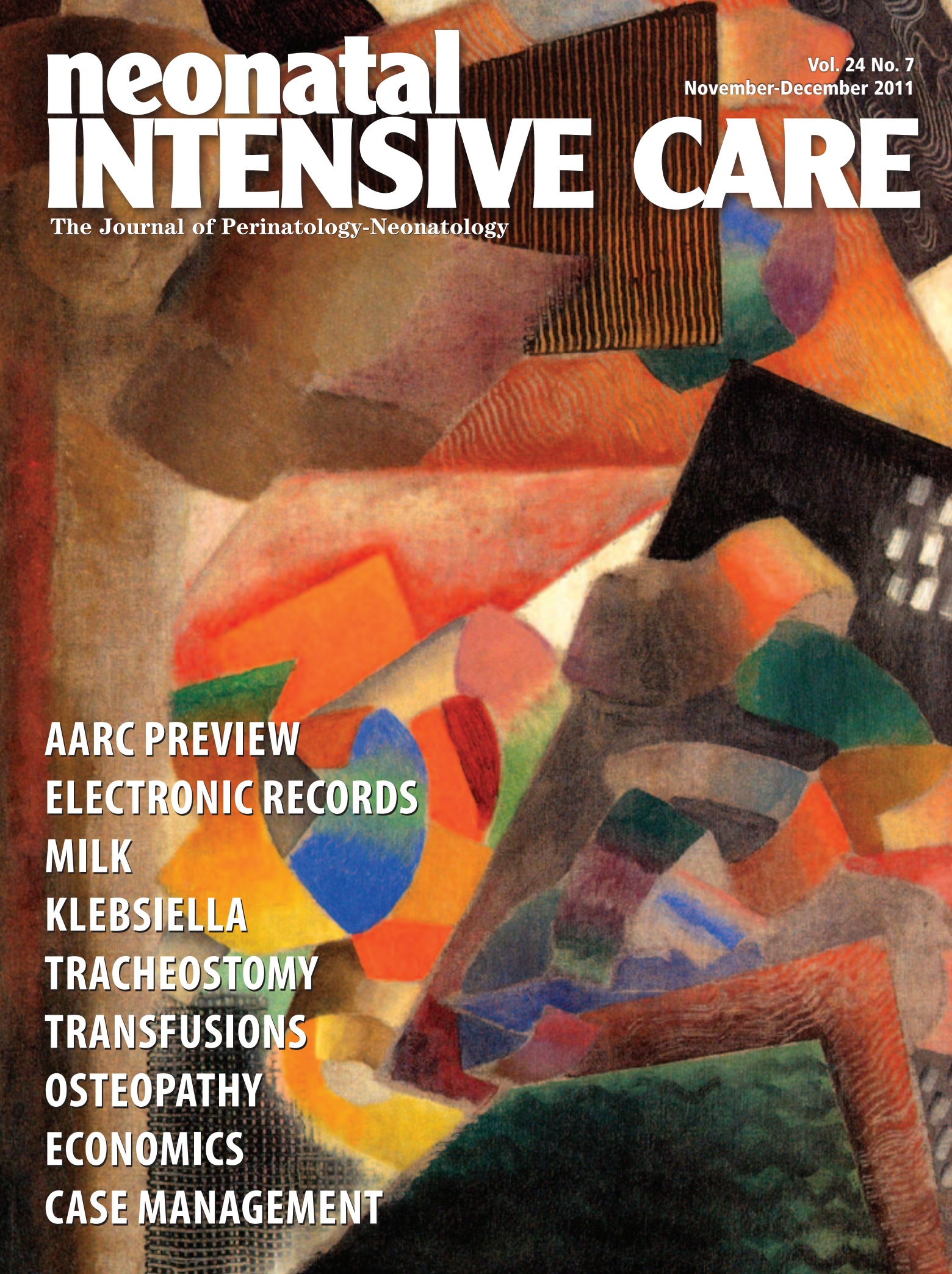
Vol. 24 No. 7
November-December 2011

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology



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ARTICLES

Editorial

Ethics Roundup

I thought you might be interested in easily accessible sources of current literature on neonatal ethics. A Google search offers many listings, but much of the material found on Google is badly out of date.

BioMed Central has several excellent journals dealing with ethics, primarily BMC Medical Ethics, though most are only tangentially relevant to neonatal/perinatal care.

Medline (PubMed, a resource of the NCBI) cites nearly 1,600 articles on the subject, though in many, ethics isn't the direct focus; rather, the subject in mentioned in passing as in the context of a more specific medical condition. However, PubMed does list 200 complete articles relevant to the subject.

For books or e-books about neonatal ethics, it might be valuable to take a look at Amazon. Our search found a number of informative books, among them: Too Expensive to Treat?: Finitude, Tragedy, and the Neonatal ICU, by Charles Christopher Camosy (2010); Neonatal Bioethics: The Moral Challenges of Medical Innovation by John D. Lantos and William L. Meadow (an oldie but goodie, from 2008); European Neonatal Research: Consent, Ethics Committees and Law by Susan A. Mason and Chris Megone (thorough but hardly current, 2001); Ethics and Newborn Genetic Screening: New Technologies, New Challenges by Mary Ann Baily and Thomas H. Murray (fairly current, 2009); Law and Ethics in Children's Nursing by Judith Hendrick (recently published, and available as a Kindle book); The Ethics of Screening in Health Care and Medicine: Serving Society or Serving the Patient? (International Library of Ethics, Law, and the New Medicine) by Niklas Juth and Christian Munthe – also fairly recent, and thorough); Compelled Compassion: Government Intervention in the Treatment of Critically Ill Newborns (Contemporary Issues in Biomedicine, Ethics, and Society) by Arthur L. Caplan, Robert H. Blank and Janna C. Merrick: not recent, but controversial – Arthur Caplan is an excellent writer on ethical issues; Uncertainty in Medical Innovation: Experienced Pioneers in Neonatal Care by Jessica Mesman, (2008); Neonatal Pain: Suffering, Pain, and Risk of Brain Damage in the Fetus and Newborn by Giuseppe Buonocore, et al, an expensive but useful Kindle reference guide at $111. This list isn't exhaustive – Amazon shows 142 items in this category. In any event, as you can see, for neonatologists looking for vital info on ethics, there's no lack of material.

Also, while we're on the subject, I would like to once more extend an open invitation to send us your thoughts about ethical or other issues relevant to neonatology and perinatology. You can reach me directly at s.gold4@verizon.net or lplesko@ucla.edu.

Les Plesko, Editor

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

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neonatal INTENSIVE CARE

ISSN 1062-2454
Published seven times each year by
Goldstein and Associates, Inc.
10940 Wilshire Blvd., Suite 600
Los Angeles CA 90024
Phone: 310-443-4109
Fax: 310-443-4110
E-mail: s.gold4@verizon.net
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http://accugraphics.net

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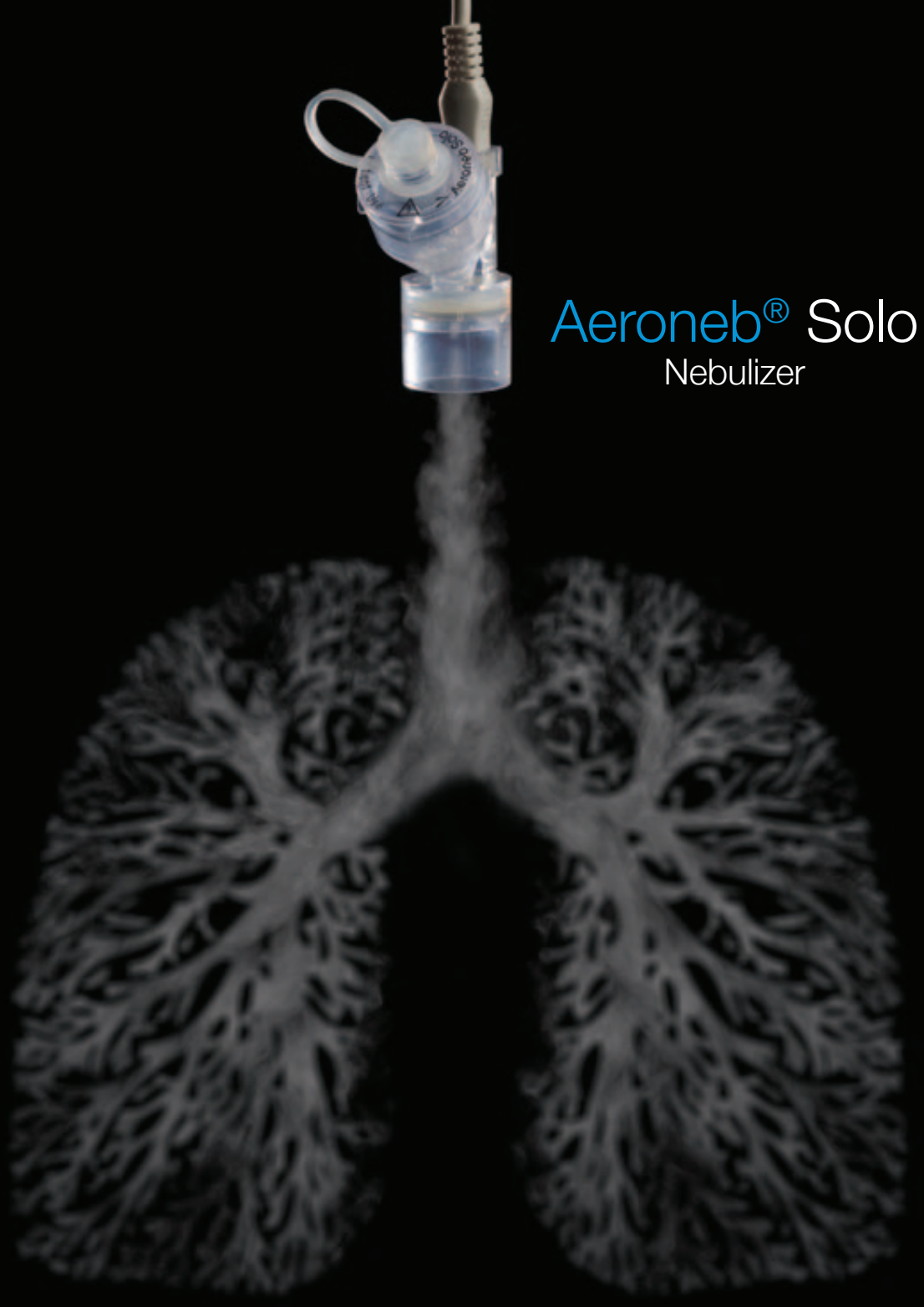

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News

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VIVE LA DIFFERENCE, NOT

Big differences in birth weights of twins increases the risk of health complications for both babies, according to a study at Rotunda Hospital in Ireland. The researchers studied a thousand women with twins over a three year period, and found that a difference of 18% or more in twin birth weights for discordant pairs was associated with an increased risk of fetal or neonatal death, bowel complications, breathing difficulties, infection and admission to the NICU. Monochorionic twins were found to be at highest risk, with the larger twin at equal risk to the smaller one. Researchers said their findings should trigger closer fetal monitoring. As a side-note, researchers found a low rate of infant morbidity and mortality among their study participants, even lower than for single births, a finding the researchers attributed to the high standards of Irish obstetric care.

IT'S A CRIME?

The Huffington Post reported that a California midwife was jailed and sentenced to three years of probation for delivering a baby after she was unable to contact a "licensed supervisor." When the midwife delivered the baby, its shoulder was stuck and the mom suffered a vaginal tear. Both mother and baby were fine, but a complaint was made to the California Medical Board, and when the case went to court, the judge said the midwife used poor judgment, and that she was motivated by money, although he noted that she hadn't had other problems with birth since she received her license. The court said it didn't accept that the midwife "had an obligation to deliver a baby without a licensed midwife there." She had faced up to three years in state prison, and prosecutors sought a 16-month term. The midwife's attorney, who took the case pro bono, had argued that she tried to get the pregnant woman to go to a hospital when hemorrhaging occurred, but that the mom refused to go. In addition to probation, the midwife was ordered to perform 280 hours of community serve and pay $10,000 to the medical board. Readers of HuffPo's article responded: Delivering babies is a serious busine$$... It's all about the money… Medical boards are kangaroo courts… So why are police officers and firemen who deliver babies not charged with practicing without a license?... I can come up with at least 20 stories of woman who were coerced into having labor induced which then (as so often does) led to c-sections because the baby and/or mom was in danger from the effects of the pitocin used to induce them. How "safe" were those services?... Oh come ON! Since when does the government have the right to tell us how to have kids?... If she would have walked away and the mother or the kid would have been hurt, then they would have prosecuted her for not helping.

WHO'S NUMBER ONE?

US News and World Reports has ranked the top 50 pediatric hospitals for NICUs. According to the magazine, the criteria are as follows: Nurse staffing in neonatal intensive care units, ability to prevent bloodstream infections, and patient volume are among the factors that made up 75% of a hospital's score. Most of the data came from a US News survey of children's hospitals. The other 25% reflects how many of 450 neonatologists surveyed in 2009, 2010, and 2011 recommended the hospital. The top ten pediatric hospitals for neonatology are: Children's Hospital of Philadelphia, Children's Hospital Boston, Cincinnati Children's Hospital Medical Center, Rainbow Babies and Children's Hospital Medical Center, Texas Children's Hospital, Lucile Packard Children's Hospital at Stanford, New York-Presbyterian Children's Hospital, Children's National Medical Center in DC, St Louis Children's Hospital – Washington University, and Johns Hopkins Children's Center. For the rest go to health.usnews.com/best-hospitals/pediatric-rankings/neonatal-care.

CONSEQUENCES

A study at Stanford University of 600,000 infants showed that preemies under 37 weeks had an increased risk of death during early childhood and young adulthood. According to a report in Medical News Today, this has important long-term implications, since the frequency of preemie births in the US has increased to more than 12%. The study comprised Swedish births over a six year period, including 28,000 preemies. Infants were also followed from their first year to their 30s. The researchers found a definitive connection between gestational age and mortality. Preemie birth was linked to higher mortality in early childhood and young adulthood, even for late preterm births. Gestational age at birth had the strongest inverse association with mortality from congenital anomalies and respiratory, endocrine, and cardiovascular disorders. The researchers couldn't say why this was so. Reported in Medical News Today, written by Grace Rattue, copyright Medical News Today.

NOT SO HEALTHY

Moms who eat low fat yogurt while pregnant may be putting their kids in danger of developing asthma and hay fever, according to a study by the Danish National Birth Cohort, as reported in Medical News Today. The researchers found that milk and dairy intake protected against asthma development but that women who ate low-fat yogurt once a day were 1.6 times more likely to have kids who had asthma by age 7. The researchers opined that perhaps the non-fat nutrients in yogurt were responsible, or that it had something to do with the lifestyles of people who ate low-fat yogurt.

FINGER FINDING

Men's ring fingers are longer then their index fingers, and women's are the opposite. Why, and so what? Researchers at Howard Hughes Medical Institute and the University of Florida have found that male and female finger lengths are determined by the balance of sex hormones during early embryonic development. Researchers say their findings could lead to an understanding of the origin of behavior and disease, which may be useful for customizing treatments or assessing risks in context with specific medical conditions. The researchers found that finger growth is controlled by androgen and estrogen receptor activity, and is thus "a lifelong signature of our early hormonal milieu." In short, our fingers can tell us about the signals we were exposed to in the womb. More androgen was found to lead to a longer ring finger, while estrogen led to ladylike hands. These hormonal signals govern the rate at which skeletal cells divide. The study used mice, who have finger ratios similar to humans. The researchers noted that in many cultures,

a proportionally longer ring finger in men was seen as a sign of fertility.

OUCH!

In yet another piece of evidence for babies' ability to feel pain, researchers at University College Hospital reported that babies can tell the difference between a normal touch and painful stimuli at 35-37 weeks gestation. Medical News Today reported that at 35 weeks, neural activity gradually changes to a nearly adult-like state, and therefore babies can then process pain like adults. The researchers added that preemies younger than 35 weeks show similar brain responses when feeling touch or something painful. Researchers looked at the brain activity of 46 babies, including 21 preemies, and used an EEG while the babies were undergoing heel sticks. Reported in Medical News Today, in an article written by Grace Rattue, copyright Medical News Today.

C-ME

AWHONN examined the growing C-section rate in its recent issue of Nursing for Women's Health. The article, by Candace Campbell, MSN-HCSM, RN, offered the suggestion that women simply refuse elective cesareans, noting the well-know potential drawbacks of the surgery. AWHONN noted, "Infants born via elective cesarean birth are exposed to greater risks, such as increased rates of prematurity, respiratory problems and developmental delays." The article noted that nurses are in a position to formulate policies, develop needed measurement tools and advocate for a better understanding of the negative effects of elective cesarean deliveries and elective repeat cesarean deliveries.

GASP!

Brain damage due to oxygen deprivation in mice fetuses can be linked to the fatty molecule LPA, according to researchers at Scripps. Researchers said their study may help understand and find new ways to address developmental disorders due to oxygen deprivation. The LPA molecular pathway can be targeted with drugs, so new medicines may be created that target these receptors. LPA acts as a signal that influences neurogenesis, and may play a role in developmental disorders linked to brain disorganization due to hypoxic insult. Scientists had assumed that the association between hypoxia and brain damage was non-specific, but the researchers found that hypoxia causes the neurons to become overstimulated, mimicking effects produced by excessive LPA exposure. Genetically removing the receptors for LPA or blocking them through drugs stopped these effects.

GIRLY MEN

Sons of male mice exposed to prenatal stress are more sensitive to stress as adults, according to researchers at the University of Pennsylvania. The researchers bred stress-sensitive males with normal females to see if the heightened stress response could be transmitted to the next generation. Even though the male offspring had no additional exposure to stress in the womb, they displayed a more pronounced reaction to stress, just like their fathers. The researchers said their study showed that the effects of maternal stress in mice are passed by the sons to the grandsons of the stressed mothers, and that the transmission is through the sons' DNA. The sons and grandsons of female mice that were stressed while pregnant showed a stress response more similar to female mice. Also, compared with other male mice, the stress-sensitive grandsons also had smaller testes, as did their fathers, suggesting they were exposed to less testosterone around birth. In addition, their genes involved in brain development were turned on and off in a pattern more similar to female than male mice. The researchers concluded that prenatal stress may disrupt masculinization of the developing mouse brain, and that this "de-masculinization" could be passed across generations.

DON'T CHEW 'EM IF YOU GOT 'EM

Babies born to snuff-smokin' moms were more likely to have breathing problems than kids born to the regular puffers, according to researchers at the Karolinska Institute in Sweden, who looked at 610,000 births. Medical News Today reported, "One or two of every 10,000 babies born to mothers who didn't use snuff or cigarettes developed apnea. For babies whose mothers lit up during pregnancy, that risk increased by about half. For those whose mothers used snuff, the rate was more than twice as high as in babies born to mothers who didn't use any kind of tobacco." Apnea was more common when mothers used snuff, regardless of whether babies were born early or not. Information is from Medical News Today, written by Sy Kraft, copyright Medical News Today.

WOOZY = DUMMY

Children of women who experience hyperemesis gravidarum, nausea persisting beyond the first trimester of pregnancy, have more attention and learning problems by age 12, according to UCLA researchers, and women with a family history of the condition were up to 17 times more likely to suffer from it. Researchers surveyed women with HG who reported on the emotional and behavioral histories of their siblings and found that 16% of siblings from the exposed group had depression, compared with 3% from the non-exposed group. Eight percent from the exposed group were diagnosed with bipolar disorder, compared with 2% from the non-exposed group, and 7% from the exposed group suffered from anxiety in adulthood, compared with 2% from the non-exposed group. Among 17 diagnoses, 38% of the cases reported psychological and/or behavioral disorders, compared to 15% of controls. Researchers concluded that adults exposed to HG in utero were significantly more likely to have a psychological and/or behavioral disorder than non-exposed adults. They posited that the high rate could be a result of the moms' prolonged malnutrition and dehydration, as well as their anxiety and stress.

THIS SUCKS

Medical News Today reports: the USA is in 41st place worldwide in infant mortality, a drop from 29th place in 1990. America's newborn death rate today is equal to that of Croatia, Qatar and the United Arab Emirates, according to a new report published in PLoS Medicine. Newborn deaths worldwide dropped from 4.6 million in 1990 to 3.3 million in 2009. The three main causes of newborn deaths are severe infections, asphyxia and preterm delivery. Newborn mortality rates increased over the last two decades in 8 countries. Each year 3.3 million babies die in the first four weeks of life. The US newborn mortality rate dropped by 26% in two decades, compared to a worldwide average of 28%. America is behind 40 others countries, with a rate of 4.3 per 1,000 live births. Reported by Medical News Today, written by Christian Nordqvist, copyright Medical News Today.

PUT IT TO REST!

There is no evidence linking vaccines to autism or type 1 diabetes, according to the Institute of Medicine, which analyzed more than a thousand research papers. Further, very few other health problems were caused by vaccines. The only concrete vaccination side effects were temporary joint pain and allergic

reactions. The report found that vaccines could not be linked to MMR and DTaP. MMR did not cause autism, and the flu vaccine does not exacerbate asthma or cause Bell's palsy. Information for the above is from an article by Christian Nordqvist, Medical News Today, copyright Medical News Today.

TWO IN ONE

An Indian woman with two wombs has given birth to two boys, one from each uterus. The Huffington Post reported that "the delighted mum Rinku Devi delivered her one-in-fifty-million babies in the northern city of Patna. Stunned doctors said giving birth to healthy babies conceived in different ovaries is so rare an average of one case is reported each year anywhere in the world. The babies, however, are not twins, as they were conceived at different times. According to gynecologist Dr Dipti Singh, 'Rinku Devi suffers from a rare medical condition known as the uterus didelphys in which the womb develops in two parts, each with its own fallopian tube. It is quite a rare congenital condition and less than 100 women around the world are known to have it.' Rinku's condition was not diagnosed until she went into labor pain, but after a one-hour long surgery she gave birth to two little boys weighing 2 kilograms and 1.5 kilograms respectively. The surgery took about an hour and the boys weighed 3 pounds, 3 ounces and 4 pounds, 4 ounces, respectively, according to Barcroft Media. Dr Singh says they can't be officially called 'twins' since one of the brothers was actually in utero three weeks longer. 'It means Rinku conceived at different times,' she said, adding that unlike some other women born with a similar condition, she did not have two vaginas. 'I got to know about having two uteruses when I was already in labor pain,' [the mom] said."

PANT AND POP

An extensive review of pregnancies over the course of more than three decades shows that women with poorly-managed asthma are at an increased risk of having a low-birth weight baby, a premature baby and other pregnancy complications such as preeclampsia. The study found that the infants of women with asthma were likely to weigh an average of 0.2 pounds less at birth compared to babies of mothers without asthma. Mothers with poorly-controlled asthma were also at a 25% increased risk of preterm birth and 50% increased risk of developing preeclampsia. "The study does not clarify the mechanism of the increased risk," said Michael Schatz, MD, asthma specialist at Kaiser Permanente Medical Center in San Diego and also a co-author on the study. "Most information suggests it is only uncontrolled asthma that increases the risk," he added. "But more information on other potential factors, such as asthma medications, is needed." The Organization of Teratology Information Specialists (OTIS), in collaboration with the American Academy of Allergy, Asthma & Immunology, recently launched an extensive study regarding asthma medications in pregnancy. It is an observational study where medications and asthma control of pregnant women will be carefully monitored and related to pregnancy outcomes. OTIS is seeking both pregnant women with asthma and pregnant women who do not have asthma. To learn more about the study or to volunteer please visit OTISPregnancy.org.

FLAME-OUT

Pregnant California women have registered some of the highest levels of the toxic flame retardant PBDE in their bodies ever recorded worldwide, according to a new study released by re-

searchers at UC San Francisco. Molly Hennessy-Fiske, writing in the Los Angeles Times, reports that the research team tested 25 second-trimester pregnant women from Northern and Central California seeking care in San Francisco in 2008 and 2009 and found that their blood showed high levels of PBDEs, or polybrominated diphenyl ethers, which studies show are harmful to the liver, thyroid and nerve development. Researchers believe that the women's high PBDE levels were due to California's strict flammability regulations enacted in the 1970s, which led manufacturers to add flame retardants to a wide variety of products, from electronics to furniture. The chemicals have largely been banned in California since 2004. US-born minority and low-income women were more likely to be exposed to the toxic chemicals, possibly because they were more likely to use secondhand furniture or live in low-income housing with poor ventilation. Paradoxically, immigrant women from developing countries such as Mexico show lower levels of exposure to the chemicals, probably because Mexico used less of them, so an immigrant's exposure in Mexico was lower than when they were in California. Researchers said pregnant women can try to reduce their exposure by dusting and wet-mopping their homes, washing their hands frequently, and avoiding foam furniture and other products.

LOOK OUT!

The FDA is informing the public that treatment with high doses (400-800mg/day) of fluconazole during the first trimester of pregnancy may be associated with a rare and distinct set of birth defects in infants. This risk does not appear to be associated with a single, low dose of fluconazole 150mg to treat candidiasis. Based on this information, the pregnancy category for fluconazole indications (other than vaginal candidiasis) has been changed from category C to category D. The pregnancy category for a single, low dose of fluconazole has not changed and remains category C. Healthcare professionals should counsel patients if the drug is used during pregnancy or if a patient becomes pregnant while taking the drug. Patients should notify their healthcare professionals if they are or become pregnant while taking fluconazole. If a patient uses fluconazole during pregnancy, the patient should be informed of the potential risk to the fetus. Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program at fda.gov/MedWatch/report.htm. or by calling (800) 332-1088.

TOO MUCH INFO

According to the Wall Street Journal: "The familiar heel prick that newborns receive is revealing more about a baby's health than ever before. But, as technology opens the possibility of screening newborns for hundreds of diseases, there is controversy over how much parents need to know. Within days of an infant being born, a few drops of blood are taken from the baby's heel and tested for signs of more than two dozen different conditions, including congenital hypothyroidism and sickle-cell diseases. In many places, babies also are given tests to identify the likelihood of hearing or vision disorders. Some states have expanded their checks, including testing for amino-acid and metabolism disorders. Many of the new conditions being looked at have no definitive treatment or it isn't clear whether immediate intervention is necessary… Proponents of broader screening programs say early intervention in a disease can improve a child's life and might speed the development of treatments for rare diseases… But critics say the additional tests may raise flags that lead to unnecessary further testing, or treatment, for babies who will not get sick. The tests can add big additional costs to the healthcare system, they say. And some people are concerned about privacy, since stored blood-spot samples can be used by researchers." The Wall Street Journal goes on to note that the government encourages tests for 30 diseases, including congenital hypothyroidism, glactosemia, congenital adrenal hyperplasia, and biotinidase deficiency. Some states also screen for Krabbe disease, Pompe disease, toxoplasmosis, and hemoglobin H disease. Many of the diseases tested for have no cure. As a result, there's controversy about the point of the tests, with some researchers and scientists claiming that it's still better to know than not to know. The above was reported in the Wall Street Journal by Amy Dockser Marcus.

PROS AND CONS

The Los Angeles Times recently reported on home births. Olga Khazan wrote: Though home births account for only about 1% of all births each year — 28,400 annually — they increased by 20% from 2004 to 2008. The practice is most popular among well-educated mothers who favor natural childbirth without the drugs or surgeries a hospital might use. The practice is frowned on by the American College of Obstetricians and Gynecologists, which issued an opinion in January saying it discourages home births because the absence of emergency medical equipment and specialists accustomed to dealing with complications means that problems during labor could cost the baby's life. ACOG acknowledged that home births are associated with fewer medical interventions than hospital births and avoid the use of drugs such as Pitocin and epidurals. Sixty-one percent of women who had vaginal delivery received an epidural in 2008. A 2006 national survey of women's childbearing experiences showed that 55% were given Pitocin to speed labor. Women also turn to home birth in order to avoid cesarean sections. According to the CDC, cesareans now account for nearly one-third of hospital births in the United States — a much higher rate than most doctors say is ideal. Also, many hospitals do not allow women who have previously had a cesarean to attempt a vaginal birth because of the risk of uterine rupture, even though a 2010 NIH advisory panel concluded that the risk of uterine rupture during a vaginal birth after one cesarean was just 1% and that more women should be offered the choice. Women wishing to have a VBAC may have no option but to do so on their own turf. Many home-birth moms also say they object to other aspects of hospital births, such as having to lie in a bed, abstain from food during labor and be monitored… The core of the home-birth debate lies with the safety of the baby. A 2005 study of 5,418 births in the US and Canada during 2000 found that the neonatal death rates of at-home births were comparable to those of births in hospitals. But a July 2010 analysis published by ACOG examined the outcomes of 12 home-and-hospital-birth studies and found that babies born at home die at two to three times the rate of those born in hospitals. Just as online communities have sprung up to promote home birth, so too have others populated by women whose home-birth attempts turned into tragedies. Much of the opposition to home births is directed at certified professional midwives. Critics say the certification for such professional midwives is inadequate for those without a prior nursing background. Certified professional midwives counter that their training is as rigorous as that of nurse midwives and that their programs are specifically geared toward low-risk home delivery. A clear answer to the safety question is hard to find because nearly every home-birth study has some flaw that is flagged by one side of the debate or the other as invalidating the results. Information for the above is from the Los Angeles Times,

copyright 2011, by Olga Khazan. It includes direct quotes and paraphrasing, and has been edited for our readers.

LONESOME YUPPIES

The Huffington Post recently reported on the so-called Latino Health Paradox. Researchers have noted that more than half the children born in the US-Mexico area of Las Cruces, NM have low income and little formal education, which would identify them as having the conditions for elevated infant mortality. But in the county, the number of deaths is lower than the national average. HuffPost went on to report that the prevailing wisdom in the US is that well educated richer people have better health, but in the case of Latinos, this isn't so. In addition, Latinos use fewer healthcare services than other populations. The National Center for Health Statistics has reported that Latinos had the nation's longest average lifespan, outliving white Americans by 2.5 years and blacks by 8 years. As far as infant mortality, the US is ranked 177th, worse than Slovenia. The white infant mortality rate in 2007 was 5.6 per 1,000 births. The rate for Latino infants in 2007 was 5.5 per 1,000, compared to 13.3 for blacks. Clinicians in Los Crucez's Dona Ana County Clinic analyzed its high-risk client files and found that high mortality was tied to a high level of social isolation or a weak support network, whereas Latinos have tight family bonds. While many explanations have been touted, it has been suggested that in addition to family support, lower infant mortality among Mexican Americans is because they have babies at an earlier, healthier age. Information for the above is from the Huffington Post.

PATCH IT UP

The Huffington Post reported that many types of monitoring equipment may soon be replaced by a "tiny, wireless patch, sort of like a temporary tattoo." Researchers at the University of Illinois have embedded electronic sensors in a film thinner than a human hair that can stick to skin without adhesives and can remain in place for 24 hours. The patches could monitor brain waves, muscle movement, larynx movement, and other functions. A company in Massachusetts, MC10 is working on developing commercial uses. HuffPo said, "The current design has a small coil and could be powered by induction – by placing it near an electrical coil – that would permit intermittent use, and for longer-term monitoring a tiny battery or storage capacitor could be used."

SAVING BABIES

The Wall Street Journal reported that some NICUs are cutting back on the high levels of oxygen traditionally given to preemies. The change is based on research indicating that such levels may contribute to ROP. Hospitals also are cutting back on prescribing several medications, including antibiotics and anti-reflux drugs, because studies show they confer few benefits and increase risk of adverse reactions. To promote such improvements, Pediatrix Medical Group, whose doctors care for about 20% of the US's preemies, launched a "100,000 Babies" campaign in 2009 in 125 hospitals. Its analysis of 13,532 infants born at 24 weeks to nearly 28 weeks from 2006 to 2008 found improvements resulted in a drop in the mortality rate in participating NICUs, from 18% in 2005 to just over 14% in 2009. The Pediatrix campaign is one of 10 neonatal quality improvement programs in the US approved by the American Board of Pediatrics, which requires quality improvement activities for neonatologists as part of their certification. By way of example, Helen DeVos Children's Hospital in Grand Rapids, MI, reduced NICU infections by more than 80% since 2005 thanks to new practices that include prohibiting parents and visitors from touching babies with artificial nails, which can harbor bacteria, and requiring staffers to change tubing only every 72 hours instead of every day, to avoid unnecessary invasive contact with the baby. As far as oxygen reduction, it is now thought that reducing blood oxygen levels to the 85% range is the safest. Other Pediatrix goals are to push the benefits of breast milk, and keeping babies warm after delivery. Reported by Laura Landro in the Wall Street Journal.

SAFE STENT

Percutaneous coronary intervention, while not typically acceptable for infants with acute coronary syndrome, has been found to be feasible and safe. Researchers at Children's Hospital San Diego conducted a retrospective review of seven children who had PCI between June 2006 and June 2010. PCI techniques included balloon coronary angioplasty and coronary stent implantation. Researchers analyzed patient data that included underlying diagnosis, comorbidites, catheterization technique, and outcomes. In all cases, successful stent placement in the proximal portion of the left or right coronary arteries with excellent revascularization was achieved. The average diameter of the heart arteries was 0.65 mm prior to the intervention. Balloon angioplasty did not completely resolve the stenosis so bare metal stents were implanted to a mean internal diameter of 2.5 mm. The average intervention-free period was 434 days after stent implantation. Restenosis and thrombosis did not occur in cases where the implanted stent diameter was greater than 2.5 mm and patients received dual anti-platelet therapy.

UNDETECTED

Researchers at Duke University are recommending pulse oximetry for early detection of CHD. The researchers noted that screening for low-blood oxygen saturation can be an effective way to identify otherwise well-appearing babies who have undetected critical CHD, but that one of the biggest challenges in implementing screening will be the follow-up after a positive screen, and noted the importance of avoiding false-positive results. For instance, researchers said, the algorithm's usual cutoff point for oxygen saturation may need to be adjusted for babies in high-altitude nurseries, where blood oxygen levels may be normally slightly lower. The Duke report was endorsed by the American Academy of Pediatrics, the American College of Cardiology Foundation, and the American Heart Association, and some states have begun such screening.

BAD HEADS AND SEX

Scientists recently reported the molecular structural basis for severe head deformities and ambiguous sex organs in babies born with Antley-Bixler syndrome accompanied by an enzyme deficiency. Researchers in Texas, Wisconsin and Prague solved the atomic structure of the human enzyme NADPH-cytochrome P450 reductase, or CYPOR. The group is the first to visualize and depict the structure of the human version of CYPOR. The scientists also reported the structure of two mutations of human CYPOR that result in congenital deformities. These mutations are responsible for severe craniofacial and steroid-production defects in humans, the latter leading to sexual ambiguities. The researchers found that the addition of a riboflavin derivative reversed the defects in the mutated enzymes. While no animal studies have yet been conducted, researchers said riboflavin therapy is worth attempting, and can be accomplished within the womb.

NO ROOM TO BREATHE

In a finding that shouldn't really be much of a surprise, researchers at Children's Hospital of The King's Daughters in Virginia, studying 327 patients, found that children with severe pectus excavatum report more incidents of shortness of breath and a higher degree of exercise intolerance. The study on lung function included 327 pre-correction sunken chest patients from hospitals around the nation. The study used standardized medical measurements to determine the severity of the pectus excavatum and a spirometer. The researchers noted that the effect was primarily from lung restriction, not airway obstruction.

DISTRACTED MICE

A multinational collaboration revealed that mice could provide an insight into how specific receptor subtypes in the brain could be responsible in increasing the risk for attention-deficit hyperactivity disorder (ADHD), and help explaining how stimulants work to treat its symptoms. One subtype variant of the dopamine D4 receptor, D4.7, has been poorly understood, and was of particular interest to the researchers because of its higher occurrence in ADHD diagnosed patients. Researchers inserted three variants of D4 receptor into cells and mice to evaluate differences in biological activities. The D4.7 variant was not able to interact with the short version of the dopamine type 2 receptor to reduce glutamate release in the brain's region that is linked to impulsivity and ADHD symptoms in humans. As such, researchers said the study showed how this genetic difference might translate into functional deficits associated with ADHD. The researchers noted that psychostimulants might reduce glutamate release by amplifying the D4/D2S interaction, and that their results might explain why psychostimulants are less efficient with patients with the D4.7 variant. Information is from Medical News Today, written by Petra Rattue, copyright Medical News Today.

PRODUCTS

DRUG DELIVERY

Ikaria, Inc, announced that the Center for Devices and Radiological Health (CDRH) branch of the FDA has granted 510(k) clearance for compatibility of its INOMAX drug-delivery systems with six additional respiratory care devices. The INOMAX DS and the INOMAX DSIR are now compatible with more than 50 makes of ventilators, anesthesia systems and other respiratory care devices. The INOMAX DS and INOMAX DSIR are proprietary drug-delivery systems that deliver INOMAX (nitric oxide) for inhalation, the only drug approved by the FDA to treat hypoxic respiratory failure (HRF) associated with pulmonary hypertension in term and near-term infants greater than 34 weeks gestational age. INOMAX selectively relaxes pulmonary blood vessels, improves oxygenation and treats HRF in this fragile newborn population. The FDA's clearance of compatibility with these respiratory care devices makes Ikaria's INOMAX drug delivery systems fully compatible with most invasive mechanical ventilation methods and non-invasive respiratory strategies used in NICUs, including CPAP and nasal cannulae. The INOMAX drug-delivery systems are now compatible with the following additional respiratory care devices: Newport e360; Impact Instrumentation EMV+ Ventilator; Teleflex Comfort Flo Humidification System and Nasal Cannula; Dräger Babylog VN500; Dräger Evita Infinity V500, and; Vapotherm Precision Flow. The INOMAX DS and INOMAX DSIR drug-delivery systems are part of a comprehensive offering known as the INOMAX therapy package. In addition to use of Ikaria's proprietary, FDA-cleared drug-delivery systems, the INOMAX therapy package includes INOMAX (nitric oxide) for inhalation, distribution, emergency delivery, technical and clinical assistance, quality maintenance, on-site hospital training, 24/7/365 customer service, and all related disposable items. Contact inomax.com or ikaria.com.

HEROIC

In a randomized study of over 3,000 preterm infants, those whose care included the Heart Rate Observation System, or HeRO monitor, experienced greater than 20% reduced mortality, effectively saving one infant's life for every 48 who were monitored. The results of this multicenter study of the HeRO monitor, co-sponsored by the National Institutes of Health and Medical Predictive Science Corporation (MPSC), appear in The Journal of Pediatrics. HeRO is a pioneering monitoring system for premature infants that detects early signs of distress, commonly caused by infection and other potentially life-threatening illnesses. HeRO generates an hourly numeric score that quantifies the prevalence of abnormal patterns in each patient's heart rate and provides a new tool for clinical assessment so that standard diagnostic and therapeutic decisions are better founded. The study, "Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: a randomized trial," was conducted from April 2004 to September 2010 at leading neonatal intensive care units at the University of Virginia, Wake Forest University, University of Alabama at Birmingham, Vanderbilt University, University of Miami/Jackson Memorial Hospital, Greenville SC Hospital System, Winnie Palmer Children's Hospital and Pennsylvania State University. There were 152 deaths (10.2%) in the group that received standard NICU care and 122 deaths (8.1%) in the group that received standard NICU care plus HeRO monitoring, an absolute risk reduction of 2.1%. The patented monitoring technology was developed at the University of Virginia and licensed to Medical Predictive Science Corporation in Charlottesville, VA. The monitor, which is made by MPSC, has been cleared by the FDA to monitor neonatal distress and is being used by hospitals across the country. Contact mpsc.biz.

TEAM TRAINING

GE Healthcare, Inc announced an agreement that grants GE Healthcare's Maternal Infant Care division (MIC) exclusive rights for distribution and marketing of the KC BioMedix NTrainer pulsatile neurostimulation system. The NTrainer System incorporates a pulsating pacifier and reinforces nonnutritive suck (NNS) in infants and then measures the progress of their ability to suck. This device, currently in use at leading US hospitals, is backed by clinical studies and world-class research. Clinically, the NTrainer enables neonatal caregivers the ability to better manage incompetent feeding in neonates by providing a standardized assessment tool to measure NNS performance. NNS is an essential neurological building block in an infant's coordination of sucking, swallowing and breathing, a capability required for independent oral feeding and the development of a healthy baby. (NTrainer System is a trademark of KC BioMedix.) Contact gehealthcare.com or kcbiomedix.com.

HAVE SOME FUN

Placebo Journal, which is ceasing publication, offers back issues of its newletter. The satirical journal notes: "Supplies are dwindling. After ten full years we have decided to discontinue

the Placebo Journal. Many people have been asking about the back issues which are soon to be collector's items. Our back issue special includes around 40 individual and random issues from over the past ten years. We would give you more but that is all we have. The cost is a measly $30 plus shipping and handling." The journal also offers its 8 posters for $30. Contact placebojournal.com.

COMPLIANT

Royal Philips Electronics announced that Philips OB TraceVue Version G.00.20 is 2011/2012 compliant and has been certified as an Electronic Health Records (EHR) module by the Certification Commission for Health Information Technology (CCHIT), an ONC-ATCB, in agreement with the hospital certification criteria adopted by the Secretary of HHS. The 2011/2012 criteria support the stage 1 meaningful use rules required to qualify eligible providers and hospitals for funding under the Health Information Technology for Economic and Clinical Health (HITECH) Act. Philips' decision to pursue ONC-ATCB certification of OB TraceVue reflects the company's commitment to helping hospitals comply with industry standards and clinical guidelines with the end objective of improving financial outcomes and helping to improve and save lives. OB TraceVue, an obstetrical information management system, is designed to ensure comprehensive coverage across the perinatal care continuum, from the first antepartum visit through delivery, postpartum, discharge, postpartum follow up, newborn nursery, and gynecological visits. The solution addresses the criteria for meaningful use related to interoperability and integration with hospital clinical workflow, and provides key benefits for caregivers and patients including EHR interfaces, eliminating duplicate entries and allowing for improved patient safety and clinical efficiency; automated flags, reminders and checklists, facilitating greater compliance with professional care standards; and access to patient data from smartphones and other mobile devices through the hospital network, supporting the complex, multi-tasking workflow of clinicians on the move. Contact philips.com.

MIGHTY MINI

GE Healthcare, a unit of General Electric Company, announced that its Mini Telemetry System has received 510(k) clearance in the US by the FDA. The GE Mini Telemetry System addresses the growing demand for mobility during labor, and is fully compatible with existing GE's Corometrics monitors and transducers, as it uses the same transducers whether the patient is in bed or mobile. The GE system is designed to enable a more ambulatory experience for the mother and increase caregiver efficiency, while ensuring continuous monitoring. A number of trends have converged to make ambulatory monitoring of mother and baby increasingly attractive, including the emergence of alternative labor-and-delivery tools and environments such as birthing balls and laboring in water. The Mini system provides maximum mobility for a minimal investment in addition to the benefits for the mother-to-be and the care provider, including compatibility with existing Corometrics monitors allowing utilization of the same transducers, regardless of the patients' location within the line of sight antenna range of 500 meters/1640 feet. Other features include: Audio monitoring of fetal heart rate via either transmitter speaker or headphones; Compact size and weight (just a pound) for the ability to move freely while maintaining constant access to monitoring; An innovative cable-management slot for enhanced patient care; One-touch marking of the baby's movements; The ability to transport mothers-to-be to other in hospital departments without needing to replace transducers within the line of sight antenna range of 500 meters/1640 feet; Three-port design allowing for multiple monitoring modes: fetal heart rate, uterine activity and ECG monitoring; Extended battery life of up to 12 hours can accommodate the full duration of most labors. The device can also be recharged during use; Waterproof 9-crystal transducers provide reliability in fetal monitoring, even while laboring in water; Industry leading line-of-sight antenna range. The GE Mini Telemetry System is now commercially available in major markets throughout the world. Contact gehealthcare.com.

TURNING A CORNER

Cornerstone Therapeutics announced findings from a study comparing all-cause, in-hospital mortality in more than 14,000 preterm infants with respiratory distress syndrome (RDS). The retrospective study evaluated Cornerstone's CUROSURF (poractant alfa) compared to other surfactant-type products. Overall, CUROSURF treatment for RDS was associated with a significantly reduced likelihood of death compared to one product, and a trend toward reduced mortality when compared to the other. The findings were published in the September 1, 2011 online issue of the Journal of Perinatology. The study was a retrospective, observational, cohort study comparing all-cause, in-hospital mortality in 14,173 preterm infants with RDS treated with one of three surfactants between 2005 and 2009. Data were collected from the research database maintained by the Charlotte, NC-based Premier healthcare alliance. When compared to infants treated with CUROSURF, the likelihood of mortality was 49.6% greater and 37% greater for other surfact patients. There were no differences in mortality observed between the other surfactant product groups. The unadjusted mortality rates were lowest for the infants treated with CUROSURF (3.61%). When stratified by birth weight, the greatest benefits were recognized by the smallest infants (500-749g), the population with the highest mortality in the study. In this group, the unadjusted mortality rate was significantly lower for CUROSURF treated infants. Limitations of this retrospective study include database restrictions, such as lack of information on the precise cause of death, number of surfactant doses and antenatal steroid use. The study was sponsored by Chiesi Farmaceutici S.p.A. Contact crtx.com.

AARC PREVIEW

Bunnell Incorporated

Booth 727

What neonatal/perinatal products will you be presenting?

Bunnell Incorporated is celebrating 25 years in the ventilator industry. The Life Pulse High-Frequency Jet ventilator has passed the test of time. Its therapeutic flexibility makes it an indispensable tool in many NICUs. Jet pulse technology, passive exhalation, and an adjustable I:E ratio makes this high-frequency uniquely effective.

What products will you be featuring that are of particular current importance, and why?

The "WhisperJet" patient box with sound reduction technology is the most timely product Bunnell will feature at the 2011 AARC Congress in Las Vegas. The most recent sound reduction upgrade has lowered the sound output from 56 to 41 dB.

Discuss educational/training/support materials you'll be promoting.
Bunnell has developed a three booklet pocket reference set that explains *What* high-frequency ventilation is, *Why* the Life Pulse is uniquely effective, and *How* the Life Pulse is used to care for patients. The Life Pulse HFV Training DVD will also be available at the AARC Congress. The DVD contains a complete in-service video, a patient management video, an alarms and troubleshooting video and more. It contains everything you need to understand how the Life Pulse works and how to use it. The DVD is organized, for your convenience, into chapters so you can focus in on the information that is important to you. All of these training materials and much more are available on the Bunnell website at www.bunl.com.

Why should neonatal/perinatal caregivers visit your display?
The number one reason NICU therapists should stop by the Bunnell booth is to hear how quiet HFV can be, just 41 dB. Noise in the NICU has become an important topic of research and debate. Bunnell is committed to continuous improvement and our new "WhisperJet" proves it. Hearing is believing. Whether you currently use HFV or not our clinical specialists can answer all your HFV questions. Stop by and give us a try.

Dräger
Booth 101

What neonatal/perinatal products will you be presenting?
Dräger will be showcasing the Babylog VN500 ventilator. The dedicated neonatal-pediatric ventilator offers an extensive array of ventilation modes including options for volume ventilation. Its ability to provide leakage compensation maintains synchrony between the patient and ventilator even during significant endotracheal tube leakages. Workflow enhancements such as suction support, day/night screens, and automatic alarm volume adjustment help support a nurturing neonatal environment. The Smart Pulmonary View can easily alert clinicians to changes in patient's pulmonary mechanics. Also on display will be the BabyFlow nasal CPAP system. Designed for use with the family of Babylog ventilators, the system is easy to apply and delivers consistent CPAP levels. The use of standard patient tubing and reusable parts keep operating costs low. Its unique prong design and innovative fixation accessories are designed to reduce the trauma associated with the delivery of nasal CPAP.

What products highlighting your recent R&D efforts will you be presenting?
Dräger will introduce the new Savina 300 ventilator with 12-inch touch screen. The Savina 300 has the versatility to meet many new challenging workplace demands in and out of the ICU, recovery room, emergency room, or skilled long term facility. It combines the independence and power of a turbine-driven ventilation system with state-of-the-art ventilation modes and appealing design. The open breathing concept lets patients' breath at any time and in any mode. To improve workflow and reduce patient risk, the Savina 300 features a simple user interface that concentrates on essential controls and parameters. The integrated safety concept was designed to protect controls and parameters.

Discuss educational/training/support materials you'll be promoting.
Dräger will offer an educational DVD discussing the topics of respiratory monitoring including gas exchange, biomarkers, work of breathing, and use of respiratory monitoring systems, available while supplies last. Our clinical booklet series including Non-Invasive Ventilation, Protective Lung Ventilation, Modes of Ventilation, and Spontaneous Breathing will also be readily available.

Why should neonatal/perinatal caregivers visit your display?
The Dräger booth will again be fun-filled and the Congress a great venue to reconnect with colleagues. We encourage attendees to stop by the booth for a demonstration of the Babylog VN500 dedicated infant ventilator and to learn more about our latest advances in technology. Visitors will also have the opportunity to play our "Make a Match" game to win a free registration to the 2012 AARC Congress. And to thank all respiratory caregivers for the work they do everyday at the bedside, Dräger will again proudly sponsor this year's AARC opening reception.

Fisher & Paykel Healthcare, Inc
Booth 1011

What neonatal/perinatal products will you be presenting?
Fisher & Paykel Healthcare, Inc understands and appreciates the critical role neonatal nurses and respiratory therapists undertake in infant care. This is the reason Fisher & Paykel is dedicated to improving patient care and outcomes for over 20 years. We are introducing Toby's Journey through the F&P Infant Respiratory Care Continuum from Neopuff Infant T-Piece Resuscitation to Optiflow Nasal Cannula for Nasal High Flow therapy. Also, learn more about the launch of our new products. The first complete Bubble CPAP System will be presented along with our new FlexiTrunk CPAP Interface and new CPAP Nasal Masks.

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

Discuss educational/training/support materials you'll be promoting.
Come and experience hands-on training with the Neopuff Infant T-Piece simulator using the new Ergonomic T-Piece Resuscitation Circuit and our Resuscitation Masks. This is highly recommended for NRP Instructors. We will be giving out Ergonomic T-Piece Resuscitation Circuit Kits to all visitors. Also, ask us about our Optimal Resuscitation workshop for your hospital staff.

Why should neonatal/perinatal caregivers visit your display?
Attendees are invited to experience all of the above-mentioned demonstrations and hands-on stations, including the opportunity to test their resuscitation skills on our simulator. Please join us at the AARC Conference in Tampa at Booth 1011 for a complete review and demonstration of all Fisher & Paykel Healthcare products and experience the F&P Infant Respiratory Care Continuum. Please visit our website at www.fphcare.com for more information.

Hamilton Medical

Booth 217

What neonatal/perinatal products will you be presenting?
The new neonatal features on the Hamilton-C2 effectively support your most fragile patient, the premature infant. Hamilton Medical has taken our 15 years of experience in advanced nasal CPAP systems, including the ARABELLA Infant NCPAP System, and incorporates this expertise into a new nCPAP-PS ventilation mode that supports even spontaneous breathing efforts. With the NEONATAL OPTION, the Hamilton-C2, with its compact design, built-in batteries and ultra quiet turbine can accompany your most fragile patient during hospital transports. The unique Ventilation Cockpit provides you with continuous patient status to ensure safe and effective ventilation therapy anywhere your patient goes. Hamilton Medical is the only ventilator manufacturer offering optional mainstream volumetric capnography as well as sidestream $ETCO_2$ measurement. This quantitative CO_2 measurement allows assessment of metabolism as an early indication of sepsis. In addition, the sidestream capnography option provides CO_2 measurement with low flow sampling and minimal added dead space. Hamilton Medical's mainstream and sidestream CO_2 measurement options, in conjunction with proximal flow measurement, provide valuable insight into the patient's condition. Quantified information about airway dead space and alveolar minute volume is provided in an intuitive way to allow the clinician a choice in determining the ideal application of CO_2 measurements for neonatal through adult populations.

What products highlighting your recent R&D efforts will you be presenting?
In addition to the NEONATAL OPTION, the Hamilton C2 now allows you the flexibility to choose your optimal care strategy with a choice between two alternative timing strategies in controlled modes or with the possibility to easily switch between conventional PSIMV+ and Intelligent PSIMV+. A 72h trend complements your monitoring possibilities.

Discuss educational/training/support materials you'll be promoting.
Hamilton Medical places a high value on education. To supplement our simulation CDs, reference cards and internet based WebEx training, Hamilton Medical will have on-line, Hamilton Medical IntelliUniversity, available for all Hamilton Medical customers. An introduction to this invaluable educational resource will be provided by our Advanced Clinical Team.

Why should neonatal/perinatal caregivers visit your display?
Hamilton Medical has continued to make technological advances in the field of ventilation and the NEONATAL OPTION on the Hamilton-C2 is one of many. We will release 6 new products in the European market by the end of 2011 with the intent that most will be available by early 2012 in the United States. Come see first-hand the difference Hamilton Medical's Intelligent Ventilation Solutions can make in your facility.

Hudson RCI, a Teleflex company

Booth 301

What neonatal/perinatal products will you be presenting?
Teleflex, through our Hudson RCI brand of respiratory products is excited to present our full line of infant care products. In particular, we will be highlighting 1) Hudson RCI Infant Nasal CPAP Cannulas and 2) Hudson RCI Infant Resuscitation & Hyperinflation bags. In regards to our new Infant Resuscitation & Hyperinflation bags, we are excited to showcase the integrated manometer, Latex free and DEHP free features.

What products highlighting your recent R&D efforts will you presenting?
At Hudson RCI, we recognize that the NICU environment is distinctly unique within the health care system. We continue to value the voice of our customer – you! We place significant investment into the NICU respiratory product line. After conducting significant market research projects and analysis, we are excited to showcase our expanded line of infant respiratory devices and our newest line of Infant Resuscitation & Hyperinflation bags.

Discuss educational/training/support materials you'll be promoting.
Teleflex is proud to offer continuing clinical education events through various media channels to all respiratory clinicians that are committed to excellence. We believe education is the primary means in providing the most safety-oriented and clinically effective outcomes to the passionate caregiver. We offer several free CRCE accredited online clinical educational programs. Please stop by booth #301 for more information regarding our online clinical education programs. A Hudson RCI representative will be happy to guide you and your colleagues to the appropriate program that caters to your specific clinical needs.

What speakers or papers will your company be featuring?
It is our great pleasure to announce Ruben Restrepo, MD, RRT, FAARC as our guest speaker. Dr Restrepo will present at our Breakfast Symposium, titled: Humidification Challenges: Strategies for VAP Risk Reduction. The event will be held on Sunday, November 6th from 6:00am to 8:30am. Please stop by booth #301 to find the location of the event. Dr Restrepo was recognized as a Fellow of the American Association for Respiratory Care. He is a member of the editorial board for Respiratory Care and the Open Journal of Allergy and the chair of the Clinical Practice Guidelines Steering Committee for the American Association for Respiratory Care. He has presented at national and international symposiums to medical, nursing and respiratory audiences. He has more than 60 peer-reviewed publications.

Why should neonatal/perinatal caregivers visit your display?
Teleflex, through our Hudson RCI brand of respiratory products

is committed to partnering with healthcare providers in respiratory care to provide solutions that help reduce infections and improve patient and provider safety. Whether it is through clinical education programs or new product development, our goal is to serve you and the patient. Please stop by our booth (#301) to learn about industry trends, advanced standards of care, as well as our clinical education programs. Furthermore, you will be able to see our next generation of products that maximize humidity and minimize challenges. In addition, you will be able to recharge your mind, body and cell phone. Stop by our booth (#301) to charge your phone at our mobile station while you recharge with a nice cup of java. We look forward to accommodating your clinical and energy needs.

MAQUET, Inc

Booth 1211

What neonatal/perinatal products will you be presenting?

MAQUET will be displaying NIV NAVA and NAVA. NIV NAVA is one of MAQUET's commitments to avoid intubation. Scientific studies suggest that in conventional non-invasive ventilation (NIV), leaks play a major role when it comes to patient-ventilator asynchrony. In infants and neonates, conventional NIV may be additionally complicated because the effort by the infant is too weak to be detected by the ventilator's pressure and flow triggers. NIV NAVA provides synchronized assist independent of conventional pneumatic sensors and leakage associated with patient interfaces. Since breath triggering and cycle off are not affected by leakage, every patient effort — independent of type of interface — is assessed, responded to, and equally effective for all patients from adult to the smallest neonates.

What products highlighting your recent R&D efforts will you presenting?

MAQUET will be showing a new tool and monitoring parameter. This new option helps increase the possibilities for clinicians to monitor parameters related to lung mechanics.

Discuss educational/training/support materials you'll be promoting.

MAQUET has long tradition of dedication to continuing education and training. We will be offering CEU accredited lectures in our booth focusing on a broad variety of subjects. In addition to this we will be hosting a breakfast symposium discussing new advances in mechanical ventilation. All our educational offerings are free of charge to our customers.

What speakers or papers will your company be featuring?

The MAQUET breakfast symposium will be hosted by prominent, key opinion leaders in mechanical ventilation.

Why should neonatal/perinatal caregivers visit your display?

In addition to NIV NAVA and NAVA, MAQUET offers several other therapies and products focusing on our smallest and most vulnerable patients. Among others we will be displaying a brand new approach to CO_2 removal as well as a complete portfolio of disposables to assist clinicians avoid intubation and still provide the best possible care for all patients categories.

Philips

Booth 401

What neonatal/perinatal products will you be presenting?

Philips is showcasing NeoPAP, a continuous positive airway pressure (CPAP) delivery and treatment system developed to treat newborns and infants who are suffering from Respiratory Distress Syndrome (RDS) or recovering from RDS. The NeoPAP system uses an innovative patient interface to provide treatment for patients less than 5kg. and automatically adjusts flow to control the delivery of nasal CPAP.

Patient comfort; clinician peace of mind. NeoPAP's leak compensation technology is coupled with a lightweight patient interface and a bonnet design that work together to deliver therapy to the patient, which may help reduce the potential for skin-related issues often seen with traditional CPAP interfaces. The NeoPAP's CPAP technology is located in the device rather than on the patient's face, resulting in an interface that is intended to be light, less bulky and more patient friendly.

Available in several sizes of nasal cannula and mask designs to accommodate various facial geometries, the NeoPAP patient interface is made of soft, skin-friendly silicone that does not contain BPA, DEHP, or natural rubber latex. It does not need to be fitted tightly to an infant's face to be secured in place, helping to minimize the discrete pressure points that often lead to irritation and, in some cases, tissue necrosis.

The patient bonnet utilizes a foam lining to help preserve the orientation of the bonnet and to help reduce any torsional stress placed on the patient interface. The adjustable bonnet clips help to maintain nostril-patient interface alignment and to reduce the potential for the interface to move or become dislodged. This unique design virtually eliminates the need to tighten the interface to the patient, a practice common with traditional CPAP patient interfaces. Coupled with an adjustable hook and loop strap, the design allows clinicians to customize the interface setup to meet the individual needs of patients.

The NeoPAP patient interface's small profile and ability to be used with both CPAP and flow modes, coupled with leak compensation technology, gives the freedom to accommodate the unique care needs of the smallest patients. The bonnet, nasal cannula and nasal mask designs work in concert to help reduce the need for adjustments during therapy, allowing clinicians to spend more time caring for patients and less time tending to the device.

Why should neonatal/perinatal caregivers visit your display?

Philips Mother and Child Care provides a wide range of products and solutions for mother and baby from pregnancy through delivery, as well as products and solutions for the obstetrician's office, the hospital's OB department, Well Baby Nursery, and Neonatal Intensive Care Units, and finally care at home. The company is committed to Developmental Care, an evidence-based framework for care that provides clinicians with innovative solutions designed especially to support and nurture the baby's growth. Developmental Care practices include creating a healing environment that reduces stress and pain and involves the family in the care of their baby. NeoPAP supports Developmental Care through: Sophisticated leak compensation technology for pressure stability in

the face of leaks, which may help reduce patient work-of-breathing, the amount of energy the patient has to expend to inflate his or her lungs during inspiration. Leak compensation allows use of tapered nasal prongs, which do not require a seal at the nostrils. This design helps decrease contact with nostrils, which could reduce irritation and enhance patient comfort.

Simple, yet developmentally-friendly CPAP patient interface that is lightweight and made of patient-friendly silicone allows for easy patient setup and may help reduce irritation and damage to the patient's nose. The patient interface does not have to be changed between CPAP and Flow mode, which may save time and reduce handling of the patient. Also, the small footprint of the nasal cannula provides a clear visual of the nasal septum to check for irritation without lifting the cannula.

The patient bonnet design helps stabilize the patient interface and may reduce the potential for pressure-related skin issues. The bonnet has a single fixation point and uses the foam lining material to hold the patient interface securely in place, which may help decrease nuisance alarms and the frequency of interface adjustment. The adjustable bonnet clips allow clinicians to change orientation of patient interface tubing to accommodate developmentally supportive positioning needs without having to loosen the bonnet.

NeoPAP's stand-by mode allows the user to stop therapy to accommodate other care procedures and re-start therapy without having to reboot the device. The pressure line at the most proximal portion of patient interface and leak compensation technology software allow pressure to be read every 100 times/second for pressure stability during leaks and changes in respiration.

NEWS FEATURES

Multicenter Trials for HIE

An article in a recent issue of Neonatology Today argues for the need for multicenter trials to general meaningful clinical results about the efficacy of hypothermia as a standard of care for neonates with HIE. To further this goal, the authors of the article reported on the creation of the Florida Neonatal Neurologic Network.*

The Florida Neonatal Neurologic Network (FN_3) will utilize centers in close geographical proxmity so that meetings and site visits can be done with limited travel and at low expense. The network will offer a centralized patient registry, providing an infrastructural for clinical trails focused on neonatal brain injury. Data will be collected on demographics, maternal information, birth histories and clinical courses, and will capture neuroimaging and EEG results, and archiving studies. A biologic repository will be established using proteomics, meto-bolomics and genomics. The network will also serve as an education hub for the dissemination of information via a web-based portal accessible by the participating centers.

According to the authors, "A major goal of the network is to ensure that every neonate in the state of Florida with HIE is in close proximity to a center which is capable of induced hypothermia therapy. Larger NICUs with Level III facilities will serve as the local hubs for neonates from smaller centers. As the authors state, "This model will essentially create cooling zones in each of the regions around the first tier participants."

In order to educate smaller nurseries and hospitals about the therapy, a "Freeze Warning" program is being created. The program involves the dissemination of an educational poster with general guidelines for hypothermia therapy, hypothermia inclusion criteria, clinical steps for care of neonates who are hypothermia candidates, and contact information. With the proposed network in place, infants with HIE born at referring centers will be identified as candidates and the hypothermia centers in the applicable region will be contact for transportation.

To make the program effective, it's necessary that a cooling device is selected that can initiate and maintain active, controlled hypothermia. The device chosen for the program is the CritiCool, which regulates core temperature very efficiently, according to the authors.

[A paper in our September issue: Neonatal Transport: Active Cooling for Infants with HIE, details how the CritiCool works in practice with several modes of transportation.] The authors state that the program using CritiCool is "the foundation of providing safe, successful and effective hypothermia to all neonates in North-Central Florida. This design, along with the education provided, will facilitate quality neonatal care, and serve as the framework for FN_3's future endeavors."

The authors note that the initial members of the program have met to discuss hypothermia protocol and establish parameters of standardization, common therapeutic management, and establishing standards of care. "This will allow the FN_3 to efficiently integrate novel diagnostic tools and therapies into the network for evaluation as they arise. To facilitate such a pipeline, the network will include a basic science component consisting of the major academic research centers in Florida. FN_3's harmonious collaboration between basic and clinical science will allow for straightforward translations to clinical trials with novel future treatments such as stem cell therapy.

"After the successful implementation within the Tier 1 sites, Tier 2 will be rolled out to other NICUs in Florida. As FN_3 moves forward in a methodical, stepwise fashion, we envision our collaborative network providing hope and promise for neonates with HIE… FN_3 is being developed in a systematic manner, from a variety of scientific contributors, with the ability to have a significant impact in the field of neonatal brain injury. The network's distinctive characteristic of combining state-of-the-art basic science with elite medical institutions within a close geographic proximity is the ideal recipe for success and represents the next evolution of the network design. Combining hope with excellence, the mission of FN_3, from regionalization of hypothermia and beyond, [is] to provide the highest level of care for all infants devastated by HIE both within Florida and worldwide." [* "A Cold Front is Sweeping Across the Sunshine State: Regionalization of Induced Hypothermia for Neonatal Hypoxia-Ischemia," by Craig B. Sussman, MD; David Auerbach, MD; Hilton Bernestein, MD; Young Byun, MD; Danilo Escoto, MD; Robert Garrison, MD; Mark Hudak, MD; Lewis Otero, MD; Richard Sheridan, MD; Rajan Wadhawan, MD; Lewis P. Rubin, MD; David J. Burchfield, MD; and Michael D. Weiss, MD. Neonatology Today, Volume 6, Issue 6, June, 2011, copyright 2011
Continued on page 50…

Use of the Passy-Muir Valve in the Neonatal Intensive Care Unit

Melanie Stevens, MS, CCC-SLP; Jennifer Finch, MA, CCC-SLP; Leslie Justice, RN, MS, CPNP, Erin Geiger, BS/RRT-NPS

Over the years there has been a trend toward increased usage of tracheostomy tubes to meet the treatment needs of neonatal and pediatric patients. The presence of a tracheostomy tube can impair a child's ability to communicate and bond with caregivers. Communication between babies and their caregivers begins at birth with crying and cooing. Normal speech and language development requires vocal exploration and social interaction, both of which may be limited when a tracheostomy tube is in place (Kalson & Stein, 1985; Simon, Fowler, & Handler, 1983). The early use of a Passy-Muir valve (PMV) with a tracheostomy tube may facilitate improved developmental outcomes for infants born prematurely, as well as outcomes for full term infants at risk for delays due to underlying medical conditions. While there is extensive experience and research to support the use of PMVs in the adult population (Suiter, McCullough, & Powell, 2003; Manzano, J., Lubillo, S., Heriquez, D., Martin, J., Perez, M. & Wilson, D., 1993), use of PMVs in the pediatric population is more limited. There is some support for use of PMVs to promote vocalizations, as well as to improve swallowing skills in pediatrics (Hull et al., 2005; Engleman & Turnage-Carrier, 1997); however additional information is needed regarding the impact on speech-language development and caregiver interaction.

Additional benefits of the PMV have been reported in the adult literature and it is suggested that the pediatric population may experience these same benefits (Hoffman, Bolton, and Ferry, 2008; Engleman, and Turnage-Carrier,1997):

- Restoration of physiological Positive End Expiratory Pressure (PEEP)
- Restoration of voice
- Improved sense of smell and taste
- Improved swallowing
- Improved secretion management
- Improved overall development and quality of life
- Aids in the weaning process from long term mechanical ventilation

This article describes a protocol for assessing and implementing PMV use in the Neonatal Intensive Care Unit (NICU) at Nationwide Children's Hospital (NCH), Columbus, OH. Assessment of candidacy and readiness for a PMV, contraindications for use, and the potential benefits of the PMV are presented. Methods for trialing the PMV and assessing progression/improvement are described. A case example at the end of this article illustrates the use of the protocol including the PMV readiness assessment, the initial trials, and progression to full time PMV use during all waking hours.

Historically, the use of PMVs at NCH with neonatal patients was limited to babies who had a tracheostomy tube while using a tracheostomy mist collar on room air. PMVs were rarely used with the ventilator-dependent baby. Beginning in Fall 2008, speech language pathologists along with an Ear Nose Throat (ENT), nurse practitioners and respiratory therapist in the NICU Bronchopulmonary Dysplasia (BPD) unit began to more consistently assess patients for Passy-Muir Valves. To promote increased use of PMVs, a standard coordinated protocol was formally established in 2010. This protocol aims to ensure a consistent referral process for PMV readiness assessments, subsequent supervised PMV trials, and progression of PMV use. Given the medical complexity of this patient population, this protocol was developed as a part of a multidisciplinary team consisting of neonatologists, speech-language pathologists, respiratory therapists and ENT nurse practitioners. Overall, working together as a multidisciplinary team has improved patient care and caused an in increase in referrals for assessment and use of PMVs in the past two and a half years.

Summary of PMV use from Fall 2008 through July 2011:

- 24 total patients in the NICU BPD unit were assessed for readiness of a PMV, including babies requiring ventilator support and/or direct tracheostomy mist collar.
- 16 of the 24 patients were found to be appropriate PMV trial candidates.
- All 16 trialed the PMV for a 4-5 day period with the Speech-Language Pathologist.
- The results showed the PMV to be safe for use with these patients without direct complications.
- Independent patient success from this protocol has been observed in the form of increased vocalizations and improved social interaction with the caregiver(s).

The multidisciplinary team identified the following criterion for referral of patients for a PMV readiness assessment:

- Post-operative tracheotomy 7 days or greater
- Medically stable
- Awake and responsive
- Patent upper airway
- Reasonably able to manage oral secretions
- Able to tolerate cuff deflation
- Trach collar or the following ventilator settings: Fraction of Inspired Oxygen (FIO_2) < 60%, PEEP $\leq$12

This article was provided by Passy-Muir.

The NCH assessment team members include: respiratory therapist, ENT-nurse practitioner, and a speech language pathologist. The respiratory therapist is present to adjust and monitor ventilator equipment and for cuff deflation (if needed). Our ENT nurse practitioner utilizes manometry testing to determine transtracheal pressures. The pressures allow us to better assess the airflow around the tracheostomy tube. Our target transtracheal pressures are <20cmH_2O. If our manometry results are >20 cmH_2O we may consider suggesting downsizing of the tracheostomy tube to support use of the PMV or wait for patient growth. The speech language pathologist is present to assess vocal ability and changes in management of secretions. All team members monitor vital signs (work of breathing (WOB), respiratory rate (RR), heart rate (HR), color, O_2 saturations) throughout the assessment.

It should be noted that manometry pressures >20 cmH_2O does not automatically disqualify a patient from trialing the PMV. Clinical information provided and clinical judgment should ultimately be the deciding factor in trialing the PMV.

Similar to previous studies, the NCH team identified the following exclusion criteria for PMV use:
- Severe airway obstruction
- Vocal cord paralysis - adducted position
- Severe neurological impairment
- Inflated tracheostomy tube cuff of any kind
- Foam-filled cuff
- Severe risk for aspiration

PMV trials are initially completed only by the speech language pathologist in order to monitor tolerance. These trials are completed daily over a 4-5 day period. The goal of the PMV trials is to monitor tolerance, increase wear time and educate caregivers. It is essential that caregivers have a full understanding of potential signs/symptoms of distress their child may exhibit if having difficulty tolerating the PMV. Caregivers are also educated during these trials to ensure they have an understanding of how the PMV works as well as cleaning and storage. Once the initial PMV trials have been completed with the Speech Language Pathologist, continued use of the PMV is handed over to the caregivers and nursing staff with an emphasis on increasing wear time and using the valve in various contexts (therapies, feeding, cares, etc).

Overall, working together as a multidisciplinary team has improved the quality of patient care and resulted in an increase in referrals for assessment and use of the PMV in our NICU BPD unit. The case study below represents the use of the protocol from inline use to tracheostomy collar. In the future we hope to use this protocol to measure caregiver/infant bonding pre and post PMV use. Future directions for research also include measurements to determine weaning from mechanical ventilation using the PMV.

Case Study

The following is a summary of Baby Boy's hospital course as it relates to the NICU BPD unit. On February 2, 2010 Baby Boy received a tracheostomy due to an inability to wean from mechanical ventilation. A cuffed tracheostomy tube was placed to accommodate high ventilator pressures. On July 28, 2010 speech therapy was initiated to address early communication skills. The patient remained ventilator dependent with a cuffed tracheostomy tube. Short periods of cuff deflation were trialed beginning on September 14, 2010. On September 30, 2010 cuff deflation was tolerated around the clock.

Assessment for Passy-Muir Readiness occurred on October 15, 2010, two weeks after the cuff was permanently deflated. Ventilator support at this time was: mode SIMV/PS, FIO_2 25%, rate of 12, pressure support 18, peak inspiratory pressure of 40 and a peep of 10. Measured expiratory pressures via manometry were 10cmH_2O. Baby Boy was deemed to be an appropriate candidate for PMV trials at this time.

PMV trials with speech therapy were initiated on October 18, 2010. Baby Boy initially tolerated a trial of 20 minutes with vocalizations. On October 19, 2010 through the 21st , 25 minutes were tolerated with vocalizations. At this point the 1 week trial period with speech therapy ended and twice a day PMV use with nursing staff began.

Baby Boy continued to use the PMV through weaning from SIMV/PS to CPAP/PS to tracheostomy collar. At time of discharge patient was wearing PMV during all waking hours.

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Driving Enterprise Efficiency Through Interoperability

Karen Triano Golin

The Institute of Medicine's 1999 report, To Err is Human, set a goal to help remedy a healthcare system compromised by preventable patient errors. One of their major recommendations to reduce medical error frequency encouraged the use of medical informatics and electronic record systems (Kohn LT, 2000). Bates and Gawande stated, "If medicine is to achieve major gains in quality, it must be transformed, and information technology will play a key part, especially with respect to safety" (Bates, 2003). The American College of Obstetricians and Gynecologists' continuing commitment to patient safety led them to classify seven objectives in 2003 (updated in 2009), two of which focused on improving communication between medical staff and patients including incorporation of technological solutions (American College of, 2003; American College of, 2009).

Centricity Perinatal remains a central component in hospitals' continuing endeavor toward excellence in managing the dynamic and complex healthcare needs of their patients. An electronic documentation system committed to providing accurate and timely information, Centricity Perinatal facilitates new levels of connectivity critical to enhancing patient care and increasing efficiency across the entire perinatal continuum of care. To further increase the reach and value delivered from the entire system, a wide variety of inbound/ADT, lab, and outbound HL7 interfacing options are offered. Shared information enables the electronic medical record and helps enhance communication, patient safety, and quality.

The United States Plays Catch Up

While many studies examining the role medical informatics play began in the 1960s and 1970s (Hon EH, 1965; Kubli et al, 1974; Rosen MG, 1978), EMR adoption in the United States has been slow and lags far behind other countries. A survey of more than 10,000 primary care physicians in 11 countries (Schoen, Osborn, Doty, Squires, Peugh, & Applebaum, 2009) found that while 46% of US primary care physicians are using an EMR, they have been embraced by more than 90% in Australia, Italy, the Netherlands, New Zealand, Norway, Sweden, and the UK. This slow growth is partly attributed to the complexity as well as the heavy investment involved: "The share of hospitals adopting either basic or comprehensive electronic records has risen modestly, from 8.7 percent in 2008 to 11.9 percent in 2009" (Jha A, 2010).

The author is a GE Healthcare Consultant.

A 10 percent increase in the adoption of basic EMRs, however, can reduce infant mortality by 16 deaths per 100,000 live births (Miller, 2011). With more than 22 years of expertise within and commitment to the perinatal continuum of care, Centricity Perinatal continues to be a leader in the industry.

Meaningful Use

In an attempt to accelerate EMR adoption in the US, the federal government has committed unprecedented resources to encourage hospitals and practitioners to integrate the appropriate EMR tools to advance patient safety and quality of care as well as improve efficiency and cost savings. Beginning in 2011, physicians who purchase and meet "Meaningful Use" criteria for EMRs were eligible for up to $44,000 in incentives. These incentives gradually decrease until expiration in 2014 with much of the stimulus coming in 2011 and 2012, so early qualifiers receive more. Requirements for Meaningful Use include structured data collection, health information exchange, clinical decision support, patient engagement, security assurance, and quality reporting.

The Certification Commission for Healthcare Information Technology has, since 2006, been certifying increasing levels of functionality for EMR systems and has been petitioned by the American Congress of Obstetricians and Gynecologists (ACOG) to incorporate their recommendations for specialty-specific functionality criteria, underscoring the need for distinct departmental solutions (McCoy M, 2010). Just as ACOG has lobbied for individualized guidelines, the American Academy of Pediatrics has recognized that many general EMR systems are of limited use in child health care as the systems are designed for adults and lack the data precision necessary, for example, to process body weight to the nearest gram which is essential to the care of all infants in the Neonatal Intensive Care Unit (NICU) (Spooner & the Council on Clinical Information Technology, 2007). Centricity Perinatal version 6.9 has received Modular Certification. Modular certification indicates that Centricity Perinatal supports some certification criteria associated with Meaningful Use objectives, helping to enable providers qualify for funding under the American Recovery and Reinvestment Act (ARRA).

Modular Certification for Centricity Perinatal 6.90 was received on March 21, 2011, Certificate Number: IG-2392- 11-0043 Certification Modular Certification, meeting the following criteria: 170.302(g) Smoking status; 170.302 (h) Advance Directives; 170.302(o) Access control; 170.302(p) Emergency

Steadfast Support of Centricity Perinatal 1975—2011

1975	1986	1990	1992	1995	1998	2005
QMI formed	QS launched	Crit Care install	L&D install	Marquette buys QMI	GE buys Marquette	QS renamed as Centricity Perinatal

access; 170.302(q) Automatic log-off; 170.302(r) Audit log; 170.302(s) Integrity; 170.302(t) Authentication; 170.302(u) General encryption; 170.302(v) Encryption when exchanging electronic health information.

Defensive Medicine

NICU and Labor & Delivery (L&D) clinicians work in a highly litigious arena with allegations of negligence or error often at the forefront (Haberman, Rotas, Perlman, & Feldman, 2007). Ob/Gyn physicians are sued 2.17 times for every Ob/Gyn as compared to .95 for every 1 physician (American Medical Assn, 2010), and this fear of lawsuits is changing the way obstetricians and gynecologists practice, with some leaving the field at an early age. Though the majority of claims are dropped or closed without payment, the litigious climate, financial and emotional stress, and time spent combating claims and suits takes a toll. Of those with closed claims, the average payment was $512,049 (Klagholz J, 2009). As the patient-doctor relationship has transformed from one of trust to one of "Show me," an EMR, with its production of a valid, reliable, and defensible medical record, adds to a physician's armamentarium. It helps provide critical safeguards and minimizes legal risk—both necessary in today's world of medicine.

Nowhere is this more evident than in the role of fetal monitor strips, which have proved so crucial that a body of decisional law has developed over their loss. The court may consider an absent fetal monitor strip as a generic missing document and impose an adverse inference charge. In this situation, the jury may draw conclusions against the defendant on any evidence related to the fetal monitor strip. The most severe impact of losing the fetal monitor strip may be a separate cause of action for spoliation, defined as "the destruction… of evidence especially by a party for whom the evidence is damaging" ("Spoliation," 2001). Intentional or negligent loss interferes with the plaintiff's ability to prove her claim. This effectively results in a default judgment, leaving only the litigation of damages. One case example found "The fetal monitoring strips would give fairly conclusive evidence as to the presence or absence of fetal distress, and their loss deprives the plaintiff of the means of proving her medical malpractice claim against the Hospital" ("Baglio v St. John's"). Centricity Perinatal helps eliminate misplaced/lost paper strips through electronic storage, managing records and preservation while improving operational inefficiencies.

Split-second Decisions

Clinicians who practice in obstetrics and neonatology face challenges that often include the involvement of two lives, a high acuity environment, and long-term consequences that may result due to care decisions. In rapid-fire clinical decision-making L&Ds and NICUs where seconds count, accuracy is non-negotiable. Situations can devolve quickly into emergencies, so immediate access to information, streaming clinical data integrated from multiple settings, and the ability to spot and intervene in deteriorating trends are vital components in the point of care continuum. In today's fast-paced environment, Mother-Baby Link (Figure 1) integrates critical maternal history and delivery data with the infant record simply by linking their medical records, sharing relevant and necessary information.

Figure 1

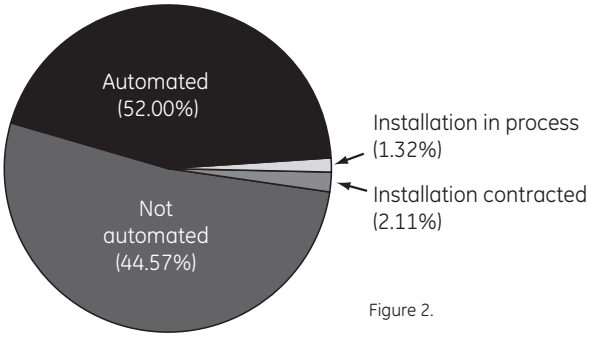

Figure 2.

Enhancing Patient Safety

This significant advantage in providing enhanced patient safety has been underutilized, with almost 45% (1,987 units) of the 4,458 US L&D units reporting that they are not using an automated system (HIMSS Analytics, 10-January-2011) (Figure 2), a statistic that extends to the NICU, validated by Drummond's research. "In late 2008, most NICUs still integrate[d] multisource clinical data at the bedside by charting each hour with pen in small boxes on folding paper flow sheets—a slow, error-prone, and imprecise method for tracking unstable situations" (Drummond, 2009). Critical care decision support systems provide functionalities and features that allow real-time integration of data with point-of-care access, streamlined clinical workflow, and data exchange that supports risk management. Point-of-Care Documentation through Centricity Perinatal annotations extends instantaneous access to critical information at the bedside when and where it is needed (Figure 3).

Care teams have an immediate source of relative patient information to visualize, access, and act more efficiently. It can help enhance the patient's health and safety at every touch point.

Figure 3

Reducing Errors and Risk

Implementing an electronic medical records system can assist in reducing error frequency through decreasing duplicate entries, improving data efficacy, performing realtime checks, providing alerts, reminders, communication improvement, calculation, and monitor assistance. Supplying more comprehensive patient information than paper-based records enables departments with EMRs to have more complete documentation, a continuity of care record, and increased time in direct patient care, in turn suggesting enhancement in patient safety and quality of care.

Centricity Perinatal's S Bar helps enhance patient safety and quality of care through increased communication among caregivers (Figure 4). Eden's pre- and post-EMR implementation study (Eden, KB, 2008) of the impact on patient record documentation completeness demonstrated that paper records were much more likely to miss significant clinical information in L&D units as evidenced in Figure 5 using data aggregated from the study.

Other studies concur: an obstetric record study demonstrated marked improvement in documentation with an 8% increase in compliance (from 77% to 85%) on a 59-item score sheet when analyzing quality of electronic medical records as compared to a paper-based system (Haberman S, 2007). Another study concluded that use of an intranet-based computerized prenatal record significantly improved communication among providers and that replacing paper obstetric records with electronic ones reduced the incidence of missing charts from 16% to 2% (Bernstein PS, 2005). And a comparison of paper to electronic fetal monitoring archival systems demonstrated higher reliability in an electronic documentation system both during the data-capture period and storage interval (Stringer, 2010).

EMR systems with embedded clinical decision support can "significantly improve access to and compliance with clinical care guidelines, reduce redundant test ordering, and ease of data sharing" (Eden KB, 2008). Centricity Perinatal's integrated Alerts & Reminders notify users of site and/or unit-specific clinical protocols or pathways at the bedside, supporting clinical decisions to help enhance safety and reduce risk. Solution response is optimized by recognizing multiple simultaneous changes tracked sequentially in clinical data streams, aligned with evidenced-based practice guidelines which identify potential complications and offer interactive assistance.

Therapeutic best practices are changing as research directs new findings; the clinical information found in EMR databases is powering quality reviews, improvement processes, productivity measurements, resource allocation, and budgets. Salt Lake City, UT-based Intermountain Healthcare began limiting labor inductions before 39 weeks after an EMR analysis proved higher admittance to the NICU and higher incidences of respiratory distress. Their revised induction strategy resulted in fewer labor complications and emergency C-sections with patient savings of $2 million (Sg2, 2010). Furthermore, as accreditation organizations continually increase focus on and request clinical performance measurements, EMRs act as a data repository.

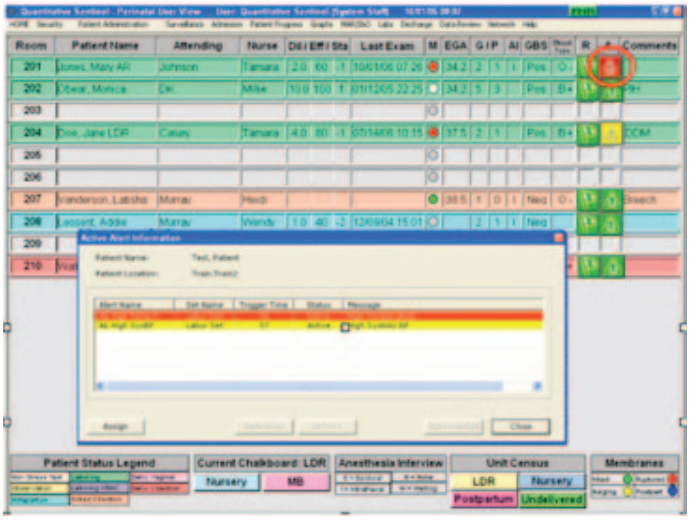

Figure 4

Clinical Data Points	Paper Missing	Electronic Missing
Bleeding	35%	2%
Fetal Movements	20%	3%
Contractions	10%	2%
Membrane Status	64%	5%
Total	129%	12%

Figure 5.

Improving Bottom Line

EMRs need to be evaluated for their return on investment. Few, if any, studies exist on "hard" ROI for L&D or within the NICU environment. However, one such example is from Fresno Community Regional Medical Center, which realized more than $70,000 in annual savings (Anderson, 2010). Miller and Tucker's study roughly estimates that healthcare IT is associated with a cost of $531,000 per infant saved (Miller, 2011).

By comparing the IT use in other industries to health care, it has been estimated that total potential savings could eventually be in excess of $81 billion annually (Hillestad R, Bigelow J, Girosi F, Scoville R, & Taylor R, 2005). A recent report from the Medical Group Management Association estimated almost $50,000 more revenue after operating cost, per full-time-equivalent physician, for non-hospital/IDS-owned practices with an EMR, and reported a 10.1% higher operating margin after five years (Medical Group, 2010).

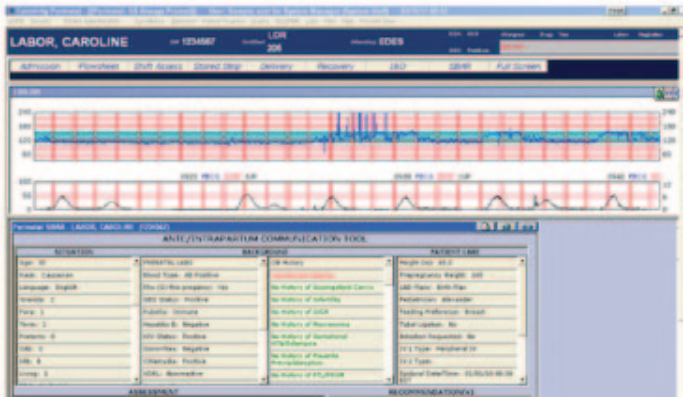

Figure 6

While "soft" ROI gains such as enhancements in patient safety, direct quality of care, process and workflow improvement, communication, compliance, stakeholder satisfaction, and legal risk minimization cannot be translated into hard dollars, an EMR's value is indisputable in terms of enhancing care delivery, and its assistance in saving lives.

Maternal Infant Care is a unique part of the hospital's care environment. It requires a special blend of technologies and capabilities to provide a seamless flow of vital information to help ensure the health and safety of these patients. Centricity Perinatal can play a major role in achieving those goals. Save time and money with Centricity Perinatal's customizable electronic documentation system. Move from paper charts to an intuitive user-friendly digital format, offering potential improvement to your bottom line. It's Power at the Point of Care.

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Human Milk Storage in the NICU – Summarizing the Research – What You Should Know

Amy O'Malley, RN, MSN

An overwhelming body of evidence demonstrates that feeding human milk to premature and other compromised infants in the NICU greatly reduces the risk of necrotizing enterocolitis, late onset sepsis, enteral feed intolerance and other serious morbidities.[1-8] Further evidence shows that human milk directly impacts the health outcomes of premature infants in a dose-response manner – greater amounts of human milk feeding offer greater protection.[8-10] Since mothers of premature infants are often pump-dependant and many have to return to work before their infant is ready to feed at breast, proper storage of human milk is essential.

There has been much research on this topic regarding both the nutritive and protective components as well as the bacterial content of human milk. Due to the variants in each study, findings may appear to conflict. It is important to note that each study should be weighed based on its particular parameters and variants. According to the 2011 Human Milk Banking Association of North America (HMBANA) Guidelines, studies recommending longer storage periods at room temperature or in the refrigerator have typically focused on bacteriological safety without considering the effects on the components of human milk.(HMBANA p. 44)[11] Alternatively, more recent studies focusing on human milk components have noted concerns on the effects of lipids, proteins and other milk components while not addressing bacterial load.[12]

HMBANA guidelines also note that to decide which storage guidelines are appropriate, the age and health of the infant as well as other factors must be considered. With high-risk infants, the safest approach is to minimize contamination and use appropriate storage conditions for the shortest storage time possible.(HMBANA p. 44)[11] This article will summarize research-based information on proper storage techniques and best practice recommendations from experts that will minimize potential contamination while best protecting the integrity of the protective benefits of the milk for infants in the NICU.

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Collection of Human Milk

Research shows human milk is not sterile as it contains bacteria including flora from the mothers' skin and that most contamination of stored milk is found to have occurred during collection.[12] While most bacteria found in human milk is safe for baby, careful collection and storage will help prevent additional contamination of the milk.(HMBANA p. 2)[11]

Manufacturers' cleaning guidelines of breastpumps, breastpump kit parts and collection containers should be followed. When using a breastpump, mothers should first clean the pump with a manufacturer approved cleaning agent. The pump should be wiped down between each use especially when shared between mothers.(HMBANA p.17)[11] Any surface that the mother touches should be cleaned. After cleaning the pump the mother should wash her hands.

Always washing hands before handling breastpump kit parts and collection containers which come in contact with human milk is an important and unfortunately sometimes forgotten step. ABM Clinical Protocol for Human Milk Storage states, "Unclean hands may transmit viruses and bacteria, some of which can cause illness. Studies show that human milk containing fewer bacteria at the time of expression develops les bacterial growth during storage and has higher protein levels compared to milk that has an abundance of bacteria."

Collection Containers

Human milk in the NICU should be collected and stored sterile FDA-approved food grade containers that are BPA-free. Research shows that while lipid-soluble nutrients may stick to the surface of these containers, the concentration of immunoglobulin A and amount of white blood cells are not markedly affected. Use of polyethylene containers was associated with a 60% drop in immunoglobulin A. Another study showed that stainless steel containers demonstrated a decline in cell count and viability compared to polyethelene and glass. Therefore, stainless steel containers should not be used.[13]

Using sterile containers helps prevent introducing additional bacteria to the milk. Milk storage bags are not recommended for storing milk for feeding in the NICU based on research which

shows milk stored in polyethylene bags loses up to 60 percent of secretory IgA(HMBANA p. 20)11 If your facility does not use sterile containers be sure to follow the manufacturer's guidelines for cleaning.

Labeling

Collection containers must be labeled properly and should be stored in a per patient section of either the refrigerator or freezer. The labels should clearly indicate patient name as well as the time and date of expression. Containers should be rotated so the oldest milk is fed first. Once that milk is thawed, a new time and date should be added to the label as thawed milk should be fed within 24 hours.(HMBANA pgs. 2, 44)11

Storing Human Milk at Room Temperature

The evidence shows that freshly expressed human milk best preserves its nutritional and bioactive components. In fresh milk, living cells work to phagocytize the bacteria and therefore the bacterial colony count in freshly expressed milk decreases over the first several hours.[14] This means that freshly expressed milk can be safely kept right at the bedside for less than 4 hours in which time often two feedings may occur. Unfortunately, in the NICU, mothers are often not able to provide freshly expressed milk. Refrigerated and frozen storage methods are a necessity.

Transporting methods will depend on length of time between the milk expression and mothers' arrival in the NICU. Mothers should be given clear instruction on proper storage during transport per their specific needs.

Feeding Colostrum

Preterm colostrum has higher concentrations of anti-infectives, anti-inflammatories, growth factors and other protective substances than does term colostrum. It should be fed as soon as possible in early feedings. The first milk is especially important and should be labeled and fed in order of expression.[15, 16]

Storing Human Milk in the Refrigerator

Over the years there have been a number of published studies regarding the refrigeration of human milk. Study results have varied with recommendations from no longer than 48 hours to others that reported evidence showed 72 hours for fortified milk maintained milk's integrity, to recommendations from HMBANA of safe refrigeration for up to eight days.[13] These studies focus on bacterial colony counts.

In a study published in 2010 in The Journal of Pediatrics, Slutzah et al looked at refrigerator storage of human milk at 4C for 96 hours in the NICU, showing that at this temperature, and for this length of time, the integrity of milk was not negatively impacted.[17] The study found that "mother's milk may be stored in the NICU at refrigerator temperature of 4C for 96 hours without compromising its overall integrity as assessed by bacterial colony counts, white blood cell counts, osmolality, pH and concentrations of sIgA, lactoferrin protein, total fat and free fatty acids."

HMBANA recommends that freshly expressed milk be fed or refrigerated immediately. If a refrigerator is not available, the milk may be refrigerated within 4 hours. Continuous feeds can therefore be given over a four hour period. If fortifiers have been added to the milk, the human milk should be fed or refrigerated right away.(HMBANA pgs 2, 44)11

Storing Human Milk in the Freezer

The process of freezing human milk destroys its living cells and interrupts phagocytosis. Studies show the viral load in milk such as Cytomegalovirus (CMV) is reduced significantly but not destroyed. In addition the bioavailability and concentration of some protective components are reduced.[14]

Some medical centers such as Rush University Medical Center, Chicago, IL recommend that NICUs store frozen human milk on site for their patients as this is the only way to ensure control over storage conditions which should be monitored on a regular basis. Industrial freezers are recommended as they are the standard of care for adult nutrition. Studies vary on suggested length of time milk should be frozen. HMBANA guidelines, based on numerous studies recommend that a three month period is optimal and should not be kept for longer than 12 months at -20C or lower.(HMBANA pgs 2, 44)11 While there is little research on refreezing human milk, experts agree that once thawed frozen human milk should be fed or discarded and not refrozen. [A note on odor: some mothers may question the odor of frozen milk; this can be a result of lipase not being inactivated during freezing so human milk can partially self-digest, resulting in a sour odor. Research demonstrates that this milk is still safe to feed. Scalding the milk prior to freezing to 180 degrees F will inactivate the lipase and decrease the odor. (HMBANA p. 31)11]

Freezing Human Milk

Do not pour room temperature human milk into a container with frozen milk; rather, chill freshly expressed milk before adding it to frozen milk. Be cautious: each time a container is opened allows another opportunity for contamination. Experts recommend filling containers only ¾ full (as frozen milk expands and a new container should be used each time a mother pumps. (HMBANA p. 22)11

Thawing Human Milk

Sterile technique for handling should be used to prevent introducing additional pathogens. Milk should be warmed to body temperature. Clinicians should note that studies show that feeding human milk at room temperature may actually be harmful to very low birth weight infants.[18]

Milk can be thawed using a number of different methods. Milk can be thawed in a container of warm water; however milk can become contaiminated by non-sterile water seeping under the lid of the container.(HMBANA p.28)11 Milk can be thawed slowly at room temperature, however, should be refridgerated before it is completely thawed and still has ice crystals. It is essential to gently agitate the thawed milk prior to feeding to ensure uniform distribution of fat and micronutrients.(HMBANA p. 28)11 Be sure to properly label when the milk is removed from the freezer. In addition, research has noted microbial contamination of hospital tap water and recommended dry-warming devices to heat fluids that come in contact with patients.[19-25] In its 2003 Guideline for Infection Control in Health-Care Facilities, the CDC recognizes that water-based solutions can serve as reservoirs for waterborne microorganisms in hospital settings.[26] Therefore, some experts suggest an optimal method is a milk warmer that circulates warm air to safely warm and thaw milk.

Conclusion

Evidence demonstrates that feeding human milk to premature and other compromised infants in the NICU greatly reduces the risk of necrotizing enterocolitis, late onset sepsis, enteral feed

intolerance and other serious morbidities.[1-8] Further evidence shows that human milk directly impacts the health outcomes of premature infants in a dose-response manner – greater amounts of human milk feeding offer greater protection.[8-10] Since mothers of premature infants are often pump-dependant and many have to return to work before their infant is ready to feed at breast, proper storage of human milk is essential. Research-based information on proper storage techniques and best practice recommendations from experts will minimize potential contamination while best protecting the integrity of the protective benefits of the milk for infants in the NICU.

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Practical Application of Osmometry for the Evaluation of Human Milk and Infant Nutritional Products in the Neonatal Intensive Care Setting

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Abstract

Understanding and monitoring the osmolality of human milk, milk fortifiers, medications, and infant nutritional products is a very relevant topic in the neonatal intensive care setting. It has been well documented that hyperosmolar substances have been associated with a wide variety of gastrointestinal illnesses in neonatal populations, including necrotizing enterocolitis (NEC). The American Academy of Pediatrics (AAP) recommends that the osmolality of formulas for "normal" infants should not exceed 450 mOsm/kg H_2O. Although no formal osmolality guideline has been set for Low Birth Weight (LBW) and Extremely Low Birth Weight (ELBW) infants, it is common practice in the neonatal intensive care unit to supplement the feedings with a host of medications, vitamins, and caloric supplements that have been shown to dramatically elevate the osmolality of the feeding well above the AAP safety threshold. Freezing point osmometry has been a well-documented tool used to accurately determine osmolality in infant formula and human milk. The purpose of this study was to evaluate the suitability and performance characteristics of the Advanced Model 3320 Micro-Osmometer over a broad sampling of infant nutritional products and human milk samples. Seventeen commercially available infant formulas were tested including ready to serve liquid, liquid concentrate, and powder formulations derived from cow's milk, soy, or protein hydrolysate based sources. Twelve (12) different human breast milk samples were tested. All were previously frozen, and were either single donor unpasteurized or pooled donor pasteurized. All samples were tested five times each to obtain a baseline reading, and then tested twenty times each to determine the range, standard deviation and coefficient of variation. The range of the seventeen infant formulas tested were between 170.0 and 385.1 mOsm/kg, and the coefficient of variation ranged from 0.5 to 1.9. The manufacturer reported osmolality claims of the feed products were consistent with experimental findings. The osmolality range of the human milk samples tested was between 261.0 and 316.1 mOsm/kg, and the coefficient of variation ranged from 0.5 to 1.2. The results indicate the Model 3320 osmometer performs well across all types of infant nutritional products and should be considered a valuable quality control tool for infant nutritional research.

The authors are with Advanced Instruments, Inc, Norwood, MA. Advanced Instruments would like to give special thanks to Indiana Mothers Milk Bank and the Mothers Milk Bank of Iowa for providing the human milk samples used in this study.

Introduction

Osmolality is an important measurement and topic of discussion with regards to infant nutrition and neonatal care. Administration of hyperosmolar feeds have been linked to a wide variety of adverse conditions including altered nutrient absorption, hypertonic dehydration, diarrhea, intestinal ischemia, as well as more severe gastrointestinal abnormalities. Hyperosmolar formulas have also been a reported factor in causing necrotizing enterocolitis.[1,2,3] To mitigate the risk, the AAP Committee on Nutrition recommends that formulas for normal infants have concentrations no greater than 400 mOsm/L.[4] This corresponds to an osmolality of approximately 450 mOsm/kg.[1] Although the osmolality of most manufactured infant formulas fall well within these guidelines, it is a routine practice in the NICU to add a host of nutritional supplements, caloric modules, and medications to the feeding. This practice occurs when using either breast milk or commercial infant nutritional products as the base feed.

Currently there is no quality control check in place to monitor the true osmolality of the feeds before they are administered to the infant. To overcome this uncertainly, many NICUs have adopted the use of osmometry as a quality control tool to avoid the incidences of hyperosmolar feedings and improve patient safety.[12]

Common feeding practices utilized in the Neonatal Intensive Care Unit

Human breast milk is widely considered the first choice for feeding preterm infants due to its nutritional superiority and growing evidence of immunological health benefits. The osmolality of human milk is tightly regulated by the body and is approximately 300 mOsm/kg, but can vary slightly for a variety of reasons. Often times mother's own milk is not available so either donor milk or artificial nutritional products must be used. Regardless of the base nutritional feed, nearly always it will be supplemented with any number of pharmaceutical medications, vitamins, supplements or fortifiers prior to administration. Because of this, the true osmolality of the feed is rarely known.

Modification of expressed breast milk (EBM) with therapeutic doses of commonly used additives can result in a significant increase in its osmolality; this could also be further worsened when used in combination with fortified EBM.[13] Previous reports demonstrated that infants requiring neonatal intensive care are exposed to a large number of medications while in the hospital. One such study found that each infant received an average of

6.2 different drugs (range of 0 to 26) while in the intensive care nursery.[5,6]

To confound the issue, studies have shown that 54 commonly used medications in the NICU had a measured osmolality in excess of 2000 mOsm/kg.[14] Several hyperosmolar medications such as calcium lactate, calcium lubionate, and caffeine citrate have even been implicated in the development of NEC.[16,17,18]

Calculated osmolality values and its inherent risks

There are available equations commonly used to calculate the theoretical estimation of osmolality for neonatal parenteral solutions based on the nutritional components of the solutions.[7] While these calculations are convenient, they may be inaccurate, especially when calculating the osmolality of a multi-component solution simply by summing up the osmolality values of starting solutions.[9] To make matters even more difficult, the same medications from different manufacturers may have vastly different osmolalities as a result of their differences in formulations. Often times manufacturers may change the drug formulation without affecting the concentration of the active ingredient. Thus, the osmotic results for some medications cannot be trusted compared to published study results.[14]

Some infant formulas come in dry powder or concentrated liquid form and require addition of water and dilution prior to use. Errors in dilution can occur and may cause hyper- or hypo-osmolar states. Osmolality of powdered formula has also been shown to vary by as much as 30% due in part to measurement technique and between different lots of the same product.[15] The addition of lipid to human milk lowers osmolality by 9% because of the displacement effect of the osmotic particles.[19] Storage time and conditions of the feed solution must also be taken into consideration. It has been noted that amylase present in the breast milk can actively break down the maltodextrin in the milk and consequently increase the osmolality.[8]

With all of the inherent variability discussed, it is clear that making assumptions of the true osmolality of liquid by using calculated results is speculative at best. A direct osmolality measurement using an osmometer is the only reliable method to measure the true osmolality of a solution.[10]

Relevance of osmometry in the milk industry

Ironically, osmometry first found commercial utility over 50 years ago in the milk dairy industry. Historically dairy farmers were paid by the quantity of milk delivered to the processor, and soon realized that adding water to the milk would increase their profits. The added water in milk caused many downstream effects in dairy food processing and degraded the quality of cheeses, yogurts, and milk products. Freezing point osmometers, or cryoscopes, were implemented as a quality control check to determine if water had been added to milk. The milk cryoscopes were extremely effective in determining added water in milk. As a consequence, dairy farmers are now paid for the quality of their milk (ie, fat content) rather than by volume.

Advantages of Freezing Point Osmometers

Osmolality is classically defined as the total number of particles (solute) in a liquid solution (solvent). It is expressed in milliosmoles of solute per kilogram of solvent or mOsm/kg H_2O. Freezing point depression is a true colligative property that can accurately measure the concentration of a liquid solution.

Freezing point osmometers have been the widely referenced and accepted as the gold standard for use in research studies involving human milk and infant nutrition products. Compared with vapor-pressure osmometry, the freezing point depression method is preferable when solvent volatile substances are suspected or measured. Vapor pressure osmometers cannot detect volatile compounds and consequently underestimate the true concentration of the sample. Since many pharmaceutical formulations contain volatile compounds and alcohols, or more commonly unknown constituents, freezing point osmometers are preferred.[10,11, 14]

Materials and Methods

Materials

Type	Description	Serial or Lot Number
Osmometer	Advanced Model 3220 Micro-Osmometer	SN 04121118A
Osmometer Supplies	50 mOsm/kg Calibration Standard (3MA005) 850 mOsm/kg Calibration Standard (00A085) 290 mOsm/kg Reference Standard (3MA029)	Lot # 0309190 Lot # 0409080 Lot # 0402010
Infant Nutritional Products	Enfamil EnfaCare Lipil Powder (Cow's Milk Based) Enfamil ProSobee Lipil Powder (Soy Based) Enfamil Lipil Nutramigen Powder (Protein Hydrolysate) Enfamil Premium Lipil 20 Powder (Cow's Milk Based) Enfamil ProSobee Lipil Ready to Use (Soy Based) Enfamil Lipil Nutramigen Concentrated (Protein Hydrolysate) Enfamil Lipil 20 Concentrated (Cow's Milk Based) Similac Alimentum Ready to Use (Protein Hydrolysate) Similac Sensitive for Spit Up Ready to Use (Cow's Milk Based) Similac Advance Ready to Use (Cow's Milk Based) Similac Sensitive for Spit Up Powder (Cow's Milk Based) Similac Sensitive Powder (Cow's Milk Based) Similac Alimentum Powder (Protein Hydrolysate) Good Start Soy Plus Concentrate (Soy Based) Good Start Gentle Plus Concentrate (Cow's Milk Based) Good Start Gentle Plus Ready to Use (Cow's Milk Based) Good Start Gentle Plus Powder (Soy Based)	Lot # QL545 Lot # BD562 Lot # MFS22 Lot # ENFG05 Lot # MLS18 Lot # MHS10 Lot # MKS07 Lot #82542RH Lot # ISADPWO Lot # SIMESPW Lot# SSRSPWD Lot# SSENFWC Lot # 82927RAD Lot # HPC3013 Lot# GGC3050 Lot# GGR3043 Lot# GGR3043
Human Milk Samples	Human Milk MMB of Iowa Pooled #1 Human Milk MMB of Iowa Pooled #2 Human Milk MMB of Iowa Pooled #3 Human Milk MMB of Iowa Single Donor #1 Human Milk MMB of Iowa Single Donor #2 Human Milk MMB of Iowa Single Donor #3 Human Milk Indiana MMB Pooled #1 Human Milk Indiana MMB Pooled #2 Human Milk Indiana MMB Pooled #3 Human Milk Indiana MMB Single #1 Human Milk Indiana MMB Single #2 Human Milk Indiana MMB Single #3	Lot # P463-4 Lot # P496-4 Lot # P474-1

Methods

The Advanced Model 3320 Osmometer was calibrated based on manufacturer's specification using the 50 and 850 mOsm/kg calibration standards. At the start of each testing day, a calibration check was performed using the 290 mOsm/kg reference solution five 5 times, and all readings were within the ±2 mOsm/kg H_2O specification for each testing day. The reference standard was also tested 20 times each to establish the 3320 instrument performance parameters.

Infant formulas were cow's milk based, soy based, or protein hydrolysate based, and the ready to use, concentrated, and powdered formulations were all represented. All powdered and concentrated infant formulas were prepared according to manufacturer instructions. All formulas were tested within the acceptable time period stated by the manufacturer once opened. Each infant formula sample was thoroughly mixed prior to testing. Human milk samples were shipped frozen and thawed prior to each testing day. The human milk was either single donor unpasteurized or pooled donor pasteurized, from two human milk banks. The thawed samples were mixed by gentle inversion prior to testing.

All samples were tested five times each to obtain a baseline reading, and then tested 20 times each to determine the range, standard deviation and CV.

Results

Table 1. Powdered Infant Formulas

Brand Name	Average Osmolality (mOsm/Kg) (n=20)	S.D.	CV	Manufacturer's Label Claim [20,21,22]	% Difference Label Claim and Calculated
Enfamil EnfaCare Lipil	333.0	2.8	0.8	300	10.4
Enfamil Prosobee Lipil	187.3	2.1	1.1	170	9.7
Enfamil Nutramigen Lipil	299.7	1.6	0.5	300	0.1
Enfamil Lipil [20]	304.8	1.9	0.6	300	1.6
Good Start Gentle plus	226.3	1.5	0.6	250	10.0
Similac Sensitive for Spit-Up	175.7	3.3	1.9	180	2.4
Similac Sensitive	229.4	1.7	0.7	200	13.7
Similac Alimentum	326.0	2.5	0.8	320	1.9

Table 1. Results for the eight (8) powdered infant formulas tested. The osmolality ranged from 175.7 up to 333.0 mOsm/kg, which showed good correlation (0.1% to 13.7% difference) with manufacturer's label claims that ranged from 170 up to 320 mOsm/kg. Coefficient of variation (CV) for all samples tested were very good and were between 0.5 up to 1.9.

Table 2. Infant Formula From Liquid Concentrate

Brand Name	Average Osmolality (mOsm/Kg) (n=20)	S.D.	CV	Manufacturer's Label Claim [20,21,22]	% Difference Label Claim and Calculated
Enfamil Nutramigen Lipil	296.4	1.7	0.6	300	1.2
Enfamil Lipil [20]	308.3	2.1	0.7	300	2.7
Good Start Gentle plus	260.1	1.8	0.7	250	3.9
Good Start Gentle Soy plus	178.1	1.5	0.8	180	1.1

Table 2. Results for four (4) liquid concentrate infant formulas tested. The osmolality ranged from 178.1 up to 308.3 mOsm/kg, which showed very good correlation (1.1% to 3.9% difference) with manufacturer's label claims that ranged from 180 up to 300 mOsm/kg. Coefficients of variation (CV) for all samples tested were very good and were between 0.6 up to 0.8.

Table 3. Ready-to-use Liquid Infant Formula

Brand Name	Average Osmolality (mOsm/Kg) (n=20)	S.D.	CV	Manufacturer's Label Claim [20,21,22]	% Difference Label Claim and Calculated
Enfamil Prosobee Lipil	170.3	1.7	1.0	170	0.2
Good Start Gentle plus	268.6	1.7	0.6	250	7.2
Similac Alimentum	385.1	2.3	0.6	370	4.0
Similac Sensitive for Spit Up	172.9	1.5	0.9	180	4.0
Similac Advance	304.8	1.8	0.6	310	1.7

Table 3. Results for five (5) liquid infant formulas tested. The osmolality ranged from 170.3 up to 385.1 mOsm/kg, which showed very good correlation (0.2% to 7.2% difference) with manufacturer's label claims that ranged from 170 up to 370 mOsm/kg. Coefficients of variation (CV) for all samples tested were very good and were between 0.6 up to 1.0.

Table 4. Pooled Donor Human Milk

Brand Name	Average Osmolality (mOsm/Kg) (n=20)	S.D.	CV
Indiana MMB Pooled #1	279.7	1.8	0.6
Indiana MMB Pooled #2	291.5	1.4	0.5
Indiana MMB Pooled #3	261.0	1.3	0.5
Iowa MMB Pooled #1	307.5	3.7	1.2
Iowa MMB Pooled #2	304.5	2.3	0.8
Iowa MMB Pooled #3	271.7	2.0	0.8

Table 4. Results for the six (6) pooled human milk samples tested. The osmolality ranged from 261.0 up to 307.5 mOsm/kg. Coefficient of variation (CV) for all samples tested were very good and were between 0.5 up to 1.2.

Table 5. Single Donor Human Milk

Brand Name	Average Osmolality (mOsm/Kg) (n=20)	S.D.	CV
Indiana MMB Single #1	312.8	1.7	0.5
Indiana MMB Single #2	310.4	1.4	0.5
Indiana MMB Single #3	283.6	2.0	0.7
Iowa MMB Single Donor #1	316.1	3.1	1.0
Iowa MMB Single Donor #2	296.2	2.7	0.9
Iowa MMB Single Donor #3	313.7	3.6	1.1

Table 5. Results for the six (6) single donor human milk samples tested. The osmolality ranged from 296.2 up to 316.1 mOsm/kg. Coefficient of variation (CV) for all samples tested were very good and were between 0.5 up to 1.1.

Discussion

The purpose of this study was to evaluate the performance of the Advanced Model 3320 Micro-Osmometer over a broad range and types of infant nutritional products and human milk samples commonly found in the neonatal care setting. The research was neither intended to assess the quality nor confirm the label claims of the commercial nutritional products and human milk samples. More importantly, the study was conducted to establish the baseline performance of the osmometer for the infant nutritional and neonatal research community.

Overall twenty-nine (29) infant formula and human milk samples were tested in the study. The samples consisted of dry powder, ready to serve liquid, and concentrated liquid infant formulations as well as both pooled and single donor human milk samples. Osmolality ranged between 170.3 and 385.1 mOsm/kg. Standard deviations ranged from 1.5 to 3.3, and the coefficient of variation ranged from 0.5 to 1.9 across all sample types.

Conclusion

The health risks associated with hyperosmolar feedings in infant nutrition have been discussed. Common feeding and supplementation practices in the neonatal intensive care unit do little to confirm the actual osmolality of individual feed samples, and in many cases can impact patient safety by increasing the risk of hyperosmolar feedings. The Advanced Model 3320 Micro-Osmometer has been shown to provide accurate test results for all types of infant nutritional products and human milk. With a 60 second test time and low cost per test, it is ideally suited for the NICU or dietary department to rapidly monitor the osmolality of infant feeding solutions including infant formula, human milk, and additives such as fortifiers, vitamins, minerals or pharmaceutical medications. The 3320 osmometer can dramatically improve neonatal patient care, eliminate the risk of unintentional hyperosmolar feedings, and quickly confirm that infant feed mixtures are below the 450 mOsm/kg safety threshold recommended by the AAP.

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Case Study: Via Christi Health

Introduction

Via Christi Health is a Catholic-sponsored health ministry affiliated with the Marian Health System and Ascension Health. The largest provider of healthcare services in Kansas, Via Christi Health serves the region through hospitals, senior villages, physician services and health services. Via Christi Health employs more than 9,000 in Kansas and northeast Oklahoma. Via Christi's three acute-care hospitals in Wichita have 1,604 licensed beds and more than 4,400 employees.

According to an annual study by HealthGrades, one of the nation's leading independent healthcare ratings organizations, the clinical performance of Via Christi Health's Wichita hospitals is among the top 5 percent in the nation. As a result, in 2011 Via Christi was recognized with a HealthGrades Distinguished Hospital for Clinical Excellence award, one of only 92 hospitals nationwide to receive the award for five consecutive years.

In addition, Via Christi received HealthGrades' Pulmonary Care Excellence Award for a fourth consecutive year, Stroke Care Excellence Award for a sixth year in a row and Critical Care Excellence Award for a third year in a row and continues to rank No. 1 in Kansas for pulmonary care, stroke treatment, critical care and gastrointestinal medical treatment.

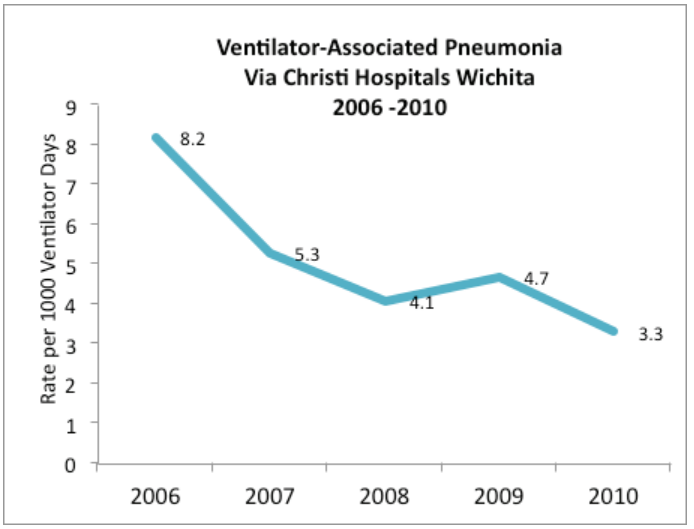
Case Example — Implementation of Kimberly-Clark KimVent Microcuff Endotracheal Tube

Via Christi's respiratory care department is made up of 125 therapists who provide care driven by clinical protocols in critical care and medical/surgical units. Ventilation includes conventional, percussive ventilation, oscillatory ventilation as well as jet ventilation in the NICU when indicated.

Since implementing new ventilator-associated pneumonia (VAP) prevention protocols, the hospital reduced the incidence rate of VAP by approximately five infections per 1,000 ventilator days from an average rate of 8.2 in 2006 to 3.3 in 2010.

The Challenge

Via Christi's Wichita hospitals provide a comprehensive range of services and tertiary care, including a Level I Trauma Center, Transplant Institute, Cancer Institute, Level III Neonatal Intensive Care Unit and Regional Burn Center as well as pediatric, cardiac, cardio thoracic, neuro critical, general and medical ICUs. As a result of its intensive care patient population, the hospital at any one time has a high volume of patients on ventilators. In 2006, the ICUs were seeing a higher than desired VAP rate of 8.2 infections per 1,000 ventilator days.



VAP is a healthcare associated infection (HAI), which is recognized as a serious problem nationwide in hospital intensive care units. Experts say that VAP can affect as many as 28 percent of patients who receive mechanical ventilation for at least 48 hours. VAP also imposes a significant financial burden, with some studies estimating the per-case cost of VAP at $12,000 to $40,000.[2] VAP increases ICU stays by up to 22 days and hospital stays by up to 25 days,[3] contributing to the high cost and toll it can take on patients, hospitals and the healthcare system. The mortality rate attributed to VAP is estimated to be as high as 27.1 percent.[4]

To reduce its VAP rates, Via Christi adopted a prevention protocol, including the use of a closed suction catheter system that keeps the ventilator circuit closed as much as possible, good hand washing, elevating the head of patients' beds, incorporating an oral care strategy, maintaining cuff pressure and selective use of heated humidification. In early 2007, the hospitals launched a formal multi-disciplinary team of individuals from infection control, hospital intensivists, ICU nursing leadership, administration and data specialists. Director of Respiratory Care Don Carden and Clinical Specialist Jeff Suderman, both registered respiratory therapists, provided leadership to the team and its efforts to reduce the VAP rate at Via Christi's Wichita hospitals.

This article was provided to us by Kimberly-Clark. Via Christi Health can be reached at www.viachristi.org.

As part of that effort, the team took a closer look at the devices and products the department was using in its VAP prevention efforts and became one of the first adopters of the Kimberly-Clark KimVent Microcuff Endotracheal Tube. The Microcuff ET Tube is designed to prevent the micro-aspiration of potentially infectious secretions into the lungs, a leading cause of VAP. The Microcuff ET Tube's unique cuff is made of an advanced microthin polyurethane material that allows the channels formed upon cuff inflation to "self-seal" within the trachea, increasing protection against fluid leakage into the lungs.

The Solution

In 2007, the Via Christi team selected the Kimberly-Clark KimVent Microcuff Endotracheal Tube and began using it on a regular basis. According to Carden and Suderman, the Microcuff ET Tube provided a solid cost-benefit advantage in that the department was able to seamlessly transition to the Microcuff ET Tube, with minimal education on how the tube works and minimal staff involvement in the training of its use. In addition, they found that when compared to competitive tubes with the same inner diameter, the Microcuff ET Tube had a smaller outer diameter. This was seen as an advantage to both RTs and patients during intubation. Also, when deflating the Microcuff ET Tube, the cuff more tightly hugs the shaft of the endotracheal tube which may allow for easier intubation. Finally, the availability of a pediatric Microcuff ET Tube option through Kimberly-Clark also made the selection more compelling for instances of treating pediatric patients.

The Results

Since implementing a strong multidisciplinary team effort, the department lowered its VAP rate to 3.3 infections per 1,000 ventilator days. Four out of 10 units have achieved a rate of zero infections per 1,000 ventilator days. "We have excellent respiratory therapists, critical care nurses, unit intensivists, advanced practice pharmacists, infection control, and microbiology," said Carden. "Assuring compliance with all elements of the VAP reduction bundle is critical." Suderman agreed, adding, "Everybody knows how important this is. It's not just the nurses' responsibility, not just the RT's responsibility, but it's everyone on the team. You have to keep VAP on the front burner."

Carden agrees, noting that every hospital needs someone to be the VAP champion to keep the issue alive. "Keeping the issue alive is an ongoing challenge, but this needs to be done in order to see successful and continued reductions in VAP," he said.

Via Christi is well-positioned to provide great care and to battle the non-reimbursement policy for never events and HAIs by Medicare, which now—more than ever—provides a further incentive to get patients off ventilators as soon as possible to cut down on the incidence of VAP to keep patients healthy and reduce hospital costs.

In addition to using the KimVent Microcuff Endotracheal Tube and KimVent TurboClean Suction Catheter, Via Christi recently began trials on Kimberly-Clark's KimVent Oral Care Kit-q4 with chlorhexidine gluconate (CHG) to help its hospitals and staff comply with the department's planned oral care strategy.

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Arthritis, Osteomyelitis, Septicemia and Meningitis Caused by Klebsiella in a Low-birthweight Newborn

Ziaaedin Ghorashi, Nariman Nezami, Hamideh Hoseinpour-feizi, Sona Ghorash, Jafar S. Tabrizi

Abstract

Klebsiella pneumoniae is in most cases a hospital-acquired infection and presents as pneumonia, septicemia and meningitis in patients with some predisposing factors, including prematurity, intravenous catheter, history of antibiotic therapy and intravenous nutrients.

Case presentation

A low-birth-weight, 33-day-old Caucasian girl with respiratory distress syndrome was admitted to our hospital. She developed septicemia, meningitis, polyarticular arthritis and osteomyelitis by nosocomial K. pneumoniae which was resistant to most antibiotics except ciprofloxacin. She was therefore treated with ciprofloxacin and co-trimoxazole for eight weeks. After completion of the treatment course, she completely improved with excellent weight gain and without any adverse effects during three years of follow-up.

In the resistant strain of K. pneumoniae, ciprofloxacin could be considered as a therapeutic option with the prospect of a good outcome, even in neonates and infants.

Introduction

Pneumonia is a type of infection that is most commonly caused outside the hospital by Klebsiella pneumoniae.[1] Mostly, K. pneumoniae is recognized as a hospital-acquired infection presenting as pneumonia, septicemia and meningitis in patients with some predisposing factors (including prematurity, intravenous catheter, history of antibiotic therapy and intravenous nutrients).[2,3] In the rare patients with underlying conditions among newborns and older adults, K. pneumoniae may result in arthritis and osteomyelitis. All Klebsiella subtypes are resistant to ampicillin, especially multi-drug-resistant (MDR) subtypes which are resistant to the majority of antibiotics, except fourth-generation cephalosporins and carbapenems. Previously, patients with MDR subtype infections usually received first-generation cephalsporins and aminoglycosides.

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Case presentation

A 33-day-old Caucasian girl was brought to the Tabriz Children's Hospital with poor breastfeeding, recurrent vomiting and anorexia. She was admitted with a primary diagnosis of septicemia.

She was born from a mother with pre-eclampsia through normal vaginal delivery at the 34th week of gestation, with a birth weight of 1670 g. Her Apgar scores at one and five minutes were five and six, respectively. During delivery and before admission to the Tabriz Children's Hospital, she had been hospitalized in the Talegani neonatal intensive care unit for prematurity, septicemia, respiratory distress syndrome and gastrointestinal bleeding. In Talegani Hospital, she had received antibiotic therapy, including ampicillin and gentamicin, then her medication was changed to cefotaxime and vancomycin, and finally her treatment continued with intravenous immunoglobulin, imipenem and ceftazidime.

Her physical examination revealed that she was pale, cachectic, anorexic and hypotonic, and her Moro and sucking reflexes were weak. She also exhibited grunting and had substernal and intercostal retraction. The patient's body weight, height and head circumference were 1700 g, 43 cm and 31 cm, respectively. Her vital signs, including pulse rate, respiratory rate, body temperature, O_2 saturation under the oxygen hood and without using the oxygen hood were 158/min, 48/min, 38.6°C, 95% and 89%, respectively.

Her cerebrospinal fluid (CSF) was purulent, and CSF analysis showed 520 mg/dL protein; 16 mg/dL glucose; many white blood cells (WBCs), with 85% polymorphonuclear cells and 15% lymphocytes; and 25 red blood cells (RBCs)/mm^3. In the CSF and blood culture, K. pneumonia was resistant to most of the antibiotics and sensitive only to ciprofloxacin and co-trimoxazole. Her chest X-ray showed bilateral humeral osteomyelitis and bilateral glenohumeral joint arthritis.

On the basis of the paraclinical evidence, diagnoses of *K. pneumoniae* septicemia, meningitis, arthritis and osteomyelitis were made, and a treatment protocol with a combination of intravenous ciprofloxacin and co-trimoxazole antibiotics was started (for 28 days). At the end of the intravenous treatment period, she weighed 2420 g, and her CSF analysis and culture were within normal range. Afterward, she was discharged with oral ciprofloxacin, co-trimoxazole and rifampicin for another 28-day period. Figures 2 and 3 show her chest X-rays obtained on the seventh and 28th days of oral antibiotic therapy, respectively.

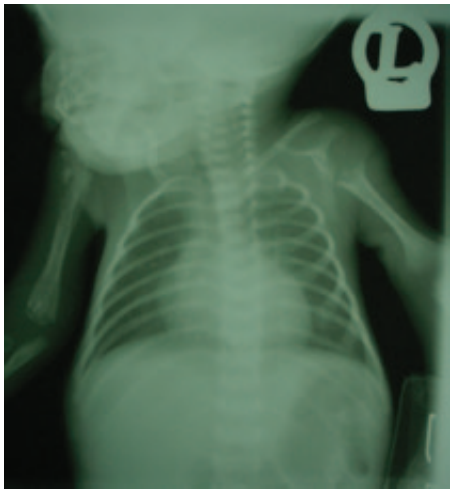

Figure 1. Chest X-ray obtained at the time of admission. Bilateral osteomyelitis in the humerus presented as osteolysis and involucrum. Also, there is sequestration because of osteonecrosis and a pathologic fracture in the proximal part of the humerus. Dislocation of right glenohumeral joint brings up the arthritis diagnosis. There is complete osteolysis in proximal metaphysis in the left humerus and arthritis in the left glenohumeral joint. The heart, lung and pleural space have a normal appearance, while the thymus is atrophic.

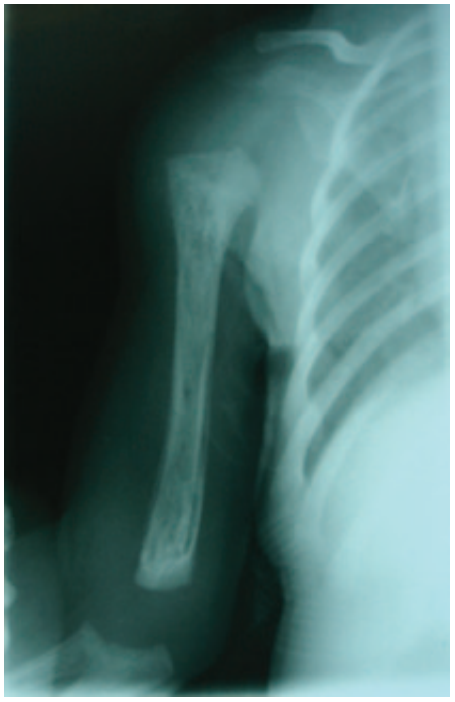

Figure 2 Chest X-ray obtained on the seventh day of oral antibiotic therapy. The lytic lesions in the proximal and distal metaphysis in the right humerus are shown

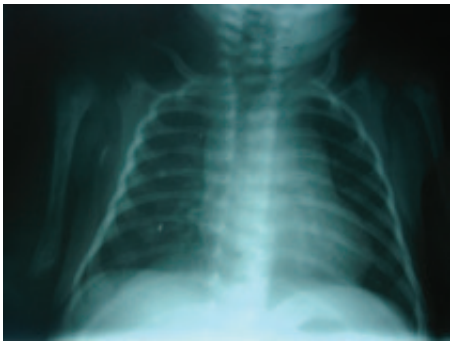

Figure 3 Chest X-ray showing complete resolution of symptoms at the end of anti-biotic therapy.

At the end of 28 days of oral antibiotic therapy (when the patient was 88 days old), her weight had reached 4250 g and normal glenohumeral joints and humerus bones were shown on her chest X-ray. During three years of follow-up, she had normal developmental milestones and was not readmitted to the hospital.

Discussion

Prolonged hospital stay, decreased gestational age, prolonged use of broad-spectrum antibiotics and inadequacy of some basic facilities and staffing carry the risk of introduction of resistant hospital pathogens.[4-6] In the present case, all of the above-mentioned factors, combined with prematurity, predisposed the neonate to a higher risk of contracting nosocomial K. pneumoniae arthritis, osteomyelitis, septicemia and meningitis, although the common cause of osteoarthritis is Gram-positive cocci.[7]

Adeyemo *et al*[8] reported an outbreak of bone infections associated with neonatal septicemia by K. pneumoniae in 12 neonates over a six month period at the Special Care Baby Unit, University College Hospital, Ibadan, Nigeria. All patients had septic arthritis, 10 of them had osteomyelitis and 50% had multiple-joint involvement.

Hospital-acquired K. pneumoniae has been reported to be resistant to multiple antibiotics.[8,9] In addition, Ghahramani and Nahaie[10] showed that K. pneumoniae is the most common cause of septicemia in the neonatal ward of the Tabriz Al-Zahra Gynecology and Obstetrics Referral Hospital in Tabriz, Iran.

The parenteral third-generation cephalosporins appear to be a major therapeutic advance in the treatment of K. pneumoniae[11] but reports of highly resistant strains that produce plasmid-mediated, extended-spectrum β-lactamases influenced therapeutic outcomes again.[12] Evidence revealed that K. pneumoniae infection, especially the nosocomial type, is resistant to the majority of antibiotics except for ciprofloxacin and ofloxacin.[13] In the present case report, the isolated K. pneumoniae was resistant to most of the antibiotics except ciprofloxacin and co-trimoxazole. Therefore, these two antibiotics were used in the treatment protocol. Because of the quinolone cartilage toxicity potential in experimental juvenile animal models, the use of ciprofloxacin among children has been restricted.[13,14] However, recent data from Bayer's ciprofloxacin clinical trials database indicate that the role of fluoroquinolones in the treatment of certain serious infections in children does not appear to be compromised by safety concerns when used appropriately.[15] In such cases, when a micro-organism is resistant to all antibiotics except ciprofloxacin, a dosage of 15 mg/kg/day to 30 mg/kg/day is advised in neonates.[16]

After completion of the treatment course, our patient completely improved and achieved normal developmental milestones and weight gain, without adverse effects or hospital readmission during three years of follow-up.

Conclusion

In neonates with delivery problems, prematurity, low birth weight and prolonged hospital admission, nosocomial K.

Table 1 Laboratory tests and results on admission[a]

Complete blood cell count		Biochemical analysis		Arterial blood gas	
WBC count (cells/μL)	6500	FBG (mg/dL)	42	pH	7.29
Hb, g/Dl	7.8	Cr (mg/dL)	0.5	HCO_3^- (mmol/L)	20
Platelets, *n*/μL	773 × 10^3	BUN (mg/dL)	24	PCO_2 (mmHg)	43
PMN cells, %	51				
Eosinophils, %	1%	Electrolytes		Other	
Lymphocytes, %	24%	Na (mEa/L)	136	CRP	2+
Monocytes, %	2%	K (mEa/L)	45	Blood group	A^+
Band cells, %	21%	Ca (mg/dL)	10.8		

[a]WBC, white blood cells; Hb, hemoglobin; PMN, polymorphonuclear cells; CRP, C-reactive protein; Na, sodium; K, potassium; BUN, blood urea nitrogen; FPG, fasting plasma glucose; Ca, calcium.

pneumoniae should be considered in the differential diagnosis of septicemia, arthritis, osteomyelitis and meningitis. Considering the multi-drug resistance of nosocomial K. pneumoniae and sensitivity to quinolones, ciprofloxacin, when used appropriately, should be considered a therapeutic option with good outcomes in patients with serious infections with resistant strains of K. pneumoniae, even in neonates and infants.

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Long-term Outcome in Relationship to Neonatal Transfusion Volume in Extremely Premature Infants

Jeannette S. von Lindern, Chantal M. Khodabux, Karien E.A. Hack, Ingrid C. van Haastert, Corine Koopman-Esseboom, Paul H.T. van Zwieten, Anneke Brand, Frans J. Walther

Abstract

Background: In premature born infants red blood cell (RBC) transfusions have been associated with both beneficial and detrimental sequels. Upon RBC transfusion, improvement in cerebral blood flow and oxygenation have been observed, while a more liberal transfusion policy may be associated with a better developmental outcome. The effect of the transfusion volume on long-term outcome is not known.

Methods: Observational follow-up study of a cohort of extremely premature born infants, treated in 2 neonatal intensive care units using a different transfusion volume (15 ml/kg in Unit A and 20 ml/kg in Unit B). The primary outcome was a composite of post discharge mortality, neuromotor developmental delay, blindness or deafness, evaluated at a mean corrected age (CA) of 24 months related to the transfusion volume/kg bodyweight administered during the postnatal hospital stay.

Results: Despite the difference in transfusion volume in clinically comparable groups of infants, they received a similar number of transfusions (5.5 ± 3.2 versus 5.5 ± 2.3 respectively in Unit A and B). The total transfused volume in unit A was 79 ± 47 ml/kg and 108 ± 47 ml/kg in unit B (p = 0.02). Total transfused RBC volume per kg bodyweight was not an independent predictor of the composite outcome (p = 0.96, OR 1.0 (CI 0.9-1.1).

Conclusion: There was no relationship between the composite outcome at 24 months CA and transfusion volume received during the post natal hospital stay. As there was no clinical advantage of the higher transfusion volume, a more restrictive volume will reduce total transfusion volume and donor exposure. Future research on the optimal transfusion volume per event to extreme preterm infants should include larger, prospective studies with a longer follow-up period through to childhood or even adolescence.

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The authors wish to thank all the neonatologists, especially Dr Hens Brouwers, and pediatricians at the University hospitals of Utrecht and Leiden and their referral hospitals for their support in this study. Reprinted from BioMed Central, BMC Pediatrics

Background

There is ongoing uncertainty whether transfusion of red blood cells (RBC) in the neonatal period influences the clinical outcome and development of premature infants. In the international literature there is discussion about the optimal transfusion volume and trigger.[1] We previously published a study comparing two transfusion dosages of the same RBC product in two Dutch tertiary care neonatal units (NICUs) using the same transfusion trigger protocols.[2] No difference in short term outcome and mortality was observed in extremely and very preterm infants when a dose of 15 ml/kg had been administered compared to a volume of 20 ml/kg bodyweight.

Little is known about the long-term follow-up of extremely premature infants after RBC transfusion. Only a few randomized trials have been published on long term outcome in premature infants with difference in transfusion practice.[3,4] However, these were studies (the PINT trial and the Iowa trial) comparing liberal and restrictive transfusion triggers, exposing the infants in the restrictive group to the possible risks of a low hemoglobin level.[5,6] In sequel to our study on short term outcome we also wanted to compare long term outcome in the same group of extremely premature infants treated with different transfusion volumes but with otherwise comparable transfusion triggers and transfusion products. In our follow-up study we evaluated post discharge mortality, neuromotor developmental outcome and disabilities in a cohort of extremely premature born infants born before 28 gestational weeks in two Dutch tertiary NICUs.

Methods

Study population: This is a follow-up study of a cohort of extremely premature infants born before 28 gestational weeks that participated in a previous study on transfusion practice and short-term outcome in two Dutch NICUs. All infants were transfused using the same transfusion triggers and with a similar RBC blood product with only a different volume per event, ie 15 and 20 ml/kg bodyweight. The study design was previously described.[2] The primary outcome measure was a composite of post discharge mortality, neuromotor developmental outcome and disabilities.

Transfusion guideline and product: All infants were transfused according to the Dutch consensus for blood transfusion 2004.[7]

Table 1 Characteristics of patients per unit included in follow-up study

	Total (n = 67)	Unit A (n = 31)	Unit B (n = 36)	p-value
Male, n	61% (41)	74% (23)	50% (18)	0.05
Gestational age, weeks mean SD	26 6/7 ± 4/7	26 6/7 ± 4/7	26 6/7 ± 4/7	0.65
Birth weight, grams mean SD	900 ± 187	906 ± 178	895 ± 197	0.59
AS 5 minutes, median (IQR)	8 (7-9)	8 (7-9)	8 (7-9)	0.88
IVH ≥ grade 3	9% (6)	13% (4)	6% (2)	0.40
BPD≥ moderate	35% (23)	29% (9)	40% (14)	0.35
ROP ≥ grade 2	12% (8)	13%(4)	11% (4)	1.0
Total number of transfusions, mean SD	5.5 ± 2.7	5.5 ± 3.2	5.5 ± 2.3	0.98
ML/per kg RBC administered, mean SD	95 ± 49	79 ± 47	108 ± 47	0.02
Composite outcome	31% (21)	29% (9)	33% (12)	0.71

AS = Apgar score, IVH = intraventricular hemorrhage, BPD = bronchopulmonary dysplasia, ROP = retinopathy of prematurity, RBC = red blood cells, composite outcome = post discharge mortality, impaired neuromotor development, deafness or blindness

The recommended transfusion triggers vary with postnatal age, degree of illness and need for respiratory support: - Hb <8 mmol/l (13 g/dl) (hematocrit (Hct) range 0.38-0.40 l/l) capillary (or <7 mmol/l arterial (11 g/dl) (Hct 0.32-0.35 l/l)): the first 24 hours after birth in all infants with clinical symptoms of anemia (tachycardia, supplemental oxygen need, apnea, bradycardia); in all infants on mechanical ventilation or severely ill. - Hb <7 mmol/l (12 g/dl) (Hct 0.32-0.35 l/l) capillary: reasonably stable infants with cardio-respiratory problems (patent ductus arteriosus, apnea, broncho-pulmonary dysplasia, need for supplemental oxygen). - Hb <6 mmol/l (10 g/dl) (Hct 0.27-0.30 l/l) capillary: stable premature infants with a postnatal age <4 weeks. - Hb <4.5 mmol/l (7 g/dl) (Hct 0.2-0.23 l/l) capillary: stable infants with a postnatal age >4 weeks if there are no signs of anemia (apnea, tachycardia, poor weight gain, poor feeding). In case of symptomatic anemia, transfusion is recommended at a higher threshold.

Transfusion volume per kg bodyweight was different between the two hospitals; 15 ml/kg in Unit A and 20 ml/kg in Unit B. This transfusion volume was part of the standard practice in the hospitals and was not chosen for study purposes. The same transfusion product was used in both hospitals. All products consisted of pre-storage filtered RBC stored in additive solution Saline Adenine Glucose Mannitol (SAG-M) (maximum storage time 35 days), with a hematocrit of 0.58 ± 0.05 l/l. The products were irradiated with 25 Gy less than 24 hours before transfusion. Preventative measures for anemia of prematurity were not standardized. Erythropoietin was not used in the study units. Iron supplementation was started 6 to 8 weeks after birth if there had been no previous RBC transfusion. After RBC transfusion iron supplementation was postponed for four weeks because of the assumed iron load given with the transfusion.

Data collection and outcome parameters: Infants with a syndrome or congenital/hereditary anomaly known to cause a neuromotor developmental delay were excluded from analysis. Data on neuromotor developmental outcome, major disabilities (deafness, blindness) and survival at a mean (± SD) corrected age (CA) of 24 ± 3.4 months were obtained from each child's outpatient follow-up physician, child-psychologist and/or pediatric physiotherapist, who were all trained in neonatal follow-up. Developmental examination was done in different hospitals. The children were assessed with various instruments depending on the hospital of follow-up. Instruments used were the Dutch 2nd version of the Bayley Scales of Infant Development-II (BSID-II-NL),[8] the Griffiths Mental Development Scales,[9] Alberta Infant Motor Scale (AIMS),[10] and the Hempel,[11] Touwen,[12] and van Wiechen[13] assessments of neuromotor development. The children were classified as normal, mildly delayed or severely delayed, using the cut-off values of each test, classifying severe neuromotor developmental delay as a score of more than 2 SD below average and mild neuromotor developmental delay as a score 1 to 2 SD below the mean. Non-cooperative children received a general assessment by the physician, pediatric physiotherapist and/or child-psychologist. A parental questionnaire was sent to the parents of the children if follow-up at age 2 years was unknown by any of the previously mentioned professionals.

Our primary outcome was the composite of post discharge mortality, severe hearing or visual impairment,

or neuromotor developmental delay at 24 months CA. Visual impairment was defined as <20/200 of best eye, hearing impairment was defined as the need for a hearing aid or cochlear implant. Neuromotor developmental delay was defined as a score more than 1 SD below the mean. The definition for bronchopulmonary dysplasia (National Institutes of health Consensus, USA) was used as described by Ehrenkranz et al.[14] For retinopathy of prematurity the revised international classification was used.[15] Intraventricular hemorrhage was graded according to Volpe.[16]

Statistical Analysis: All variables were analyzed by univariate analysis for continuous variables and Chi-Square or Fishers exact probability test for nominal variables. Backward step wise logistic regression analysis was used for the independent effect of the following factors: hospital (representing transfusion dose and unknown factors), number of RBC transfusions, total transfused RBC volume per kg bodyweight, gender, gestational age, birth weight, CRIB II score and Apgar- score at 5 minutes. (SPSS 17 Chicago, United States of America). A p-value of less than 0.05 was considered significant.

Results

Eighty-seven extremely premature infants were included in our earlier cohort study (44 in Unit A, 43 in Unit B). Four infants died the first day of life and were excluded from this follow-up study (1 lung hypoplasia, 1 massive pulmonary hemorrhage, 1 severe perinatal asphyxia and 1 cause unknown). None of these children had received a RBC transfusion. Twelve other patients died in the neonatal period for various reasons; they had all received RBC transfusions. They were also excluded from follow-up. Seventy-one of the 87 infants (82%) left the hospital alive (in total 9 in unit A and 7 in unit B died (p = 0.78). There were no deaths after discharge from the units. One other patient

Table 2 Predictors of the composite outcome of neuromotor developmental delay, post-discharge mortality, blindness or deafness

	P-value	OR	CI of OR (95%)
Hospital	0.8	1.6	0.1-24.7
Number of RBC transfusions	1.0	1.0	0.2-4.8
ML/kg RBC transfused	1.0	1.0	0.9-1.1
Gender	0.2	0.4	0.0-1.6
Gestational age	0.8	1.0	0.9-1.1
Birth weight	0.4	1.0	1.0-1.0
CRIB II score	0.6	1.0	1.0-1.0
Apgar score 5 min	0.3	1.2	0.8-1.9

RBC = red blood cells

was excluded from follow-up analysis because of a severe myopathy. Three children were lost to follow-up in the first year of life; one due to emigration, of the other two (twins) the reason is unknown, leaving 67/70 (96%) of the eligible infants surviving the post-natal period for neuromotor developmental follow-up.

There were no statistically significant differences when comparing the baseline characteristics of the patients from both units (Table 1). The number of transfusions administered was similar, 5.5 ± 3.2 (Unit A) versus 5.5 ± 2.3 (Unit B) respectively. As the volume per transfusion event per center differed, the mean total volume transfused in unit A and B was significantly different (79 ± 47 ml/kg versus 108 ± 47 ml/kg (p = 0.02) respectively). Neuromotor development was evaluated at a mean 24 ± 3.4 months CA. One infant had a severe visual impairment and one child had severe hearing loss. Forty-seven out of 67 (70.1%) infants showed normal neuromotor development for corrected age. Seventeen infants (25.4%) had a mild developmental delay and three infants were severely impaired (4.5%).

There was no statistically significant difference in the transfused volume for the primary outcome (composite of post discharge mortality, neuromotor developmental delay, blindness or deafness) compared to children with a normal outcome (105 ± 52 ml versus 90 ± 47 ml respectively) (p = 0.96, OR 1.0 (0.9-1.1). In multivariate analysis none of the tested variables reached statistical significance for an independent association with the composite outcome (Table 2).

Discussion

Transfusion of RBC has been associated with negative and positive effects on clinical outcome. Our study showed no significant differences between a smaller and a larger transfusion volume regarding a composite outcome of post discharge mortality, neuromotor developmental outcome and disabilities at 2 years CA. This would imply that a smaller transfusion volume rather has advantages (generally limiting donor exposure and costs), than negative effects on neuromotor developmental outcome. It is possible that no effects were seen because the difference in transfusion volume per transfusion event was not large enough. On the other hand, the total transfusion volume/kg during the post natal hospital stay was significantly different in the two NICUs. Several studies associated RBC transfusion with the development of retinopathy of prematurity[17-20] and chronic lung disease.[21-23] It is hypothesized that iron overload, caused by multiple RBC transfusions, increases oxidative stress leading to free radical-induced injury to the premature retina and developing lungs.[24,25] However, anemia has been associated with negative effects as well and in particular the brain may be susceptible to low hemoglobin levels. Bell et al, in a randomized study, found a statistically significant higher incidence in the number of infants with intracranial hemorrhage grade IV or periventricular leukomalacia when a restrictive transfusion threshold was applied as compared to a more liberal threshold.[5] On the other hand, neither Chen[24] nor Kirpalani (PINT trial)[6] found a statistically significant difference in the occurrence of (severe) intracranial pathology. However, the follow-up study by Whyte et al of infants included in the PINT trial, suggested that preterm infants treated with a more liberal transfusion regime may have a better developmental outcome.[4] The premature infants included in this multicenter PINT trial were analyzed at18-21 months CA with regard to mortality, cerebral palsy, severe visual impairment, hearing-loss, a Bayley-Mental Developmental Index (MDI) score <70, and a composite of these variables. Although there was no statistically significant difference in composite outcome (45% in the restrictive and 38% in the liberal group), the difference in cognitive delay (MDI score <70) approached statistical significance in favor of the liberal group. A post-hoc analysis with cognitive delay redefined (MDI score more than 1SD below the age-standardized mean) showed a significant difference favoring the liberal threshold group. This suggests that premature infants may benefit from a higher hemoglobin threshold for transfusion.[4] In the study by Nopoulos et al on the brain structure of 12 year old children previously enrolled in the Iowa trial by Bell and colleagues, only 44 of the 100 children participated.[3] The children who were exposed to the liberal transfusion threshold appeared to have a substantially smaller intracranial volume compared to the children transfused according to the restrictive guideline. Nopoulos mentions unpublished data on long-term cognitive follow-up showing (non-significant but) overall poorer outcome in the group of liberal transfused children.

Another recent study has shown that RBC transfusions increase cerebral oxygenation, thereby decreasing the risk of tissue hypoxia.[26] Mercer et al showed that premature male infants after delayed cord clamping, had a better developmental outcome at seven months CA compared to infants after immediate cord clamping.[27]

It is conceivable that upon transfusion of a larger volume, an increase in cerebral flow and better oxygenation can be obtained with a similar effect as described by Mercer.

In transfusion guidelines, the range of recommended RBC volume per kilogram bodyweight is rather wide, 10-20 ml/kg. Given the variation in hematocrit between used RBC products, the guidelines result in a huge variation in actually transfused RBC.

We observed no influence of transfused volume RBC per kg bodyweight on a composite of impaired neuromotor development, post discharge mortality and deafness or blindness in extremely preterm born infants evaluated at 24 months CA. This finding remained unchanged after logistic regression analysis correcting for other factors relevant for outcome.

The two Dutch NICUs participating in this study used the same transfusion guideline, transfusion trigger and transfusion product, which virtually excludes important differences in degree of anemia between infants. Our study has its limits being a retrospective, non-randomized trial. The neuromotor development was assessed using various different tests. In Unit B all children were assessed by the same special educator who is also a pediatric physiotherapist (ICvH) using the same

test (BSID-II-NL) in 95% of the children. The children from Unit A were assessed using various validated tests, performed in different hospitals by different professionals. It may be an incentive to perform a larger, prospective randomized controlled trial, focusing not only on the transfusion trigger but also on the total transfused RBC volume to recommend an optimal transfusion trigger and dose.

Conclusion

A high total transfused volume of RBC per kg was not correlated with the composite outcome of impaired neuromotor developmental outcome, post discharge mortality, blindness or deafness when analyzed at 24 ± 3.4 months CA, hereby questioning the previously presumed possible detrimental effects of RBC transfusions. Due to differences in neonatal transfusion practice, conclusions on the effect of maintaining a higher Hb value by the use of liberal transfusion triggers or a larger volume of RBC per transfusion are not based on strong evidence. A larger transfusion volume may not be associated with deleterious effects, whereas a smaller transfusion volume may limit donor exposure. Through randomized clinical studies, the effect of more liberal or restrictive triggers on long-term outcome can be studied, as well as the combination with a low (10 ml/kg) or high (20 ml/kg) transfusion volume. A longitudinal study to school age or even adolescence looking for instance at academic competencies might give further insight in the effects of different transfusion volumes.

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Measuring Economic Consequences of Preterm Birth

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Abstract

This study aims to identify the impact of a preterm birth on financial and emotional burden from the families' perspective. Additionally, a comprehensive schedule of recommendations for a sufficient evaluation of all aspects of burden is developed. Based on the results of a literature search relevant categories and sub-domains for a questionnaire covering multiple aspects of associated financial and emotional burden are identified and converted into a recommendation scheme. Results of the literature search illustrate the large extend of burden of prematurity on parents. This results in substantial out-of-pocket expenditures (OOPE) and emotional distress to the parents besides the medical problems and further financial costs to the health insurance system. According to the results on infants' state of health, OOPE and emotional distress are significantly increased with decreasing gestational age. OOPE for transportation often amounts to the main parental cost dimension. Moreover there is some evidence for a high magnitude of reduced income and missed work days. The family perspective has to be taken into account when calculating the overall costs of preterm births from a societal point of view. However, in recent years economic evaluations were performed rather inhomogeneously in this field. For future studies a) direct medical costs, b) direct non-medical costs, c) indirect costs as well as d) intangible costs (in terms of emotional distress and reduced quality of life for caregivers and children) are the main categories that should be evaluated measuring personal burden of preterm birth on families adequately. A detailed list of specific sub-domains is given. Additionally, the recommendations are not restricted to application in infants born preterm and/or at low birth weight.

Introduction

Although the number of births in most industrialized countries remained relatively stable in recent years, an increasing incidence of infants with low gestational age (≤36 weeks of gestation) and low birth weight (<2,500 g) can be observed. For example, in Germany the proportion of infants with low birth weight rose by nearly a fourth from the 1980 level. Increasing maternal age and fertility treatments in many western countries are only two of several possible reasons for this development. For example, in Germany the percentage of infants born preterm is about 9-10% of all newborn children, which comes to approximately 60,000 infants per year. About 1-2% is even born before the 32nd week of gestation. Regarding the entirety of all newborns, 6,8% are weighing less than 2,500 g and 1.2% less than 1,500 g (8,090 infants in 2005). Similar trends can be observed in other industrialized countries.

Those children who do survive have a higher risk of future health-related and developmental problems ranging from severe motor and sensory impairments to attention deficit disorders (ADHD) and learning difficulties. Clinical complications may include chronic lung disease, acute respiratory and/or gastrointestinal prob-lems as well as visual impairments or severe infections. On the other hand dramatic advances in neonatal care and perinatal practices have resulted in increased survival chances of low gestational age and birth weight infants. Together these effects increase the cost of care provided to these children during the neonatal period and in later periods of life as well.

Recently the Institute of Medicine (IOM) in the US has prepared a comprehensive report called "Preterm birth, causes, consequences, and prevention" describing prematurity as an important public health issue. In the US this was elevated to the government and the "Preemie Act" signed in December 2006 decreed an expansion of research related to care, treatment and outcomes of preterm birth and low birth weight infants as well as public and provider education. A fundamental recommendation of the IOM report was to increase efforts aimed at understanding all aspects in the provision and perception of health care related to preterm birth. One of the issues envisaged is the burden posed by preterm infants on parents and families. Moreover, in a recent study van Exel et al emphasized that the overall healthcare sector strongly depends on informal care provided by families and other caregivers. According to their analyses informal caregivers may experience significant burden as well as health and well-being effects. Resource allocation decisions should always account for these "invisible-hands"-effects in the social environment of patients.

So far, existing research on costs of prematurity primarily focused on the (high) costs for initial hospitalization and

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Table 1 Applicable domains to measure burden of disease: direct medical costs, direct non-medical costs, indirect costs, and quality of life aspects

Resource utilization domain	Possible contents and practical issues
Health care co-payments or OOPE (direct medical costs)	
Outpatient	*Co-payments or deductibles; health care services not covered by health plans and paid for by the parents*
- visits to physicians (general practitioners and specialists)	Additional services like German "IgeL"; (follow-up) visits causing a surgery fee or other co-payments
- visits to non-physicians	E.g. physiotherapy, ergotherapy, logopedics, osteopathy, massages, animal/music therapy, psychotherapy etc. (co-)paid for by the parents
- medication	Parental drug expenses (OTC drugs not covered by the insurance plan or co-payment for Rx)
- aids and devices	E.g. inhalators, home monitor, glasses, orthotics, wheelchair, specialized pushchair, sitting aid, hearing aid, corset etc. (co-)paid for by the parents
- outpatient/home care	Nursing staff, specialized bed (co-)paid for by the parents
Inpatient	*Co-payments or deductibles; health care services not covered by health plans and paid for by the patient*
- initial hospitalization	Co-Payments/deductibles for extra therapies/services
- re-hospitalization	Co-Payments/deductibles for extra therapies/services
- rehabilitation/regimen	Co-Payments/deductibles for extra therapies/services
Other disease-related OOPE (direct non-medical costs)	
- transportation	Travel costs for hospital visits (initial hospitalization, re-hospitalization) and transport to therapies/ specialists, including parking
- accommodation	Lodging costs during the infants' hospital stays
- home or car remodeling	Adaptations to the families' home or car
- meals	Physician-ordered food
- other/special medical approaches	Alternative therapies: naturopathy, homeopathy, light therapy etc. (possibly overlapping with visits to non-physicians, see above)
- childcare/babysitting for other siblings	During absence of parents while accompanying the preterm child to hospital visits or therapies
- special education/schooling	Coaching/tutoring (not relevant for infants, but in later years)
- home help	For housekeeping as parent time is required caring for the preterm child
- higher insurance premiums	In private health insurance or supplementary insurance
Indirect costs	
- income losses	Due to change in work status of parents; lost wages (in very later life this is relevant for the preterm child as well: indirect costs caused by future limited ability to work)
- missed working days	Does not automatically mean reduced income, but often absence causes problems at work (psychologically and perhaps financially in the long run as well)
- time losses (opportunity costs)	For care, travelling, hospital visits (asking how much of this time would otherwise have been spent to work)
Intangible costs: Quality of life aspects	
- QoL of children	Development problems, infections, disabilities with influence on physical, emotional and social functioning
- QoL/physical and emotional burden on parents or other caregivers	Prenatal phase (anxiety, self-reproaches), perinatal phase (stress related to birth, separation from baby on NICU), postnatal phase (psychological distress: fear of losing child/infections/development problems, self-reproaches, burden on relationship to siblings, marital stress, maternal depression, restricted social contacts, feeling of isolation etc.)

associated neonatal intensive care for preterm infants from a health insurance perspective. In contrast, only little is known about the magnitude of the public burden beyond this early hospitalization (re-hospitalization, outpatient services, and medication) and non-medical costs like expenses for special education or indirect costs because of lost productivity, especially from the families' perspective. Aim of this paper is therefore to explore this issue further by reviewing existing literature in order to describe the financial and emotional burden of prematurity on parents. Additionally this study aims to develop recommendations on how to measure familial burden of disease in future studies.

Methods

Based on a literature search, the objective is to gather a deeper insight into the medical and associated financial (out-of-pocket expenditures (OOPE)) and emotional burden (quality of life (QoL)) of a preterm birth and/or low birth weight on families. For this first part, a narrative literature search was conducted covering the time until April 2009. Main objective of this first part is not a complete evaluation or classification of all relevant studies, but to identify and to analyze different methods to quantify burden on parents. The following databases and search engines were used: MEDLINE, German Medical Science, Karger, Kluwer, Thieme and Springer bibliographic databases as well as Scirus search engine. The keywords used for the search were: (preterm OR premature OR low birth weight) AND (parent OR caregiver OR mother OR father) AND (cost OR out of pocket expenditure OR OOPE OR out of pocket payment OR OOPP OR quality of life OR burden of disease). Relevant publications needed to analyze at least one category of burden on parents or other caregivers and not only the perspective of the health care system. Because of expected scarceness of studies other inclusion or exclusion criteria were not defined. All different topics or cost domains that are identified through that process will be classified and listed in structured table.

Based on the findings, the results of the review are used to complete a comprehensive list of recommendations for a sufficient evaluation of all burdens of preterm births on families concerned. The particular choice of which costs to include always depends on the respective perspective of a study: From the perspective of a family a) medical direct costs, b) non-medical direct cost, c) indirect cost and d) intangible costs (in terms of QoL aspects) are four the major categories, which have to be filled with information. The major categories were defined a priori. They were derived from general standards/ basics of health economic evaluation and cover all possible types of burden. The main objective is to fill these four heading with special sub-domains covering all relevant aspects of personal burden and simultaneously to avoid double counting which is achieved by the analyses of the literature.

Results

Financial aspects: Valuing the economic burden of prematurity to society, it is very important to understand the full extent of costs as different cost domains are affected. However, it is accepted that these conditions impose a substantial financial burden not only on the health insurance, but on families and caregivers of the infants. There are several different cost categories that might be of importance.

A recent report by the IOM estimated that the societal economic burden associated with pre-maturity (≤36 weeks of gestation) in the US was at least 26.2 billion USD annually in 2005, or 51,600 USD per infant born preterm. These costs capture the annual discounted value of resources consumed per year in excess of what is projected to be used by infants born at term. Nearly two-thirds of these costs (33,200 USD) were accounted for by medical care services, with more than 85% of those delivered during early childhood (0-5 years). Maternal delivery costs accounted for an additional 3,800 USD per infant, early intervention service costs (for programs on the emotional, physical, and developmental outcomes, eg interventions for speech and language acquisition in very young children up to 3 years of age) contributed 1,200 USD annually and special educational services associated with a higher prevalence of disabling conditions among premature infants added 2,200 USD per person. Finally indirect costs, in terms of future lost productivity in the household and the labor force associated with disabling conditions of the children, contributed 11,200 USD per every preterm child. These cost components do not include costs of the caregivers for individuals with disabilities like out-of-pocket payments for education or loss of earnings during childhood which would have to be added.

Additional studies confirm an inverse relationship of neonatal and post-discharge costs with birth weight and gestational age. According to the results of a comparable study for the European context the average overall 2-year-costs are 104,635 EUR for surviving infants born preterm (< 1000 g), compared to 3,135 EUR for normal birth weight children in Finland. Initial hospital costs alone accounted for 64% of total costs, whereas costs during the first and second year accounted for 20% and 13%, respectively.

However, evidence on financial burden (OOPE) is very limited. Costs during the neonatal period (mainly for initial hospitalization and associated OOPE, eg for transportation, child care or accommodation) can be distinguished from long-term costs after this period (co- and out-of-pocket payments for re-hospitalization, outpatient visits, pharmaceuticals, medical aids as well as non-medical costs for transportation, special education or time and earning losses).

Costs during the neonatal period: Several studies found an inverse relationship between gestational age or birth weight and hospital service costs during the neonatal period (initial hospitalization). Moreover they also showed that neonatal costs tended to be higher for preterm infants who survive compared with those who die. Furthermore hospital service costs during this period are highly related to the degree of surgical intervention performed on the infant and the level of assisted ventilation. Gilbert et al estimated total per-patient neonatal hospital costs of 202,700 USD for a surviving baby born during the 25th week and 46,400 USD for babies born during the 30th week, decreasing to only 1,100 USD for a 38-week newborn.

Besides these studies on the expenses covered by the insurance system, there are also some analyses assessing the parental expenses in this neonatal period: Travel expenses incurred by parents visiting their children in neonatal care units may be considerable if travel to a hospital is entailed. McLoughlin et al showed that 88% of mothers visited their newborn baby daily and estimated that the median travel expenditure ranged between 101 and 200 GBP. Additionally, there are also other OOPE incurred to families, such as costs related to child care and babysitting for siblings, accommodation expenses during the neonatal hospital stay or lost earnings during this time. Referring to this, Tommiska et al calculated parental mean costs before initial discharge for extremely low birth weight infants (< 1000 g) at 2,755 EUR or 4% of total costs. Travel costs are the main cost category: Travelling induces 64% (1,763 EUR) of all expenses, 30% are earnings losses (827 EUR) and 6% (165 EUR) are payments for accommodation. Gennaro estimated that families spend 2% - 4% of their gross annual income on non-reimbursed out-of-pocket payments, attributable to their infants' condition. OOPE incurred by families of low birth weight infants average 433 USD during the initial hospitalization, with the largest part accounting for transportation (271 USD).

Costs after the neonatal period (longer term economic factors): Most relevant cost components after the neonatal period are expenses for re-hospitalization, outpatient visits, pharmaceuticals, medical aids and non-medical costs for education, travelling, accommodation, child care as well as indirect costs (mainly parental time and/or wage losses). Only few studies have analyzed the long-term economic burden of preterm birth following the initial discharge from the neonatal unit so far. Existing studies are varying with regard to methodological quality, sample size, study design and duration of follow-up.

As for the short-term costs, post-discharge resource utilization is inversely related with gestational age as well. The majority of costs accrue in the first year of life and costs for re-hospitalization are higher than outpatient costs. For example, McCormick et al and Stevenson et al both report that infants born preterm are more likely to incur hospital and other health services (like family practitioner services) during the first years of life than children born at full term and at normal birth weight. For the UK Petrou estimated that the adjusted number of hospital inpatient admissions, days and costs over the first 10 years of life was 1.3, 0.77, and 4.43 higher, respectively, for children born before the 28th week. The impact of low gestational age on hospital admissions applied mainly to the first two years of life as opposed to the subsequent period.

Most studies do not provide specific disaggregation of the sources of payment for costs incurred by preterm birth, however, some focus on post-discharge parental OOPE and lost productivity. In addition to direct resources consumed, there are also other long-term economic consequences for parents: As a result of additional healthcare contacts during the first years of life, there are remarkable direct non-medical expenses that become a burden on families. An important point are indirect costs: Parents who intended to return to work after the birth often have to reduce their working hours, postpone their return or miss working days to care for their child. Tommiska et al report parental wage losses of 5,990 EUR in extremely low birth weight infants (< 1,000 g) in the first year of life and 8,175 EUR in the second year - compared to only 880 EUR and 595 EUR for controls, respectively.

Travelling costs are estimated at 75 EUR in the first year and at 85 EUR in the second year (compared to 15 EUR in both years for controls). Additionally these authors also report higher OOPE in this group for home aid as well. McCormick et al have assessed travel costs at 180 USD per year and child care costs at 563 USD. Further substantial costs are special education expenses. Chaikind and Corman, for example, calculated that, compared to children who were of normal birth weight, infants who weighted less than 2,500 g at birth were almost 50% more likely to be enrolled in any type of special education than children who were of nor-mal weight at birth.

Health-related quality of life (HRQoL) is an individuals' subjective perception of health status on physical, emotional and social functioning. In pediatric patients this assessment must be seen in the context of the family and interacting influences. On the one hand, the health status of the child has an impact on QoL of the rest of the family, particularly on social and psychological domains. On the other hand, the family situation is influencing the children's well-being very strongly, because the child is dependent on his/her caregiv-ers.

QoL of parents: The birth of a premature infant is a critical event in the life of a mother and the rest of the family. A multiplicity of studies tried to describe some of the intangible costs associated with the birth and caring for pre-term and low birth weight children in later life. These studies suggest that the impact is often negative, because of the physical and emotional burden associated with physical illness and the process of caring for the child. Particu-larly the mothers of such infants are at greater risk of psychological distress than mothers of full-term infants.

Prenatal and perinatal phase: There have been a wide variety of studies on postpartum depression in mothers of infants born preterm. Depending on study design and included population, there are estimates of between 28% and 70% of preterm mothers as having clinically significant degrees of psychological distress. In a more recent study Davis et al. found that 40% of mothers of preterm infants (< 32 weeks) reported significant depressive symptoms on the Edinburgh Postpartum Depression Scale (EPDS) one month after the birth. This is higher than the population norms of 10% - 15%. Moreover, the estimated percentage is very similar to other studies which have indicated that mothers of premature infants are likely to experience significant depressive symptomatology while their infant is in a neonatal unit. During this time parents are negatively influenced by the stress and disappointment of the early birth, self-reproaches, the separation from their fragile child on a neonatal intensive care unit (NICU) with only limited opportunities to interact, the ongoing medical crisis and the possibility of death or continued health and developmental problems of their child.

Postnatal phase: In the long run (weeks, months and years later) there are also QoL impacts on family members as well: The need for caregivers to provide a high level of vigilance and to maintain this support over months or years may have significant consequences on their own QoL. This may result in maternal depression, self-reproaches, upheaval in the family routine leading to instabilities, marital stress, anxiety of losing the child, emotional and behavioral concerns of siblings, restricted social contacts or sometimes even the feeling of isolation.

QoL of infants: There are numerous studies looking at preterm children's HRQoL. As a rule, for preschool-aged children questionnaires such as TAPQOL or Peds-QL were completed by parents. These parent-proxy versions are used, because it can be assumed that children cannot understand the complex theoretical construct of HRQoL in this early age. Sometimes these parent-interviews are used in older ages as well, but normally in school-aged children, adolescents and young adults the HRQoL is self-reported. Most indicate that these persons born preterm are, on average, significantly less healthy (objective QoL) than their normal birth weight peers. They perform more poorly in respect of their physical, emotional and social functioning (eg having eating disorders, motor functioning, communicational skills or tend to have problems with anxiety). On the other hand the majority of interviewed children or adolescents born preterm do not perceive their own subjective HRQoL significantly different from peers at their age, whereas proxy reports of parents reported significantly poorer performance in their child's global health, behavior and physical functioning. Maybe this difference can be explained by an 'emotional' bias parents might have towards their experience and expectations for their children as well as coping mechanisms by the children over time. A further possible reason is that severe (or even mild or moderate) problems in early childhood are not

present to the children as they forgot them or were too young to memorize.

Discussion

Economic burden of preterm birth and low birth weight go far beyond the expenses e.g. a health care insurance has to cover as the birth of a preterm child may have an economic impact over many years also on other parties. In fact, this condition imposes a substantial financial burden on the families and caregivers of these infants and then growing children. Despite several studies already targeted costs covered by the insurance system, there is only limited information assessing OOPE, lost productivity and/or impact on QoL for caregivers.

Based on the results of the literature search, a recommendation scheme or a tool box for researchers when constructing a study design, is developed. It includes a set of four separate major categories to measure additional healthcare needs and further burden of disease from families' perspective. Each category is divided into several domains covering all relevant aspects of personal burden. For every domain some applicable contents are highlighted, but depending on the respective study design or perspective the selection of individual cost components might differ. Moreover this matrix is not restricted to the application to infants born preterm and/or at low birth weight. These recommendations could be applied to most neonatal diseases like congenital heart defect or RSV infections.

The following components should be considered: Hospital admissions or re-admissions, increased contacts to general practitioners and other healthcare providers or special requirements on care for everyday living are often connected with individual expenses or at least co-payments for the parents. These *direct medical costs* can be divided into outpatient and inpatient cost areas. In addition, *direct non-medical costs* may arise for additional transportation to the hospital and other therapies. Furthermore additional educational needs and care for siblings may have to be arranged. Usually these direct non-medical costs are the most important cost components regarding parental expenditures.

When developing a questionnaire, researchers should define the reported OOPE very precisely to avoid double counting or overlapping between cost categories (particularly between outpatient health care OOPE and other disease-related OOPE).

Moreover, parents or other caregivers may have to reduce other productive activities, such as paid work, in order to spend more time with their children. These lost earnings, missed working days and time losses by parents or other caregivers who are unable or less able to work represent *indirect costs*.

Other problems subsequently may arise through *intangible costs*, in terms of reduced QoL of parents. The instruments which can be used to evaluate caregivers' QoL or distress level can roughly be divided into instruments for the acute hospitalization period (regarding mainly feelings of the mother) and those for continued evaluation in later months or years for the whole family. Some examples for frequently used instruments in studies evaluating feelings of parents with preterm infants are:

Impact on parents during neonatal period (infants' hospitalization): *Parental Stressor Scale: Neonatal Intensive Care Unit (PSS:NICU)*. This questionnaire measures parental perception of stressors arising from the physical and psychosocial environment of the NICU due to alterations in the parental role, staff relationships, infant behavior and appearance, and unit sights and sounds. There is both an interview and a self-reported format available. The instrument has shown evidence of internal consistency, reliability, and validity. *Edinburgh Postpartum Depression Scale (EPDS):* This 10-item self-report scale is a well-validated and widely used screening tool for depression after birth of a child. The questionnaire focuses on the cognitive and affective features of depression rather than somatic symptoms. The EPDS is not diagnostic, but gives an estimate of psychological disturbance and alerts health care professionals that further assessment is required. The score is ranging from 0 to 30, whereas a cut-off level of 12 has been used in several studies to indicate probable depressive disorder. *Spielberger State-Trait Anxiety Inventory (STAI):* A self-report instrument designed to measure and to differentiate between anxiety as a state and a trait. It assesses overall stress reactions (state anxiety: 20 items) and personal stress traits (trait anxiety: 20 items). The measure has been used previously to assess parental anxiety with a child's hospitalization.

Impact on the family in following months and years: *Impact on Family Scale*: This scale measures the impact that a child's illness has on family function. Financial burden, familial/social impact, personal strains, and mastery abilities are assessed to subscales that can be summed to a total score as well. Reliability and validity in evaluations with premature or low birth weight infants are proven in former studies. *Family Adaptability and Cohesion Evaluation Scale II (FACES II):* This 30-item measure evaluates parental perceptions of family adaptability and cohesion. Higher scores on the adaptability subscale indicate higher flexibility, whereas higher scores on the cohesion subscale indicate better emotional family connection.

In addition to these generic scales without any disease-specific background, there is a recently developed questionnaire assessing the impact on parents of an infants' hospitalization for bronchiolitis. This disease usually affects infants of less than two years, particularly following preterm birth. The Impact of Bronchiolitis Hospitalization Questionnaire (IBHQ) contains 65 items, which were organized into 8 sections: parent emotional impact, infants' reactions, parent physical reactions, impact on daily organization, siblings' reactions, parent behavior with infant and siblings, impact on couple, and financial consequences. Of course, not every premature infant is hospitalized for bronchiolitis, but these dimensions might also be adequate to measure the impact on families in case of prematurity in general.

Besides the instruments regarding parental well-being, there are some studies assessing the QoL of preterm children as well. Depending on the age, there are several instruments questioning the child directly, whereas others prefer to use a parent as a proxy respondent. It is estimated that children can begin reporting more complex domains of their own HRQoL between the age of 4 and 6 years. In very young children and preschoolers, judgment about their own QoL is only possible by parent-proxy reporting. Although this is necessary, parental ratings are influenced by their own feelings towards and expectations for their children. For school-age children and adolescents instruments questioning directly should be preferred.

One frequently used proxy instrument is the 43-item TNO-AZL Preschool Children Quality of Life Questionnaire (TAPQOL) as a generic instrument for assessing HRQoL of preschool children age 1 to 5 years. It is consisting of 12 multi-item scales that cover the domains physical, social, cognitive, and emotional functioning. It is commonly used for research among preterm infants and after hospitalization for RSV. Other generic instruments regularly used are Pediatric Quality of Life Inventory (Peds-QL), Health Utility Index II (HUI2) or Child Health Questionnaire (CHQ). In later life the usage of more global generic instruments like EQ-5D or SF-36 is possible as well.

It is to emphasize that at least the direct medical and non-medical cost dimensions should be included in any health economic evaluation regarding neonatal problems. The additional consideration of indirect costs and QoL aspects allows an even more detailed and comprehensive view on the total burden from the families' perspective. Deviations may occur due to different views but should be justified with a detailed description of chosen study design. A more standardized assessment according to these suggestions would be an important step to a higher level of comparability of results from different countries. On the contrary, in particular OOPE are highly depended on legal framework. Parental payments may vary widely between different health care systems so that an unadjusted transfer of results is not appropriate.

Empirical studies always pose challenges with regard to recall bias and selection of the survey group. It is difficult to verify the reliability and validity of the responses. However, findings should be based on a large cohort of parents in a geographically defined area and include a comprehensive record of out-of-pocket payments as well as other fields. Reports should always be checked for face validity and internal logic. Ideally information on in- and outpatient visits, medication or aids should be confirmed directly with the health insurance or the physicians' office. On the contrary, reported OOPE, changes of income or QoL variations are difficult to verify. The identification of cost attributable to the preterm birth, in comparison to costs which would have been induced by a normal term birth as well, would be possible by the inclusion of a control group (infants born at term), especially considering that it is difficult for parents to separate these costs in an interview.

A preferable way to evaluate the economic and emotional burden of a preterm birth on the family is to ask combined closed- and open-ended-questions about medical and non-medical services not covered by their health plan and paid for by the parents (OOPE, co-payments, and deductibles). These information as well as missed working days, reduced income, lost time and especially subjective rating of own stress level or QoL are ideally assessed from the parents themselves.

Potential questions regarding the different cost dimensions should be tested with some adequate respondents to verify their completeness and relevance. In this pretest participants should be encouraged to give a detailed answer and to speak about their experiences. Thereby researchers' assumptions about the economic and social burden of disease are reassessed.

Ideally the questions would not be limited to the parents' own experiences so that burden on other persons concerned was evaluated as well. However, the integration of multiple caregivers could potentially lead to confusion, most notably if parents were asked to estimate OOPE or time spent by other volunteers (e.g. additional, non-paid childcare for other siblings). This is why the collected information should be restricted to burden on the main caregiver (usually parents), keeping in mind that this limitation could potentially underestimate total societal burden, because other persons affected are not included.

Generally, a questionnaire is only able to capture a limited period of time. To minimize negative effects, parental burden should be derived from very detailed and separated questions (eg travelling distances, medication, therapies etc). Parents are only able to give valid information on their own expenses for a limited de-fined period. For example, information on parental transportation and accommodation costs should be evaluated directly on the day of discharge or, even better, daily during the hospitalization. Long-term non-reimbursed costs of ongoing medical and non-medical needs provided by families, additional loss of income or an enduring feeling of stress and anxiety should be evaluated by separated and regularly repeated interviews. Primarily cost-calculations for later life would be very interesting; in the literature there is only scarce evidence as to whether costs remain higher in future life. A long-term longitudinal study, with parents surveyed periodically over several years, would be valuable to follow the development of preborn infants. Realizing this, there is a need for specific questionnaires representing different periods of life (infant vs. later childhood vs. adolescence). For example, educational costs or payments for therapies like logopedics are only relevant in later life and not in the first weeks.

It also should be discussed, what form of questionnaire is really adequate for the evaluation of complex and detailed economic burden, particularly if a QoL questionnaire for parents and/or children is included in the study. For measuring QoL or the long-term consequences with regard to a changed income situation, an evaluation only once a month or maybe just several times per year may be sufficient. Particularly QoL aspects should not be measured via internet, because most of the instruments are only validated for a written (or sometimes an oral) survey.

To address certain limitations and to gain a deeper insight into this topic additional research should be conducted in the future. Developed recommendations need to be discussed and tested: this includes research on the feasibility of included dimensions as well as validation of parent-reported information on burden. Moreover, the sample size of future studies or surveys should be big enough in order to yield several subgroups within the study sample. This could be combined with an international study incorporating more countries in the survey. It would be most interesting to explore whether there are diverging results in different health care systems and to explore the reasons and resulting incentives.

Future research should also try to identify cost-effective interventions which have the potential to prevent preterm births and reduce morbidity and mortality of infants and mothers once a preterm birth occurs. It is important that the economic impact (including parental OOPE, productivity losses as well as QoL impact of prematurity and connected diseases such as RSV on infants and their families) is recognized in future studies evaluating pre-, peri- and neonatal treatment strategies. To identify an efficient allocation of resources, data on incremental costs and health benefits attributable to particular interventions are needed. RSV infections could be chosen as an example

at this point, because they are a prevalent and more or less well investigated health problem associated with prematurity. They are a good example for an area where health economic evaluations already exist, but investigators frequently neglect to include the family perspective when calculating burden. With a full health economic evaluation, including total burden on families, it could be analyzed whether preventing or treating infections in the at-risk infants offers a cost-effective approach in order to reduce costs on society and parents.

Conclusions

In conclusion, this study has illustrated the large extent of burden on parents of a child born pre-term. There is a significant (economic) burden on the families besides the medical burden and further financial burden to the health insurance system. It was shown that preterm birth and low birth weight result in substantial OOPE and emotional distress to the parents. The largest part of parental burden occurs in the long run after infants are discharged from the neonatal unit. Nevertheless emotional stress is on a very high level during initial hospitalization and significantly increases with decreasing gestational age.

Economic evaluations are performed rather inhomogeneously in this field and seemingly were a rather neglected topic in recent years. Generalized recommendations including all important domains to measure financial and emotional burden on families have been developed. Further research should follow these methodological introductions to get a more detailed, comprehensive, standardized and comparable view from the families' perspective.

It is important that decision-makers, health-insurers and healthcare providers are aware of the total clinical, financial and emotional burden borne by parents at this critical time in the parent-child relationship. At this moment evidence is missing to convince decision makers of the seriousness of parents' perspective. The existence of comprehensive information on total costs to society (including parental burden) would help to make decisions on a broader basis. Considering different sources of expenditures and personal distress could lead to decisions targeted on a reduction of total societal burden and not on health insurance burden alone.

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by Neonatology Today. The article was provided to us by Michael D. Weiss and Mennen Medical.]

Oxygen Protocols Can Decrease the Rate of Retinopathy of Prematurity

Justin Tse, BS, RT-NPS, reports in the latest issue of Hamilton Medical's newsletter: Oxygen supplementation has long been used in the treatment of the premature newborn in the Neonatal Intensive Care Unit. Oxygen administration has many possible side effects. Constant monitoring is required to prevent hypoxia or hyperoxia. Two main problems associated with oxygen administration are potential lung injury and retinopathy of prematurity. There are 5 stages of ROP: 1. Stage I: There is mildly abnormal blood vessel growth. 2. Stage II: Blood vessel growth is moderately abnormal. 3. Stage III: Blood vessel growth is severely abnormal. 4. Stage IV: Blood vessel growth is severely abnormal and there is a partially detached retina. 5. Stage V: There is a total retinal detachment. A study in Pediatrics International* looked into an oxygen protocol and the incidence of ROP in infants of < 33 weeks gestation. The study included 137 patients and for the first part of the study collected data using the standard protocol in existence. The SpO_2 alarm limits were set at 92% and 98% for all infants. The second part of the study included a new protocol which the alarm limits were set at 88% and 92%. The staff was educated on the new protocol. The study reported a significant decrease in the threshold of incidence of ROP in patients < 33 weeks gestation. The results showed a decrease from 32.2% to 16.7% ($p< 0.05$). The authors also concluded that further observation should be conducted to confirm long term prognosis. Protocols are instituted in hospitals all over the world. Unfortunately, due to increasing workloads, decreased staffing and budget cuts, protocols are not always followed. A solution that is on the horizon is Closed loop FIO_2. Closed loop FIO_2 can help maintain normal oxygen saturation by continuously monitoring SpO_2 and titrating oxygen delivery to stay within the protocol. Automation of these functions may be the future of medicine. [*Reduced Oxygen Protocol decreases the incidence of threshold retinopathy of prematurity in infants of < 33 weeks gestation. Pediatrics International (2009) 51, 804-806. Reported by Justin Tse, BS, RRT-NPS, Clinical Support Specialist, Hamilton Medical, Inc.]

Effect of Osteopathic Manipulative Treatment on Gastrointestinal Function and Length of Stay of Preterm Infants

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Abstract

Background: Organizational improvement of neonatal intensive care units requires strict monitoring of preterm infants, including routine assessment of physiological functions of the gastrointestinal system and optimized procedures for the definition of appropriate discharge timing.

Methods: We conducted a prospective study on the effect of osteopathic manipulative treatment in a cohort of N=350 consecutive premature infants admitted to a neonatal intensive care unit without any major complication between 2005 and 2008. In addition to ordinary care, N=162 subjects received osteopathic treatment. Endpoints of the study were differences between study and control groups in terms of excessive length of stay and gastrointestinal symptoms, defined as the upper quartiles in the distribution of the overall population. Statistical analysis was based on crude and adjusted odds ratios from multivariate logistic regression.

Results: Baseline characteristics were evenly distributed across treated/control groups, except for the rate of infants unable to be oral fed at admission, significantly higher among those undergoing osteopathic care (p=.03). Osteopathic treatment was significantly associated with a reduced risk of an average daily occurrence of gut symptoms per subject above .44 (OR=0.45; 0.26-0.74). Gestational age lower or equal to 32 weeks, birth weight lower or equal to 1700 grams and no milk consumption at admission were associated with higher rates of length of stay in the unit of at least 28 days, while osteopathic treatment significantly reduced such risk (OR=0.22;0.09-0.51).

Conclusions: In a population of premature infants, osteopathic manipulative treatment showed to reduce a high occurrence of gastrointestinal symptoms and an excessive length of stay in the NICU. Randomized control studies are needed to generalize these results to a broad population of high risk newborns.

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Background

Significant improvements in neonatal technology utilized in neonatal intensive care units (NICUs) over the last two decades, along with evidence-based care guidelines, have significantly improved hospitalization and survival for both low birth weight (LBW) infants and the residual preterm population, albeit at a high cost. A major proportion of pediatric hospital stays in the United States is attributable to neonatal conditions that rank among the most expensive items in the list of services provided for children. The average cost per infant is highest for preterm newborns with gestational age (GA) between 24-31 weeks, and next highest for those between 32-36 weeks, as opposed to the general population. Costs per surviving infant generally decrease with increasing GA. In the United States, preterm/LBW infants account for half the hospitalization costs of all newborns and one quarter of overall pediatric costs. Length of stay (LOS) in NICUs is strongly associated with GA and birth weight. Infants delivered at the earliest GA have the longest hospital stays, partly because of the higher incidence of medical complications in very low birth weight (VLBW) infants. However, compared to term infants, premature infants are unique in their need to attain not only medical stability but also physiologic maturity, including adequate temperature control, cessation of apnea and bradycardia, and adequate feeding behavior, before they are safely discharged to home. Patterns of hospitalization of preterm infants are also associated with the presence of clinical

Table 1. General characteristics of the study population.

	Study Group	Control Group	p value
N	162 (46.3)	188 (53.7)	
Gender			
Females	81 (50.0)	89 (47.3)	
Males	81 (50.0)	99 (52.7)	0.70
Gestational Age			
≤32	39 (24.1)	43 (22.9)	
>32, ≤35	69 (42.6)	72 (38.3)	
>35	54 (33.3)	73 (38.8)	0.56
Weight (grams)			
At Birth			
≤1700	27 (16.7)	36 (19.2)	
>1700, ≤2200	62 (38.3)	63 (33.5)	
>2200	73 (45.0)	89 (47.3)	0.62
At Admission*	2148 (486.7)	2212 (562.3)	0.25
Oral feeding at admission			
No	129 (79.6)	129 (68.6)	
Yes	33 (20.4)	59 (31.4)	0.03

Numbers in Table are N (%), p values from Chi Square test
*=mean, (standard deviation); p value from t test

Table 2. Results for Average Daily Gut Symptoms: Crude and Adjusted Odds Ratios from Multivariate Logistic Regression

	Average Daily Gut Symptoms*		Univariate O.R.		Adjusted O.R	
	≤0.44	>0.44	O.R. (95%CI)	p> χ^2	O.R. (95%CI)	p> χ^2
N	262 (74.9)	88 (25.1)				
Gender						
Females [R.C]	129 (75.9)	41 (24.1)	1	-	1	-
Males	133 (73.9)	47 (26.1)	1.11 (0.68-1.80)	0.759	1.08 (0.65-1.79)	0.777
Gestational Age						
≤32	57 (69.5)	25 (30.5)	1.20 (0.65-2.21)	0.670	1.02 (0.43-2.40)	0.965
>32, ≤35	112 (79.4)	29 (20.6)	0.71 (0.40-1.25)	0.293	0.72 (0.39-1.32)	0.292
>35 [R.C]	93 (73.2)	34 (26.8)	1	-	1	-
Birth Weight (grams)						
≤1700	39 (67.2)	19 (32.8)	1.54 (0.80-2.96)	0.265	1.39 (0.55-3.46)	0.481
>1700, ≤2200	100 (76.9)	30 (23.1)	0.95 (0.55-1.63)	0.952	1.03 (0.55-1.93)	0.927
>2200 [R.C]	123 (75.9)	39 (24.1)	1	-	1	-
Oral feeding at admission						
No	192 (74.4)	66 (25.6)	1.09 (0.63-1.90)	0.860	1.18 (0.67-2.13)	0.583
Yes [R.C]	70 (76.1)	22 (23.9)	1	-	1	-
OMT						
No [R.C]	128 (68.1)	60 (31.9)	1	-	1	-
Yes	134 (82.7)	28 (17.3)	0.45 (0.27-0.74)	0.002	0.45 (0.26-0.74)	0.002

R.C.=Reference Category
* No. of episodes of Vomit, Regurgitation, Gastric residual and Enema

symptoms of abnormal gastrointestinal function. In particular, vomit and regurgitation were found to be associated with increased esophageal acid occurrence among NICU patients, as well as gastric residuals (GR), which can be linked to feeding behaviors and definitely improved by targeted feeding strategies. In VLBW infants, feeding tolerance algorithms are based on pre-prandial GR volume measurement. High pre-prandial volumes of GR are regarded as significant markers of feeding intolerance. Previous studies in NICUs show that neonates under stress have a higher incidence of stress-induced gastric mucosal damage. Functional constipation and hard stools are common conditions in both term and preterm infants, usually leading to changes in feeding formulas and use of enemas in specific settings.

Noninvasive treatments to improve feeding tolerance and to reduce clinical complications of premature infants may represent a convenient option in the absence of standard procedures for specific subgroups of patients. The present report describes the activity of a research team investigating the effects of Osteopathic Manipulative Treatment (OMT) in preterm infants, including monitoring of physiological functions of the gastrointestinal system and LOS.

Methods

Objective and endpoints of the study: To evaluate the efficacy of OMT on premature infants during hospitalization. Endpoints of the study were differences between study and control groups in terms of changes in gastrointestinal function and LOS. Primary endpoints were measured over the entire period of NICU hospitalization as follows: I. High frequency of gut symptoms, defined as the upper quartile of the average number of episodes of vomit, regurgitation, GR and enema per measurement visit per subject. II. Excess duration of LOS, defined as the upper quartile of LOS in NICU per subject.

Study Design and Population: The study was based on a non-randomized, longitudinal observational design investigating outcomes in a cohort of newborns admitted to the NICU of the main public hospital in Pescara, Abruzzo, Italy.

Eligible subjects included all infants consecutively admitted between January 2005 to June 2008 (N=663). A total of N=359 passed the following exclusion criteria: GA less than 29 weeks, or greater than 37 weeks; osteopathic treatment performed more than 14 days after birth; newborn transferred to/ from other hospital/unit; newborn from an HIV seropositive and/or drug addicted mother; newborn with any of the following clinical conditions: genetic disorders, congenital abnormalities, cardiovascular abnormalities, neurological disorders; proven or suspected necrotizing enterocolitis with or without gastrointestinal perforation; proven or suspected abdominal obstruction; pre- and/or post- surgery patients; pneumoperitoneum and/or atelectasis. Among the 304 subjects excluded, 232 infants had a GA below 29 or above 37, while 78 subjects presented with severe clinical conditions.

After enrollment, 4 additional infants were dropped because of an unrecorded birth weight, and 5 infants (2 from the study group; 3 from the control group) because of complications arising during hospitalization. The final total number of infants analyzed in this study was 350. A total of 188 preterm infants were non-randomly assigned to routine neonatal care; while 162 subjects received routine care plus OMT. All patients from both groups were transferred from the delivery and/or operating room to the NICU immediately after birth. No prior manipulation provided by any physical and/or massage therapist was performed on any infant.

Data collection: Data collection was performed by undergraduate osteopaths from the Accademia Italiana Osteopatia Tradizionale (AIOT). Measurements were recorded twice a week (Tuesdays and Fridays) based upon NICU's clinical charts completed by nursing staff who provided care on the same day. Additional infant information was included: date of birth, admission/discharge from NICU, GA at birth (based on best obstetrical estimate), birth weight at admission and discharge, formula and/or breast milk intake volume. Gastrointestinal function was measured as regurgitation (defined as the passage of refluxed gastric contents into the oral pharynx), or vomiting (defined as the expulsion of the refluxed gastric contents from

Table 3. Results for Length of Stay (LOS): Crude Odds Ratios (p value from Cochran Mantel Haenszel Chi Square Test of Zero Correlation) and Adjusted Odds Ratios from Multivariate Logistic Regression (p value from partial test on regression coefficient)

	LOS (days)		Univariate O.R.		Adjusted O.R.	
	<28	≥28	O.R. (95%CI)	p> $\|\chi^2$	O.R. (95%CI)	p> $\|\chi^2$
N	267 (76.3)	83 (23.7)				
Gender						
Females [R.C]	128 (75.3)	42 (24.7)	1	-	1	-
Males	139 (77.2)	41 (22.8)	0.90 (0.55-1.47)	0.765	1.40 (0.63-3.10)	0.412
Gestational Age						
≤32	21 (25.6)	61 (74.4)	38.10 (16.40-88.20)	<0.001	10.90 (3.53-33.72)	<0.001
>32, ≤35	128 (90.8)	13 (9.2)	1.33 (0.55-3.22)	0.680	0.76 (0.27-2.15)	0.609
>35 [R.C]	118 (92.9)	9 (7.1)	1	-		
Birth Weight (grams)						
≤1700	9 (15.5)	49 (84.5)	120.60 (42.70-340.60)	<0.001	43.23 (11.63-160.66)	<0.001
>1700, ≤2200	103 (79.2)	27 (20.8)	5.80 (2.40-13.80)	<0.001	3.01 (1.05-8.68)	0.041
>2200 [R.C]	155 (95.7)	7 (4.3)	1	-	1	-
Oral feeding at admission						
No	186 (72.1)	72 (27.9)	2.85 (1.44-5.66)	0.003	3.11 (1.05-9.25)	0.041
Yes [R.C]	81 (88.0)	11 (12.0)	1	-	1	-
OMT						
No [R.C]	133 (70.7)	55 (29.3)	1	-	1	-
Yes	134 (82.7)	28 (17.3)	0.51 (0.30-0.85)	0.012	0.22 (0.09-0.51)	<0.001

R.C.=Reference Category

the mouth, ie feeding tolerance), or GR finding (milky, bilious and bloody; measured only on infants with oro/naso-gastric tube, recorded as present/not present), frequency of stooling and enema administration per patient care encounter. A neurological/developmental evaluation at entry/discharge was not available for this study as it does not constitute part of routine assessment in the NICU. Data were directly entered on an Excel spreadsheet. Osteopathic treatment was administered to the intervention group on Tuesdays and Fridays. Subjects in the study arm received osteopathic care within 14 days after birth, regardless of the application of any other procedure (ie mechanical ventilation, blood transfusion or phototherapy). OMT was performed by a group of osteopaths certified by the Registro degli Osteopati d'Italia with at least five years of clinical experience. Treatment duration ranged between 20-30 minutes. The infant's entire body was evaluated and manipulative procedures were provided as indicated by the osteopathic palpatory structural examination results. Osteopaths performing OMT were trained to use only indirect and fluidic techniques which included: indirect myofascial, sutural spread, balanced membranous tension and balanced ligamentous tension.

Clinical procedures and discharge strategy: Feeding regimen, feeding strategies and enema administration were based on the application of standard international guidelines to both study arms. As distinct from UK/US hospitals, enema prescription used by the study NICU included 5% glucose glycerin enemas (10:1 mixture, 5mL/kg), administered twice a day, until infants spontaneously expel at least 1 stool per day.

Physiological conditions required for discharge included: maintenance of body heat at room temperature, coordinated sucking, swallowing, and breathing while feeding; sustained pattern of weight gain; and stability of cardiorespiratory function (no episodes of apnea/bradycardia for 2–5 days, free of supplemental oxygen support).

Statistical analysis: Main results are expressed in terms of odds ratios between each level of a potential risk factor and a set reference category (RC), with primary endpoints classified as binary outcomes (low/high). Potential confounders included the following characteristics (categories): gender, GA (≤32; >32-≤35;>35 weeks), birth weight (≤1700;>1700-≤2200;>2200 grams), oral feeding at admission (No/Yes). Univariate statistical tests included formal tests of the differences between study and control groups using chi-square for categorical variables and unpaired t-tests for continuous measurements. Multivariate logistic regression was used to estimate the independent effect of OMT on primary outcomes, simultaneously adjusting for all potential confounders. Statistical significance was based on a probability level (α) equal to 0.05. Results were expressed in terms of point estimates (odds ratios: OR) and 95% confidence intervals (C.I.). All analyses were performed using the statistical programming language R.

Results

No significant imbalances were found among treated and control groups in terms of main characteristics measured at admission, except for milk at admission (p=0.03), showing a higher percentage of infants unable to be oral fed at entry into this study among those treated with OMT. Upper quartiles led to the definition of the following thresholds for the outcomes of interest: 1) average daily occurrence of gut symptoms per subject above .44; 2) LOS of at least 28 days. None of the risk factors considered as potential correlates were found to be associated with an high rate of gut symptoms, except for OMT (OR=0.45;0.27-0.74). Multivariate logistic regression confirmed OMT to be independently associated with a 55% reduction of gastrointestinal symptoms (Adjusted OR=0.45;0.26-0.74). Univariate odds ratios showed the following categories to be associated with increased rates of LOS equal or above 28 days: GA ≤32 weeks (OR=38.10;16.40-88.20; R.C.:GA>35 weeks), birth weight ≤1700gm vs >2200gm (OR=120.60;42.70-340.60) and birth weight >1700gm, ≤2200gm (OR=5.80;2.40-13.80; R.C.: birth weight>2200gm), oral feeding at admission (OR=2.85;1.44-5.66) and OMT (OR=0.51;0.30-0.85). Multivariate logistic regression showed similar patterns, confirming an independent effect of OMT, simultaneously adjusted for all factors, corresponding to more than a 75% reduction in excessive LOS (Adjusted OR=0.22;0.09-0.51)

Discussion

The main objective of this exploratory study was to investigate the effects of OMT in a population of premature infants in terms of gastrointestinal functions and LOS. The medical literature lacks information of any potential benefits of complementary treatments in this area. To the best of the authors' knowledge, OMT in premature newborns has never been documented by pediatric specialty journals. Studies carried out in pediatric patients suggested positive effects of OMT in very young children. In the broader field of manual therapy, specialists of massage therapy and kinesthetic stimulation showed positive results in premature infants. However, such findings were inconsistent and obtained with heterogeneous methods, showing only minimal differences in terms of clinical significance.

The present study suggests that OMT may reduce the occurrence of frequent symptoms of abnormal gastrointestinal functionality. Precise mechanisms for such positive effects generated by OMT are difficult to specify, but several hypotheses can be offered on the basis of neurological, tissue and neuroendocrine factors.

In terms of neurology, there is evidence of an association between autonomic nervous system function and OMT, showing a significant direct relation between myofascial release technique and modifications in the autonomic nervous system activity. Regarding the interaction between OMT and tissue modification, in-vitro models highlight a possible decrease in the production of inflammatory factors.

A possible role of neuroendocrine factors can be hypothesized as indicated by the evidence of the effect of OMT on pain biomarker modification in patients affected by low back pain. This study also shows that a significantly higher rate of premature infants receiving osteopathic care can be discharged before 28 days regardless of gender, GA, birth weight and oral feeding at admission.

Such a result may have important implications for the optimization of health care in premature infants. Focusing on the percentage of patients discharged before a given threshold, rather than looking at the average reduction in LOS, may be very relevant for health optimization and cost control. Reducing the rate of long stays would reduce the number of patients in the NICU, allowing for more cribs to become simultaneously available for those infants who require specialized care. From an epidemiological point of view, the potential benefit may also spread beyond discharge, considering that hospitalization can influence nutrition and morbidity of gastrointestinal infections.

An understanding of the differential advantage of OMT on specific subgroups, in particular within specified classes of GA, will require ad hoc studies with an adequate sample size. In the present study, it was not possible to perform subgroups analyses on subjects with very low GA, due to the very limited number of patients available for enrollment.

Finally, some intrinsic limitations of the present study need to be outlined. This report is based on measurements implemented at the local NICU at the start of the study. Additional relevant confounding variables such as maternal/delivery factors (including breast feeding), respiratory support, method of feeding and gastric emptying time could not be included in this study. Treatment allocation was neither randomized nor structured, as it was based on matters of convenience within the constraints of the proposed two days per week of osteopathic care. Furthermore, due to the current logistics and procedures it was not possible to "blind" nurses and neonatologists to treatment regimen. This study, which was conducted in only one NICU, cannot capture the intrinsic variability of organizational strategies across multiple clinical centers managing the complexities of the overall population of newborn infants. From a methodological point of view, sample size was not based on formal power estimation, treatment was not allocated using a random procedure, and the population of preterm infants may not be representative of the entire population of cases. The above limitations affect our ability to check for bias and duly rely on the precision of our estimates. In other terms, both the size of the effect of OMT (point estimate) and its level of uncertainty (95% confidence interval) are more likely to be inconsistent with further results obtainable under more general conditions. To evaluate the efficacy of OMT more studies are required using formal experimental methods, such as randomized and placebo controlled clinical trials. The best endpoint of a well designed three armed study would be the difference between the sham and the actual treatment. However, to make it possible, osteopaths should collaborate with NICU managers to revise the application of operational procedures, so that OMT can be smoothly applied on large populations, across multiple clinical sites.

Despite the above limitations, and given the current lack of information on the possible effects of OMT in preterm infants, the finding of this report sets an interesting ground for new developments. Among these, the standard measurement of all relevant parameters represents an essential aspect that deserves attention for future investigations. Key characteristics and outcomes that can be easily monitored on a daily basis by clinicians, nurses and even parents of preterm infants have been identified. Their adoption for the construction of electronic data base registers can offer a sustainable means to improve both analysis and management of NICU activity, allowing to carry out more detailed exploratory studies while providing a basis for ongoing trials.

Conclusion

The study suggests that osteopathic treatment may reduce a high occurrence of gastrointestinal symptoms and the rates of long-term stays. Randomized control studies are needed to confirm these results and to generalize them to a broader population of high risk newborns.

Effect of Case Management on Neonatal Mortality Due to Sepsis and Pneumonia

Anita K.M. Zaidi, Hammad A. Ganatra, Sana Syed, Simon Cousens, Anne C.C. Lee, Robert Black, Zulfiqar A. Bhutta, Joy E. Lawn

Abstract

Background: Each year almost one million newborns die from infections, mostly in low-income countries. Timely case management would save many lives but the relative mortality effect of varying strategies is unknown. We have estimated the effect of providing oral, or injectable antibiotics at home or in first-level facilities, and of in-patient hospital care on neonatal mortality from pneumonia and sepsis for use in the Lives Saved Tool (LiST).

Methods: We conducted systematic searches of multiple databases to identify relevant studies with mortality data. Standardized abstraction tables were used and study quality assessed by adapted GRADE criteria. Meta-analyses were undertaken where appropriate. For interventions with biological plausibility but low quality evidence, a Delphi process was undertaken to estimate effectiveness.

Results: Searches of 2876 titles identified 7 studies. Among these, 4 evaluated oral antibiotics for neonatal pneumonia in non-randomized, concurrently controlled designs. Meta-analysis suggested reductions in all-cause neonatal mortality and neonatal pneumonia-specific mortality. Two studies evaluated community-based neonatal care packages including injectable antibiotics and reported mortality reductions of 44% and 34%, but the interpretation of these results is complicated by co-interventions. A third, clinic-based, study reported a case-fatality ratio of 3.3% among neonates treated with injectable antibiotics as outpatients. No studies were identified evaluating injectable antibiotics alone for neonatal pneumonia. Delphi consensus (median from 20 respondents) effects on sepsis-specific mortality were 30% reduction for oral antibiotics, 65% for injectable antibiotics and 75% for injectable antibiotics on pneumonia-specific mortality. No trials were identified assessing effect of hospital management for neonatal infections and Delphi consensus suggested 80%, and 90% reductions for sepsis and pneumonia-specific mortality respectively.

Conclusion: Oral antibiotics administered in the community are effective for neonatal pneumonia mortality reduction based on a meta-analysis, but expert opinion suggests much higher impact from injectable antibiotics in the community or primary care level and even higher for facility-based care. Despite feasibility and low cost, these interventions are not widely available in many low income countries.

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Background

Deaths occurring in the neonatal period each year account for 41% (3.6 million) of all deaths in children under 5 years. The majority of these deaths occur in low income countries and almost 1 million of these deaths are attributable to infectious causes including neonatal sepsis, meningitis and pneumonia. These deaths occur because of lack of preventive care (clean birth care, breastfeeding) and appropriate case management. Delays in treating neonatal infections of even a few hours may be fatal. Delays in illness recognition and care seeking, a dearth of primary health care providers, and limited access to facility care contribute to these deaths. Recent trials have demonstrated the effect of community-based packages for prevention and treatment of neonatal bacterial infections, with the potential to save many lives.

Therapy with appropriate antibiotics and supportive management in neonatal nurseries is the cornerstone of management of neonatal sepsis and pneumonia, with strong biological plausibility that such therapy saves lives. Yet the quality of evidence is understandably affected by the ethical impossibility of undertaking randomized trials of antibiotic management compared with no antibiotic management. Nevertheless, given the limited access to care for sick neonates in low income countries, it is important to assess the potential mortality effect of oral antibiotics and injectable antibiotics delivered in domiciliary or primary care settings. Case management for hospitalized neonates is more expensive, but to guide policy and program investments we also need to know how much more effective it is compared to care delivered at home or in primary care settings.

The objective of this review is to provide estimates of the effectiveness of three interventions in preventing neonatal deaths from severe infection: (i) case management with oral antibiotic therapy alone for pneumonia and sepsis; (ii) case management with injectable antibiotics (± oral antibiotics) as an outpatient or at home for neonatal sepsis /meningitis and pneumonia; and (iii) hospital-based case management, including

injectable antibiotics, intravenous fluids, oxygen therapy, second line injectable antibiotics if needed, and other supportive therapy (Table 1). These mortality effect estimates are used in the Lives Saved Tool (LiST) software, a user-friendly tool that estimates the number of lives saved by scaling up key interventions and helps in child survival planning in low income countries.

Methods

We searched all published literature as per CHERG systematic review guidelines.[7] Databases searched were PubMed, Cochrane Libraries and WHO regional databases from 1990 until April 2009 and included publications in any language (Figure 1). Search terms included various combinations of: sepsis, meningitis and pneumonia. For sepsis and pneumonia management at a hospital level we conducted two parallel searches. These were broader as we also wanted to identify studies reporting incidence and case fatality ratios (CFR) for a related study on global burden of neonatal sepsis. Titles and abstracts were reviewed and studies were included if data on one of the following outcomes was provided: all-cause mortality, sepsis/meningitis/pneumonia mortality and/or CFR. Furthermore, extensive efforts were made to contact investigators and program managers for unpublished data.

We reviewed all available observational studies, randomized controlled trials, systematic reviews, and meta-analyses, which included neonates and principally involved the management of serious neonatal infections. We examined studies published from 1990 until April 2009.

We included randomized controlled trials, studies with concurrent controls, and observational studies with no control group if mortality outcomes were reported. All studies meeting final inclusion criteria were double data abstracted into a standardized form. We abstracted key variables with regard to the study identifiers and context, study design and limitations, intervention specifics, and mortality outcomes. We assessed the quality of each of these studies using a standard table employing an adapted version of GRADE developed by the Child Health Epidemiology Reference Group (CHERG).[7] For studies which reported mortality outcomes that were not neonatal specific, we contacted the authors to request the neonatal-specific data.

During our review of selected studies we were unable to find a standard definition for clinical neonatal sepsis or pneumonia. Each study used different criteria although most are a variation on WHO IMCI approach. We therefore decided to accept authors' definitions of sepsis and pneumonia, recognizing that these non-specific definitions lower mortality outcome estimates as many "non-sepsis" cases are included in an effort to maximize sensitivity.

All studies reporting mortality data for pneumonia and sepsis management, in community and hospital settings, were summarized according to the overall quality of evidence for each outcome and each data input type using an adapted version of the GRADE 21 protocol table. When appropriate, we conducted meta-analyses to obtain pooled estimates of the risk ratios, using either the Mantel-Haenzsel or, when there was evidence of heterogeneity, the DerSimonian-Laird random effects estimator. 95% confidence intervals (CI) were also calculated.

For intervention-outcome combinations for which we did not identify moderate quality evidence, we sought expert consensus via the Delphi method. Individuals invited to participate were experts in newborn health and sepsis representing six WHO regions, and including multiple disciplines: international health, pediatric infectious diseases, clinical neonatology, and general pediatrics. Twenty experts agreed to participate in the Delphi process. The questionnaire was developed by JL, AZ, SC and SS, and refined after several rounds of pilot testing. The questionnaire was sent by email and included the background and aims of the Delphi and estimates of effect that were available from the literature for different scenarios. The median response and range were determined for each question. Consensus was defined a priori as an interquartile range in responses of not more than 30% for each question. For those estimates not reaching consensus, the plan was for results to be electronically distributed to the panel, virtual discussion allowed, and a second round of email questionnaires sent. However, consensus was achieved after one round of questionnaires and subsequent rounds were not necessary.

Results

Our systematic searches for community management of sepsis and pneumonia identified 2876 titles and after screening of titles, abstracts and relevant full texts, we located 7 studies of interest (reported in 8 papers). We identified 4 non-randomized concurrently controlled studies, which evaluated oral antibiotics for pneumonia. Three of these studies did not report disaggregated neonatal outcomes in the primary papers, but neonatal outcomes were available through abstracted forms from an earlier meta-analysis by Sazawal et al. For management of neonatal sepsis using injectable antibiotics, we located 3 studies (reported in 4 papers). There was one observational primary clinic-based study without a control group, one RCT and one non-randomized, concurrently controlled study. The fourth paper reported observational data from individual infants evaluated during the RCT mentioned above and was not a separate study. All the studies were from high neonatal mortality regions.

In our search for hospital-based studies of sepsis we found 55 studies from a total pool of 13998 studies which reported sepsis and/or meningitis mortality outcomes. For pneumonia, we found two studies from a total pool of 94 studies.

Unpublished neonatal data were obtained from the principal investigators of the four studies identified and a new meta-analysis was done to update that of Sazawal et al. We performed meta analyses for two outcomes: oral antibiotics were associated with reductions in both all-cause mortality and pneumonia-specific mortality. Limitations included non-randomization, estimation of intervention coverage as precise coverage estimates were not available; and variability between studies of the intensity of co-interventions. We found no studies of the effect of oral antibiotics on sepsis-specific mortality. The Delphi consensus (median) was for a 28% reduction in sepsis-specific mortality with an interquartile range of 20% to 36.25%.

Three studies reported in four papers, were identified. One, an RCT, evaluated the impact of a perinatal care package which included the administration of injectable antibiotics in domiciliary settings in situations where referral to hospital was not possible. This trial reported a reduction in all-cause neonatal mortality of 34%. A second paper from the same study reported that the CFR for neonates who were evaluated and actually treated with injectable antibiotics was 4.4%. A non-randomized, concurrently controlled study also evaluated the impact of a

home-based neonatal care package in which septic neonates were treated with injectable antibiotics when referral to hospital was not possible. The overall mortality reduction in the intervention arm of the trial was calculated to be 44%. A third, uncontrolled study based in a primary care clinic reported a CFR of 3.3% among septic children treated with injectable antibiotics.

In both of the community-based studies injectable antibiotics were only one component of comprehensive community-based newborn care packages, and therefore the effectiveness of injectable antibiotics alone in the community cannot be reliably estimated. The Delphi consensus for the effect of injectable antibiotics was for a 65% reduction in sepsis-specific mortality and 75% reduction in pneumonia-specific mortality in community-based settings.

We found no trials assessing the impact of hospital-based case management and the observational studies of hospital management showed wide variation in effect. Searches conducted for studies reporting CFRs in neonates with pneumonia in health facilities revealed very few data. Two studies were identified with author-defined neonatal pneumonia; both were from low income, non-industrialized settings and reported CFRs of 14.4% and 30.8%.

CFRs for neonatal sepsis, adjusted for the proportion of very low birth weight babies in the study, were plotted against national percentage skilled delivery, as a proxy for access to hospital-based case management of neonatal sepsis. In countries with a high proportion of births attended by skilled attendants, the predicted CFR for sepsis was 9.5%, whereas in countries with a low proportion (<30%) skilled birth attendance, the predicted CFR for sepsis with hospital care is 20-30%. A 68% reduction in the CFR for neonatal sepsis is predicted as one moves from 0% to100% skilled birth attendance. This reduction is likely to under estimate the effect of hospital-based case management since skilled birth attendance is likely to be a poor surrogate for effective facility case management of neonatal infections, but was used in the absence of coverage data for case management.

Although the quality of evidence is low according to GRADE criteria, the recommendation for case management of neonatal infections is strong, and this is standard practice globally. Therefore the Delphi process was used to provide estimates for the effect of hospital care. The Delphi consensus was for a 80% reduction in sepsis-specific mortality and a 90% reduction in pneumonia-specific mortality.

Discussion

Infections including sepsis, meningitis and pneumonia are responsible for almost a million neonatal deaths annually. Neonates are more susceptible to severe infections and the progression of disease is more rapid due to developmental immunodeficiency, resulting in high CFRs. Also, a significant proportion of infections may arise early, after vertical transmission from the mother.[73] Therefore, timely identification and appropriate management with antibiotics is an important strategy to reduce the burden of neonatal mortality due to infections. We have previously reported the evidence from observational and experimental studies in low income countries for community-based management of neonatal infections (pneumonia and sepsis) with oral and injectable antibiotics. We have now undertaken a systematic review of available evidence, including from industrialized countries and facility settings, and where the quality of evidence is low we have undertaken a Delphi expert process to estimate the cause-specific mortality effect.

This review of effectiveness of the interventions is shaped in large part by the needs of the LiST model. In that model, increasing coverage of an intervention results in a reduction in deaths due to one or more specific causes or in reduction of a risk factor. Therefore the reviews and the GRADE process used were designed to develop estimates of the effect of an intervention in reducing death due to specific causes.

To our knowledge, this is the first review providing effectiveness estimates for case management options to reduce neonatal deaths due to neonatal sepsis/meningitis and pneumonia, in both community and facility settings. Theodoratou et al have previously estimated effectiveness of pneumonia case management in children under 5 years but they did not disaggregate neonatal mortality data from later child mortality. The estimated effect of community case management on pneumonia mortality in children under 5 years of age in the analysis by Theodoratou et al is 70%. Oral antibiotics in community settings for neonatal pneumonia in our analysis were associated with a 42% reduction in pneumonia-specific mortality and a 25% reduction in all-cause neonatal mortality based on a meta-analysis of available trials. There is no evidence to estimate the effect of oral antibiotics on sepsis-specific mortality, but our Delphi process suggested a 28% reduction. Delphi-derived estimates for the effects of management using injectable antibiotics delivered in home or primary care settings came out at 65% for sepsis-specific mortality and 75% for pneumonia-specific mortality. These estimates are biologically plausible and consistent with published studies which reported reductions in all-cause neonatal mortality (sepsis plus other causes) of 34% and 44% respectively with community-based packages including injectable antibiotics. CFRs reported from observational studies of hospital case management varied widely, from 6.7 to 67%. Our Delphi estimates suggested an 80% mortality reduction in sepsis deaths and a 90% reduction in pneumonia deaths with hospital case management.

There were 4 effectiveness trials assessing the impact of oral antibiotics on pneumonia-specific mortality in the community. Only one of these studies was randomized and the programmatic coverage of the intervention had to be estimated as coverage data were not routinely assessed or reported. The selection and intensity of co-interventions was not uniform between the studies. An additional limitation was the lack of clearly defined cause-of-death definitions by the authors. However, the effect sizes were remarkably consistent with each other, and therefore the evidence level was upgraded to moderate.

GRADE guidelines rank the evidence relating to the effect of injectable antibiotics on sepsis-specific mortality as low quality. The 3 studies identified were not uniform with respect to study designs; one was an effectiveness RCT, one was a non-randomized concurrent trial and the third was an observational study describing the experience from primary care clinic without a control group. Both the RCT and the non-randomized concurrent trial, involved concurrent co-interventions alongside the administration of injectable antibiotics. This made it impossible to assess the impact of injectable antibiotics alone on sepsis mortality. Neither study reported the change in the sepsis-specific mortality rate in the intervention arm compared

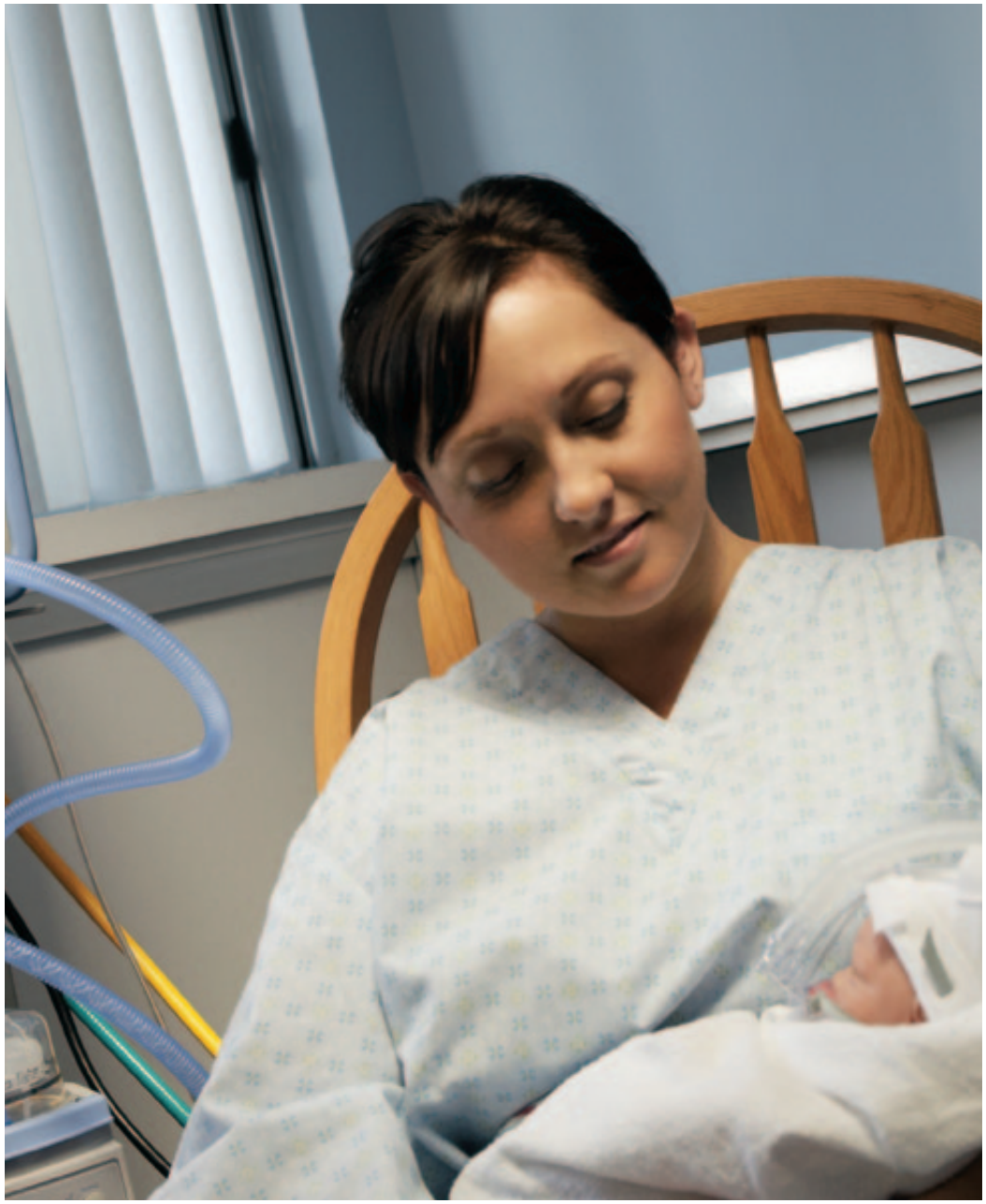
to control arm, and reported the impact on all-cause neonatal mortality only. The absence of randomization in one of the trials is a further limitation.[9] The main limitation to the observational study in a primary care clinic[13] was the absence of a control arm in the study.

We identified no controlled trials assessing the effect of hospital-based case management of neonatal infections. Such studies would be difficult or impossible to implement in an ethical fashion. Thus studies were limited to reporting CFRs for neonatal sepsis and meningitis. The studies were from varied settings, from both industrialized and low income countries, and reported widely varying CFRs. Only 2 of these observational studies reported CFRs for pneumonia. One of these studies reported a very high CFR for pneumonia due, we believe, to the high proportion of LBW babies in the sample (60%).

We found some moderate quality evidence for intervention packages including antibiotics in community settings but ironically data are most lacking at facility level, and district hospital level is a critical gap. Unlike the LiST review on neonatal resuscitation which identified several before-after studies of facility based neonatal resuscitation reporting mortality data, we were unable to find similar before-after studies on the effect of hospital-based case management of sepsis/meningitis/pneumonia. An understandable reason for this might be the ethical constraints precluding such studies. However, historical reviews from the pre-antibiotic era provide an insight into the CFR associated with untreated sepsis in facility settings. The best available evidence comes from the series of papers from Yale Medical Center reporting time trends for neonatal sepsis. These data show that in the 1920s and 1930s the CFR for blood culture confirmed sepsis stood at 90%. With the introduction of antibiotics, the CFR decreased to 45% by 1965, and with the subsequent introduction of intensive care units and advanced life support it came down to 16% by 1988 and 3% by 2003. Such data highlight the effectiveness of hospital-based management in preventing neonatal mortality from sepsis.

Conclusion

As evident from our results, even oral or injectable antibiotics alone are highly effective in reducing deaths from neonatal sepsis or pneumonia. These interventions hold great potential to reduce the 1 million neonatal deaths each year. If substantial reduction in neonatal mortality is desired, both, community and facility-based interventions are required, linked by functioning referral systems, giving the potential to prevent hundreds of thousands of avoidable newborn deaths every year.



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