cultures and not from blood cultures or other sites. Our patient suffered from grade V reflux, that may lead to an ascending kidney infection. However, it is reported that amongst clinical signs for systemic disease isolated candiduria may be the only indication for candidaemia. Studies confirmed that blood cultures are 40–75% false negative in patients with candidiasis, as demonstrated in patients with autopsy proven candidiasis. In addition to clinical signs of systemic disease, our patient had renal involvement as well, such as parenchymal changes on ultrasound. An ascending infection would be expected to result in isolated pelviccalyceal disease, and it is known that hematogenous spread is the most common route for renal candidiasis. Therefore, it is conceivable, that patients may have transient candidemia that may lead to organ involvement. Nevertheless, it is known that blood cultures are often no longer positive when renal candidiasis becomes manifest. As candiduria is regarded as a risk factor for invasive candidiasis clinicians should be aware of this, even though blood cultures might remain negative.

Up to now Candida kefyr is considered as not pathogenic to healthy individuals, but has been discussed as an emerging pathogen in patients with risk factors. Pediatric data are sparse, reporting isolation of Candida kefyr from 1.8% to 4% of all isolated Candida species from mainly preterm und low birth weight neonates. In adults Candida kefyr has been reported to cause systemic Candida infection in patients with neutropenic leukemia and in a woman with underlying heart disease. Very recently Candida kefyr was described as a pathogen causing invasive fungal enteritis in a patient with underlying haematological disease following bone marrow transplantation.

Of note, Sendid et al report a twofold detection rate of Candida kefyr isolates from adult patients in oncohematology wards compared to patients in other wards (4.8% vs 1.9%). Up to now, it is not known why Candida kefyr is found more often in these patients. Induced selection of Candida kefyr following antimicrobial therapy or prophylaxis is discussed, as well as factors that might influence gastrointestinal homeostasis in favour of Candida kefyr. Furthermore, as Candida kefyr is commonly found in dairy products, dietary habits might influence or promote colonization and subsequent infection in patients as well.

Conclusion
As clinicians are confronted with an increasing number of non-albicans Candida species, knowledge about these pathogens and their sensitivities is of major importance. In children with recurrent candiduria systemic infection and organ involvement should be ruled out, even though blood cultures might remain negative.

Figure 1 Renal ultrasound. Hyperechogenic renal parenchyma due to persistent Candida pyelonephritis and massive pelviectasis.
References


Infant Flow Biphasic Nasal Continuous Positive Airway Pressure (BP-NCPAP) vs Infant Flow NCPAP for the Facilitation of Extubation in Infants ≤ 1,250 Grams

Karel O’Brien, Craig Campbell, Leanne Havlin, Lisa Wenger, Vibhuti Shah

Abstract

Background: The use of mechanical ventilation is associated with lung injury in preterm infants and therefore the goal is to avoid or minimize its use. To date there is very little consensus on what is considered the “best non-invasive ventilation mode” to be used post-extubation. The objective of this study was to compare the effectiveness of biphasic nasal continuous positive airway pressure (BP-NCPAP) vs NCPAP in facilitating sustained extubation in infants ≤ 1,250 grams.

Methods: We performed a randomized controlled trial of BP-NCPAP vs NCPAP in infants ≤ 1,250 grams extubated for the first time following mechanical ventilation since birth. Infants were extubated using preset criteria or at the discretion of the attending neonatologist. The primary outcome was the incidence of sustained extubation for 7 days. Secondary outcomes included incidence of adverse events and short-term neonatal outcomes.

Results: Sixty-seven infants received BP-NCPAP and 69 NCPAP. Baseline characteristics were similar between groups. The trial was stopped early due to increased use of non-invasive ventilation from birth, falling short of our calculated sample size of 141 infants per group. The incidence of sustained extubation was not statistically different between the BP-NCPAP vs NCPAP group (67% vs 58%, P = 0.27). The incidence of adverse events and short-term neonatal outcomes were similar between the two groups (P > 0.05) except for retinopathy of prematurity which was noted to be higher (P = 0.02) in the BP-NCPAP group.

Conclusions: Biphasic NCPAP may be used to assist in weaning from mechanical ventilation. The effectiveness and safety of BP-NCPAP compared to NCPAP needs to be confirmed in a large multi-center trial as our study conclusions are limited by inadequate sample size.

Keywords: Biphasic NCPAP, Infants, Extubation, Weaning, Neonatal Intensive Care

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functional residual capacity is recruited by the upper CPAP level and maintained with the lower baseline CPAP level, thus decreasing the work of breathing. To date there have been no studies comparing the use of these two modes of non-invasive ventilation in preterm infants to facilitate sustained extubation following an initial period of intubation and positive pressure ventilation at birth.

The primary goal of this study was to compare the effectiveness of BP-NCPAP vs NCPAP using the Infant Flow SiPAP system in facilitating sustained extubation in preterm infants < 1,250 grams. The secondary goals were to compare the adverse events and short-term neonatal morbidities between the two groups.

**Methods**

In this randomized controlled trial we included intubated infants with birth weight < 1,250 grams. Infants with congenital abnormalities of the upper airway tract, acquired nasal septum injury and major congenital or chromosomal abnormalities were excluded. The study was conducted at a tertiary care NICU, Mount Sinai Hospital, Toronto, Ontario, Canada, during the period from April 2006 to November 2008.

Parents of eligible infants were approached for participation in the trial and written informed consent was obtained prior to extubation. A marker was then placed at the bedside of eligible infants whose parents had given consent. Randomization cards were generated using a computer generated random numbers list. The cards were sealed in sequentially marked opaque envelopes and opened immediately prior to the first extubation. Infants were randomized to one of two groups: BP-NCPAP or NCPAP delivered by the Infant Flow SiPAP. The assigned mode of support was continued until the infant was ready to be placed in room air or supplemental oxygen. The study was approved by the local Research Ethics Board.

Preset criteria were used to guide extubation using a consensus approach amongst neonatologists in our NICU. For conventional ventilation the criteria included: a ventilator rate of < 20 breaths per minute (bpm), peak inspiratory pressure (PIP) < 16cm H2O and fractional inspired oxygen (FiO2) of < 0.35. For high frequency ventilation the criteria were: frequency of 9-13 Hz, amplitude < 20 percent, mean airway pressure (MAP) of < 8cm H2O and FiO2 < 0.35. Once an infant reached these preset criteria, the medical team was approached for consideration of extubation. In the event of accidental extubation in eligible consented infants, face mask CPAP was applied for no more than 15 minutes until a decision was made either to reintubate based on the clinical condition or to randomize to the study group. All infants had the appropriate bonnet, nasal prong interface and Cannulaide (Beevers Manufacturing Inc, McMinnville, OR) applied.

In the BP-NCPAP arm the respiratory rate was set at 20 bpm with an inspiratory time of 1.0 second. The upper level of CPAP was set 3 cm above the lower (baseline) level of CPAP. In both modes the lowest baseline CPAP was set at 5 cm H2O and the CPAP was titrated according to the infant’s FiO2 needs based on an algorithm (Table 1). Neither mode of NCPAP was synchronized with the infant's respiratory effort. Weaning in both groups was left at the discretion of the attending neonatologist. If the infant remained clinically stable in FiO2 < 0.25 with no evidence of increased work of breathing and/or apnea of prematurity, then attempt was made to trial off CPAP.

Criteria for reintubation included: presence of severe apnea (defined as need for positive pressure ventilation), > 4 minor apneic episodes per hour requiring moderate stimulation, required supplemental oxygen of > 60% to maintain oxygen saturation > 88%, developed uncompensated respiratory acidosis (defined as pH < 7.25) or a combination of the above. Apnea was defined as cessation of respiration for > 20 seconds or a shorter pause if associated with bradycardia (heart rate < 100 beats per minute) or desaturation (< 85%). Reintubation was also allowed at the discretion of the attending medical team for other reasons, e.g., concerns regarding sepsis. Data were collected for the duration of their in-hospital stay. Other medical therapy and interventions were provided at the discretion of the medical team.

In our unit, caffeine is usually commenced in the first week of life even if the infant requires positive pressure ventilation via endotracheal tube. A loading dose of 10mg/kg followed by maintenance dose of 2.5 mg/kg is administered within 24-36 hours. Based on the clinical response the maximum dose of maintenance caffeine used is 5 mg/kg.

Data were collected on maternal characteristics including age, gravidity, parity, pregnancy induced hypertension, essential hypertension, preterm prolonged rupture of the membranes (> 18 hours), antenatal steroids (complete and partial course), and clinical and histological diagnosis of chorioamnionitis from maternal health records and placental pathology.

The primary outcome was the incidence of sustained extubation for 7 days. Secondary outcomes included incidence of adverse events such as: nasal septal injury/erythema, eyelid edema, abdominal distension, feeding intolerance and pneumothorax. Nasal septal injury/erythema and eyelid edema were monitored and recorded every 4 hours by the respiratory therapists and the nursing staff. Data on feeding intolerance (defined as aspires of > 30% of a single feed administered) and abdominal distension (defined as >10% increase in abdominal girth) were recorded by the nursing staff every 4 hours and/or prompted by clinical concerns. Data on the other clinical outcomes including the incidence of BPD [oxygen dependency at 36 weeks post menstrual age (PMA)], patent ductus arteriosus (PDA) (diagnosed clinically or by ECHO and treated with indomethacin + surgery), necrotizing enterocolitis (NEC) (Bell's stage 2 or greater),13 grade 3/4 intraventricular hemorrhage (IVH)16 or periventricular leucomalacia (PVL) and retinopathy of prematurity (ROP) were abstracted from the chart. Retinopathy of prematurity was classified according to the international classification.17 Infants who died were excluded from the analysis for ROP and for BPD if they died before they reached 36 weeks PMA. In our unit, PDA is treated pharmacologically (with indomethacin) based on the presence of clinical symptoms and signs. Prior to administration of a second course of indomethacin or referral for surgical ligation, infants undergo echocardiography. Both caregivers administering the interventions and research assistants were not blinded to the group assignment.

The sample size calculation was based on the results obtained from a previous study that compared the rate of sustained extubation using NCPAP vs high flow oxygen in our unit. The rate of sustained extubation with NCPAP was 85%.18 To demonstrate a clinically significant increase in the rate of sustained extubation by 10% between groups (i.e. from 85% to
93.5%) with 80% power and an alpha value of 0.05, we estimated a sample size of 141 patients in each arm for a total of 282 patients.

The analysis was performed using the intention-to-treat principle. Baseline maternal and infant characteristics and outcomes of the infants randomized to both modes were compared using 2 test for categorical data and Student’s t test for continuous data. The Wilcoxon rank sum test was used to compare continuous data with highly skewed distributions. All reported P values are two sided. A planned secondary analysis examined the predictors of successful extubation using multivariate logistic regression to control for possible confounders including birth weight, sex, age, at the time of first extubation, accidental extubation and use of antenatal steroids. All statistical analyses were performed using the computer program Statistical Package for the Social Sciences v.12 (Chicago, IL). A P value of 0.05 was considered significant.

Results
Of the 534 infants ≤ 1,250 grams admitted to the NICU during the study period, 348 infants were eligible for the study. Parents of 190 infants were approached of whom 43 declined and 147 consented. Four infants died and 7 were transferred to another site prior to randomization. Thus, a total of 136 neonates were enrolled (Figure 1). The trial had to be stopped prematurely prior to enrolment of the intended sample size due to a change in clinical practice in our unit that resulted in fewer infants being intubated from birth. Results are presented for the recruited subjects. No interim analysis was performed.

The demographic characteristics (birth weight, gestational age and sex) did not differ between participants and non-participants. Sixty-seven infants were randomized to BP-NCPAP and 69 to NCPAP. Baseline maternal and neonatal characteristics of the participants are presented in Tables 2 and 3, respectively. There were no significant differences between the two groups.

Discussion
In our study, we were unable to demonstrate the effectiveness of BP-NCPAP in facilitating sustained extubation. Further, the incidence of adverse events, reasons for reintubation and short-term neonatal morbidities except forROP were similar in both groups. There may be several reasons for our inability to show a difference in the primary outcome. Firstly, we were unable to recruit the predetermined sample size to demonstrate a difference due to increasing use of non-invasive ventilation from birth. This is a major flaw of our study. Secondly, the overall rate of sustained extubation in our infants was much lower than anticipated. The rate of sustained extubation in our study ranged from 58% to 67% compared to a rate of 85% used to determine our sample size. Using these revised rates of sustained extubation and an effect size of 10%, we would need to recruit a total of 870 infants to demonstrate a difference. Obviously conducting such a trial requires a collaborative effort and is a major undertaking.

Our a priori hypothesis was to demonstrate/achieve a clinically significant increase in the rate of sustained extubation of 10% with the use of BP-NCPAP. With our limited sample size we were able to demonstrate an increase in the rate of sustained extubation by 9% in the BP-NCPAP group even though this difference was not statistically significant. We cannot rule out the possibility that if we had indeed achieved our targeted sample size we may have been able shown a statistically significant difference. In clinical practice, this difference of 9% may be considered clinically significant as there is increasing trend of using non-invasive ventilation to avoid the consequences of mechanical ventilation.

To our knowledge, there are no previous published studies that have evaluated BP-NCPAP for facilitating successful sustained extubation following intubation and ventilation at birth, ie, used as a secondary mode. The trial was initiated at our site when infants ≤ 1,250 grams were routinely intubated and ventilated at birth and administered prophylactic surfactant if < 27 weeks gestation. Biphasic-NCPAP is considered a form of nasal intermittent positive pressure ventilation (NIPPV) and therefore we compared the results of our study to those of NIPPV when used as a secondary mode. In an updated Cochrane review in 2008, Davis et al. compared NIPPV vs CPAP for preterm infants after extubation. They demonstrated a reduction in extubation failure rate [relative risk (RR) 0.38; 95% confidence interval (CI) 0.16, 0.97] with the use of synchronized NIPPV (data from 3 trials with N = 159) and concluded that it may potentially be a way of augmenting NCPAP when used to prevent extubation failure. Further evidence that NIPPV facilitates successful extubation comes from a recent randomized controlled trial by Moretti et al. in which 94% (30/32) of infants in the NIPPV group were successfully extubated (defined as no reintubation within 3 days) compared with 61% (19/31) in the NCPAP group (P = 0.01). The details of the 4 published trials on NIPPV are presented in Table 7.

The above findings are in contrast to the results of our study. Possible explanations for the difference in the effectiveness of NIPPV compared to BP-NCPAP include variations in the: 1) definition of sustained extubation, 2) the median age of extubation and 3) ventilatory parameters used to prevent reintubation. The duration of successful extubation in the NIPPV trials was defined as 48 hours21 to 72 hours20,22,23 vs 7 days in our study. Further, the median age of extubation was day 3 in our study vs 7 days20,22,23 and 18.5-21 days22 in the NIPPV studies. This later age of extubation may have resulted in resolution of co-morbidities such as a clinically significant patent ductus arteriosus in the first 7-10 days, which could contribute to successful sustained extubation.

As BP-NCPAP is considered to be a form of NIPPV, we conducted a meta-analysis including data from the 4 published studies and our results (Figure 2). The incidence of extubation failure was lower with the use of NIPPV and BP-NCPAP compared to NCPAP [Relative risk (RR), 0.27; 95% confidence interval (CI), 0.17, 0.43; P < 0.01]. No significant statistical heterogeneity was noted for this outcome. The risk difference was -0.30, 95% CI (-0.38, -0.21; P < 0.01). The number needed to prevent one infant from being reintubated was 3 (95% CI, 2, 5).

When we designed our study, there were no previous studies to guide us in our choice of ventilatory parameters to be used to provide effective BP-NCPAP. The maximum upper level of CPAP that can be set with BP-NCPAP is less than that used for NIPPV and with the use of endotracheal tube and ventilation. In our study, the upper level of CPAP varied from 8 to 10 cmH2O based on the oxygen requirements of the infant. The inspiratory and expiratory time were set at 1.0 and 2.0 seconds respectively resulting in a pressure exchange rate of 20 breaths per minute (cycle/minute at upper level). We were unable to synchronize the delivery of the upper level of CPAP with this device. The combination of lack of synchronization with low pressure exchange rate and upper level of CPAP may have been critical.
factors contributing to our failure in facilitating sustained extubation. With most modes of NCPAP or indeed NIPPV synchronization is imperfect, using either a Graseby capsule on the infant’s abdomen or most recently a flow detector at the nares. When a higher rate of ventilation is used as in most modes of NIPPV then synchronization happens more often just by chance. Synchronisation may be important for entrainment of tidal volumes both on inspiration and expiration and that this may in part explain the clinical benefit of synchronized NIPPV.

Recently, BP-NCPAP has been evaluated for infants with moderate respiratory distress syndrome as a primary mode of ventilation. Infants between 28-34 weeks gestation were randomized to either BP-NCPAP or NCPAP in the first hour of ventilation. The use of BP-NCPAP was associated with shorter respiratory support and oxygen dependency with no difference in weight at discharge. The investigators used a pressure exchange rate of 30 bpm, inspiratory time of 0.5-0.7 seconds and upper and lower CPAP levels of 8 and 4.5 cm H2O respectively.

Adverse events such as increased risk of pneumothorax, nasal septal trauma, feeding intolerance, abdominal distension and gram-negative sepsis secondary to nasal mucosal barrier breakdown have been described in the literature with the use of various forms of NCPAP. The incidence of pneumothorax was reported to be 6.8% and 9% respectively in the Supportive Care of Preterm Infants trial.362:1970-1979. When a higher rate of ventilation is used as in most modes of NIPPV then synchronization happens more often just by chance. Synchronisation may be important for entrainment of tidal volumes both on inspiration and expiration and that this may in part explain the clinical benefit of synchronized NIPPV.

**Conclusion**

BP-NCPAP may be used safely and effectively to assist in weaning from mechanical ventilation. However, the effectiveness and safety of BP-NCPAP compared to NCPAP needs to be confirmed/refuted in future studies.

**References**


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**Figure 1. Flow diagram of study participants.**

**Figure 2. Comparison of the effectiveness of NIPPV vs NCPAP to prevent extubation failure.**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NIPPV Events</th>
<th>Total Events</th>
<th>NCPAP Events</th>
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<td>M-H, Fixed</td>
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<td>Barrington 2001</td>
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<td>27</td>
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<td>Friedlich 1999</td>
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<td>7</td>
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<td>0.12 [0.02, 0.91]</td>
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<tr>
<td>Khalaf 2001</td>
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<td>34</td>
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<td>17.5%</td>
<td>0.15 [0.04, 0.60]</td>
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<td>Moretti 2008</td>
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<td>12</td>
<td>31</td>
<td>16.7%</td>
<td>0.16 [0.04, 0.66]</td>
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<tr>
<td>O'Brien 2011</td>
<td>11</td>
<td>67</td>
<td>29</td>
<td>69</td>
<td>39.1%</td>
<td>0.39 [0.21, 0.72]</td>
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<tr>
<td>Total (95% CI)</td>
<td>182</td>
<td>176</td>
<td>100.0%</td>
<td></td>
<td>0.27 [0.17, 0.43]</td>
<td>0.27 [0.17, 0.43]</td>
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<tr>
<td>Total events</td>
<td>20</td>
<td>72</td>
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<td>Heterogeneity: Chi² = 3.36, df = 4 (P = 0.50); I² = 0%</td>
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<td>Test for overall effect: Z = 5.71 (P &lt; 0.000001)</td>
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Favors NIPPV Favors NCPAP


Paracetamol Serum Concentrations in Preterm Infants Treated with Paracetamol Intravenously

Christ-jan J.L.M. van Ganzewinkel, Thilo Mohns, Richard A. van Lingen, Luc J.J. Derijks, Peter Andriessen

Abstract

Introduction: Until now, studies on paracetamol given intravenously have mainly been performed with the pro-drug propacetamol or with paracetamol in preterm babies above 32 weeks of gestation. Studies in these babies indicate that intravenous paracetamol is tolerated well, however studies on the efficacy of intravenous paracetamol are lacking. There are no pharmacokinetic data on the administration of multiple doses of paracetamol in preterm babies with a gestational age below 32 weeks.

Case presentation: We present a case series of nine Caucasian preterm babies, six boys and three girls, with a mean gestational age of 28.6 weeks (range 25.9 to 31.6 weeks). Case one, a girl with a gestational age of 25 weeks and six days, presented with necrotizing enterocolitis. In the second case, a female baby with a gestational age of 26 weeks and two days presented with hematoma. In case three, a female baby with a gestation of 26 weeks and one day developed intraventricular hemorrhage. In case four, a male baby with a gestational age of 31 weeks and four days presented with pain after vacuum delivery. Case five, a female baby born after a gestation of 29 weeks and six days presented with hematoma. In case six, a male baby with a gestation of 30 weeks and six days presented with hematoma. In case seven, a male baby with a gestational age of 30 weeks and six days, presented with caput succedaneum and hematoma. In case eight, a male baby, born with a gestational age of 30 weeks and six days, presented with hematoma. In case nine, a female baby, born with a gestational age of 29 weeks and six days presented with hematoma. These babies were treated with intravenous paracetamol 15mg/kg every six hours. Serum concentrations and aspartate transaminase were determined after prolonged administration. Pain scores were assessed using the Premature Infant Pain Profile.

Conclusion: Paracetamol serum concentrations ranged from 8 to 64mg/L after eight to 12 doses of intravenous paracetamol. Adequate analgesia was obtained in seven babies. During paracetamol therapy the median serum level of aspartate transaminase was 20U/L (range 12 to 186U/L). This case series indicates that prolonged intravenous administration of paracetamol in preterm babies with a gestational age of less than 32 weeks is tolerated well in the first days after birth. However, in the absence of proper pharmacokinetic data in this age group we cannot advocate the use of paracetamol intravenously.

Introduction

Pain management in newborns is limited by the availability of only a few analgesics. The use of opiates in newborns is limited because of potential clinical side effects. As an alternative to opiates, paracetamol is a well-known analgesic in children without significant side effects. There are only limited data on the use of paracetamol in the newborn. The first drafts of the evidence-based guideline regarding pain management in children of the Dutch Pediatric Society supported the intravenous administration of paracetamol (15 mg/kg every six hours) in babies. In advance of the guideline we introduced intravenous administration of paracetamol to preterm babies in our neonatal intensive care unit to reduce the use of opiates. As a safety precaution we determined serum levels of paracetamol and aspartate transaminase in babies with intravenous paracetamol.

After the release of the final version of the nationwide evidence-based guideline on pain assessment and management in children, it became clear that the guideline restricted intravenous administration of paracetamol to term babies after the first month. After the release of the final guideline we discontinued the local policy of intravenous administration of paracetamol in preterm babies. The Institutional Review Board/Independent Ethics Committee was informed afterwards and concluded that the presented data were obtained legally according the Dutch Law on Medical Research with Humans (WMO).

Though the case series of nine is achieved in an unusual manner, we consider the data on paracetamol levels in preterm babies below 32 weeks of gestation as relevant information for future clinical studies.

Case presentations

Case one: A Caucasian female baby was admitted to our NICU after a gestation of 25 weeks and six days. Although delivery started in the hospital the one minute apgar score is not available because no health care provider was present at the time of birth. Her five minute apgar score was six and her birth weight was 890 grams (p50-75). During the third week of life she developed...
necrotizing enterocolitis grade one according to Bell’s criteria. She received 15mg/kg intravenous paracetamol every six hours, with a total of four doses. Co-medications were antibiotics and ranitidine. Pain score, as measured with the Premature Infant Pain Profile (PIPP) decreased from 10 to eight (12 or more reflects moderate to severe pain). After 24 hours paracetamol was discontinued because of low PIPP scores. The paracetamol serum level determined four hours after the last dose was 24mg/L.

**Case two:** A Caucasian female baby, born with a gestational age of 26 weeks and two days, was admitted with respiratory failure to our NICU. She was intubated shortly after delivery. Apgar scores were one and five after one and five minutes respectively. Birth weight was 680 grams (p5-10). Because of hematoma she received 15mg/kg intravenous paracetamol every six hours. Therapy was started four hours after birth. She received a total of six doses. Pain scores decreased from 10 to nine only. Co-medications were antibiotics and caffeine. The paracetamol serum level, which was determined three hours after the last dose, was 29mg/L.

**Case three:** A Caucasian female baby was admitted to our NICU after a gestation of 26 weeks and one day. Shortly after birth she developed respiratory failure and was intubated. Apgar scores were one and five after one and five minutes, respectively. Her birth weight was 800 grams (p25-50). She developed a grade three intra-ventricular hemorrhage for which morphine was started. Further co-medications were antibiotics. In an attempt to stop morphine, paracetamol was started, in a dose of 15mg/kg every six hours. Pain scores were below six during morphine and remained so during paracetamol mono-therapy. She received six doses of paracetamol and the serum level was determined 20 hours after the last dose. The serum level was 12mg/L.

**Case four:** A Caucasian male baby, born with a gestational age of 31 weeks and four days, was admitted to our NICU after vacuum delivery. Apgar scores were eight and nine after one and five minutes, respectively. His birth weight was 1600 grams (p25-50). He received 15mg/kg of intravenous paracetamol every six hours for a total of eight doses. Pain scores decreased from 14 before start of therapy to nine during therapy. The paracetamol serum level was determined 10 hours after the last dose and was 25mg/L.

**Case five:** A Caucasian female baby, born after a gestation of 29 weeks and six days, was admitted with hematoma due to traumatic birth and breech delivery to our NICU. After birth she received cardiopulmonary resuscitation because of apnea and bradycardia. Apgar scores were one and six after one and five minutes, respectively. Her birth weight was 1300 grams (p25). She was diagnosed with hematoma and received 15mg/kg of intravenous paracetamol every six hours starting five hours after birth. She received a total of nine doses of paracetamol. One hour after the last dose her paracetamol serum level was 46mg/L. Thirty hours later the serum level was determined again and was <5mg/L. Co-medications consisted of antibiotics and caffeine. Pain scores decreased from 16 before start of paracetamol to nine during therapy.

**Case six:** A male Caucasian baby was admitted to our NICU after a gestation of 30 weeks and six days. Birth took place in a peripheral hospital and was complicated by breech presentation and forceps delivery. Apgar scores were two and seven after one and five minutes, respectively. Birth weight was 1480 grams (p25). In the first hours of life he developed respiratory failure and was intubated. The baby showed extensive hematoma for which 15mg/kg of intravenous paracetamol every six hours was started. He received a total of 10 doses. Three hours after the last dose his paracetamol serum level was 64mg/L. Co-medications were antibiotics and caffeine. Pain scores decreased from 10 before therapy to six during therapy.

**Case seven:** A Caucasian male baby, born with a gestational age of 30 weeks and six days, was admitted to our NICU after an uneventful preterm delivery. The apgar scores were nine and 10 after one and five minutes, respectively. His birth weight was 1755 gram (p50-75). He was diagnosed with caput succedaneum and also had a small hematoma on one of the upper limbs. Due to high pain scores he received 15mg/kg of intravenous paracetamol every six hours starting two hours after birth. He received a total of 11 doses of paracetamol. His serum paracetamol level was 37mg/L four hours after the last dose. He received no co-medication. Pain scores decreased from 14 before start of paracetamol to seven during analgesic therapy.

**Case eight:** A Caucasian male baby, born after a gestation of 28 weeks and four days, was admitted with respiratory failure due to respiratory distress syndrome to our NICU. Apgar scores were four and eight after one and five minutes, respectively. His birth weight was 860 grams (p25-50). He developed severe abdominal distention on the second day of life and received 15mg/kg of intravenous paracetamol every six hours for a total of 14 doses. There were no radiological signs of necrotizing enterocolitis and his condition improved over the next few days. Co-medications were antibiotics and caffeine. Five hours after the last dose his paracetamol serum level was 8mg/L. Pain scores decreased from 14 before starting paracetamol to three during therapy.

<table>
<thead>
<tr>
<th>Table 1 Clinical data of the case series</th>
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<td>Cases</td>
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below 50 mg/l, the upper margin value reported by Palmer. In two subjects serum values were around 60 mg/l. During neurotic rupture of membranes and an uncomplicated delivery. Apogar scores were six and nine after one and five minutes, respectively. Her birth weight was 990 gram (p50). Due to hematoma and subsequent high pain scores (14) she received 15mg/kg of intravenous paracetamol every six hours. She received a total of 17 doses. Due to inadequate analgesic effect 10μg/kg/hour morphine was started during paracetamol therapy. Her paracetamol serum level, determined seven hours after the last dose, was 61mg/L.

Table 1 summarizes the clinical data of the nine babies. Figure 1 shows the paracetamol serum concentrations of the nine babies, related to the number of doses. In seven babies the serum levels of paracetamol (the black dots) are < 50 mg/l (grey area), the upper margin value found by Palmer for babies > 32 weeks of gestation. The highest serum concentration (64 mg/l) was far below 150 mg/l (indicated by the dotted grey horizontal line), which has been reported as a toxic value in children [3].

Case nine: A Caucasian female baby, born with a gestational age of 27 weeks and three days was admitted to our NICU after preterm rupture of membranes and an uncomplicated delivery. Apogar scores were six and nine after one and five minutes, respectively. Her birth weight was 990 gram (p50). Due to hematoma and subsequent high pain scores (14) she received 15mg/kg of intravenous paracetamol every six hours. She received a total of 17 doses. Due to inadequate analgesic effect 10μg/kg/hour morphine was started during paracetamol therapy. Her paracetamol serum level, determined seven hours after the last dose, was 61mg/L.

Table 1 summarizes the clinical data of the nine babies. Figure 1 shows the paracetamol serum concentrations of the nine babies, related to the number of doses. In seven babies the serum levels of paracetamol (the black dots) are < 50 mg/l (grey area), the upper margin value found by Palmer for babies > 32 weeks of gestation [2]. The highest serum concentration (64 mg/l) was far below 150 mg/l (indicated by the dotted grey horizontal line), which has been reported as a toxic value in children [3].

Discussion
We administered intravenous paracetamol in a dose not supported by literature. The dose we used in preterm babies of less than 32 weeks gestation is being used in term babies, and is not a result of miscalculation due to the differences in formulations of propacetamol and paracetamol [4].

Until now, most studies on intravenous paracetamol have been performed with propacetamol in preterm babies above 32 weeks of gestation. Propacetamol is a pro-drug of paracetamol and is hydrolyzed by plasma esterases after intravenous administration such that 1 g of propacetamol is hydrolyzed to 0.5 g of paracetamol [4]. To our knowledge this is the first report of paracetamol concentration data in preterm babies below 32 weeks of gestation, in whom multiple dose intravenous paracetamol (Perfalgal®) was administered for non-surgical analgesia in the first hours after birth. This case series indicates that in preterm babies below 32 weeks intravenous paracetamol is tolerated well. In seven babies we found serum concentrations below 50 mg/l, the upper margin value reported by Palmer [2]. In two subjects serum values were around 60 mg/l. During paracetamol therapy we found no indications for liver failure. Although the therapeutic window for paracetamol in children is assumed to be 10-20 mg/l, there is no consensus on dosage regimen for intravenous administration of paracetamol in babies. Allegaert, using propacetamol, suggests a maintenance dose of 20 mg/kg every 12 hours for babies below 31 weeks gestational age after a loading dose of 30 mg/kg propacetamol [4]. Using this dose, Allegaert was not able to show significant analgesic effect. However, with a maintenance dose of 12.5 mg/kg every six hours Allegaert showed analgesic effects [6]. Autret suggests a maximum of 7.5 mg/kg every 6 hours after a loading dose of 15 mg/kg propacetamol in newborns for antipyretic effects. Autret did not study the analgesic effect. In term newborns, de la Pintière describes a maintenance dose of intravenous propacetamol of 120 mg/kg/day, equivalent to paracetamol 60 mg/kg/day [8]. Limited data is available concerning the pharmacokinetics of propacetamol and paracetamol [2,5,6,10]. Both Allegaert and Palmer found serum levels of paracetamol between < 6 and 50 mg/l, after a single dose of paracetamol and multiple doses of intravenous paracetamol, respectively. Note that Palmer included preterm babies above 32 weeks of gestation [4]. In a letter to the editor, Bartocci et al report their Stockholm experience of postoperative analgesia with intravenous morphine and paracetamol (maintenance dose 7.5 mg/kg every eight hours) in newborns with a postconceptional age between 25 and 42 weeks [11]. From the letter, however, it is unclear at what postnatal age paracetamol is given and no paracetamol concentration data are shown. Several cases report accidentally given overdoses of propacetamol or paracetamol. Two doses of approximately 300 mg/kg propacetamol (equivalent to 150 mg/kg propacetamol) at a 6 hour interval given to a term baby, resulted in a serum level of 166 mg/l without signs or symptoms of liver failure [9]. Two babies born prematurely after maternal overdose of paracetamol had serum concentrations of 76 and 260 mg/l respectively, without apparent adverse effects [12,13]. A paracetamol overdose in a preterm baby resulted in a serum concentration of 121 mg/l [14].

Recently, Bristol-Myers Squibb Pharmaceuticals Ltd issued a letter with drug safety information concerning accidental overdose in 23 world wide cases. All were babies younger than one year, one of whom died. Scope of the letter was a raising concern on the possible confusion in prescribing ml/kg instead of mg/kg, leading to a tenfold overdose [15]. The letter does not provide information on serum levels or liver functions in these cases.

Conclusion
This case series is no formal pharmacokinetic study. Obviously, the small sample size and the single serum concentration limit
a pharmacokinetic interpretation of paracetamol therapy in preterm babies. Still, this case series of nine very preterm babies indicates that paracetamol administration in a maintenance dose of 15 mg/kg/day every six hours results in paracetamol concentrations that are in the range of others.2,5,10 It suggests that intravenous paracetamol is tolerated well in the first hours after birth in very preterm babies. However, since proper pharmacokinetic data in this age group is still lacking, we cannot advocate the use of paracetamol intravenously based on our observations. It is obvious that future studies should target determination of dosing regimens to achieve maximum analgesic effect (efficacy) without adverse effects (tolerance) in newborns in the first four weeks after birth.

References

15 Campello-Iddison V: Direct Healthcare Professional Communication on serious cases of accidental overdose reported in infants and children with intravenous paracetamol 10 mg/mL solution for infusion 2010. Middlesex, Bristol-Myers Squibb Pharmaceuticals Ltd.
Population Based Trends in Mortality, Morbidity and Treatment for Very Preterm and Very Low Birth Weight Infants Over 12 Years

Christoph Rüegger, Markus Hegglin, Mark Adams, Hans Ulrich Bucher

Abstract

Background: Over the last two decades, improvements in medical care have been associated with a significant increase in survival and better outcome of very preterm (VP, < 32 completed gestational weeks) and very low birth weight (VLBW, < 1500 g) infants. Only a few publications analyze changes of their short-term outcome in a geographically defined area over more than 10 years. We therefore aimed to investigate the net change of VP- and VLBW infants leaving the hospital without major complications.

Methods: Our population-based observational cohort study used the Minimal Neonatal Data Set, a database maintained by the Swiss Society of Neonatology including information of all VP- and VLBW infants. Perinatal characteristics, mortality and morbidity rates and the survival free of major complications were analysed and their temporal trends evaluated.

Results: In 1996, 2000, 2004, and 2008, a total number of 3,090 infants were enrolled in the Network Database. At the same time the rate of VP- and VLBW neonates increased significantly from 0.87% in 1996 to 1.10% in 2008 (p < 0.001). The overall mortality remained stable at 13%, but survival free of major complications increased from 66.9% to 71.7% (p < 0.01). The percentage of infants getting a full course of antenatal corticosteroids increased from 67.7% in 1996 to 91.4% in 2008 (p < 0.001). Surfactant was given more frequently (24.8% in 1996 compared to 40.1% in 2008, p < 0.001) and the frequency of mechanical ventilation remained stable at about 43%. However, the use of CPAP therapy increased considerably from 43% to 73.2% (p < 0.001). Some of the typical neonatal pathologies like bronchopulmonary dysplasia, necrotizing enterocolitis and intraventricular hemorrhage decreased significantly (p ≤ 0.02) whereas others like patent ductus arteriosus and respiratory distress syndrome increased (p < 0.001).

Conclusions: Over the 12 year observation period, the number of VP- and VLBW infants increased significantly. An unchanged overall mortality rate and an increase of survivors free of major complication resulted in a considerable net gain in infants with potentially good outcome.

Background

Very preterm birth is a major cause of mortality and morbidity for newborns and imposes a considerable burden on limited health care resources. Over the last two decades, changes in perinatal management have been associated with a significant increase and better outcome of these infants. However, the majority of these reports are based on single centers or neonatal networks not representing the whole population. In addition data may be biased by different criteria for referral, admission or treatment. Only a few publications analyze the short-term outcome of these infants on a nationwide basis over more than ten years. On these grounds, the Swiss data from 1996, 2000, 2004, and 2008 were analyzed, focusing on temporal trends in mortality, morbidity and treatment for VP- and VLBW infants. Special importance was attached to the short-term survival free of major complications. Beyond that, temporal changes in the length of hospital stay as a substitute for the resources needed were followed. These results were finally compared with studies in other countries. Referring to previous population-based studies, we hypothesized that improvement in obstetric and perinatal management led to a decrease in mortality resulting in more survivors with disability.

Methods

The Swiss Neonatal Network & Follow-Up Group, a non-profit voluntary collaboration of health care professionals was founded by the Swiss society of Neonatology in 1995 with the goal to improve the quality of neonatal care. Today, the Network comprises all nine Neonatal Intensive Care Units (NICUs), most of the smaller Neonatal Units (NUs) and most Neuropediatric Centres caring for VP and VLBW infants in Switzerland under the auspices of the Swiss Society of Neonatology. The Network maintains a Minimal Neonatal Data Set (MNDS) collecting anonymous information about the demographics and outcome of all live born infants between 400 and 1500 g birth weight and/or between 23 0/7 and 31 6/7 gestational weeks, born at or transferred to a participating hospital. Data were collected on all infants until death or discharge home. Mortality rates were calculated for all infants born alive. Morbidity rates and treatments however were based only on those infants admitted to an NICU, and encompass the following diagnoses: intraventricular hemorrhage (IVH), based on the most severe ultrasound result during the hospital stay using the classifications defined by Papile et al; cystic periventricular...
leucomalacia (PVL) defined by de Vries et al.\(^5\) retinopathy of prematurity (ROP) using the international classification published by the committee for the classification of ROP,\(^6\) bronchopulmonary dysplasia (BPD) defined as an oxygen requirement at 36 weeks gestational age (GA) according to the NICHD consensus conference paper;\(^7\) necrotizing enterocolitis (NEC) defined as clinical signs (abdominal distension, bilious aspirates and/or bloody stools) confirmed by radiographically visible intramural gas or at laparotomy (Bell stage 2 and 3);\(^8\) patent ductus arteriosus (PDA) which was symptomatic and required indomethacin or surgery; sepsis with clear clinical, radiological, or histological evidence of infection as well as at least one microbiologically relevant positive blood culture. A survival free of major complications was determined as survival without grade 3 and 4 IVH, cystic PVL, ROP stage 3 or 4 or BPD. The years 1996, 2000, 2004 and 2008 were chosen because the Swiss Neonatal Network and Follow-up Group made a special effort to ensure that data for these years were complete and correct. To assess the completeness of our data, the number of infants having been enrolled since 1996 were compared to the birth registry of the Swiss Federal Statistical Office.\(^9\) Data was collected for 89% of all VLBW infants in 1996, 90% in 2000, 97% in 2004 and 90% in 2008.

### Statistical analysis

A two-sided paired Student’s t-test was performed to compare mean values of two independent, normally distributed variables. To determine temporal changes in the distribution of a variable, the Pearson’s Chi-square test was used. Probability levels below 0.05 were considered significant. To determine a temporal trend we used linear regression models with the coefficient b indicating the slope of a linear regression line. All statistical analyses were carried out with R release 2.13.0.

### Results

**Demographics:** According to the Swiss National Registry, there were 83,007 live born babies in 1996, 78,458 in 2000, 73,082 in 2004, and 76,691 in 2008. Concurrently the rates of VLBW infants in Switzerland increased significantly from 0.76% to 0.97% (p96-08 < 0.001, b = 0.06%). 3,090 infants with less than 32 completed gestational weeks and/or with a birth weight less than 1500 g were included for further analysis. For the demographic details of the study population and their changes over the years see Table 1.

**Mortality:** Neonatal mortality rate: 412 (13.3%) infants died during the study period, 96 (3.1%) in the delivery room. We observed 292 (9.4%) early neonatal (perinatal) deaths, defined as a death of a live born child within the first 7 days of life. A late neonatal death, occurring after 7 but before 28 completed days was found in 81 (2.6%) cases. The sum of early and late neonatal deaths amounted to an average of 12.1%. The rates for early-, late- and neonatal deaths did not change significantly during the 12 years of observation.

**Survival analysis:** The survival rate was 86.8% in 1996, 84.1% in 2000, 86.7% in 2004, 88.2% in 2008, and on average 86.5%. The increase from 1996 to 2008 was not significant (p96-08 = 0.22, b = 0.70%) even though the Kaplan-Meier analysis (Figure 1) showed an overall better survival in 2008 resulting from considerably higher survival rates during the first 48 days of life. The mean duration till death amounted to 13.4 days in 1996, 12.7 days in 2000, 7.0 days in 2004 and 7.5 days in 2008. During the whole study period only a trend towards a lower mean duration till death was found (p96-08 = 0.09, b = -2.3 days).

**Gestational age:** When stratifying the study population according to the GA we could observe significant lower mortality rates in 2008 for the two youngest GA groups (< 26 weeks of gestation: p96-08 = 0.02, and 26-27 weeks of gestation: p96-08 = 0.04). For the two older GA groups the difference between 1996 and 2008 was not statistically significant (p-values > 0.05). Infants with < 26 completed gestational weeks had a seven times higher relative risk (RR) to die than those who were at least 26 completed gestational weeks old (RR = 6.8). A detailed analysis of survival regarding gender, mode of delivery, location of birth, number of infants, GA and birth weight is given in Table 2.

**Morbidity:** The incidence of typical neonatal morbidities and their temporal trends are given in Table 3. This table also analyzes these morbidities in combination with other variables, such as gender, birth weight, GA, location of birth, and mode of delivery.

### Table 1 Demographic changes of the study population from 1996 to 2008

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<tr>
<td>Very preterm infants(^1)</td>
<td>2665 (86.2)</td>
<td>606 (84.2)</td>
<td>0.07</td>
<td>674 (97.1)</td>
<td>0.24</td>
<td>662 (87.8)</td>
<td>0.04</td>
<td>723 (95.9)</td>
<td>0.23</td>
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<tr>
<td>Very low birth weight infants(^2)</td>
<td>425 (13.8)</td>
<td>114 (15.8)</td>
<td>0.03</td>
<td>100 (12.9)</td>
<td>0.57</td>
<td>92 (12.2)</td>
<td>0.09</td>
<td>119 (14.1)</td>
<td>0.18</td>
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<td>Small for gestational age(^3)</td>
<td>576 (18.6)</td>
<td>146 (20.3)</td>
<td>0.06</td>
<td>136 (17.6)</td>
<td>0.90</td>
<td>134 (17.8)</td>
<td>0.36</td>
<td>460 (19.0)</td>
<td>0.35</td>
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<td>Gender</td>
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<td>- female</td>
<td>1507 (48.8)</td>
<td>342 (47.5)</td>
<td>0.11</td>
<td>390 (50.4)</td>
<td>0.22</td>
<td>363 (48.1)</td>
<td>0.65</td>
<td>412 (48.9)</td>
<td>0.41</td>
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<td>- male</td>
<td>1583 (51.2)</td>
<td>378 (52.5)</td>
<td>0.11</td>
<td>384 (49.6)</td>
<td>0.22</td>
<td>391 (51.9)</td>
<td>0.43</td>
<td>450 (51.1)</td>
<td>0.15</td>
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<td>Location of birth</td>
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<tr>
<td>- inborn(^4)</td>
<td>2806 (90.0)</td>
<td>652 (92.6)</td>
<td>0.07</td>
<td>686 (88.6)</td>
<td>&lt; 0.001</td>
<td>711 (94.3)</td>
<td>0.30</td>
<td>787 (93.5)</td>
<td>&lt; 0.001</td>
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<td>- outborn</td>
<td>284 (9.2)</td>
<td>98 (13.6)</td>
<td>0.11</td>
<td>88 (11.4)</td>
<td>0.43</td>
<td>43 (5.7)</td>
<td>0.55</td>
<td>55 (6.5)</td>
<td>0.15</td>
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<td>Mode of delivery(^5)</td>
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<tr>
<td>- spontaneous</td>
<td>567 (18.3)</td>
<td>174 (24.2)</td>
<td>&lt; 0.001</td>
<td>143 (18.5)</td>
<td>0.24</td>
<td>127 (16.8)</td>
<td>0.09</td>
<td>123 (14.6)</td>
<td>&lt; 0.001</td>
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<td>- caesarean section</td>
<td>2395 (75.5)</td>
<td>521 (72.4)</td>
<td>&lt; 0.001</td>
<td>595 (76.9)</td>
<td>&lt; 0.01</td>
<td>610 (80.9)</td>
<td>0.29</td>
<td>669 (79.5)</td>
<td>&lt; 0.001</td>
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<td>Number of infants</td>
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<tr>
<td>- singleton</td>
<td>2144 (69.4)</td>
<td>541 (75.1)</td>
<td>&lt; 0.01</td>
<td>546 (70.5)</td>
<td>0.13</td>
<td>513 (68.0)</td>
<td>0.03</td>
<td>544 (64.6)</td>
<td>&lt; 0.001</td>
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<td>- multiples</td>
<td>946 (30.6)</td>
<td>179 (24.9)</td>
<td>0.11</td>
<td>282 (37.5)</td>
<td>0.11</td>
<td>241 (32.0)</td>
<td>0.54</td>
<td>298 (35.4)</td>
<td>0.11</td>
</tr>
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</table>

\(p_{0.5} = 50th\) percentile = median, \(p_{0.05} = 5th\) percentile, \(p_{0.95} = 95th\) percentile, \(^1\) infants born < 32 weeks of gestation, \(^2\) infants born ≥32 weeks of gestation with a birth weight < 1500 g, \(^3\) birth weight < 10th percentile, \(^4\) born in one of the nine perinatal centres, \(^5\) cephalic forceps and cephalic ventouse deliveries were not listed separately.
Neonatal outcome: The overall survival free of major complications was 68.6%, 66.9% in 1996, 68.0% in 2000, 67.5% in 2004 and 71.7% in 2008, reflecting a significant improvement in the short-term outcome over time (p96-08 < 0.01, b = 1.4%). The age-stratified survival free of major complication is evident from Figure 2.

Length of stay: The mean length of stay (LOS) was based upon the survivors only and amounted to 59.7 days in 1996, 58.5 days in 2000, 55.0 days in 2004 and 60.1 days in 2008. For the overall study period, an average in-hospital stay of 58.4 days was calculated (p96-00 = 0.81, p00-04 = 0.17, p04-08 < 0.01, p96-08 = 0.81, b = -0.2 days). The GA was inversely correlated with the LOS and reached up to 108 days for infants < 26 weeks i.e. 21, 42 and 63 days longer than for infants born between 26-27, 28-29 and 30-31 completed gestational weeks respectively. Between 1996 and 2008 we found a significant increase in the LOS for infants born < 26 weeks (p96-08 = 0.045). The overall mean duration of CPAP administration was 9.7 days, as well as a significant decrease for infants born between 26-27 gestational weeks (p96-08 = 0.04, b = -2.9 days). The age stratified LOS are shown in Figure 3. Male infants and singletons were significantly longer hospitalized than females and multiples (59.6 vs 57.1 days, p = 0.047 and 60.2 vs 54.4 days, p < 0.001). Over the twelve years of observation, there were no significant changes in the LOS regarding gender, number of infants, mode of delivery, and location of birth (all p96-08 > 0.05).

Therapies: Information about administration of antenatal steroids, surfactant treatment and oxygen therapy are presented in Table 4.

CPAP treatment: Continuous positive airway pressure (CPAP) was given to 63.6% of the included infants namely 43.0% in 1996, 60.7% in 2000, 75.8% in 2004 and 73.2% in 2008, resulting in a significant increase of 70.4% between 1996 and 2008 (p96-08 < 0.001, b = 10.6%). Most of the newborns who had to be treated with CPAP were those with a GA between 26-27 weeks namely 79.8%, whereas the figures for infants born > 26, 28-29, and 30-31 completed gestational weeks accounted for 65.4%, 76.8% and 60.4% respectively. All GA groups showed a significant shift towards a more frequent use of CPAP therapy (all p96-08 < 0.001, b < 26 GA = 13.0%, b26-27 GA = 8.4%, b28-29 GA = 11.5%, b30-31GA = 12.4%). This change could most impressively be documented in the age group of infants born between 30-31 gestational weeks. With 36.2% in 1996 and 71.2% in 2008, the incidence of CPAP therapy nearly doubled. There was no difference in the use of CPAP regarding gender (females vs males, p = 0.78), number of infants (singletons vs multiples, p = 0.70), mode of delivery (spontaneous vs cesarean section, p = 0.60) and location of birth (inborn vs outborn, p = 0.38), but again, the same significant increase of CPAP treatment was found when analyzing all four variables separately over time. The overall mean duration of CPAP administration was 9.7 days, taking into account the surviving infants only. The respective figures were 3.9 days in 1996, 8.2 days in 2000, 12.8 days in 2004 and 13.8 days in 2008, which is equal to a 3.4 days’ increase every four years (p96-00 < 0.001, p00-04 < 0.001, p04-08 = 0.36, p96-08 < 0.001). The cumulative percentage of survivors per year treated with CPAP can be seen in Figure 4.

Mechanical ventilation: The frequency of infants who were mechanically ventilated was 45% in 1996, 39.6% in 2000, 41.8% in 2004 and 45.6% in 2008, which corresponded to an average rate of 43%. Altogether we found significant changes between 1996 and 2000 and between 2004 and 2008 (p96-00 < 0.01, p00-04 = 0.23, p04-08 = 0.03, p96-08 = 0.74). Mechanical ventilation was inversely correlated with GA: 84.2% of the infants with < 26 completed gestational weeks, 71.2% of those with 26-27 weeks, 51.4% of those with 28-29 weeks and 28.0% of those with 30-31 weeks were ventilated. We found only one significant difference towards a less frequent use of mechanical ventilation regarding infants born < 26 completed gestational weeks (p96-08 = 0.045).
However there was no difference concerning mechanical ventilation regarding gender (females vs. males, p = 0.50), number of infants (singleton vs. multiples, p = 0.29), mode of delivery (spontaneous vs. caesarean section, p = 0.81), and location of birth (inborn vs. outborn, p = 0.29), mode of delivery. This trend probably reflects the improved chance of survival these infants now have, justifying the greater risk to which the mother is exposed to when undergoing surgery compared to natural childbirth. The number of outborn infants decreased significantly, reflecting an existing trend to centralize high-risk pregnancies in perinatal centers. As a matter of fact, this corresponds to findings of different studies showing that infants who were born in NICUs had lower mortality rates than infants who were transported extrauterinely. As expected, the increasing rates of VP- and VLBW had lower mortality rates than infants who were transported extrauterinely. As expected, the increasing rates of VP- and VLBW infants discharged home without major complications in a stable population over 12 years. This added value is composed of three factors: 1) Increase of the absolute (122) and relative (16.9%) number of VP- and VLBW infants, stable overall mortality rate and higher rate of survivors without major complications (absolute increase 122, relative 25.3%). This finding was not expected and differs in various aspects from previously published results. We will discuss methodological issues and compare the results with those of other studies for the four main topics, population characteristics, mortality, in-hospital morbidity and therapies. Comparison of such global population based trends must be considered with caution as inclusion criteria, definitions of referral, morbidities, treatments, and discharge policies may vary.

**Obstetrics/delivery/birth characteristics:** Obstetric management changed with respect to the percentage of mothers who were treated with antenatal corticosteroids as well as with respect to the mode of delivery. This trend probably reflects the improved chance of survival these infants now have, justifying the greater risk to which the mother is exposed to when undergoing surgery compared to natural childbirth. The number of outborn infants decreased significantly, reflecting an on-going trend to centralize high-risk pregnancies in perinatal centers. As a matter of fact, this corresponds to findings of different studies showing that infants who were born in NICUs had lower mortality rates than infants who were transported extrauterinely. As expected, the increasing rates of VP- and VLBW infants discharged home without major complications in a stable population over 12 years. This added value is composed of three factors: 1) Increase of the absolute (122) and relative (16.9%) number of VP- and VLBW infants, stable overall mortality rate and higher rate of survivors without major complications (absolute increase 122, relative 25.3%). This finding was not expected and differs in various aspects from previously published results. We will discuss methodological issues and compare the results with those of other studies for the four main topics, population characteristics, mortality, in-hospital morbidity and therapies. Comparison of such global population based trends must be considered with caution as inclusion criteria, definitions of referral, morbidities, treatments, and discharge policies may vary.

**Discussion**

Our study shows a considerable net gain in VP- and VLBW infants discharged home without major complications in a stable population over 12 years. This added value is composed of three factors: 1) Increase of the absolute (122) and relative (16.9%) number of VP- and VLBW infants, stable overall mortality rate and higher rate of survivors without major complications (absolute increase 122, relative 25.3%). This finding was not expected and differs in various aspects from previously published results. We will discuss methodological issues and compare the results with those of other studies for the four main topics, population characteristics, mortality, in-hospital morbidity and therapies. Comparison of such global population based trends must be considered with caution as inclusion criteria, definitions of referral, morbidities, treatments, and discharge policies may vary.

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42
cohort including VP infants between 1997 and 2003. This difference was inexplicable as our study population consisted not only of VP- but also of VLBW infants resulting in more infants with birth weights under the 10th percentile.

**Mortality:** The overall mortality rate of our study population remained stable over time on an average of 13.3%. Excluding the VLBW infants, a mortality rate of 15% was found. Both rates remained stable over time on an average of 13.3%. Excluding mortality:

- infants who died in the delivery room were excluded;
- born in one of the nine perinatal centres;
- cephalic forceps and cephalic ventouse deliveries were not listed separately;
- children born > 32 completed gestational weeks were not listed separately;
- bronchopulmonary dysplasia;
- necrotising enterocolitis;
- intraventricular haemorrhage grade III or IV;
- cystic periventricular leukomalacia;
- patent ductus arteriosus;
- respiratory distress syndrome;
- retinopathy of prematurity grade 3 or 4

In spite of better detection techniques and more ultrasound examinations being routinely made nowadays, the incidence of serious IVH decreased and the rate of cystic PVL remained stable. Again, there might be a positive influence of antenatal intensive care treatments for extremely preterm infants. The third argument of the authors, namely, reaching the limits of current technology to support pre-term infants at gestational ages near the limits of viability, might not be applicable to Switzerland, as recent data show better survival of these infants. Extending this study by children born in 2012, as we plan to do, may confirm this finding.

**Morbidity:** Regarding the results of other studies examining the relation between antenatal steroids and respiratory distress syndrome (RDS), we expected to find a decrease in the incidence of RDS, which however, increased significantly by 8% to 84.6%. Ensh et al demonstrated similar findings in their survey of a geographically limited neonatal population. They found that the incidence of RDS in infants admitted to neonatal units doubled over the last 30 years, which was ascribed to the corresponding increase in the rate of cesarean section. We suggest that in our cohort, given the above-mentioned constant mortality rate, the severity of RDS must have been reduced by the increasing antenatal treatment with corticosteroids. The rising survival of the most immature infants and the infants with RDS did not result in an increased number of infants with BPD, which was unexpected and quite contrary to other reports, where an increased survival resulted in more morbidity, mainly BPD.

<table>
<thead>
<tr>
<th>Year</th>
<th>BPD No. (%)</th>
<th>NEC No. (%)</th>
<th>IVH No. (%)</th>
<th>PVL No. (%)</th>
<th>PDA No. (%)</th>
<th>RDS No. (%)</th>
<th>ROP No. (%)</th>
<th>Sepsis No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996-2008</td>
<td>470 (15.7)</td>
<td>76 (2.5)</td>
<td>176 (5.9)</td>
<td>66 (2.2)</td>
<td>584 (19.6)</td>
<td>2428 (81.4)</td>
<td>38 (1.2)</td>
<td>291 (9.8)</td>
</tr>
<tr>
<td>1996 (n = 702)</td>
<td>125 (17.8)</td>
<td>23 (3.3)</td>
<td>43 (6.1)</td>
<td>12 (1.7)</td>
<td>105 (15.0)</td>
<td>550 (78.3)</td>
<td>13 (1.9)</td>
<td>60 (8.5)</td>
</tr>
<tr>
<td>2000 (n = 750)</td>
<td>104 (13.9)</td>
<td>22 (2.9)</td>
<td>51 (6.8)</td>
<td>18 (2.4)</td>
<td>128 (17.1)</td>
<td>584 (77.9)</td>
<td>4 (0.5)</td>
<td>81 (10.8)</td>
</tr>
<tr>
<td>2004 (n = 728)</td>
<td>123 (16.9)</td>
<td>17 (2.3)</td>
<td>49 (6.7)</td>
<td>21 (2.9)</td>
<td>148 (20.3)</td>
<td>615 (84.5)</td>
<td>9 (1.2)</td>
<td>65 (8.9)</td>
</tr>
<tr>
<td>2008 (n = 803)</td>
<td>118 (14.7)</td>
<td>14 (1.7)</td>
<td>33 (4.1)</td>
<td>15 (1.9)</td>
<td>203 (25.3)</td>
<td>679 (84.6)</td>
<td>12 (1.5)</td>
<td>85 (10.6)</td>
</tr>
</tbody>
</table>

Table 3 Incidence of neonatal morbidities and their temporal trends over the years
corticosteroids on the incidence of IVH and PVL as was shown in the previously mentioned meta-analysis by Crowley. The diagnosis of a patent arterial duct (PDA) was made more frequently over time. This is most likely due to an intensified diagnostic workup, especially by systematic echocardiographs in VP- and VLBW infants. The incidence of necrotizing enterocolitis (NEC) decreased significantly to 1.7% mainly due to the preventive administration of probiotics in Switzerland since 2006.

The survival free of major complications which represents, besides mortality, the most crucial variable defining neonatal outcome, significantly increased. This finding is remarkable as it was neither adversely affected by an increasing number of VP infants nor by better survival rates of the youngest GA groups. Zeitlin et al investigated the short-term outcome of live births before 32 weeks of gestation in 10 European regions and found large differences in neurologic and respiratory morbidity despite similar standards of living and healthcare provision. They reported rates between 71.2 and 89.7% for a survival without IVH/PVL or BPD, raising questions about variability in treatment decisions and population characteristics. Fanaroff et al defined a survival without major neonatal morbidity as survival without IVH, NEC, and BPD and found a stable rate of 70% between 1995 and 2002 regarding VLBW infants only. Despite stricter criteria including the absence of IVH, cystic PVL, BPD, and ROP, our results are similar to those of other European and American groups.

**Therapies:** The increasing antenatal application of corticosteroids as well as the wide use of rescue surfactant therapy led to a change in respiratory support strategy towards early use of nasal CPAP starting in the delivery room, thereby reducing the need for intubation in preterm babies. In our study the increased use of antenatal corticosteroids was not associated with a decreased use of surfactant. That was unexpected and could most likely be explained by additional indications for surfactant administration, namely early administration in the delivery room based on risk, not on severity of RDS.

We additionally documented an impressive 70% increase in the use of CPAP as well as a far longer duration of CPAP therapy, by approximately 10 days, between 1996 and 2008. Despite this, the use of mechanical ventilation did not change in terms of period and number of ventilated infants. Taken together, we think that the increasing rates of antenatal corticosteroid- and postnatal surfactant administration, the decreasing use of supplemental oxygen as well as lung-protective ventilation strategies are among the most important factors to explain our lower BPD rate in 2008. This rate of 14.7% is similar to those reported in the two population-based cohort studies EPIPAGE in 1997 (14.4%) and MOSAIC in 2003 (15.3%).

Strengths and limitations of the study: Strengths of our study are 1) Prospective definition of inclusion criteria and specific morbidities remaining unchanged over the whole observation period. 2) The recruitment of subjects based on a homogenous, geographically defined population. 3) An observation period of 12-years, 4) a special effort to enhance data quality by on-site visits and matching with the official population statistics, and 5) presenting temporal trends not only of mortality and morbidity but also of therapies used in a large sample of VP- and VLBW infants.

Our study is limited by the lack of information about the long-term outcome of our infants. However, there is an association between major complications and neurodevelopmental outcome. This data is currently being collected and will be reported later.
**Table 4 Treatment of the liveborns**

<table>
<thead>
<tr>
<th>Year</th>
<th>supplemental oxygen No. (%)</th>
<th>surfactant No. (%)</th>
<th>antenatal steroids No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996-2008¹</td>
<td>1933 (64.8)</td>
<td>972 (32.6)</td>
<td>2311 (77.5)</td>
</tr>
<tr>
<td>1996¹</td>
<td>472 (67.2)</td>
<td>174 (24.8)</td>
<td>475 (67.7)</td>
</tr>
<tr>
<td>2000¹</td>
<td>489 (65.2)</td>
<td>221 (29.5)</td>
<td>508 (67.7)</td>
</tr>
<tr>
<td>2004¹</td>
<td>492 (67.6)</td>
<td>255 (35.0)</td>
<td>594 (81.6)</td>
</tr>
<tr>
<td>2008¹</td>
<td>480 (59.8)</td>
<td>322 (40.1)</td>
<td>734 (91.4)</td>
</tr>
</tbody>
</table>

*p-value 1996-2008*< 0.001< 0.001< 0.001

<table>
<thead>
<tr>
<th>Gender</th>
<th>No. (%)</th>
<th>p-value</th>
<th>No. (%)</th>
<th>p-value</th>
<th>No. (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>- female</td>
<td>922 (63.1)</td>
<td>0.77</td>
<td>435 (29.8)</td>
<td>0.50</td>
<td>1132 (77.4)</td>
<td>0.99</td>
</tr>
<tr>
<td>- male</td>
<td>1011 (66.5)</td>
<td>0.49</td>
<td>537 (35.3)</td>
<td>0.49</td>
<td>1179 (77.5)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of birth</th>
<th>No. (%)</th>
<th>p-value</th>
<th>No. (%)</th>
<th>p-value</th>
<th>No. (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>- inborn²</td>
<td>1728 (64.0)</td>
<td>0.48</td>
<td>865 (32.0)</td>
<td>0.49</td>
<td>2144 (79.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>- outborn</td>
<td>205 (72.2)</td>
<td>0.76</td>
<td>107 (37.7)</td>
<td>0.38</td>
<td>167 (58.8)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mode of delivery³</th>
<th>No. (%)</th>
<th>p-value</th>
<th>No. (%)</th>
<th>p-value</th>
<th>No. (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>- spontaneous</td>
<td>327 (62.0)</td>
<td>0.76</td>
<td>141 (26.8)</td>
<td>0.38</td>
<td>392 (74.4)</td>
<td>0.71</td>
</tr>
<tr>
<td>- caesarean section</td>
<td>1537 (65.5)</td>
<td>0.49</td>
<td>789 (33.6)</td>
<td>0.49</td>
<td>1852 (78.9)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of infants</th>
<th>No. (%)</th>
<th>p-value</th>
<th>No. (%)</th>
<th>p-value</th>
<th>No. (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>- singleton</td>
<td>1387 (67.2)</td>
<td>0.49</td>
<td>722 (35.0)</td>
<td>0.49</td>
<td>1525 (73.8)</td>
<td>0.35</td>
</tr>
<tr>
<td>- multiples</td>
<td>546 (59.5)</td>
<td>0.49</td>
<td>250 (27.2)</td>
<td>0.49</td>
<td>786 (85.6)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestational age⁴</th>
<th>No. (%)</th>
<th>p-value</th>
<th>No. (%)</th>
<th>p-value</th>
<th>No. (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 26</td>
<td>234 (88.0)</td>
<td>1.67</td>
<td>167 (62.8)</td>
<td>0.20</td>
<td>201 (75.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>26-27</td>
<td>435 (89.5)</td>
<td>0.28</td>
<td>286 (58.8)</td>
<td>0.37</td>
<td>377 (77.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>28-29</td>
<td>534 (78.0)</td>
<td>0.26</td>
<td>261 (38.1)</td>
<td>0.35</td>
<td>536 (78.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>30-31</td>
<td>234 (20.8)</td>
<td>0.24</td>
<td>234 (20.8)</td>
<td>0.24</td>
<td>903 (80.3)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

¹ infants who died in the delivery room were excluded, ² born in one of the nine perinatal centres, ³ cephalic forceps and cephalic ventouse deliveries were not listed separately, ⁴ children born > 32 completed gestational weeks were not listed separately

**Conclusions**

Over the 12-year observation period, the number of VP- and VLBW infants increased significantly. An unchanged overall mortality rate and an increase of survivors free of major complication resulted in a considerable net gain in infants with potentially good outcome. This improved short-term outcome was associated with a shorter hospital stay and therefore less cost. Follow-up of this cohort will show whether this benefit will persist.

**References**


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The VICI-Trial: High Frequency Oscillation Versus Conventional Mechanical Ventilation in Newborns with Congenital Diaphragmatic Hernia

Lieke van den Hout, Dick Tibboel, Sanne Vijfhuize, Harma te Beest, Wim Hop, Irwin Reiss

Abstract
Background: Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly of the diaphragm resulting in pulmonary hypoplasia and pulmonary hypertension. It is associated with a high risk of mortality and pulmonary morbidity. Previous retrospective studies have reported high frequency oscillatory ventilation (HFO) to reduce pulmonary morbidity in infants with CDH, while others indicated HFO to be associated with worse outcome. We therefore aimed to develop a randomized controlled trial to compare initial ventilator treatment with high-frequency oscillation and conventional ventilation in infants with CDH.

Methods/design: This trial is designed as a multicenter trial in which 400 infants (200 in each arm) will be included. Primary outcome measures are BPD, described as oxygen dependency by day 28 according to the definition of Jobe and Bancalari, and/or mortality by day 28. All liveborn infants with CDH born at a gestational age of over 34 weeks and no other severe congenital anomalies are eligible for inclusion. Parental informed consent is asked antenatally and the allocated ventilation mode starts within two hours after birth. Laboratory samples of blood, urine and tracheal aspirate are taken at the first day of life, day 3, day 7, day 14 and day 28 to evaluate laboratory markers for ventilator-induced lung injury and pulmonary hypertension.

Discussion: To date, randomized clinical trials are lacking in the field of CDH. The VICI-trial, as the first randomized clinical trial in the field of CDH, may provide further insight in ventilation strategies in CDH patient. This may hopefully prevent mortality and morbidity. Trial registration: this trial is registered in the Dutch trial register (number NTR 1310)

Background
Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly of the diaphragm, which occurs in approximately one in 3000 live births. In CDH, the diaphragmatic defect allows abdominal organs to herniate into the chest cavity. As a consequence, underdevelopment of the lungs and abnormal pulmonary vasculature growth may occur, resulting in pulmonary hypoplasia and pulmonary hypertension.

Children with CDH mostly present with immediate cardiorespiratory distress during the first hours of life. The initial therapy for these children is mechanical ventilation and cardiorespiratory stabilization in support of optimal management of the pulmonary hypoplasia and pulmonary hypertension. Thereafter, surgical repair of the diaphragmatic defect is indicated. Although many advances in treatment for CDH patients have been made throughout the years, CDH remains a life-threatening condition with a reported mortality rate of 20-70%, depending on case selection.

Survivors of CDH are at risk of developing secondary morbidity, such as gastrointestinal, neurodevelopmental and pulmonary sequelae. Throughout infancy and childhood, a broad spectrum of pulmonary morbidity may occur, such as bronchopulmonary dysplasia (BPD), persistent pulmonary hypertension, recurrent respiratory tract infections and asthmatic symptoms. BPD is characterized by disturbances of the normal alveolarization.

Ventilator induced lung injury, oxygen toxicity, pulmonary inflammatory responses, and severe pulmonary hypertension predispose infants with CDH to develop BPD. A recent report of the CDH Registry reported the prevalence of BPD to be 4% in infants with CDH. About half of the CDH survivors with BPD are reported to have moderate to severe BPD. Moreover, lung function anomalies are often present in these patients.

Optimizing ventilation strategies in patients with CDH may help to prevent chronic respiratory disease. However, evidence-based standardized treatment protocols based are lacking in the field of CDH. Consequently, ventilation strategies may differ between centers and ventilatory support is often based upon expert opinion. To date, conventional ventilation is the most widely used initial ventilation mode in newborns with CDH, while in many institutions high frequency oscillatory ventilation (HFO) is used as rescue therapy. In some centers, however, HFO is used as the initial ventilation mode. HFO achieves adequate gas exchange by an oscillatory pump, which combines very high respiratory rates and low tidal volumes. HFO may improve gas exchange, promote uniform lung inflation, reduce barotrauma, and decrease the presence of inflammatory mediators. HFO has been used in preterm infants with respiratory distress syndrome, either as an elective ventilation strategy or as a rescue therapy. A Cochrane review, on the use of elective HFO compared to CMV...
in preterm infants, found a borderline significant reduction in the rate of chronic lung disease with the use of HFO. A second Cochrane review described the use of HFO as a rescue therapy in term and near term infants with severe pulmonary dysfunction. Only one trial compared these two ventilation strategies prospectively, resulting in no significant difference in outcome, need for extracorporeal membrane oxygenation (ECMO), or complications.

In infants with CDH, retrospective and observational studies reported improved survival and a lower incidence of chronic lung disease with elective use of HFO. HFO was reported to provide better oxygenation and higher MAP without increasing the incidence of barotraumas. In one study, the use of HFO avoided hyperventilation as well as the need for ECMO. Moreover, inhaled nitric oxide was documented to result in better gas exchange following recruitment of the lungs by HFO. On the contrary, HFO may cause lung hyperinflation in some patients, which may induce higher alveolar and mean airway pressures. This may result in an increased risk of pulmonary barotrauma and hemodynamic instability. A recent study by the CDH Registry reported HFO as initial ventilation mode to be associated with an increased rate of mortality and BPD. In this study, it is speculated that infants who received initially HFO were more severely ill from the start.

Conclusively, chronic pulmonary morbidity and high mortality rates are major problems in infants with CDH. Several retrospective and observational studies have reported that mechanical ventilation strategies may have an impact on outcome and pulmonary morbidity in CDH patients. Therefore, we aimed to develop a randomized controlled trial to compare initial ventilatory treatment with HFO and conventional ventilation in infants with CDH. The acronym VICI is deducted from the words: HFO versus conventional Ventilation in Infants with Congenital diaphragmatic hernia: an International randomised clinical trial. In Latin vici means “I have conquered,” which refers to our patients with CDH who are very vulnerable and ill and sometimes have to struggle to survive.

The primary objective of this trial is to determine if there is a difference in the incidence of BPD and/or death within the first 28 days of life between newborns with congenital diaphragmatic hernia treated with high frequency oscillatory ventilation (HFO) and those treated with conventional mechanical ventilation (CMV) as initial ventilation mode. Secondarily, we also aim to compare the severity of BPD, ventilator-induced lung injury and pulmonary hypertension by using clinical and laboratory parameters.

Methods/Design
This study is designed as a prospective, randomized controlled multicenter trial. All participating centers are member of the CDH-EURO Consortium. This is a collaboration between European tertiary centers which have an expertise in the field of CDH. The CDH-EURO consortium was started in 2006 and aims at cooperation between centers, enhancement of research in the field of CDH and development of standardized evidence-based treatment protocols.

Outcome measures: The primary outcome measure is BPD and/or death within the first 28 days of life. Secondary outcome parameters are overall mortality, severity of BPD, number of days on the ventilator, number of treatment failures, ventilation-induced lung injury and pulmonary hypertension according to clinical and laboratory parameters and need for ECMO (only for ECMO centers). BPD is defined as oxygen dependency at day 28, according to the definition of Jobe and Bancalari. The severity of BPD is also defined according to this definition.

Inclusion and exclusion criteria: The study population consists of all infants antenatally diagnosed with CDH born at one of the participating centers. Exclusion criteria are: birth before a gestational age of 34 weeks, severe chromosomal anomalies, like trisomy 18 or trisomy 13, which may imply a decision to stop or not to start life-saving medical treatment; severe cardiac anomalies, expected to need corrective surgery in the first 60 days of life; renal anomalies associated with oligohydramnios; severe orthopedic and skeletal deformities, which are likely to influence thoracic, and / or lung development; and severe anomalies of the central nervous system.

Statistical analysis: We estimated that a total of 400 newborns can be included within a period of three years. In a previous study of the CDH study group, the incidence of BPD and/or death within the first 28 days of life is reported to be about 50%. Assuming a difference of 15% in BPD and/or death within the first 28 days between both treatment groups, 186 patients are required per arm for a power of 80% at two-sided alpha is 0.05. To allow for some non-evaluable patients and dropouts, 200 patients per group will be included. To achieve equal distribution of the two ventilation modes among the participants, block randomization stratified per center will be carried out. The data-analysis will be carried out at the Erasmus MC, Rotterdam. An intention-to-treat analysis will be performed. A p-value (two-sided) < 0.05 will be considered significant in all analyses.

The primary endpoint will be evaluated using multiple logistic regression analysis taking account of: center, lung-to-head ratio, position of the liver (intra-abdominal or intra-thoracic) and the side of the defect (left, right or central). A subgroup analysis will be carried out in operated infants to evaluate the defect size, according to the CDH study group defect size scale. The secondary endpoints will be evaluated by using the following statistical tests. Overall mortality in the first year of life will be analyzed by Kaplan-Meier curves and Log rank tests. The chi-square test will be used to analyze number of treatment failures, presence of pulmonary hypertension according to echocardiographic parameters, requirement of medication at discharge and during the first year of life, and need for ECMO therapy (in ECMO centers). The Mann-Whitney test is used to evaluate the severity of chronic lung disease, number of days on the ventilator and the fraction of days with required medical treatment for pulmonary hypertension during the hospital admission. In the evaluation of the severity of chronic lung disease and the number of days on the ventilator, deaths are counted as worst outcome according to the intention-to-treat principle. Repeated measures ANOVA is used to evaluate levels of laboratory markers for ventilator-induced lung injury or pulmonary hypertension and pulmonary function at the age of six and twelve months. This analysis allows for missing data at different time points and is considered as the optimal way for evaluation of longitudinal data. All the above-mentioned analyses will allow for center by stratification.

Study procedures: Parental informed consent will be obtained antenatally to enhance quick randomization. Following antenatal diagnosis, the parents are to be counseled and will receive
information about the study, including a patient information letter and an informed consent form. If both parents decide to participate in the study, as soon as possible after birth central randomization will take place by the treating physician using a website. This way concealed allocation is guaranteed. Within two hours after delivery, the allocated ventilatory treatment has to be started.

The patient receives the allocated ventilation treatment during the entire admission period on the intensive care unit. During surgery, the child preferably remains on the allocated ventilation type, provided the treating surgeon agrees. Should the surgeon opt for the other ventilation mode, the patient is switched to the allocated ventilation treatment again after surgery. If the patient has to be re-intubated within the first 60 days after the start of the allocated treatment, the patient receives the allocated treatment again. Patients are observed up to day 60 after birth or until discharge whichever comes first.

**Standardized treatment and ventilation settings:** All infants participating in the VICI-trial are treated according to the same standardized treatment protocol which has been published recently. This protocol of standard practice was decided upon available evidence and consensus between the participating centers. After birth, all infants are immediately intubated. In general, our goals are to achieve preductal saturations between 85 and 95%, postductal saturation levels above 70% and arterial CO₂ levels between 45-60 mmHg (permissive hypercapnia). Conventional mechanical ventilation is provided by a neonatal ventilator capable of positive pressure ventilation or triggered modes (Babylog ventilator, Dräger Medical, Germany). High frequency oscillatory ventilation (HFO) is provided by a high frequency oscillatory ventilator (Sensormedics 3100A/B HFO Ventilator, CareFusion). If the allocated treatment is conventional ventilation, the following settings are used: a peak inspiratory pressure (PIP) of 20-25 cm H₂O, a positive end-expiratory pressure (PEEP) of 2-5 cm H₂O and a frequency of 40-60 per minute. In case of HFO, the settings are: a mean airway expiratory pressure (PEEP) of 2-5 cm H₂O and a frequency of 40-60 per minute. In case of HFO, Dp amplitude (Dp, cm H₂O) of 30 to 50 obtaining chest vibrations, and an inspiration/expiration rate (I:E) of 1:1.

According to our standardized treatment protocol, a chest radiograph is made as soon as possible after birth to assess the initial condition and is repeated guided on the patient’s condition. In case of HFOV, a chest radiograph is also made after this ventilation mode is started to confirm that the lungs are not overinflated, as defined by a contralateral lung expansion of over 8 ribs. Also, echocardiography is performed within the first 24 hours after birth to assess pulmonary arterial diameter and right heart function. In all patients, a chest radiograph and echocardiography are repeated at day 28.

Weaning from conventional ventilation is done by means of decreasing PIP. Frequency and/or the PIP-PEEP were modified to achieve PaCO₂ levels above 45 mmHg. In case of HFOV, Dp was decreased if the paCO₂ was below 45 mmHg and FiO₂ was decreased if preductal saturation levels were above 95%.

In case of hypovolemia and/or cardiogenic shock, saline fluid therapy is started (10 to 20 ml/kg of NaCl 0.9% up to three times during the first two to one hours), which is followed by inotropic therapy if necessary. At an oxygenation index of 20 or higher and/or a pre- and postductal saturation difference of 10% or more, 10-20 ppm iNO is given for at least one hour. Intravenous prostacyclin or prostaglandin E1 may be considered in case of no response to iNO. Sildenafil may be considered in the chronic phase of pulmonary hypertension. Surgery is performed if the patient is physiologically stable according to the criteria described in our protocol [4]. No routine paralysis is used.

**Treatment failure:** In case of one or more failure criteria, the allocated ventilatory treatment may be switched. Also, an ECMO procedure may be started in centers where ECMO is available. After the ECMO-procedure has ended, the patient preferably receives the initial allocated ventilation mode. Because an intention-to-treat analysis will be performed, data from these patients are stored and analyzed the same way as data from patients in whom no switching of ventilation mode or ECMO procedure took place.

The following failure criteria are applicable to the study patients: inability to maintain preductal saturations above 85% (± 7 kPa or 52 mmHg) or postductal saturations above 70% (± 3.5 kPa or 40 mmHg); increase in CO₂ > 65 torr or mmHg (8.5 kPa) despite optimization of ventilator management; PIP > 28 cm H₂O or MAP > 17 cm H₂O; inadequate oxygen delivery with metabolic acidosis defined as lactate ≥ 5 mmol/l and pH < 7.20; hypotension resistant to fluid therapy and adequate inotropic support, resulting in a urine output < 0.5 ml/kg/hour; oxygenation index consistently ≥ 40.

**Laboratory analyses:** During the study, blood, urine and tracheal samples are collected. Separate parental informed consent is asked for taking, analysing and storing these samples. Blood, urine and tracheal samples are taken within the first 2 hours of life and on days 3, 7, 14 and 28. Blood sampling is only done if a central or peripheral line is present and in combination with routine laboratory measurements. Urine sampling is only done if the patient has a urine catheter. Sampling of tracheal aspirates is only done during routine suctioning. In that way, sampling of laboratory markers are of minimal burden for the patient.

**Blood samples:** Blood markers are determined by immunoassay analysis and are necessary support evidence of chronic lung disease and to further evaluate its severity.

The following laboratory markers are measured: markers for inflammation and pulmonary vascular endothelial dysfunction and pulmonary hypertension (intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), sP- and sE-selectine, pro-brain natriuretic peptide (Pro-BNP), vascular endothelial growth factor (VEGF), von Willebrand factor, thrombomodulin, factor VIII and Asymmetric Dimethylarginine (ADMA); markers for the nitroxide pathway (nitrate and nitrite).

**Urine samples:** Two urine samples from an 8-hour urine collection are taken to measure desmosine, an elastolytic degradation product of elastin. It gives an indication of the degradation of lung elastic fibers in ventilated neonates. One sample of 20 ml containing 0.2 % boric acid and one sample of 10 ml will be stored at ~20 degrees Celsius. Desmosine will be measured by massspectrometry, a highly sensitive way of measuring this laboratory marker.

**Tracheal aspirate:** Protein profiling by proteomics are used for identifying specific groups of proteins, which are involved in the
pathogenesis of chronic lung disease. During routine tracheal suctioning, flushing with 0.5-1.0 ml saline is performed according to standard practice. The tracheal aspirates are centrifuged for 10 minutes at 3000 rpm and are stored at –80 degrees Celsius.

Follow-up: At all participating centers, routine follow-up takes place at the age of 6 months, 12 months, 24 months, 5 years, 8 years, 12 years and 18 years in all patients with CDH, including participants of the VICI-trial. During follow-up visits, routine physical examination and additional testing (e.g. lung function tests or developmental tests) take place. For the purpose of this study, parents complete a patient diary card on a daily basis for one month at the age of six and twelve months. By using this diary card information about whether their child coughed, wheezed and/or needed medication is collected. This gives a quantitative assessment of morbidity. In a subgroup of patients born at the Erasmus Medical Centre and King's College Hospital, lung function tests are performed at the age of six and twelve months. Only these two centres have the equipment and expertise to measure lung function in children below the age of one. At King's College, FRC (functional residual capacity) and LCI (lung clearance index) are measured by using helium gas dilution. The LCI is the cumulative expired volume required to clear an inert gas from the lungs, divided by the FRC. Also, lung function tests are performed before and after bronchodilatation at this center. Therefore, a bronchodilator is administered by a face mask and a spacer. At the Erasmus Medical Centre, the FRC is determined by SF6 measurements. Since the methods of lung function measurements differ between the two centres, these measurements will be analyzed separately for both centers.

Safety reporting: An adverse event or complication is defined as any undesirable occurrence in a patient. Mortality is regarded a serious adverse event. Adverse events or complications are reported to the study coordinator within 24 hours. Thereafter, the study coordinator informs the data safety monitoring board, who monitors the incidence of mortality on a continuous base. If at some point a large difference in mortality between the two treatment groups is noticed, the data safety monitoring board may recommend ending the study.

Data collection: Demographic and neonatal characteristics as well as data on the clinical course and treatment of all patients will be collected in a central database in Rotterdam. Corporeal material collected during the study is stored at the local centers. Since it should be impossible to identify a specific patient, data are sealed by a code and a patient number replaces personal data. All centers keep a logbook of the number of eligible non-participants, including the reasons for not participating. Patient data are stored during the study and for fifteen years after the study has ended. If the parents consent, corporeal material is also stored for fifteen years after the study has ended. This material may be used in future for a study with the same research aims.

Discussion
Congenital diaphragmatic hernia (CDH) is associated with a high risk pulmonary morbidity. Several previous studies have reported a wide range of pulmonary problems throughout childhood in these patients. A recent study of our group in collaboration with the CDH Registry reported a 41% prevalence of bronchopulmonary dysplasia (BPD) in survivors of CDH. This study reported the initial ventilation mode to be possibly associated with BPD in these patients. This formed the rationale for our study, which aims at comparing HFO and conventional ventilation as initial ventilation modes in infants with CDH.

Our study is the first randomized clinical trial in the field of CDH. Previous studies were retrospective or observational reports, mostly from single centers. Moreover, progress in CDH research is hampered due to small numbers of patients and lack of evidence-based treatment strategies. Cooperation between centers is therefore highly important to enhance research, exchange knowledge and compare data in larger groups of patients. The CDH Study Group is an example of a worldwide network which has established a large database on CDH patients. To date, the CDH Study Group has published numerous reports in the field of CDH, which contain valuable information on survival, treatment strategies and morbidity in infants with CDH. Another example is the CDH-EURO consortium, a European collaboration between tertiary centers with an expertise in treatment of CDH, which also initiated the VICI-trial. The consortium also developed a recently published standardized treatment protocol. This treatment protocol makes valuable comparison of patient data possible, since all CDH patients, including the VICI-trial patients, born in these centers are treated according to this protocol.

HFO and conventional ventilation are both safe, effective and widely used strategies to ventilate infants with respiratory distress. Although observational and retrospective studies have suggested that HFO may improve survival and pulmonary outcome in infants with CDH, no prospective randomized controlled trials have been carried out to compare initial ventilation strategies in these patients. Therefore, no specific conclusions about certain benefits or disadvantages of either HFO or CMV can be made.

As the first randomized clinical trial in CDH infants, the VICI-trial will provide a clearer view on ventilatory treatment strategies and possible prevention of mortality and morbidity. Still, there are many questions left in the field of CDH and clinical trials are highly needed to improve care and establish standardized treatment. Cooperative networks between centers, such as the CDH-EURO consortium, play a major role in this.
A Decision Aid for Considering Indomethacin Prophylaxis vs Symptomatic Treatment of PDA for Extreme Low Birth Weight Infants

Khalid M. AlFaleh, Eman Al Luwaimi, Turki M. AlKharfi and Saleh A. Al-Alaiyan

Abstract
Background: Decision Aids (DA) are well established in various fields of medicine. They can improve the quality of decision-making and reduce decisional conflict. In neonatal care, and due to scientific equipoise, neonatologists caring for extreme low birth weight (ELBW) infants are in need to elicit parents’ preferences with regard to the use of indomethacin therapy in ELBW infants. We aimed to develop a DA that elicits parents’ preferences with regard to indomethacin therapy in ELBW infants.

Methods: We developed a DA for the use of the indomethacin therapy in ELBW infants according to the Ottawa Decision Support Framework. The development process involved parents, neonatologists, DA developers and decision making experts. A pilot testing with healthy volunteers was conducted through an evaluation questionnaire, a knowledge scale, and a validated decisional conflict scale.

Results: The DA is a computer-based interactive tool. In the first part, the DA provides information about patent ductus arteriosus (PDA) as a disease, the different treatment options, and the benefits and downsides of using indomethacin therapy in preterm infants. In the second part, it coaches the parent in the decision making process through clarifying values and preferences. Volunteers rated 10 out of 13 items of the DA positively and showed significant improvement on both the knowledge scale (p = 0.008) and the decisional conflict scale (p = 0.008).

Conclusion: We have developed a computer based DA to assess parental preferences with regard to indomethacin therapy in preterm infants. Future research will involve measurement of parental preferences to guide and augment the clinical decisions in current neonatal practice.

Background
Burden of Illness: Due to its high rate of mortality and morbidity, prematurity is by far the most important issue in modern perinatal medicine. Patent ductus arteriosus (PDA) is very common among very low birth weight infants (VLBW); the delay in closure of the ductus is inversely related to gestational age varying from 20% in premature infants greater than 32 weeks up to 60% in extreme low birth weight infants (ELBW < 1000 g).1,2 PDA results in a significant left to right shunt with an increase in left ventricular output. Although it usually closes spontaneously by 5 days of age in most infants > 30 weeks’ gestation, it remains patent by 5 days of age in more than two thirds of infants < 30 weeks.3 Although controversial, observational data failed to show an association of PDA with necrotizing enterocolitis (NEC).4 Failure of the ductal constriction has been shown to be associated with low superior venacaval flow (SVC) and subsequent occurrence of late intraventricular hemorrhage (IVH).5 Lastly, large left to right ductal shunting is associated with a significant increase in pulmonary blood flow and serious pulmonary hemorrhage.6,9

Indomethacin prophylaxis vs treatment for symptomatic PDA; the clinical dilemma: There is now a substantial body of literature available to evaluate the role of indomethacin prophylaxis in the management of the premature infant. Indomethacin prophylaxis reduces the incidence of symptomatic PDA by 55%, severe grade III and IV IVH by 35%, and the need for surgical PDA ligation by 50%.11,12 In addition a recent ancillary analysis on the database of the trial of indomethacin prophylaxis in the preterm infants (TIPP trial), showed a significant reduction of serious clinically significant pulmonary hemorrhage during the first week of life.11 However, this significant reduction in symptomatic PDA, severe IVH, and serious pulmonary hemorrhage did not translate in reduction of mortality, BPD, and more importantly the rates of long term neurosensory outcome.

As a result of the data presented above, clinicians caring for premature infants are left uncertain of what would be the most sensible approach to the use of indomethacin prophylaxis in the preterm. Some clinicians would justify its use based on the reduction of important intermediate morbidities. On the other hand, others would refrain employing a prophylactic strategy...
Patient decision aids can improve the quality of decision-making, reduce decisional conflict and help patients become involved in decision making by providing information about the options and outcomes and by clarifying personal values. They are designed to complement, rather than replace, counseling from a health practitioner. The medical literature has observed an increasing number and utilization of decision aids in patients management in various fields of medicine.15-17

Objective: To develop a decision aid to elicit parents of premature infants’ preferences with regard to indomethacin prophylaxis vs. symptomatic treatment in the management of their infants.

Methods: Structural development: The framework is an evidence-based, practical, midrange theory for guiding parents making health or social decisions. It follows the Ottawa Decision Support Framework, and is based on the Ottawa Personal Decision Guide (OPDG).18 The DA supports decision making through providing information about the disorder, its management and its outcomes through a computer based interface.

Evidence Sources: Information about the outcomes of indomethacin prophylaxis in ELBW infants were driven from the best evidence reported in the published meta-analysis of indomethacin prophylaxis use in preterm infants. Morethan 19 randomized trials were included in the report.11,12

Platform design: A web-based DA format was chosen to allow for broader utilization, easier access. A professional web designing establishment developed the platform of the DA using PHP scripting language and MySql database and made available on the World Wide Web.

Experts’ feedback: Feedback of the DA structure and content was sought of neonatologists, DA experts commenting on the structure and content of the DA. Eight experts were approached by e-mail (5 international and 3 local). Experts provided constructive feedback with some modification regarding the scientific data presented, language and general layout of the DA.

Parents’ feedback: We conducted interviews with 10 expecting mothers (ten mothers of infants in our NICU were randomly selected to participate in this pilot study). Each participant answered specific questions and provided general comments. An example of a general comment; “it was a simple and an interesting way to understand the condition of my child, it is nice to see such interactive tools to cover our health concerns about our children”. Modifications were made based on the participant feedback. Modifications were mainly related to the DA language, numeric data presentation, and other scientific information.

Pilot testing of the Decision Aid: Ten mothers (other than those involved in the parents feedback) used the DA as if they were to make a real life decision about the use of indomethacin therapy. Initially, they were introduced to the concept of prematurity and PDA followed by explaining the role of indomethacin therapy as a management option. These participants then completed 3 instruments: (1) an evaluation questionnaire; (2) a knowledge scale before and after use; and (3) a validated decisional conflict scale (before and after use).18 The evaluation questionnaire addressed 9 features of the DA that participants rated on 5-point Likert scale (1 for highest value, 3 for neutral value and 5 for lowest value). The knowledge scale consisted of 8 questions we developed specifically about prematurity, PDA, the required time and the need for assistance in using the DA.

Statistical analysis: Tests utilized in this study were a one sample t-test for the 5-point Likert scale and paired t-test to compare the pre and post means for the knowledge and decisional conflict scales. A two sided P value < 0.05 was considered statistically significant.

Results

The Decision Aid (DA): Structure: DA was structured in two parts; the first part provides medical information about: the use of the DA, prematurity and its complications, PDA, and the use of indomethacin therapy in ELBW infants (prophylactic indomethacin and symptomatic PDA treatment), chance of intermediate outcomes (risk of PDA, surgical PDA ligation, severe IVH), chance of long term outcomes (survival, neurosensory impairment) for both options, and potential adverse effects (gastrointestinal perforation, renal impairment) associated with indomethacin prophylaxis use, all presented in a systematic and balanced way through a series of screen shots, that included several images and simplified language in both paragraphs and bullet points.

In the second part; the DA coaches the parents in the decision making process regarding the use of indomethacin for their preterm infants through: case scenarios of the PDA and side effects of indomethacin, clarification of the patient’s own values for each benefit and harm; and assistance in the final decision making, a verbal description of uncertainty was utilized (e.g. likely) rather than a numeric one (eg 0.80) in order not to overload participants with numbers and because evidence shows that verbal is as effective as numeric communication. However, numeric values were displayed on the decision aid instrument.17

Rating values: The parents will assign the value of each potential outcome associated with indomethacin therapy. The DA presents the values as a horizontal feeling-thermometer with values ranging from 0 (worst outcome imaginable i. e. death) to 100 (best health condition imaginable) by increments of 1 unit. The parents move the cursor of the scale to assign the value for a specific outcome. Their assigned value will show in the box adjacent to the scale.

Table 1 Baseline characteristics of pilot testing mothers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Respondents (N = 10)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (SD)</td>
<td>36.2 (7.76)</td>
<td></td>
</tr>
<tr>
<td>Educational level N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>1(10)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>1 (10)</td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Graduate degree</td>
<td>6 (60)</td>
<td></td>
</tr>
<tr>
<td>Computer user</td>
<td>8 (80)</td>
<td></td>
</tr>
<tr>
<td>Internet user</td>
<td>8 (80)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 Results of pilot testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>1.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>User friendliness</td>
<td>1.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pictures</td>
<td>1.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Understandability</td>
<td>1.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Amount of information</td>
<td>1.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Knowledge improvement</td>
<td>1.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Perceived required time</td>
<td>1.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Decision Aid helpfulness</td>
<td>1.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>1.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Knowledge scale pre*</td>
<td>1.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Knowledge scale post</td>
<td>7.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Decisional Conflict scale pre**</td>
<td>25.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Decisional Conflict scale post</td>
<td>0.6</td>
<td>1.349</td>
</tr>
<tr>
<td>Number of minutes to complete DA mean (SD)</td>
<td>19 (5.164)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| Need for assistance to use the DA n (%) | 4 (40%) | *knowledge scale total score is 10
| ** Decisional conflict scale total is 40 **

Decision making models: Later, the DA allows the parents to choose one of the two possible decision making models. After integrating the information provided, their values the parents will provide a choice “to use” or “not to use” indomethacin as prophylaxis for their ELBW infant as an individual choice. The parents have the choice to leave the decision aid at any stage andleave the decision to their health care provider.

Navigation: User friendly navigation was utilized. The parent can access the first page of any section from any page of the DA, and all pages of a particular section from any page of that section.

Pilot testing of the Decision Aid: Characteristics of the mothers who participated in the pilot testing of the DA are listed in Table 1. The results of the pilot testing are listed in Table 2. Positive feedback regarding the design, pictures, understandability, user friendliness, perceived required time, explanations, and amount of information in the DA was provided by the participants. They felt comfortable and satisfied while using it. Both the knowledge and the decisional conflict scales improved significantly after review of the DA. The mean time needed to finish reviewing the DA was 19 minutes, only one of the volunteers needed assistance in using the appropriate buttons to navigate the DA.

Discussion
We have developed a computer based interactive DA for considering indomethacin therapy in the management of ELBW infants following a detailed well structured methodology based on the Ottawa Decision Support Framework. The DA will help parents of ELBW infants have an informed decision without the presence of their health care provider with regard to whether to offer or decline indomethacin prophylaxis in the management of their infants. The DA will also augment further research in evaluating parents preferences with regard to indomethacin therapy based on a reliable tool which will then completes the three circles (experience, research evidence, and patient preferences) of evidence based medicine in the area of indomethacin prophylaxis in preterm infants. Parents evaluated our DA rated most of its features positively and showed a significant improvement in their knowledge, decisional conflict scales.

Our DA is the first to our knowledge in neonatal care; it followed a rigorous well defined developmental process, and offers the ease, accessibility and convenience to users since it is web based. It can be utilized in the care of preterm infants starting at the antenatal visit. Our DA however has some limitations; first, our pilot testing involved ten subjects that makes it difficult to generalize the results for a widespread use. Second, the computer, web based design although advantageous to many parents in the modern age makes it difficult to be utilized by non computer users. Third, a limitations of the DA development process is the lack of real life decision making of a parent of a preterm infant admitted in the intensive care unit, our future research will involve measurement of parental preferences with regard to indomethacin therapy in ELBW infants in a large representative sample to help guide the practice of neonatal practitioners.

Conclusion
We have developed a computer based DA to assess parental preferences with regard to indomethacin therapy in preterm infants. Future research will involve measurement of parental preferences to guide and augment the clinical decisions in current neonatal practice.

References
5 Rojas MA, Gonzalez A, Bancalari E, Claure N, Poole C, Silva-Neto G: Changing trends in the epidemiology and


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