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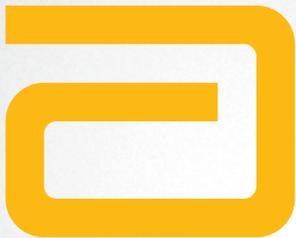
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References: 1. Carver JD, et al. *Pediatrics*. 2001;107:683-689. **2.** O'Connor DL, et al. *Pediatrics*. 2001;108:359-371. **3.** Groh-Wargo S, et al. *Pediatr Res*. 2005;57:712-718.

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Editorial

Fetal wound healing and stem cells

Boris Petrikovksy, Jeffrey Karsdon

Stem cells have varying potential: only those in the fertilized oocyte are totipotent. After 4 days these totipotent cells begin to specialize, forming a blastocyt and the inner wall mass (ICM). The ICM cells are considered to be pluripotent, able to differentiate into almost all cells that arise from the three germ layers (ecto- endo- and meso-derm). Most adult tissues have multipotential stem cells, cells capable of producing a limited range of differentiated cell lineages, eg small intestinal stem cells. We also recognize unipotenial stem cells, cells capable of generating one specific cell type. Examples include stem cells in the basal layer of the interfollicular epidermis that produces only keratinized stratified squamous epithelium.

When cells are continually being produced to replace worn-out cells, there is often a unidirectional flow of cells, with stem cells at the beginning of the flux. For example, in the epidermis, stem cells are at the lower end of the cell escalator in the basal layer, with cells being shed at the surface. Stem cells are a small percentage of the total cellularity. When studied in vitro, colonies formed of tightly packed undifferentiated cells are considered to represent stem cell colonies, named "holoclones" (fewer than 5% of the colonies formed by the cells of a holoclone abort and terminally differentiate),[1] first described for human epidermal cells.[2]

Stem cells are defined by their ability to produce more stem cells and cells that differentiate. Symmetrical stem cell divisions provide a mechanism to increase the stem cell population after cell loss. Extrinsic signals that govern asymmetrical cell division can emanate from the stem cell niche. All stem cells are thought to exist in specialized microenvironments known as niches. Well characterized stem cell niches include the bulge region of the hair follicles, where highly clonogenic multipotential stem cells are located, capable of forming all the cell lineages of the hair follicle and sebaceous gland.

The skin is lined by a stratified keratinizing squamous epithelium, the interfollicular epidermis. Normally, cell proliferation is confined to the basal layer of cells that make contact with the underlying basement membrane. In the hair follicle, the bulge region is clearly the stem cell niche.

The skin is the body's outer covering that keeps the inside of body moist and protects from outside assaults by physical, environment and biological factors. This waterproof skin barrier and its associated hair follicles and glandular structures, sebaceous and sweat glands, are formed by a stratified epithelium where the position of the cell in the tissue relates to its state of differentiation. By definition, adult stem cells have the ability to both self-renew and produce differentiated progeny. In healthy skin, epidermal stern cells divide infrequently but upon skin injury, stem cells rapidly divide to repair the wound. Although stem cells have the capacity to differentiate into all epidermal lineage in the skin, evidence suggests that the interfollicular epidermis, hair follicles, and glands are all maintained by their own, distinct, stem cell compartments. In addition to epidermal stem cells, other stem cell populations reside in the skin, including specialized groups of dermal cells found in the dermal sheath and dermal papilla. As the skin is an easily accessible organ, the regulation, maintenance, and differentiation potential of skin stem cells have been subjects of intense research in recent years.

Several approaches have been taken in the effort to identify epidermal stem cells. In vivo epidermal stem cells have been considered to be a population of slow-cycling, long-lived cells.

A number of strategies have been used to isolate bulge stem cells and compare the RNA profile of those cells to the surrounding "non-bulge" cells by array analysis. Less

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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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[1] Shah N et al. Anesthesiology, 2006; 105:A929. [2] Castillo A et al. Pediatric Academic Societies Annual Meeting. 2007. [3] Ash-Bernal R et al. Medicine. 2004. [4] Tsutumi T et al. Critical Care Medicine. 2006. [5] Baquero H, Alviz R, Castillo A, Neira F, Sola A. Acta Paediatrica . 2011.

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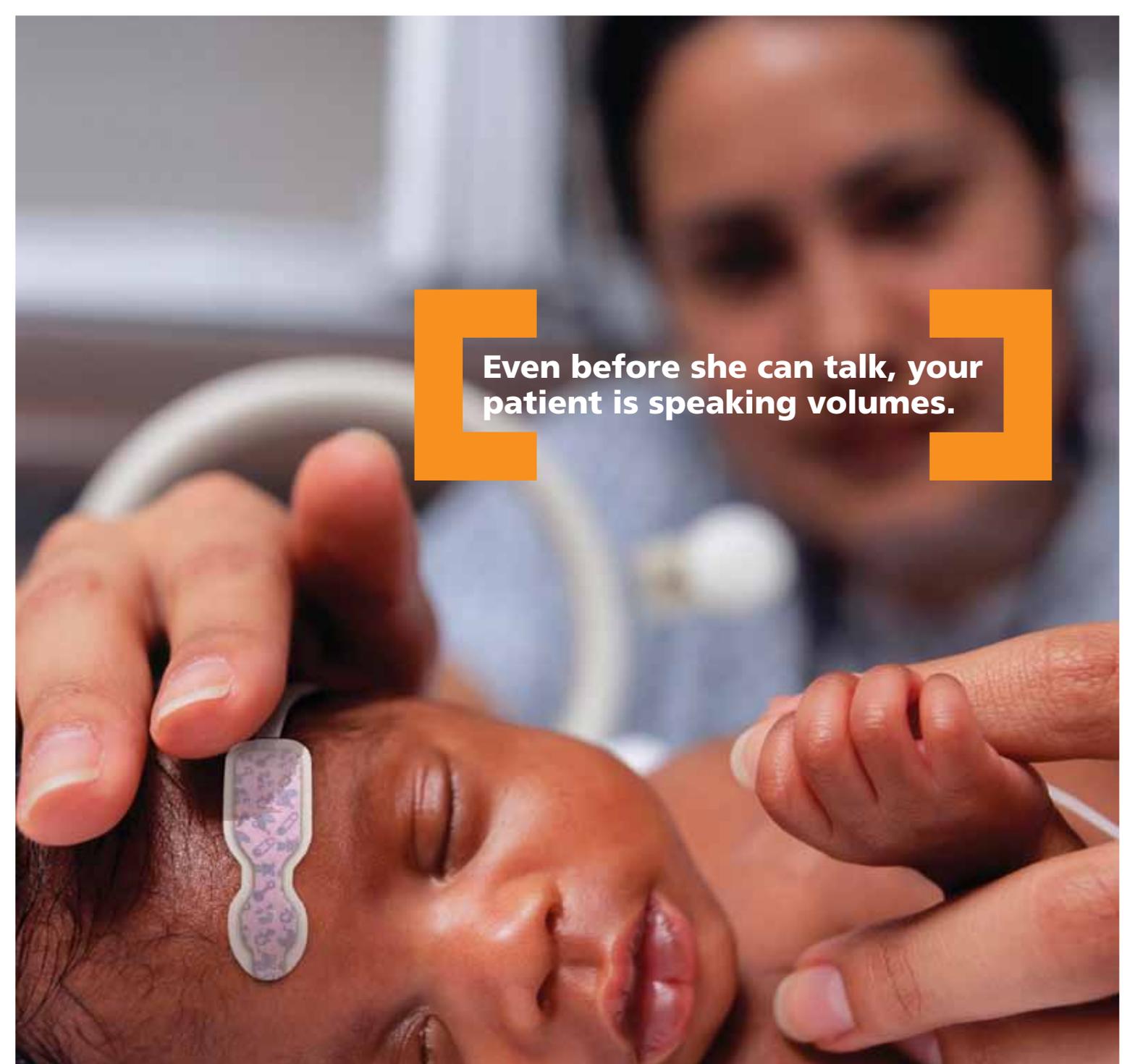
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News

NOT SHAKEN OR STIRRED

The University at Albany's Professional Development Program (PDP) has won a gold award from the US Distance Learning Association (USDLA) for an e-learning course on shaken baby syndrome developed for day care providers. The hour-long, fully narrated course, Preventing Shaken Baby Syndrome, emphasizes the message "never, ever shake a baby." Developed under contract to the New York State Office of Children and Family Services, the course is part of a growing suite of free e-learning courses created for day care providers. The USDLA award recognizes the course as a best practice in distance learning programming. Since 2000, PDP's training programs through the New York State Office of Children and Family Services have reached more than 2,800 individuals who protect the well-being of children, especially in day care facilities. PDP's work plays a vital role in the licensing, registration, and inspection of day care facilities. PDP is affiliated with UAlbany's Rockefeller College of Public Affairs and Policy.

WHY HOME BIRTH?

Susie Madrak reports on the website Crooks and Liars about why there's an increase in home births, and why CDC misses the obvious reason: Madrak says, "Some women are giving birth at home because they don't have health insurance and can't afford to pay cash up front for a delivery. That was true back in the 1970s, when I apprenticed as a lay midwife, and it's even more true now. There's no question that home delivery is much cheaper, and in low-risk births, just as safe when you have a qualified midwife. (For one thing, you don't pick up those antibiotic-resistant superbugs in your own home.) The medical restraints of hospital births can trigger a cascade of complications and interventions that might account for the US's disgraceful 32% C-section rate. The standard line is that American doctors are jumping the gun to avoid legal liabilities, but I think there's more to it than that: C-sections have become so commonly used that most medical students don't ever learn non-surgical alternatives to managing a complication, and thus don't know any other way to treat them… The other factor in choosing home delivery is that the quality of prenatal care is usually much higher, since midwives are famously reluctant to chance a high-risk home delivery. Consider the typical profit-driven ob-gyn 'assembly line' visit of 20 minutes or so. My visit with my lay midwife was more likely to last a couple of hours, including detailed questions about my protein intake, any unusual symptoms that might indicate nutritional deficiencies, blood pressure sitting and standing, and internal and external examinations. Midwives also recommend positions to encourage a breech baby to flip. (My midwife diagnosed twins in the last trimester that the ob-gyn had missed. Just sayin'!) So instead of moaning and wringing their hands as they've been doing for decades now, it might make more sense for ACOG to offer more affordable – and safe – alternatives to women." Reported by Crooks and Liars.

TAKING CARE

The Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) released a new publication, Perioperative Care of the Pregnant Woman. Based on the best available evidence, this resource describes how nurses and patient care facilities can provide safe care for pregnant women who require surgical procedures and for pregnant women who have cesarean births. Developed by a team of AWHONN nurse experts, Perioperative Care of the Pregnant Woman includes recommendations for: evidence-based practice and competencies for obstetrical (OB) and operating room (OR) nurses; interventions to promote family-centered care before, during and after surgery; assessment and care of women recovering from regional and general anesthesia; appropriate staffing levels to safely care for pregnant women requiring surgery; assessment and interventions for post-cesarean complications such as pulmonary embolus, wound infection and endometritis; care of high-risk patients, including special considerations for safe care of the obese pregnant woman; and patient safety measures unique to the OB/OR setting. Perioperative Care of the Pregnant Woman includes 2.1 continuing education contact hours and a Quick Care Guide, a handy bedside reference tool that summarizes key practice recommendations for nursing care. It is available for purchase on AWHONN's website.

UTERUS TO MY-TERUS

Agence France-Presse reported that the world's first mother-daughter uterus transplant could take place next year in Sweden. Doctors are investigating ten pairs of moms and daughters. One daughter under consideration was born without a uterus. She could receive a uterus from her 56-year-old mother, who said she no longer had any use for the organ and that it felt natural to do everything she could to help her daughter. Transplanting a womb from a woman to her daughter would be a world first, although a uterus transplant between two unrelated women took place in Saudi Arabia in 2002 when doctors transplanted the womb of a 46-year-old woman to a 26-year-old. Although blood clots forced the doctors to remove the transplanted organ after 14 weeks, they claimed technical success in the procedure. In 2007, scientists planned the first uterus transplant in the United States, but the procedure never went beyond the screening stage.

ANOTHER BIG BABY

California news media reported on the birth of a boy who weighed 14 pounds, 3.8 ounces when he was born in Salinas, CA. The infant's mother was in labor for two days before doctors at Natividad Medical Center performed a cesarean. The mother said, "They took him out and the doctor started saying 'damn,' so they put him on the scale," according to NBC. But the kid wasn't the biggest. The Guinness Book of World Records claims that in 1878, a Canadian mother birthed a son who weighed 23 pounds, 12 ounces. PS: As we went to press, an even bigger baby was born in Texas, at 16 pounds, and two feet tall. Mom said: "a lot of stuff we bought him is too little."

SUICIDE

JoNel Aleccia of MSNBC reported on the case of nurse Kimberly Hiatt, who gave too much medication to a baby, got fired, and killed herself. But there was more to the story than just the facts. The facts were that Hiatt, a 50-year-old RN at the Cardiac Intensive Care Unit of Seattle Children's Hospital, gave a baby 1.4 grams of calcium chloride instead of 140 milligrams. It was her first – and last – medical mistake. Doctors and nurses who make medical mistakes are often traumatized, Aleccia reports. Surgeons who thought they made medical mistakes were three times as likely

to consider suicide, based on a survey of 8,000 doctors. In Hiatt's case, she had cared for the infant, who had severe heart problems, since its birth, and was close to the family. There was some doubt as to whether the drug overdose killed the baby, since it was in such poor shape to begin with. In any event, Hiatt was escorted from the hospital right after her error, put on administrative leave, then fired. Since then, the hospital said, it has initiated a program that wouldn't automatically terminate a doctor or nurse for simple human error, and would also investigate systemic problems that might have contributed to the error. But Aleccia writes that there were other factors contributing to Hiatt's firing. A co-worker had previously filed a sexual harassment claim against Hiatt, who was a lesbian, alleging Hiatt acted inappropriately by hugging her and kissing her on the cheek. Hiatt denied there was anything sexual about the action, which she said was meant to comfort the co-worker during a tough time, and described the investigation as a "witch hunt." She said the Human Resources department had a history of discriminating against her because of her sexual orientation. Aleccia notes, "Records show that Hiatt was stunned to be terminated for what she believed was a single medical error in nearly a quarter-century of service. Investigation records reveal multiple glowing reviews. Just two weeks before [the infant's] overdose, an evaluation identified Hiatt as a 'leading performer,' earning a mark of 4 on a 5-point scale." Her error, though, attracted much media attention, and resulted in a state nursing commission investigation about whether Hiatt's license should be revoked. The agency fined her $3,000, and ordered 80 hours of coursework. Given the notoriety of her case, she thought she wouldn't be able to find any other jobs in the area. "Faced with the prospect of not working again as a nurse," Aleccia writes, "Hiatt was overcome with despair… Kimberly Hiatt hanged herself in her family's home… Nearly 500 people, including many nurses, attended her memorial ceremony a week later." A survey of Washington State Nurses Association members conducted after Hiatt's case became public found that half of the respondents believe their mistakes will be held against them personally. A third said they would hesitate to report an error or patient safety concern because they were afraid of retaliation or harsh discipline. As such, firing workers after they make mistakes actually leaves patients at greater risk, because those who make mistakes would be less likely to report them. According to a colleague who quit the hospital after seeing how Hiatt was treated, "I thought [Hiatt's dismissal] was sending the exact wrong message: If you make a mistake, you better keep your mouth shut about it." Reported by msnbc, © 2011 msnbc.com.

SUDDEN SIDS
The Vancouver Sun reported that there were more sudden infant deaths in British Columbia in the first half of 2011 than for all of 2010, according to the Ministry of Public Safety and the Coroners Service. Twenty-one sudden infant deaths occurred between January 1 and the end of June. In 2010, there were 16 such deaths for the whole year. In each of this year's cases, the infant was found unresponsive after having been placed to sleep at night or for a nap. Reported by the Vancouver Sun.

TO D OR NOT TO D
Marissa Cevallos writes, on HealthKey/For the Booster Shots blog, in the Los Angeles Times: A debate rages over how much vitamin D adults, children and pregnant women should consume for health benefits and disease prevention. Now research suggests that infants who are born with low levels of vitamin D may be

at higher risk for lung infections caused by a common virus. In a study published online in Pediatrics, researchers in the Netherlands assessed vitamin D levels in 156 babies at birth by measuring concentrations in their cord blood. After one year, 18 babies had developed a lower respiratory tract infection caused by a respiratory syncytial virus (RSV). These babies, researchers found, were more likely to have had lower levels of vitamin D. The researchers acknowledged that the relatively small number of babies – again, 18 – who became ill certainly limited the strength of their conclusions, and that the newborns with lower levels of vitamin D could have developed lung infections for other reasons. In an earlier study, newborns with low amounts of vitamin D were more likely to wheeze and develop respiratory infections than those with higher levels. The researchers said that, especially during pregnancy, doses up to 4000 IU per day may be needed to maintain optimal maternal and neonatal health. At the same time, the FDA has cautioned that giving babies too much vitamin D could lead to kidney disease.

TO D OR NOT, II
ACOG says there isn't enough good evidence to support routinely screening all pregnant women for vitamin D deficiency, and that most pregnant women can help ensure they're getting enough vitamin D through prenatal vitamins. Proponents of the vitamin have suggested that all pregnant women be screened for D deficiency, but the problem is that there's no consensus about what the optimal level of the vitamin should be during pregnancy, nor about the safe upper limit of supplemental doses. ACOG said only those pregnant women thought to be at increased risk for vitamin D deficiency should be tested.

OUTLIERS
The Arizona Republic, in an article by Richard Ruelas, reported that a Phoenix woman gave birth to a baby she had carried just outside her uterus, a feat so rare that doctors couldn't say for sure whether such a birth had ever occurred before. According to the newspaper, "Azelan Cruz Perfecto began the day in a precarious position, surrounded by a thin wall of membrane and muscle just outside the safety of his mother's womb. Doctors knew they needed to operate to get him out, fearing that if they waited too long, his protective bubble would burst. His mother, Nicollete Soto, 27, of Phoenix, had been advised by doctors that carrying the baby brought risk to both his life and hers, but she wanted to see the pregnancy through… Azelan Cruz was born at 32 weeks, weighed 2 pounds, 14 ounces… Doctors originally thought that Soto was carrying the baby in her abdomen, completely outside her uterus. They feared that even if the baby were delivered successfully, there would be grave risk for the mother. The placenta might have attached itself to a vital organ, making its removal tricky, if they could detach it at all. But after delivering the baby, doctors found that Soto didn't appear to have an abdominal pregnancy, as they thought. Instead, the embryo had attached itself to the area where the fallopian tube meets the uterus, or what is known as a cornual pregnancy. That area of the uterus is not supposed to stretch enough to accommodate a pregnancy, said one of the surgeons in the operating room. Pregnancies of that type usually end at the 12- to 14-week mark, with the tube rupturing… The placenta was not attached to a vital organ but instead was mostly attached to a uterine wall. Removing it was much simpler than the doctors expected. There had been a team of vascular, trauma, urology and radiology surgeons assembled for any possibility… The unusual pregnancy was not discovered until the couple qualified for the state's insurance plan for indigents. By then, the baby was 18 weeks along. The mother was hospitalized.

Doctors did not want to risk a rupture with her away from a hospital. Up until then, she was working a nine-hour daily shift at day care, lifting toddlers and toys. She needed no special medical intervention and didn't even lose much blood. The only unusual aspect of her surgery will be a larger-than-normal abdominal scar." (The above is from the Arizona Republic; it has been slightly edited.)

RESPONSIBILITY
Doug Farrago, MD, in Authentic Medicine Journal, writes: "'We need to stop paying fees for the process of treatment and instead reward the successful results of that treatment.' This is what the Director of Medicaid in Arkansas is saying. Recognize it? You should. It is parroted over and over again from every administrator in this country. It sounds great. Learn it. You will hear it a million times over and over again. Until one day the whole philosophy crumbles. Why? Because medical treatments do not exist in a vacuum. It is not that simple. It is not just putting in an equation and having a computer spit out the answer. Treat someone's diabetes too well and he has an hypoglycemic episode because he forgot to each lunch. He hits his head and gets a subdural hematoma. Or… over-aggressively treat a presumed pneumonia in a ER setting only to set off a bad case of C. Diff. Even better, concentrate on the 'successful' treatment of those measures for which you are being graded to the detriment of those you are not and that person commits suicide due to his or her severe case of depression. Read that top line again. You will hear this happy horse**** over and over again. It comes from those who are remoras living off the medical system. They never actually see or treat patients. They are not doctors (the few who were quit their regular jobs years ago). They are businessmen and politicians and administrators. The quickest and easiest way to save money in the healthcare system is to remove them. Here is that line again: 'We need to stop paying fees for the process of treatment and instead reward the successful results of that treatment.' How would this work, by the way, for the field of psychiatry? I rest my case." Authentic Medicine Journal was formerly Placebo Journal and can be found at placebojournal.com.

HARMFUL HERBICIDE
The Huffington Post reported that the world's most widely used herbicide, Roundup weedkiller, causes birth defects, specifically its active ingredient, glyphosate, but industry regulators have ignored this. A review released by Earth Open Source suggests that industry regulators in Europe have known for years that glyphosate, originally introduced by American agricultural biotechnology giant Monsanto in 1976, causes birth defects in the embryos of laboratory animals. Earth Open Source's study is the latest report to question the safety of glyphosate, which is the top-ranked herbicide used in the United States, according to the Huffington Post. The EPA says the agricultural market used 180 to 185 million pounds of glyphosate between 2006 and 2007, while the non-agricultural market used 8 to 11 million pounds between 2005 and 2007. Earth Open Source revealed that by 1993 the herbicide industry knew that visceral anomalies such as dilation of the heart could occur in rabbits at low and medium-sized doses. The report further suggests that since 2002, regulators with the European Commission have known that glyphosate causes developmental malformations in lab animals, but the commission's health and consumer division approved its use in Europe for the next 10 years. The European Commission decided late last year not to review information on the herbicide until 2015, and won't apply its new standards to it until 2030. The Commission told Huffington Post that it is sticking by its stand that the herbicide is safe. Earth

Open Source said that government approval of the ubiquitous herbicide has been rash and problematic, and that its examination of the evidence led it to conclude that approval of glyphosate and Roundup is flawed and unreliable. While Roundup has been associated with deformities in a host of laboratory animals, its impact on humans remains unclear. One laboratory study done in France in 2005 found that Roundup and glyphosate caused the death of human placental cells and abnormal embryonic cells. Another study, conducted in 2009, found that Roundup caused total cell death in human umbilical, embryonic and placental cells within 24 hours. HuffPost reports that authorities have criticized Monsanto in the past for soft-peddling the dangers of Roundup. In 1996 New York State's Attorney General sued Monsanto for describing Roundup as "environmentally friendly" and "safe as table salt." Monsanto agreed to stop using the terms for promotional purposes and paid New York state $250,000 to settle the suit. The EPA has requested that Monsanto submit human health and ecotoxicity data and said it will review information and data from independent researchers. Argentina has published a report: "Roundup and birth defects: Is the public being kept in the dark?" years after Argentine scientists and residents targeted glyphosate, arguing that it caused health problems and environmental damage. Argentine farmers used the weed-killer on genetically modified Roundup Ready soy, which covers half of the country's cultivated land area. In 2009 farmers sprayed fifty million acres with 200 million liters of glyphosate. Several years after the first big harvests, residents near where the soy cop grew began reporting high rates of birth defects and cancers, as well as the losses of crops and livestock as the herbicide spray drifted across the countryside. Another study found that glyphosate causes malformations in frog and chicken embryos at doses far lower than those used in agricultural spraying and that malformations

caused in frog and chicken embryos by Roundup and its active ingredient glyphosate were similar to human birth defects found in genetically modified soy-producing regions. Argentina hasn't publicized the research, and instead mounted a defense of Monsanto, but the Defense Ministry forbade the planting of genetically modified glyphosate-resistant soy on lands it rents to farmers, and a group of environmental lawyers petitioned the Supreme Court of Argentina to implement a national ban on the use of glyphosate, including Monsanto's Roundup product. The ban wasn't adopted. Meanwhile, in the US, researchers at Purdue University found that genetically-modified crops used in conjunction with Roundup contain a bacteria that may cause animal miscarriages. Genetically modified crops are now immune to Roundup, and farmers spray the herbicide liberally to kill weeds. One problem with any type of regulation is that the USDA oversees genetically modified crops, while the EPA watches herbicides, creating a potential regulatory loophole for products like Roundup, which relies on both agencies. Furthermore, the EPA is relying on agribusiness companies which manufacture the product to supply data about its safety and regulation. Major portions of the foregoing report are taken verbatim or edited from a report on the website Huffington Post, written by Lucia Graves.

CALLING ALL MIDWIVES

The United Nations reported that midwives are desperately needed to help preserve life in developing countries, saying an additional 112,000 midwives need to be deployed in 38 countries to meet their target to achieve 95% coverage of births by skilled attendants by 2015. Globally, 350,000 midwives are still lacking. The UN noted that up to 3.6 million deaths could be avoided each year in 58 developing countries if midwifery services are upgraded, and added that if midwives are in place and can refer the most

severe complications to specialized care, up to 90% of maternal deaths could be prevented. Each year, 358,000 women die while pregnant or giving birth, some two million newborns die within the first 24 hours of life and there are 2.6 million stillbirths. Among the 38 countries most desperately in need of midwives, the hardest up are Cameroon, Chad, Ethiopia, Guinea, Haiti, Niger, Sierra Leone, Somalia and Sudan. One success story is Mozambique, whose healthcare system was devastated after a 16-year civil war during which one in ten women died in childbirth. There were only 18 obstetricians for a population of 19 million. In 2004, Mozambique introduced a new initiative to train midwives in emergency obstetric care. These midwives now perform major surgeries including cesareans and hysterectomies. The country is on track to reduce its maternal death rate by 75% by 2015. This news item is based on information from an article by Sy Kraft in Medical News Today, copyright Medical News Today.

MOSTLY BREASTFED
The percentage of newborn babies in the UK who are breastfed has increased significantly since 2005, from 78% to 83% in England, 67% to 71% in Wales and 70% to 74% in Scotland. There was no change in Northern Ireland. The National Health Service also reported that the percentage of pregnant mom smokers dropped from 33% in 2005 to 26% in 2010. Last year, 54% of regular female smokers gave up during their pregnancy, compared to 48% in 2005. Twelve per cent of mothers smoked throughout their pregnancy in 2010, versus 17% in 2005. Young moms smoked more, at 57% of moms under 20. The above is from an article written by Christian Nordqvist, Medical News Today, copyright Medical News Today.

RIPE AIN'T NORMAL
Cervical ripening that instigates preterm labor is not the same as what happens at the onset of normal term labor, researchers at UT Southwestern Medical Center have found, challenging the premise that premature cervical ripening and remodeling is merely an accelerated version of the labor process, and that normal term ripening is caused primarily by activation of inflammatory responses. The researchers reported that premature cervical remodeling can occur by more than one mechanism and is not necessarily an acceleration of the physiologic process in term labor. The notion that in labor, white blood cells flow into the cervix and release enzymes that break down tissue support and remodel the cervix is only half-right, they said, and that the immune system or inflammatory response isn't necessary for reconfiguration of the cervix to prepare it for birth. UT Southwestern researchers compared preterm birth models in mice. They injected lipopolysaccharide (LPS) to promote infection-like conditions and an inflammatory response in one mouse model. They administered mifepristone (RU486) to simulate the withdrawal of the gestation-supporting hormone progesterone, which normally takes place at the end of a pregnancy. They reported that cervical changes in inflammation-induced conditions are caused by an influx of white blood cells and an increased expression of pro-inflammatory markers with no increase in the expression of genes induced in term ripening. Preterm ripening induced by progesterone withdrawal results from the combined activation of processes that occur during term ripening and shortly postpartum. These findings, at least if women are like mice, suggest that one therapy may not be effective for all preterm births, and that early identification of the cause of prematurity is necessary to determine the correct therapy.

FROM FETUS TO FAT
Researchers at Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center found that altering the levels of insulin and leptin in utero changes the cellular development in the region of the brain that regulates appetite. Altered levels of leptin or insulin may have marked effects on offspring brain development. The researchers said these findings provide further clues to the causes of obesity. The researchers found altering the levels of leptin caused neural stem cells from animal model to develop more neurons, while changing the levels of insulin promoted the creation of more astrocytes. Each process occurred at the expense of the development of other brain cells. Importantly, levels of leptin and insulin are altered in infants of mothers with gestational diabetes, obesity or inadequate nutrition during pregnancy. The new study builds on research which found nutritionally deprived newborns are programmed to eat more because they develop fewer neurons in the region of the brain that controls food intake. That study suggested overeating is programmed at the level of stem cells before birth if the mother has poor or inadequate nutrition. The present results suggest that additional infant and child brain functions may be altered or impaired under conditions of suboptimal pregnancy nutrition. Using an animal model, the researchers found less division and differentiation of the neural stem cells of a newborn with low birth weight as compared to normal birth weight.

ECG FOR ACIDOSIS
University of Granada researchers have shown that fetal ECG is the best method for detecting early acidosis and the risk of loss of fetal wellbeing. Researchers conducted a prospective randomized study with 180 women in labor and found that those monitored with fetal ECG and with recorded CTG compatible with risk of loss of fetal wellbeing, recorded a lower cesarean rate (30% vs 46.7%), obtained better fetal Apgar test results and better values in fetal umbilical cord gas analysis at birth than those recorded with pulse oximetry. They also observed greater real-time monitoring, adequate signal, fetal ECG providing more continuous information, thus helping the obstetrician to control the state of the fetus. The two methods, researchers said, operate at different levels of fetal physiology and therefore give some very precise data. Furthermore, fetal ECG was said to detect acidosis at an earlier stage.

NO INDUCEMENT NEEDED
Researchers at Herning Hospital in Denmark and the Danish Medical Birth Registry revealed that inducing labor in the weeks around term, or from week 39 to week 41, is not connected with higher rates of cesarean section compared with waiting for a later spontaneous or induced labor. They analyzed data from 230,528 women delivering between 2004 and 2009, a considerably larger population-base that previous studies. Overall induction rates were 15% and C-section rates were higher among the induced compared to spontaneous labors, but after adjustment for confounding factors such as age, parity, smoking and use of epidural analgesia and adjusting for each gestational week, the results showed that in induced women, induction of labor did not convey an increased risk of cesarean section when comparing outcomes in gestational weeks 39, 40 or 41, as compared to women who waited longer for a spontaneous or later induced labor. The study further confirmed that there is a higher cesarean rate among the more obese women (higher BMI) and with older age in both nulliparous and parous women. Researchers said their study showed that it's necessary to take gestational length into account when induction of labor and expectant management are being compared, but that the decision to induce labor around term seems not to be dependent on timing for success at term and

during the week before or after, when the end-point of emergency cesarean section is considered.

GET IT OUT!

More than half of the women in a survey by Ohio State University reported that they tried to induce labor near the end of their pregnancy by walking, having sex, eating spicy food or stimulating their nipples. Of the 201 women who responded to the survey, 102 used these or other methods to try to bring on labor. Other techniques they tried included exercise, laxative use, acupuncture, masturbation and herbal supplementation. Women who tried these techniques tended to be younger, having their first baby, and pregnant beyond 39 weeks. Most of the women said they received info about these methods to spur labor from their family and friends, and less than half asked their doctor if these methods were a good idea. The researchers noted that clinicians should probably be aware that their patients might be trying to take labor matters into their own hands, so to speak, and that these methods were unlikely to make any difference, though they admitted that the exact mechanism of labor initiation remains unknown, likely due to hormones produced by the fetus. So, hands off: the baby is in charge. FYI, the attempts at labor induction broke down as follows: 87 tried walking; 46, sex; 22 ate spicy food; 15 tried nipple stimulation, four exercised, five used a laxative, two got acupunctured, one masturbated, and one took an herbal supplement. Some women tried more than one method. Sex, some women believed, could ripen the cervix or lead to contractions while spicy food and laxatives, they believed, could cause intestinal activity that might give the kid in the uterus a budge. In this study, no one tried other methods reported in the literature, like starving or enemas, the former said to "make a hungry baby escape the womb in search of food." The one method that was said to have some possible effect was nipple stimulation, which leads to the release of oxytocin, which can cause contractions. As to the breakdown of where the women said they got their info, 26 said their doctor said so, six said a nurse did, and 11 said the Internet. The foregoing is from an article in Medical News Today, written by Emily Caldwell.

FORTIFIED FLOUR

Fortifying corn masa flour with B vitamin folic acid could prevent birth defects of the brain and spine in the Hispanic community, according to the March of Dimes. Such fortification of enriched cereal grains such as bread and pasta was mandated has been mandated by the FDA since 1998, and since then, the rate of NTDs, including spina bifida and anencephaly, has dropped by a third. Nonetheless, about 3,000 annual pregnancies in the US still are affected by NTDs, with Hispanics having the highest rate. Corn masa flour is made from specially treated corn and used to make products such as corn tortillas and tamales. Hispanic women are about 20% more likely to have a child with an NTD than non-Hispanic white women.

TROUBLE AHEAD

Preemies turn out less healthy, have more social and school struggles, and face great risk of heart problems in adulthood, according to a study at the University of Rhode Island. The foundation of the study is based on the fetal origins hypothesis, which says that the stress response of pre-term infants, the hypothalamic-pituitary adrenal (HPA) axis, is the mechanism underlying fetal origins of adult chronic diseases. Pre-term birth sets up a stress response, which produces higher levels of cortisol. The Rhode Island study compared cortisol levels in the adults who were born pre-term versus those born full-term and is assessing if cortisol levels among adults who were the sickest as premature infants are higher than those less medically and neurologically compromised. Preliminary findings indicate that male gender and birth weight affect early adult pulmonary function. The poorest pulmonary outcomes and higher resting blood pressure were for those born at extremely low birth weight. Data culled at age 17 revealed that physical health, growth, and subtle neurological outcomes were poorer in the preterm groups. Infants with medical and neurological impacts had a 24 to 32% increase in acute and chronic health conditions. The researchers also noted that the effects of preterm birth don't disappear after age 2, and that learning disabilities often don't appear until second grade and middle school. or even after preterm children catch up physically with full-term babies. Preterm infants with no medical conditions have more learning disabilities, struggles with mathematics and need more school services than full-term babies. Some pre-termers are less coordinated, which may be related to brain development and effects of neonatal intensive care. They have fewer friends and boys have more difficulty in school. On the plus side, preterm kids have a persistent drive to succeed, and moms of preemies often provide a strong push for nurturing academic, social and physical performance.

POOR CARE FOR SAD SACKS

Depressed pregnant women are likely to receive inconsistent treatment, said researchers at the Georgia Health Sciences University Education Discovery Institute. They tracked 20 healthcare providers in six Michigan clinics and revealed a lack of uniformity in addressing perinatal depression. Care providers said they had no guidelines on how to deal with depressed women, and that there was no system-level support. Researchers said this was likely why fewer than half of women who need special depression treatment don't get it. As such, the University's Education Discovery Institute is conducting a pilot project to develop and test tailored educational interventions in perinatal depression care, in hopes of quickly implementing the content into clinical practice. A related study discovered that depressed women had significantly longer-than-average hospital stays: more than 24 hours prior to delivery.

PRODUCTS

NOT THAT WE'RE COMPLAINING!

Researchers who are submitting poorly written papers to medical journals (not to us, of course!) can now make use of a professional proofreading service to ensure that academic and professional work is written in good English. The company says it will check the grammar and style of your work and return it to you to meet your requirements. The company notes: "If your research has too many English spelling and grammar errors, or if the publisher's style guide has not been followed, your research may be rejected without due regard to its content. We strongly suggest sending the document to us for editing and proofreading before submission, particularly if English is not your first language. We can provide you with a professional proofreading service at a very reasonable rate. All our proofreaders are highly qualified native English speakers. Many work as leading academics in their fields and all have extensive experience of proofreading to the highest standards. We are one of the largest proofreading and editing services worldwide for research documents covering all academic areas. If you are interested in our service, please take a look at our website. All you have to do is send us your document as a Word/LaTeX attachment with the deadline and we will guarantee

delivery of a perfectly written document to give you complete confidence when you submit your work. The fee is worked out on a flat rate (£7.49 per thousand words or 0.749 pence per word), so you know exactly how much the proofreading will cost in advance." Contact proof-reading-services.org.

NEONATAL CONFERENCE

Dräger will be offering a complimentary conference focusing on neonatal care on Monday, October 17, 2011 at the Radisson Hotel in King of Prussia, PA. The conference is open to nurses, respiratory therapists, and physicians throughout North America who are interested in neonatal care. Nationally known speakers from across the country will present topics focused on the pulmonary and cardiac care of the sick newborn. Conference faculty includes Dr Daphne DeMello of Phoenix Children's Hospital, Lisa Johnson, MS, RRT-NPS of SUNY Stony Brook Respiratory Care Program, Dr Donald Null of Primary Children's Hospital, Dr Lance Parton of Westchester Medical Center, Lori Ives-Baine of The Hospital for Sick Children, and Dr Thomas Shaffer of Temple University. The company recently released its dedicated infant ventilator, the Babylog VN500. Contact ww.draeger.com/neonatal-care-today.

REINTUBATION & SURFACTANT

Discovery Laboratories, Inc announced that the Journal of Neonatal-Perinatal Medicine recently published a manuscript reviewing an important data analysis from the Surfaxin (lucinactant) Phase 3 clinical trial program. The manuscript is entitled "Reintubation and risk of morbidity and mortality in preterm infants after surfactant replacement therapy" (Guardia et al, Volume 4, Number 2, 2011). This is the first peer-reviewed manuscript describing neonatal patient compromise following reintubation. The analysis demonstrates that, for preterm infants at risk for respiratory distress syndrome (RDS) who received prophylactic surfactant therapy and were extubated, subsequent reintubation is a highly predictive risk factor for mortality and major complications of prematurity. The analysis also indicates that infants treated with Surfaxin had a significantly lower incidence of subsequent reintubation and improved survival without reintubation, compared with infants who received animal-derived surfactants Survanta (beractant) and Curosurf (poractant alfa), the current standard of care. Infants who are extubated following surfactant therapy often relapse and require reintubation. Although increased mortality and morbidity in adults requiring reintubation is well described in medical literature, the consequences of reintubation in preterm infants have not been previously reported. Data from Discovery Labs' Phase 3 RDS clinical trials were assessed in a post-hoc analysis to evaluate the consequences of reintubation as well as the potential effect of surfactant choice on reintubation rates and subsequent clinical outcomes in preterm infants. The recently published manuscript highlights the following observations: Infants who were successfully extubated and did not require reintubation experienced low mortality rates across all treatment groups, while infants who were subsequently reintubated had a statistically significant higher mortality rate, 0.5% vs 18%, respectively (p<0.05). Infants who required reintubation had significantly higher rates of six major complications of prematurity, including BPD, necrotizing enterocolitis, sepsis, and intraventricular hemorrhage. Infants treated with Surfaxin demonstrated a significantly lower reintubation rate compared with those infants treated with animal-derived surfactants, Curosurf (33% vs 47% respectively; p<0.05) and Survanta (35% vs 43% respectively; p<0.05). Infants treated with Surfaxin demonstrated a significantly higher combined outcome of survival without reintubation compared with those infants treated with animal-derived surfactants, Curosurf (67% vs 53% respectively; p<0.05) and Survanta (65% vs 57% respectively; p<0.05). Surfaxin is an investigational drug product that has not been approved by the FDA or any other world health regulatory authority. Top-line data of this post-hoc analysis was previously presented at the 2008 AARC International Respiratory Congress. Contact www.discoverylabs.com.

THE FUTURE

Astodia, from Futuremed, is the latest innovation in neonatal transillumination. Designed specifically for the NICU/High-Risk Nursery environments, Astodia combines a slim handset with red and yellow LEDs for maximum target illumination. The nine-stage dimmer insures optimum brightness for various tissue densities and pigments, as well as different room lighting. Astodia is placed underneath the extremity, leaving the other hand free after setting appropriate LED color and illumination level. The device comes equipped with a four-foot cord for the illumination wand, so patients in layettes and isolation incubators of any depth are accessible. The one-handed operation means minimal patient movement. The control unit easily fits into a lab coat or scrub pocket for complete portability. Astodia is also ideal in helping diagnose hydroceles, pneumothorax, and hydroperitoneum. For further information on Astodia, contact Futuremed at (800) 222-6780 or futuremed.com.

LISTEN UP

The Maico MB11 newborn hearing screening system incorporates the latest technological advances based on years of research. Using fast rate ABR technology with a unique, CE chirp acoustic stimulus, MB11 stimulates an ABR that is almost two times larger than the response from a traditional click stimulus. This can translate into faster test times. MB11's "green technology" features an integrated, reusable earphone and electrodes, avoiding the exorbitantly high costs and medical waste associated with use of disposable electrodes and ear couplers. The cost for the supplies to perform an MB11 screening is approximately 25 cents compared to $9-$12/screening with competitive systems. Visit booth 226, at the NANN expo; contact maico-diagnostics.com.

BREATHE

MAQUET Cardiovascular announced the launch of its QUADROX-i Neonatal and Pediatric oxygenators and reservoirs in the United States. Oxygenators are an integral part of a cardiopulmonary bypass system and function as an artificial lung during surgical procedures. The company noted that these oxygenators and reservoirs provide new options for ensuring the best care for small children requiring cardiopulmonary bypass. The QUADROX-i Neonatal and Pediatric oxygenators and reservoirs enable selection of the appropriate-sized oxygenator and reservoirs for the smallest patients needing surgery for congenital heart disease by presenting new opportunities in circuit size reduction for patients who weigh from 2 to 30 kilograms, which may significantly reduce the need for blood transfusions in the operating room. The QUADROX-i Neonatal and Pediatric oxygenators offer significant improvements over currently comparable oxygenators. During open-heart surgery on neonatal and pediatric patients, the integrated arterial filter, low pressure drop and minimal priming volume of the MAQUET oxygenators contribute to improved quality of perfusion. Contact maquet.com.

SAFE AND CONTINUOUS

Aerogen of Galway, Ireland, has launched a new syringe and

tube-set that enables medical personnel to safely continuously nebulize a patient by completely eliminating the danger of tubing misconnections. Luer connector systems, common to many healthcare catheters, tubes, administration sets, extension sets, and syringes, have been at the heart of many catheter/tubing misconnections. The ease of connection between these luer lock connectors have led to misconnections that have inadvertently linked unrelated systems, and at times, have resulted in serious adverse events. Until now, this risk was inherent in continuous nebulization set-ups. Aerogen's new continuous nebulization tube set incorporates non-standard connectors that cannot be misconnected onto any other device being used with the patient. The new tube set is compliant with the European Harmonised Standard EN 13455-1 and with the FDA guidelines on prevention of tubing misconnections. Contact www.aerogen.com, or Tri-anim, Aerogen's US distributor.

PERFORMANCE

Kimberly-Clark Health Care and I-Flow Corporation (a Kimberly-Clark company) announced that they're winners of the sixth annual Performance Award presented by the Premier healthcare alliance. Premier has contracts with more than 800 suppliers, and Kimberly-Clark Health Care and I-Flow are two of only 38 contracted suppliers to receive the Performance Award. Winners are recognized for their outstanding management of Premier agreements and drive toward the mutual goal of providing clinical and financial value to Premier alliance members. Premier's Performance Award applauds the efforts of contracted suppliers to meet and exceed operational expectations. In selecting recipients, performance data is collected and scored over four successive calendar quarters. Owned by hospitals, health systems and other providers, Premier maintains a comprehensive repository of clinical, financial and outcomes information and operates a leading healthcare purchasing network. Contact kchealthcare.com.

CE RECEIVED

Siemens Healthcare Diagnostics has received CE marking outside the US for its Neonatal Total Bilirubin (nBili) test on the RAPIDPoint 405 Blood Gas Analyzer, with Version 3.7 Software. The nBili assay requires a small amount of blood— only 100 µL—and offers test results in about 60 seconds. With one small blood sample, a full range of analytes can be measured on the RAPIDPoint 405 system, including bilirubin, blood gases, electrolytes, glucose, total hemoglobin and other critical care parameters required to assess critically ill infants. Siemens Neonatal Total Bilirubin test on the RAPIDPoint 405 Blood Gas Analyzer is intended to measure the concentration of bilirubin in an infant's blood as an aid for assessing the risk for kernicterus in a point-of-care setting. The RAPIDPoint 405 offers a no-maintenance, cartridge-based solution for critical care testing. Contact siemens.com/bgbilirubin.

SPOTLIGHT ON VENTILATION

NONINVASIVE

Hamilton Medical has announced the availability of neonatal capability and capnography on the Hamilton C2 Ventilator system, which now offers nasal non-invasive ventilation of neonates with nCPAP-PS. Nasal CPAP effectively supports the breathing patterns of preterm infants. Synchronized nasal intermittent positive pressure ventilation results in decreased work of breathing, stabilizes the chest wall and reduces asynchronous motion

between the chest and abdomen and improves tidal volumes and minute ventilation. Hamilton offers the full range of accessories and consumables for successful nCPAP-PS therapy. Contact hamilton-medical.com.

INSPIRATIONAL

eVent Medical's Inspiration neonatal to adult ventilators are versatile, high performance ventilators designed with the clinician in mind. The patented Swiss pneumatic design allows high performance PSOL valves to provide outstanding breath delivery. Users find exceptional value in the straightforward interface, ease of transport, comprehensive monitoring and simple preventive maintenance. Practical advantages include standard battery, emergency backup compressor, integral nebulizer, Heliox and extreme ease of use. A unique capability within the Inspiration line is the ability to use eVent's CliniNet and CliniNet Virtual Report viewing system to bring centralized, real-time data and patient management to the entire care team. Contact event-medical.com.

VERSATILE

The original Infant Flow nCPAP from CareFusion has been shown to provide gentle and noninvasive method of breathing support, which works for, and with, the respiratory compromised infant. The Infant Flow SiPAP system is a product evolution that offers a comprehensive selection of modalities including CPAP, Biphasic, and Biphasic tr. This selection, combined with the patented fluidic flip generator technology designed specifically for infants, provides a complete solution for noninvasive ventilatory support. The AVEA ventilator system from CareFusion is a versatile critical care ventilator for neonatal, pediatric and adult patients featuring both invasive and non-invasive applications, including infant nasal CPAP. The 3100A High Frequency Oscillatory Ventilator (HFOV) from CareFusion is the only high frequency oscillatory ventilator approved in the United States for early intervention in the treatment of neonatal respiratory failure. Contact carefusion.com.

COMPANY PROFILE

Advanced Instruments, Inc

Describe your neonatal/perinatal products and their features.

Advanced Instruments, Inc is a leading supplier of instrumentation for clinical, pharmaceutical, biotechnology, microbiology and food laboratories around the world. Quality, reliability, service and support have been the company's guiding principles since our founding in 1955. Advanced Instruments continues to be the world's foremost authority for the application of osmometry utilizing freezing-point depression technology. Advanced Instruments invites you to learn more about the **Advanced Model 3320 Osmometer**. Place it in the NICU or dietary department to rapidly monitor the osmolality of feeding solutions including infant formula, human milk, and additives such as fortifiers, vitamins, minerals or pharmaceutical medications. The 3320 eliminates the risk associated with hyperosmolar feedings by providing quantitative results that infant feed mixtures are below the 450 mOsm/kg safety threshold recommended by the AAP. 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 uncertainty, many NICUs have adopted the use of osmometry as a quality control tool to avoid the incidences of hyperosmolar feedings and improve patient safety.

The 3320 is very easy to operate and requires very little training. The sample size requirement is only 20µl and the total test time is less than a minute, making the 3320 an ideal screening tool for the NICU or infant nutrition feeding station. We encourage you to learn more about our products and services and to request our latest Technical Whitepaper "Practical Application of Osmometry in the Neonatal Intensive Care Setting." Let us work with you to determine the ideal solution for your NICU.

Discuss your technical support and services.
Advanced Instruments Hot-Line Service and worldwide distributor network provide comprehensive customer service and technical support. Advanced Instruments products are available from a worldwide distributor network. For more information on our products and services or to find your nearest distributor, visit us at aicompanies.com or e-mail us at info@aicompanies.com.

NANN PREVIEW

Acacia Neonatal
Booth 215

What products do you plan to exhibit?
• NuTrio Enteral Feeding System including: NuTrio Syringes, NuTrio GraviFeed, NuTrio Extension Sets, NuTrio Feeding Tubes, NuTrio Pump
• MedSafe and Multi Access Sets
• ClosedCare IV System
• NICU Specialty Tubing
• SafeSample Blood Gas Sampling Set

What's new this year? What R&D advances will you be presenting?
• NuTrio Enteral Pump
• NuTrio Enteral Syringes
• NuTrio Enteral Combo Syringes

What educational or training materials will be available?
Literature, catalogs, DFUs and visual techniques.

Tell us about any speakers or in-booth promotions.
• Sandy Beauman – Poster presentation
• Promotions – I-pad and Starbucks card giveaway

Why should our readers stop by your display?
Acacia Neonatal prides itself on being an innovation leader. Keeping with this principle we are introducing three new breakthrough products at the 2011 NANN Conference. On display in our booth will be the NuTrio Enteral Pump, the first and only non-electrical enteral only pump on the market. Also at this year's show we will be unveiling the NuTrio Combo Syringe, the most flexible syringe available today with the ability to meet a number of needs all with a single syringe including pump feeding, gravity feeding and venting. The NuTrio Enteral only syringe, a single piece design offering the highest level of enteral safety, will be on display as well. Contact www.AcaciaNeonatal.com.

Baxa Corporation
Booth 209

A leading provider of devices and systems for the preparation, handling, packaging and administration of liquid medications, Baxa Corporation will be displaying the NeoThrive Enteral Feeding System at the upcoming National Association of Neonatal Nurses 27th Annual Educational Conference in Orlando, FL. This complete system includes both the NeoThrive Enteral Feeding Pump and the NeoThrive Enteral Syringe. Together they eliminate any potential cross-use between common IV pumps and the syringes and tubes designed specifically for enteral feeding. Visit Baxa Corporation in Booth 209 at NANN or online at www.baxa.com/neothrive for more information.

CareFusion
Booth 119

What products do you plan to exhibit?
This year, CareFusion will be showcasing Pyxis Infant Care Verification, a solution that identifies and tracks breast milk in the hospital setting to help increase positive patient identification. A versatile platform that seamlessly combines patient identification and tracking, this application matches and verifies the patient with the designated breast milk using a mother/infant match functionality. By identifying mother to infant and infant to breast milk/supplemental nutrition, Pyxis Infant Care Verification helps reduce the risk of infection transmission and mislabeling. This easy-to-use, handheld tool adds an extra layer of verification in the NICU/PICU, giving providers and families peace of mind.

What's new this year? What R&D advances will you be presenting?
Pyxis Infant Care Verification offers many advanced features to help hospitals safeguard newborns through positive patient and breast milk identification. One new feature we'll be presenting is Discharge Inventory, which matches the correct milk to the correct family at the time of discharge.* We'll also be highlighting the new Audit Trail report, which allows facilities to see all Pyxis Infant Care Verification user activity, including when users make errors, to support training opportunities in near real-time.* [*This product is currently in Limited Release. The company may not make this unreleased product available for commercial sale.]

Why should our readers stop by your display?
Stop by the CareFusion booth to learn how Pyxis Infant Care Verification can help caregivers help prevent errors related to breast milk administration. In the life of an NICU patient, there are many obstacles. NICU staff does everything within their power to protect their patients from harm. Most hospitals have systems implemented that provide protection from medication errors, laboratory mistakes and more. There remains one less protected area that is unique to the NICU—breast milk administration—that can leave the door wide open for neonatal exposure to life-threatening bacteria and viruses. A mother's breast milk offers vital nutrients and immunological aid to a preemie. However, it also has the potential to carry Cytomegalovirus (CMV), group B streptococcus (GBS) and HIV, among other pathogens. The administration of the wrong mother's milk to a patient can introduce these bacteria and viruses to a body that has a very immature immune system. These pathogens are life threatening to an adult with a strong immune system; for an infant with an underdeveloped, susceptible immune system, these diseases can be fatal. Therefore it is vital to ensure that NICU patients receive the correct breast milk to reduce the risk of dangerous bacterial and viral exposure. Pyxis Infant Care Verification helps hospitals address this concern by:

- Managing breast milk inventory, donor milk tracking and expiration date tracking
- Helping eliminate breast milk administration errors
- Helping reduce infection transmission
- Helping complete combined inventory for multiple infants from one mother and fortification by recipe
- Safeguard newborns with Check to Family/Check to Care feature
- Capturing real time wireless data at the point of care
- Helping support Joint Commission patient confirmation standards

CSZ Medical
Booth 229

What products do you plan to exhibit?
We plan on exhibiting our Blanketrol III (Hyper-Hypothermia device), our Kool-Kit Neonate (for infant whole body cooling and re-warming) and our Gelli-Roll (Hyper-Hypothermia blanket with the comfort of Akton polymer).

What educational or training materials will be available?
We will have a clinical staff available to those who have questions and would like more information.

Why should our readers stop by your display?
We will be giving away CSZ stuffed penguins to those who stop by our booth and want to learn about our products.

Cornerstone Therapeutics
Booth 308

What products do you plan to exhibit?
CUROSURF (poracant alfa) Intratracheal Suspension.

What educational or training materials will be available?
Publications, printed User's Guides, administration video.

Tell us about any in-booth promotions.
For each visitor to the booth, Cornerstone will donate $10 to the March of Dimes.

Why should our readers stop by your display?
Learn about the data and advances in the use of surfactant for the treatment of RDS in premature infants.

Dräger
Booth 319

What products do you plan to exhibit?
At Dräger, we believe technology for the NICU should be perfectly suited for enabling NICU clinicians to deliver care that is life-sustaining, non-invasive, and supportive of developmental care. Technology should provide a quiet and serene environment to promote growth and brain development. Dräger provides a wide range of products and accessories specifically designed for the neonate. A fine balance must be built that maintains a warm, humidified, constant environment for the neonate, while providing access and visualization for care provider. We encourage all clinicians to come to booth 319 to see how we accomplish this.

What's new this year? What R&D advances will you be presenting?
Technological support does not end with the infant. Dräger greatly values the role of the clinician and to support you in your day to day work we have tools and references at your finger tips. Heat Balance is a stimulation application that is a dynamic program that lets you change environmental conditions for an infant using the parameters you want, not what a chart tells you.

What educational or training materials will be available?
Babyfirst.com brings lectures from around the world on the hot topics of neonatal care, wherever and whenever you want them. Knowing that continuing education credit time is a vital part of your career, we are also offering access to over 9 hours of approved (ANCC) credit hours for nurses and 6 hours (AARC) for respiratory therapists.

Kentec Medical, Inc
Ameritus Medical Products
Booth 425

What products do you plan to exhibit?
Kentec Medical will be exhibiting its own Ameritus branded products including the complete Ameritus Safety Enteral Feeding System composed of safety enteral feeding tubes, extension sets, syringes and a milk straw. ECG Neonatal electrodes as well as temperature probes and temperature probe covers will also be on display. Ameritus also offers Pediatric, Infant and Neonatal Limb-Boards in two styles. In addition to the Ameritus brand, Kentec distributes a wide range of neonatal products on behalf of its manufacture partners; from PICC lines and introducers, customer oral care kits, and radiation collimation shields, to Preemie Pouch ostomy products and hi-flow nasal cannulas.

What's new this year? What R&D advances will you be presenting?
The new Ameritus products include a complete Safety Enteral Feeding System. Within the last year, Ameritus has launched a brand new feeding tube with its own unique connector design. Ameritus also launched its own one piece enteral syringe with an orange plunger and self-righting cap.

What educational or training materials will be available?
Copies of our various brochures, literature pieces and pamphlets will be available in our booth.

Tell us about any speakers or in-booth promotions.
Stop by and talk to us. We'll enter you in our drawing for a special prize on the last day of the show. Please visit our booth for detailed information.

Why should our readers stop by your display?
Readers should stop by our display to check out our newly launched products and enter into our raffle drawing.

MAQUET
Booth 105

What products do you plan to exhibit?
We will be exhibiting the SERVO-i ventilator with NAVA and NIV NAVA. MAQUET will also be showing its new portfolio of non-invasive ventilation interfaces for infants and neonates.

What's new this year?
New from MAQUET this year is the possibility of using NAVA (Neurally Adjusted Ventilatory Assist) in non-invasive ventilation.

What R&D advances will you be presenting?
MAQUET will be showing non-invasive NAVA (NIV NAVA). NIV NAVA provides assist levels capable of matching patients' neural demands regardless of leakage or user interface.

What educational or training materials will be available?
MAQUET is offering an extensive portfolio of educational materials. For SERVO-i with NAVA, MAQUET has launched web-based training that can be accessed through www. criticalcarenews.com.

Why should our readers stop by your display?
MAQUET's NAVA technology and monitoring of the activity of the diaphragm is one of the most interesting new technologies available for neonatal ventilation today. The SERVO-i ventilator is one of the most versatile ventilators available in the US today, offering the standard modes of ventilation, Heliox, NAVA, non-invasive ventilation, as well as transportability. The SERVO-i can be used conditionally in the MR environment allowing ICU standard ventilation for all patients throughout the hospital.

Medela
Booth 411

Medela's comprehensive system of evidence-based products, services and education – helping you get more human milk to your patients from hospital to home: In the Neonatal Intensive Care Unit the need for the protective benefits of human milk is perhaps more evident than anywhere else. Human milk is considered to be a crucial medication to help premature infants grow and protect them from serious complications. Medela's system of innovative, evidence-based products, services and education helps you deliver more milk to your vulnerable patients every step of the way. From breastpumping, to human milk storage, transport and preparation to diagnostics and feeding our comprehensive system will help you • improve outcomes, • reduce costs, • improve patient satisfaction.

Research leads to innovation: Visit booth 411 and learn more about the research showing that higher doses of human milk can help NICU professionals achieve better outcomes for their patients. Learn about the clear dose-response effect between the dose of human milk and a reduction in risk for several disabling morbidities such as necrotizing enterocolitis, late onset sepsis and enteral feed intolerance.

Understanding the research led to innovative new products that make feeding human milk even easier with innovations such as Symphony Preemie+, the first pumping program clinically shown to produce more milk for NICU moms. Check out our Baby Weigh II scale which helps accurately measure infant milk intake. Knowledge of milk intake may improve the clinical diagnosis of feeding problems while providing essential information for precise supplementation of infants who may be at risk for under or over consumption. In addition, Medela's new Waterless Milk Warmer is the safer, easier way to warm human milk. The Waterless Milk Warmer: • Eliminates risk associated with warming in water, • Consistently warms milk to temperatures of that of expressed human milk, • Safely thaws human milk.

Educating our clinicians and patients: Medela Education provides the latest breastfeeding research through its extensive education programs. Our evidence-based programs detail best practices and are designed to impact and improve practice in hospitals nationwide. Visit www.MedelaEducation to learn more about our evidence-based education programs geared toward the NICU clinician.

Supporting you and your patients from hospital to home: Research shows feeding more human milk can help reduce costs, yet we know getting enough milk can be a challenge. Medela can help overcome these challenges as the only manufacturer that provides a comprehensive human milk support system that includes solid evidence-based education and extends from breastpumping through storage and into feeding, diagnostics and milk preparation. Medela supports your efforts every step of the way. And when your patients go home, Medela is there to support them with a full line of breastfeeding and breastpumping products available at retailers nationwide. Mothers can benefit from of a continuum of care with the same technology and benefits they enjoyed in the hospital. Medela's Breastfeeding Division exists to enhance mother and baby health through the life-giving benefits of breastmilk. This is more than a vision, this is Medela's destiny.

Mercury Medical
Booth 429

What products do you plan to exhibit?
Mercury Medical will be exhibiting Neo-Tee, the industry's first disposable Infant T-Piece Resuscitator with Built-In Pressure Relief and Color-Coded Manometer on the Tee. Mercury will also be showing the neonatal CO_2 detector, Neo-StatCO2 with expanded weight range of 0.25 kg – 6 kgs. Also on display will be Mercury's high-quality hyperinflation and infant CPR bags with and without manometers as well as Mercury's new disposable infant sizes of air-Q (Masked Laryngeal Airways): 1.0, 1.5 and 2.0.

What's new this year? What R&D advances will you be presenting?
A new Neo-Tee configuration, with the adjustable PIP controller closer to the TEE will be displayed. This enhancement adds convenience to changing inspiratory pressures anytime in close proximity to the patient. The development of the Neo-Tee will be very important as hospitals begin changing their protocols for safer and more affordable infant resuscitation solutions. The Neo-Tee infant T-Piece resuscitation single-patient-use device allows practitioners to deliver required volumes for neonatal lung expansion with simultaneous patient monitoring of airway and/or PEEP pressures. The new Neo-Tee affords the clinician more consistent PIP and PEEP pressure. Additionally, there is no "bag" to squeeze so the clinician will not experience bag squeezing fatigue. Furthermore, the Neo-Tee includes a built-in pressure relief valve as an added safety measure when releasing high ventilatory pressures over 40 cm of H_2O. The stay-put PEEP valve allows for quick and easy gas flow adjustments, when needed. The adjustable PIP controller, which regulates pressure, is much smaller and compact than competitive capital equipment. Neo-Tee does not require cleaning and it's completely disposable. As compared with expensive capital equipment, Neo-Tee will be affordable for any hospital (small or large) to incorporate at every NICU and L & D bedside.

What educational or training materials will be available?
Full product training will be provided at the booth by Mercury Medical Product Specialists. We will provide Neo-Tee product information brochures with specifications and offer free samples. The samples will be provided by fully trained sales representatives who will provide full product in-servicing at the attendees' facilities. Additionally, Mercury Medical has partnered with Innovative Respiratory Concepts to provide customers with FREE AARC accredited CEU courses. Just go to www.mercurymed.com and click on the Educational tab. Click on the IRC link to access the CEU course, particularly the Neonatal Resuscitation featuring Neo-Tee.

Why should our readers stop by your display?
Mercury is a leading manufacturer of resuscitation products that commands the number 1 market position in infant CPR resuscitation bags. Mercury pays special attention to customer needs and develops high-quality products to meet those customer requirements. Mercury's slogan, "Your Need . . . Our Innovation!" sums up the company positioning. Neonatal/perinatal caregivers should visit our display to get a first-hand view and advantages of Neo-Tee, the industry's first disposable infant T-Piece resuscitator with built-in pressure relief and color-coded manometer on the Tee.

NeoMed, Inc
Booth 316

What Products do you plan to exhibit?
NeoMed, Inc is proud to present a unique line of products specifically designed to enhance the safety and outcome of the patient. Our products include our comprehensive Enteral Safety System (Extension Sets, Feeding Tubes, and Oral Dispensers), Closed System NeoBottle, NeoDrape, SafeBaby Breast Milk Tracking System, Catheterization Trays, Urinary Drainage Kits/Catheters, Umbilical Vessel Catheters, Lumbar Puncture Products and Specialty Kits. Our product line supports the latest clinical innovations that meet or exceed enteral safety recommendations set forth by the FDA, Joint Commission and ASPEN (American Society of Parenteral and Enteral Nutrition).

What's new this year? What R&D advances will you be presenting?
NeoMed is excited to introduce the first closed-system storage container that combines collection, storage, fortification and delivery of fresh human breast milk (HBM) or enteral/oral liquids through a single device. Featuring collapsible floor technology and a unique airtight, leak-proof lid, the NeoBottle may extend the shelf life of fresh HBM or oral liquids by allowing users to evacuate excess air reducing the risks of oxidization and exposure to bacteria prior to delivery.

What educational or training materials will be available?
NeoMed will provide clinical documentation from the American Society for Parenteral and Enteral Nutrition (ASPEN), The Joint Commission, the Institute for Safe Medication Practices (ISMP) and various case studies that highlight the importance of patient safety and how our products eliminate or mitigate misconnections, mis-feeds, enteral contamination, and patient misidentifications.

Tell us about any speakers or in-booth promotions.
NeoMed will be providing a hotel room drop including a tote bag with a 60ml oral/enteral syringe and our new closed system NeoBottle. All attendees will be eligible to register for a chance to win prizes such as Apple iPods and an iPad, plus much more.

Why should our readers stop by your booth?
NeoMed is committed to providing the highest quality and most cost effective neonatal and pediatric products that promote patient safety by protecting against misconnections and misidentifications while improving clinical outcome of the patient. Please visit our website: www.neomedinc.com for more details.

Fisher & Paykel Healthcare, Inc
Booth 432

What products do you plan to exhibit?
Fisher & Paykel Healthcare, Inc understands and appreciates the critical role neonatal nurses 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 and 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's new this year? What R&D advances 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.

What educational or training materials will be available?
Come and experience hands-on training with the Neopuff Infant T-Piece simulator using the new Ergonomic T-Piece Resuscitation Circuit and our Resuscitation Masks. This is highly recommended for NRP Instructors. Also, ask us about our Optimal Resuscitation CNE workshop for your hospital staff.

Tell us about any speakers or in-booth promotions.
Fisher & Paykel Healthcare will be giving out Ergonomic T-Piece Resuscitation Circuit Kits to all visitors. Also, we will be providing flash drives containing Neopuff Infant T-Resuscitator and Bubble CPAP educational material.

Why should your readers stop by your booth?
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 NANN Conference in Orlando at Booth 432 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.

Bosentan Role in Severe Refractory Pulmonary Hypertension in an Extremely Low Birth Weight Infant

Musaddaq Inayat, MD; Rebecca Yeasted, MD; Eric Schultz, MD; John Cleary MD; Anthony C. Chang, MD

Abstract

Pulmonary hypertension (PH) is one of the known complications of bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD) in extremely low birth weight (ELBW) infants. The incidence of secondary complications of BPD and CLD is increasing as the survival of extreme low birth weight neonates is improved in modern neonatal intensive care units. Pulmonary hypertension (PH) in infants can be devastating and can result in long-term morbidity and mortality. An infant with PH can be a therapeutic challenge in the emergency room with mild URI or even during a relatively benign surgical procedure. The treatment options for PH in neonates are very limited due to lack of large randomized controlled trials. Available therapeutic data comprise animal studies, case reports and few studies in pediatric and adult population. Sildenafil and iNO has been used for the treatment of PH. There is some promising evidence for the use of Bosentan as a treatment modality. Bosentan is an active, dual endothelin (ET) receptor antagonist, which helps to decrease pulmonary vascular resistance. We describe a case of severe PH in an ELBW with BPD who had pulmonary hypertension crisis after bilateral inguinal hernia repair and was treated with Sildenafil, iNO and Bosentan. We have successfully used Bosentan in this patient without any adverse effects with significant clinical improvement.

Introduction

As neonatal medicine is growing with emerging new techniques and improved management strategies, survival of extremely low birth weight (ELBW) infants has increased. Though the overall mortality for ELBW infants has decreased over the past decade, their survival is associated with significant morbidities.[1] One of the most common complications is bronchopulmonary dysplasia (BPD), which affects approximately 40% of ELBW infants.[2] BPD is associated with other conditions related to prematurity, which include pulmonary hypertension (PH), growth failure, metabolic disease of prematurity, neurodevelopmental impairment and retinopathy of prematurity.

One of the most challenging complications of BPD is pulmonary vascular remodeling leading to PH. Over the past decade,

different strategies have evolved to manage PH.[4] Although use of oxygen, inhaled nitric oxide (iNO), sildenafil and prostacyclin has helped to improve survival, neonatologists still continue to encounter cases where these strategies are either minimally successful or fail to improve the patient's condition. With this in mind, neonatologists are constantly striving to improve treatment regimens.

Bosentan is an active, dual endothelin (ET) receptor antagonist with effects on both ETA and ETB receptors. Blocking these receptors has shown to decrease pulmonary vascular resistance in adult and pediatric populations.[5,6,7] We report case of a 5-month-old ELBW infant with severe, life-threatening PH, which was treated with Bosentan in addition to iNO and sildenafil. To our knowledge there is only one reported case of Bosentan use for pulmonary HTN secondary to BPD for patient less than 1 year old.[21]

Case

Our patient is a Hispanic male born at 26 weeks' gestation with severe IUGR (birth weight 390 g) via C-section for late decelerations with oligohydramnios. Mother did receive one course of antenatal steroids. He was intubated in the delivery room and received surfactant. On DOL 11, his chest Xray showed cystic lucencies consistent with pulmonary interstitial emphysema. Subsequently, he was changed to high frequency jet ventilation (HFJV). On DOL 44, he was extubated to nasal synchronized intermittent mandatory ventilation (nSIMV), and 8 days later to nasal continuous positive airway pressure (nCPAP). During this hospitalization, he underwent PDA ligation on DOL 10. Head ultrasound showed no intraventricular hemorrhage. TORCH infection workup was negative.

The patient underwent bilateral laser treatment for his retinopathy of prematurity (ROP) and bilateral inguinal hernia repair on DOL 150 (5 months). Following these procedures, patient had persistent respiratory distress. An echocardiogram showed PH with pulmonary artery pressure of 58mm Hg. At that time, sildenafil was started at 0.25 mg/kg/dose Q6hours. Two weeks later, sildenafil was increased to 1mg/kg/dose Q6hours. A second echocardiogram showed improved pulmonary arterial (PA) pressures with mild right ventricular dilation. Five days later, the patient began requiring increased oxygen. A third echocardiogram showed worsening PH.

The patient was then referred to our institution at 5-½ month of life (CGA 48 wks, weight = 3.64 kg) for management of

refractory PH in the setting of BPD. He was maintained on high flow nasal cannula (HFNC) at 3L/min. His medications included Aldactazide, Sildenafil, L-albuterol and Budesonide. Echocardiogram showed equal pulmonary and systemic pressures. His sildenafil dose was increased to 2mg/kg/dose Q6hours. The following day, it was increased further to 3mg/kg/dose Q6hours. Throughout the first 4 days, he remained on high flow nasal cannula, 3L/min at 100% FiO_2.

On day 5 of admission, patient was placed in an oxyhood with 100% FiO_2 along with 3L/min nasal cannula for persistent desaturations, tachypnea and increased work of breathing. B-type natiuretic peptide (BNP) level sent and was high at 670. Due to this, sildenafil dose increased to 4mg/kg/dose Q6hours. The following day, the patient continued to decompensate and was intubated for hypoxic respiratory failure. He was transitioned from SIMV to High Frequency Oscillatory Ventilation due to decreased lung volumes and pulmonary edema. Inhaled nitric oxide was started at 20ppm. He became hypotensive, required multiple normal saline boluses, milrinone, and epinephrine drips. Fentanyl and versed drips were started for sedation. Septic workup was initiated with blood and urine cultures and ampicillin and cefotaxime were started. Chest x-ray showed right upper lobe infiltrate, concerning for aspiration pneumonia. His antibiotic coverage was changed to gentamicin and piperacillin/tazobactam. Echocardiogram pre- and post-nitric oxide showed equal pulmonary and systemic pressures, with an estimated PA pressure of 71mm Hg. Three days later, the patient was extubated to nCPAP, continuing on iNO. By the following day, he was taken off pressors, and his iNO oxide was weaned by 5ppm every 12 hours to level of 5ppm. Repeat echocardiogram showed persistent PH with estimated PA pressures of 55-60mm Hg. Two days later, he was weaned to high flow nasal cannula (2 L/min) with 100% FiO_2 and given four doses of Furosemide 1mg/kg Q12hrs for pulmonary edema. Despite being on iNO at 5ppm and on maximum Sildenafil dose at 4mg/kg/dose Q6, repeated echocardiograms demonstrated persistent PH with elevated RV and PA pressures and septal deviation along with significant TR. After discussion with cardiology and parents, Bosentan was started at 1 mg/kg/dose (3mg) twice a day. This dose was extrapolated from adult and pediatric dosing data based on the patient's age and weight.[5,8,9] Liver function tests obtained prior to starting Bosentan and during therapy remained normal. Nitric oxide was weaned by 1ppm every 24 hours until it was discontinued 5 days later. Two days into the nitric oxide wean, the Bosentan dose was increased to 1.3 mg/kg/dose (4mg) twice

a day. The patient was then weaned to 1L/min nasal cannula with 100% FiO_2. Adding Bosentan in the management regimen helped to improve clinical status in 2-3 days and six days later a repeat echocardiogram showed improved PA pressures (figure 1). He was then weaned to 0.5L/min NC, only requiring 1L/min during feeds and physical therapy. Baby was discharged home on Bosentan, Sildenafil and Aldactazide. Patient has slow but gradual improvement of respiratory status and has shown no adverse effects of Bosentan including no abnormalities of liver function tests at follow up visits to pulmonary hypertension clinic up to 9 months of life.

Discussion

Pulmonary hypertension (PH) is a devastating entity that is characterized by an increase in pulmonary vascular resistance (PVR), which can lead to progressive deterioration, right heart failure, and death. Common etiologies include congenital heart anomalies, parenchymal lung disease like BPD and idiopathic pulmonary fibrosis.[9] PH and chronic pulmonary vascular changes are expected complications of BPD in young infants and children. Therapies available currently include oxygen, iNO, oral Sildenafil and parenteral Prostacyclin. These therapies are suboptimal and may be unsuccessful in treating these patients. Recently, oral endothelin receptor blockers and phosphodiesterase-5 inhibitors have been used successfully for pediatric patients who have PH secondary to BPD.[10]

Endothelin-1 is a smooth-muscle mitogen and a potent vasoconstrictor. PH is associated with the loss of endothelin B-mediated vasodilation and increased endothelin A-mediated vasoconstriction.[11,12,13] Experimental studies have shown that intrauterine blockage of endothelin A-receptor resulted in a decrease in pulmonary artery pressure, right ventricular hypertrophy and distal muscularization of small pulmonary arteries.[14] In experimental models of pulmonary hypertension, endothelin receptor blockade caused sustained improvement in hemodynamics and oxygenation.[15] Endothelin-1 may play a major role in the pathophysiology of PH.

Bosentan is an antagonist of both endothelin-1 receptors A and B. This dual effect on both endothelin receptors results in diminishing or eliminating the inflammatory, fibrotic and proliferative effects of endothelin-A.[5,8] Bosentan may have immediate effects on pulmonary circulation. In an experimental newborn lamb model with PPHN, endothelin-A receptor antagonist effect resulted in markedly decreased pulmonary vascular resistance.[15] Bosentan has also been shown to prevent and reverse developing hypoxic PH in rats.[16] It has been successfully used in both pediatric and adult populations.

Bosentan has been used successfully and safely in pediatric and adult patients and has been shown to reduce PVR and pulmonary arterial pressure.[5,6] One study in pediatric patients with congenital heart disease emphasized the use of Bosentan to reduce PVR in PH.[7] There have been case reports describing the use of Bosentan in smaller children with secondary PH due to BPD.[18] Bosentan has been shown to be safe at 1 yr follow up study done in 2002.[14] Administration of intravenous Bosentan can cause dose dependant fall in total PVR within hours.[17] The pharmacokinetics, safety and efficacy of bosentan are very similar in pediatric PH patient as compared to adults.[8]

There are two documented cases in the literature reporting the use of Bosentan in neonates with PPHN[19] and another case

Fig 1: Trend of estimated PA pressure and Medications
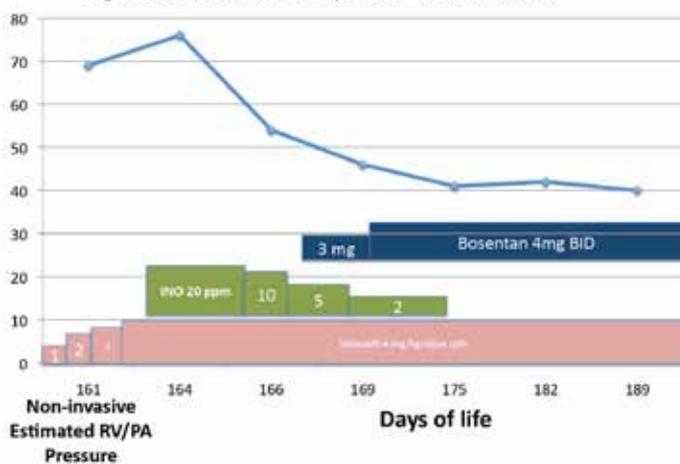
report demonstrating use of Bosentan for PH in the presence of congenital heart defect ie TOGA.[20] In the past there is only one reported case of Bosentan use for PH secondary to BPD for patient less than 1 year old.[21] Bosentan was started in that particular case at 9 month of age concomitant to Epoprostenol use. The dose administered was higher at 3mg/kg/dose BID compared to our case where we used lower dose at 1 mg/kg/dose BID. Use of Sildenafil in that case was at 12 month of age in an attempt to wean Bosentan and Epoprostenol. Sildenafil was started in our patient at 5 months of age, was maximized prior to starting Bosentan while patient was on iNO. Our patient showed decrease in estimated pulmonary pressure to half systemic pressure with the use of Bosentan. In our case, Bosentan was well tolerated and the diagnostic laboratory tests including liver function remained normal at follow-up visits.

Conclusion

In conclusion, we believe that this case supports the use of Bosentan as an adjunct treatment for neonates with refractory PH in the setting of BPD. Although Bosentan is not currently used as a standard adjunct therapy, it may be useful in the newborn population with PH due to its beneficial effects shown in this case report. Further studies are warranted to assess the efficacy, pharmacokinetics, and pharmacodynamics of Bosentan use in neonates. In addition, we need to establish criteria for the selection of patients who will benefit from Bosentan use. Studies are also required to evaluate whether Bosentan use is superior in isolation or as an adjunct with other agents like Sildenafil and iNO.

References

1   Claas MJ, Bruinse HW, van der Heide-Jalving M, Termote JU, de Vries LS. Changes in Survival and Neonatal Morbidity in Infants with a Birth Weight of 750 g or Less. Neonatology. 2010 May 7;98(3):278-288.

2   Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 2007;196(2):147.e1–.e8.

3   Eichenwald EC, Stark AR. Management and outcomes of very low birth weight. N Engl J Med Apr 17 2008;358(16):1700–11.

4   Ivy D. Diagnosis and treatment of severe pediatric pulmonary hypertension. Cardiol Rev 2001;9:227-37.

5   Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002; 346: 896–903.

6   Galie` N, Rubin LJ, Hoeper MM, Jansa P, Al-hiti H, Meyer GMB, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomized controlled trial. Lancet 2008; 371: 2093–100.

7   Maiya S, Hislop AA, Flynn Y, Haworth SG. Response to bosentan in children with PH. Heart 2006; 92: 664–70.

8   Barst R, Ivy D, Dingemanse J, Widlitz A, Schmidt K, Doran A, Bingaman D, Nguyen N, Gaitonde M, vean Giersbergen P (2003) Pharmacokinetics, safety, and efficacy in pediatric patients with pulmonary arterial hypertension. Pharmacol Ther 73:372–382.

9   Beghetti M, et al; Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: the FUTURE-1 study. Br J Clin Pharmacol. 2009 Dec; 68(6): 948-55.

10 Usha K, Sankaran K, Michael G. Treatment of PH in Children with Chronic Lung Disease with Newer Oral Therapies.

Pediatr Cardiol (2008) 29:1082–1086.

11 Ivy D, Le Cras T, Horan M, Abman S (1998) Increased lung prepro ET-1 and decreased ETB-receptor gene expression in fetal PH. Am J Physiol 274:L535–L541.

12 Ivy D, Ziegler J, Dubus M, Fox J, Kinsella J, Abman S (1996) Chronic intrauterine PH alters endothelin receptor activity in the ovine fetal lung. Pediatr Res 39:435–442.

13 Galié N, Manes A, Branzi A. The endothelin system in pulmonary arterial hypertension. Cardiovasc Res. 2004 Feb 1;61(2):227-37.

14 Sitbon O, Badesch DB, Channick RN et al. Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: a 1-year follow-up study. Chest 2003;124:247–54.

15 Ivy D, Parker T, Kinsella J, Abman S (1998) Endothelin A receptor blockade decreases pulmonary vascular resistance in premature lambs with hyaline membrane disease. Pediatr Res 44:175–180.

16 Chen SJ, Chen YF, Meng QC, Durand J, Dicarlo VS, Oparil S. Endothelin-receptor antagonist bosentan prevents and reverses hypoxic PH in rats. J Appl Physiol 1995; 79: 2122–31.

17 Williamson D, Wallman L, Jones R, Keogh A, Scroope F, Penny R, Weber C, Macdonald P (2000) Hemodynamic effects of bosentan, an endothelin receptor antagonist, in patients with PH. Circulation 25:411–418.

18 Nakwan N, Choksuchat D, Saksawad R, Thammachote P, Persistent PH of the newborn with transposition of the great arteries: successful treatment with bosentan. Journal Compilation 2009 Acta Pædiatrica 2009 98, pp. 1683–1685.

19 Goissen C, Ghyselen L, Tourneux P, Krim G, Storme L, Bou P, et al. Persistent PH of the newborn with transposition of the great arteries: successful treatment with bosentan. Eur J Pediatr 2008; 167: 437–40.

20 Rugolotto S, Errico G, Beghini R, Ilic S, Richelli C, Padovani EM. Weaning of epoprostenol in a small infant receiving concomitant bosentan for severe pulmonary arterial hypertension secondary to bronchopulmonary dysplasia. Minerva Pediatr 2006; 58: 491–4.

21 Ivy D, Parker T, Ziegler J, Galan H, Kinsella J, Tuder R, Abman S (1997) Prolonged endothelin A receptor blockade attenuates chronic PH in the ovine fetus. J Clin Inv 99:1179–1186.

Current Breast Pump Recommendations for NICU Mothers: 2011 HMBANA Guidelines – an Essential Resource

Jean Rhodes, PhD, CNM, IBCLC

Helping mothers of NICU infants establish and maintain adequate milk production is a challenging task for health care providers. Many of these mothers have preexisting medical conditions with superimposed pregnancy complications, some of which – such as diabetes, obesity, and thyroid disease – can negatively impact milk production.[1] The emotional stress associated with preterm delivery is also known to impact milk production. Compounding these obstacles, many of these mothers did not plan to breastfeed, much less pump. Thus, hospital and community practitioners have very important roles in breastfeeding education, advocacy and support.

In the past six years alone, the lactation literature has exploded with clinical studies, scientific discoveries and professional practice protocols. Along with this new information comes concern – especially in neonatal intensive care (NICU) settings – that practices be kept current and evidence based. Therefore, an essential resource for clinicians is the Human Milk Banking Association of North America's (HMBANA) 3rd edition of Best Practice for Expressing, Storing and Handling Human Milk in Hospitals, Homes, and Child Care Settings.

While the HMBANA guidelines cover many topics, the focus of this paper is to examine the 2011 HMBANA breast pump recommendations for situations in which infants are unable to breastfeed for extended periods of time. The 2011 HMBANA guidelines recommend a hospital-grade breast pump for mothers whose infants cannot breastfeed "for an extended period of time" or when an infant "is not feeding effectively."[2]

Breast pumps work through a combination of suction strength (vacuum pressure) and suction pattern (frequency of cycles per minute). By observing term infants at breast, Kent et al[3] found infant sucking patterns change over the course of a breastfeeding session. At the beginning of breastfeeding and prior to milk ejection, infants suck rapidly. This pattern changes to a slower and deeper suction pattern as the milk ejects. Using ultrasound imaging, Kent et al[3] verified milk ejection is critical to the overall process of milk removal from the breast. And by comparing the effect of different pumping patterns on milk ejection, they were able to determine the most effective pumping patterns for milk expression. Hospital-grade pumps with computer technology

Jean Rhodes, PhD, CNM, IBCLC has 30 years of experience as a nurse, lactation consultant, nurse-midwife, educator and researchers. Formerly of the Medical University of South Carolina, she is now an independent consultant. This article was provided by Medela.

have been programmed to mimic variations in infant sucking thereby improving the degree and speed of breast emptying.[4]

Breast pump suction control and suction patterns are important factors in removing adequate amounts of milk to stimulate milk synthesis. Both are also important factors in patient comfort. In a 2008 study[5] involving a hospital-grade electric pump, researchers determined each mother had a maximum level of suction that is still comfortable for her. To find this level, pumping women increased the pump suction to the point of beginning discomfort, and then decreased the suction to a point of comfort. When women used their own maximum, but still comfortable, vacuum levels they obtained higher milk volumes and milk higher in fat. Pain with pumping may indicate the suction level is too high (though there may be many reasons for nipple pain). Obviously, the more comfortable a woman is while pumping, the more likely she is to continue.

As a large percentage of NICU infants immediately post birth are simply unable to breastfeed and their mothers may have difficulty for many reasons establishing milk supply, a hospital-grade pump is recommended because as HMBANA states:
- Mid-sized electric pumps sold for individual use tend to work best for mothers who have established a milk supply and are breastfeeding on a regular basis as well as pumping.
- Small electric/battery operated/and hand pumps may work for occasional use once the milk supply is well established.

Sisk et al[6] support these sentiments in a recent qualitative study. In this study of the supports and barriers to milk expression, the authors interviewed 32 mothers of very low birth weight infants. While subjects included women who planned to breastfeed as well as who did not plan to breastfeed or pump, all women in the study ultimately chose to pump for their preterm infants. The authors noted that NICU mothers who used primarily small electric or manual breast pumps had great difficulty establishing a pumping routine and adequate milk supply because pumps were ineffective at emptying their breasts.

In addition, for more than twenty years, research has found that hospital-grade pumps also express a greater volume of breastmilk than hand expression or manual pumps. The research has shown that hospital-grade pumps empty the breasts better, increasing the fat content of composite milk.[7-9] In a study cited by HMBANA, Slusher et al[10] compared expressed breastmilk volumes obtained via pumping to those obtained by hand expression. This study was conducted in a Nigerian NICU where

hand expression was the norm. Their results suggested mothers who used a hospital grade breast pump expressed significantly more milk than mothers who hand expressed. In general, improved volumes of expressed milk indicate better breast emptying.

Daly et al[11] studied the degree of breast emptying and the effect of timing between pumping sessions on rates of milk synthesis. They found the degree of breast emptying impacted breast milk synthesis more than the frequency of breast pumping. Thus they concluded mothers produce more milk if they are able to more fully empty the breast. Lastly, Slusher et al[9] in another study of Nigerian NICU mothers found a hospital-grade electric pump facilitated the collection of hindmilk. During a weeklong hindmilk intervention, mothers increased their average daily milk volumes using a hospital-grade electric breast pump when compared to their milk volumes via hand expression. Furthermore, the infants fed pump-expressed hindmilk had improved weight gains, both during the intervention and after discharge. For example, the mean infant weight gain prior to the hindmilk intervention was 10.1 grams/day. During the intervention mean weight gains increased to 18.8 grams/day and remained elevated over pre-intervention baseline for at least two weeks after discharge.

For the first time, the new HMBANA guidelines include a discussion of "hands on pumping" or the combination of breast massage, hand expression and pumping with an effective pump. Morton et al[12] described an increase in milk removal in mothers of preterm infants <31 weeks who consistently practiced manual colostrum expression and breast massage along with breast pumping. Most lactation practitioners have observed mothers spontaneously augmenting breast pumping with a variety of manual techniques. The combination of methods makes sense in the context of pumping as healthy infants express milk from the breast by a combination of suction and breast compression. Hands on pumping, therefore, helps compensate for the absence of breast compression in pump dependent mothers.

A new recommendation in the 2011 HMBANA guidelines is evaluation of pump flanges for proper fit. In 2004, Meier et al[13] discussed problems associated with poorly fitted breastshields. These included incomplete milk removal, nipple trauma and pain. The majority of hospital-grade pumps come with the option of different size breastshields. Meier and colleagues recommended evaluating NICU mothers frequently for flange fit as their nipples can change size more than once over the course of extended breast pumping. Indicators of a properly fitted breastshield include: the nipple is centered and will move easily in the tunnel of the flange, none of the areola (or only a small amount) will be pulled into the tunnel, there is a gentle rhythmic motion of the breast with each cycle of the pump, pumping is comfortable, the nipples are not painful, blanched or cracked and the breasts are well drained.[13]

Listening to what women say about their breast pumping experiences is also important. A 2008 Cochrane Review: Methods of Milk Expression for Lactating Women[14] examined the issues of efficiency and acceptability of all methods of expressing human milk. Twelve studies on milk expression met their criteria for review. Most studies either compared sequential to simultaneous pumping or compared methods of expression (hand expression, manual pump or electric pump) to one another. No studies compared two or more hospital-grade pumps. The authors concluded, "…no one type of pump…is suitable for all mothers and all circumstances." More importantly, they identified in the milk expression literature a lack of attention to the issue of maternal satisfaction.

Since 2008, qualitative researchers have looked more closely at the experiences of women who are breast pumping. Like the study by Sisk et al[6] above, other studies have explored mothers' perceptions of breast pumping. Clemons et al[15] in 2010 questioned breastfeeding mothers about their experiences of milk expression, either by hand or by pump. While the majority of women preferred breast pumps to hand expression, reasons given for not liking a pump included that it was ineffective or painful. Certainly these concerns should inform practice and breast pump standards. Studies like these as well as those by Meier et al[16,17] and Kent et al[5] – all of which highlight the importance of maternal feedback – are needed if our goal is to advocate for mothers expressing milk for their hospitalized infants.

In summary, we have reviewed the research evidence supporting the 2011 HMBANA guidelines on breast pump selection for NICU mothers. Current best practice standards continue to recommend the use of hospital-grade electric pumps when infants cannot go to breast or when they cannot breastfeed effectively.

References

1 Lawrence RA, Lawrence, RM. Breastfeeding: A Guide for the Medical Profession. 7th ed. Maryland Heights, Missouri: Elsevier Mosby; 2011.

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

3 Kent JC, Ramsay DT, Doherty D, Larsson M, Hartmann PE. Response of breasts to different stimulation patterns of an electric breast pump. J Hum Lact. May 2003;19(2):179-186; quiz 187-178, 218.

4 Mitoulas LR, Lai CT, Gurrin LC, Larsson M, Hartmann PE. Effect of vacuum profile on breast milk expression using an electric breast pump. Journal of human lactation : official journal of International Lactation Consultant Association. Nov 2002;18(4):353-360.

5 Kent JC, Mitoulas LR, Cregan MD, et al. Importance of vacuum for breastmilk expression. Breastfeed Med. Mar 2008;3(1):11-19.

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

7 Boutte CA, Garza C, Fraley JK, Stuff JE, Smith EO. Comparison of hand- and electric-operated breast pumps. Hum Nutr Appl Nutr. Dec 1985;39(6):426-430.

8 Green D, Moye L, Schreiner RL, Lemons JA. The relative efficacy of four methods of human milk expression. Early human development. Apr 1982;6(2):153-159.

9 Slusher T, Hampton R, Bode-Thomas F, Pam S, Akor F, Meier P. Promoting the exclusive feeding of own mother's milk through the use of hindmilk and increased maternal milk volume for hospitalized, low birth weight infants (<1800 grams) in Nigeria: a feasibility study. Journal of human lactation : official journal of International Lactation

Neonatal Transport: Active Cooling for Infants with HIE

The journal Air Medical Journal recently published the paper, Active Cooling During Transport of Neonates with Hypoxic-Ischemic Encephalopathy.*

Background
The authors note that hypoxic ischemic encephalopathy (HIE) attributable to perinatal asphyxia continues to be a major cause of neonatal morbidity and mortality, and that limited therapeutic interventions for HIE are available: "Infants who survive HIE often have long-term developmental disabilities, including mental retardation, seizures, and cerebral palsy. Total body cooling has emerged as a therapy for these affected infants. Three multicenter trials demonstrated that treatment with mild hypothermia results in improved neurodevelopmental outcomes in infants of 36 weeks' gestation or greater who have suffered a hypoxic-ischemic event."

Initiation of hypothermia must occur within six hours. This is achievable if the baby is born in a center with the necessary cooling equipment; otherwise the infant must be transported to an NICU that has hypothermia therapy. Therefore, passive cooling during transport becomes necessary. This involves keeping the infant from external heat sources and monitoring its temperature, typically using gel packs – not the most effective method in terms of providing a continuous-feedback loop. As a result, infants often arrive at the NICU with a temperature outside the desired range of 32 to 35°C.

The authors stated, "Therapeutic hypothermia has emerged as state-of-the-art treatment for neonates with HIE. As a result, clinicians must have a reliable and controlled method to cool these neonates during transport to centers with hypothermia programs. Often these neonates are inadvertently overcooled because of the resultant changes in metabolism and heat production from HIE. Both passive cooling and active cooling with gel packs can cause this overcooling. Overcooling has the potential to increase serious side effects associated with cooling, such as: arrhythmias, electrocardiogram changes, electrolyte abnormalities, thrombocytopenia, and coagulopathies."

The authors of this study employed the CritiCool, a microprocessor-controlled temperature management unit, to achieve the desired temperature range, and concluded, "In this report, we demonstrate that the servo-controlled CritiCool is feasible for use during both ground and air transports."

The authors noted that their program served as a hypothermia treatment referral area, and that the transport of infants could last six hours round trip. As such, they wanted to implement a method to provide active cooling at the optimum temperature range. They used the CritiCool during transport by ambulance, aircraft, and helicopter.

According to the authors, "The system uses a control algorithm that monitors skin and core temperature to make adjustments to the circulating water temperature to maintain the patient's core temperature at a target of 33.5°C." The unit, although not designed for transport, per se, is the right size for conveying the infant to the NICU. They presented three cases detailing specific transport modalities.

Aircraft Transport
This case involved an infant born by cesarean, unresponsive on delivery, heart rate less than 60 bpm, who required intubation and ET epinephrine administration, with Apgar scores 1, 3 and 4. Passive cooling was initiated and transport to the authors' NICU arranged, via an aircraft with CritiCool equipment. The baby's temperature was 31.5°C at the start of transport, and temperature management begun with gradual rewarming. At the destination, the baby was transferred to an ambulance for ground transport, and active cooling continued. Passive cooling was briefly employed in the transfer from the ambulance to the

NICU, as with the other two cases below, where active cooling resumed. At this point the infant's temperature was 33.5°C. Physical examination classified the infant as Sarnat stage III; MRI showed decreased brain volume and etiology consistent with HIE. The infant was ultimately discharged to hospice care.

Helicopter Transport

The infant was born by C-section after placental abruption, without fetal heart tones. Apgar scores were 1, 2, 4 and 7, arterial pH at 30 minutes was 6.60. The infant was ventilated and resuscitated, and given a diagnosis of encephalopathy, and its condition qualified it for systemic hypothermia therapy. The infant was passively cooled, and on the transport team's arrival, the baby's temperature was 34.1°C. The infant was placed on the CritiCool and transported on a 50 minute flight by helicopter without event. His temperature was 34.1°C on arrival. The infant's subsequent complications were mild, without seizures, and a subsequent MRI showed no neurologic injury.

Ground Transport

A term girl was born by C-section, with fetal bradycardia and Apgar scores 1, 3 and 5. She was intubated but self-extubated and left that way because of improved respiration. She developed seizures and was re-intubated and given phenobarbital. Passive cooling was initiated during transport to the referral hospital, where the need for hypothermia was established. The authors' hospital sent an ambulance with a CritiCool device, by which the infant was cooled during the transport at between 32.5 and 33.1°C, with an on-arrival temperature of 33.3°C . She was classified as Sarnat stage III with seizures and without a gag reflex and actively cooled for 72 hours, wherein her clinical course improved and she was extubated, with her neurological status returning to normal.

Summary

A comparison of patient temperatures as recorded during the ambulance, fixed-wing, and helicopter transports revealed the following: "During the ambulance transport, the patients' temperature stayed very consistent and within the target range during the entire transport. In both the fixed-wing and helicopter transports, the patients were below the target temperature on arrival at the referring facilities. The CritiCool device rewarmed both patients with user inputs so that they were within the target range on arrival to Shands Teaching Hospital." The authors and the manufacturer initiated several adjustments to improve the ease of use in neonates below the target temperature, including temperature monitoring during transfers between a facility and fixed wing aircraft to avoid temperature fluctuations associated with passive cooling. During the ground transport from the hospital to the airport for the fixed-wing transport, the authors eventually opted to place a separate continuous rectal probe monitor and provide passive cooling. If the neonate's temperature fell below 33.5°C, they noted that the incubator should be turned on to 0.5°C above the neonate's current temperature. On arrival to the aircraft the rectal probe would then be replaced with the rectal probe for the CritiCool.

The authors concluded, "This report demonstrates the first use of a servo-controlled cooling device during multiple modes of transport. The device enables the user to tightly regulate and control the neonate's temperature in a controlled and tightly monitored fashion."

Consultant Association. May 2003;19(2):191-198.

10 Slusher T, Slusher IL, Biomdo M, Bode-Thomas F, Curtis BA, Meier P. Electric breast pump use increases maternal milk volume in African nurseries. J Trop Pediatr. Apr 2007;53(2):125-130.

11 Daly SE, Kent JC, Owens RA, Hartmann PE. Frequency and degree of milk removal and the short-term control of human milk synthesis. Exp Physiol. Sep 1996;81(5):861-875.

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

13 Meier P, Motykowski JE, Zuleger JL. Choosing a correctly-fitted breastshield for milk expression. Medela Messenger. Vol 21. McHenry IL: Medela, Inc; 2004:1.

14 Becker GE, McCormick FM, Renfrew MJ. Methods of milk expression for lactating women. Cochrane database of systematic reviews. 2008(4):CD006170.

15 Clemons SN, Amir LH. Breastfeeding women's experience of expressing: a descriptive study. Journal of human lactation: official journal of International Lactation Consultant Association. Aug 2010;26(3):258-265.

16 Meier PP, Engstrom JL, Hurst NM, et al. A comparison of the efficiency, efficacy, comfort, and convenience of two hospital-grade electric breast pumps for mothers of very low birthweight infants. Breastfeed Med. Sep 2008;3(3):141-150.

17 Meier P, Hurst N, Rodriguez N, et al. Comfort and effectiveness of the Symphony breast pump for mothers of preterm infants: comparison of three suction patterns. Advances in experimental medicine and biology. 2004;554:321-323.

The University Hospital of Lausanne

This article reports on how MetaVision helps The University Hospital of Lausanne, Switzerland (CHUV) increase the quality of nutritional support in ICUs and improves newborn care with MetaVision to reduce malnutrition, minimize ICU patient weight loss, and identify potentially dangerous conditions in newborns.

The University Hospital of Lausanne (CHUV) is a leading hospital in Switzerland which admits 43,500 patients annually. Through its collaboration with the Faculty of Biology and Medicine at the University of Lausanne, CHUV plays a leading role in the areas of medical care, medical research, and training. MetaVision is installed in the hospital's cardiovascular, burn, surgical, neonatal and pediatric intensive care units.

The need

CHUV sought a clinical information system to increase the accuracy of their patient data and reduce their nurses' clerical workload. Hospital management needed a system to facilitate quality control initiatives, and provide notifications of potentially dangerous events. As a university teaching hospital, CHUV required the ability to easily extract information from the patient database for research purposes and for reporting.

The solution

In 1999, MetaVision was first implemented in the hospital's surgical ICU, extending to the entire ICU (32 beds) over three years, and later to the cardiac surgery intermediate care. In 2006, the Clinic of Neonatology implemented MetaVision, and became the hospital's largest user of the system, with 37 units installed. The Clinic of Neonatology serves as the tertiary perinatal center for a perinatal network with about 14,000 live births annually, serving most of the French speaking area of Switzerland.

According to Dr Matthias Roth-Kleiner, PD & MER, Staff Neonatologist, one of the greatest advantages of using MetaVision in the Clinic of Neonatology is that patients benefit from uninterrupted data recording for the entire duration of their hospitalization. Beginning directly after the resuscitation procedure in the delivery room the patient's data, including vital parameters, incubator and ventilator settings, and laboratory results, is registered and displayed by MetaVision. As a result of this comprehensive recording process, clinicians can monitor patients closely and survey the complete dataset of each patient's hospitalization from birth until discharge home or to Level II or Level I clinics.

This article was provided to us by MetaVision.

CHUV's staff has reported ease of use and customization as key advantages of MetaVision. The hospital was able to implement functionalities tailored to the specific workflows of their different units, while maintaining single standardized patient database across clinical departments. CHUV has saved on integration costs due to MetaVision's interoperability with other systems.

Results

Clinicians at CHUV report that MetaVision improves patient safety and treatment accuracy and has a significant impact on their daily workload. MetaVision gathers data from many disparate sources and presents a unified patient record, reducing the chances of clinicians missing essential data. MetaVision sends out warnings about potentially life-threatening situations and assists with prescriptions by suggesting alternatives according to a given algorithm.

At CHUV MetaVision shortened the time required for computations and clerical reporting by 30 minutes per shift, enabling clinicians to spend more time on patient care. Additionally, MetaVision helps quality control efforts by mandating adherence to established guidelines.

Better nutrition for ICU patients

CHUV studied the impact of MetaVision on malnutrition, revealing a significant improvement in care. MetaVision in ICU patients is a serious concern, associated with increased infectious morbidity, prolonged hospital stay, and increased mortality. They showed that the use of MetaVision led to improved nutritional support through easy visualization of the nutritional intervention and prescription standardization. These improvements led to better follow-up, a nutrient delivery closer to energy target (mean increase of energy delivery by 415 calories per day in all patients), and less weight loss for burned patients (5 kg less weight loss per patient). In fact, their study showed that use of MetaVision almost doubles the percentage of patients who receive adequate nutrition within 4 days in the ICU.[1]

Safer, more accurate testing for newborns

CHUV's clinicians have praised MetaVision's rich source of reliable data and unique querying capabilities as extremely effective for research purposes. Based on data gathered by MetaVision, CHUV has now published more than twelve papers in international journals, resulting in improved care quality.
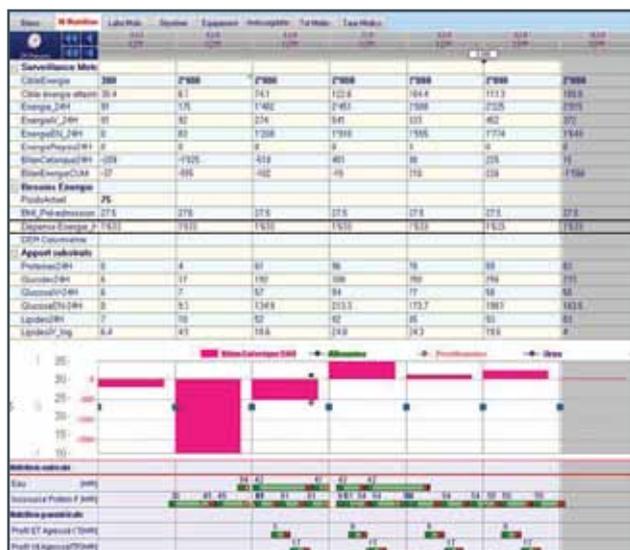
Graph showing the progression of the daily energy balance, with rate and type of feeding shown in the Gantt.

systems. All patients hospitalized in the NICU are connected to a data acquisition system (DAS; Metavision, iMDsoft, Boston, MA) which records automatically every minute clinical and laboratory data. Additionally, the nurses introduce manually information about diagnostic and treatment interventions (eg blood sampling). We thus know exactly the timing of blood sampling in the NICU and result validation in the central laboratory as well as the results obtained by the different measurement methods. For the period between December 2006 and December 2007, the DAS allowed us to screen retrospectively 29,350 blood glucose values."

CHUV performed research on newborns that was only possible by querying cases using MetaVision, and which resulted in better patient care. Low blood sugar (hypoglycemia) is a dangerous condition for babies, which can have devastating effects on their long-term development. However, this condition is difficult to detect, as often there are no symptoms. Clinicians are faced with the challenge of how to test for hypoglycemia without extracting excessive amounts of blood from newborns. Using their database of 30,000 glycemia entries in MetaVision, CHUV was able to determine the accuracy of new point-of-care blood testing devices without performing potentially detrimental blood testing of neonates.[2] As a result of this study, an ineffective point-of-care blood testing device was determined to be inaccurate, and was taken off the market for neonatal hypoglycemia screening purposes.

References

1   Berger MM, Bouvry S, et al. Impact of a computerized information system on quality of nutritional support in the ICU. Nutrition 22 (2006): 221–229.
2   Roth-Kleiner M, Stadelmann DC, et al. Evaluation of different POCT devices for glucose measurement in a clinical neonatal setting. European Journal of Pediatrics 169:11(2010): 1387-95.

Addenda

The article, referenced above, [Roth-Kleiner, et al] noted: "Hypoglycemia is a major cause of neonatal morbidity and may induce long-term developmental sequelae. Clinical signs of hypoglycemia in neonatal infants are unspecific or even absent, and therefore, precise and accurate methods for the assessment of glycaemia are needed. Glycemia measurement in newborns has some particularities like a very low limit of normal glucose concentration compared to adults and a large range of normal hematocrit values… In this retrospective study, we identified over a 1-year study period 1,324 paired glycemia results."

The authors of the study used MetaVision by iMD soft to compare glucose results. The authors stated:

"We therefore have quite often the opportunity to compare glucose results of the reference method with one of the POCT

So What is the Difference?

Ray Braxton, RRT; Paul Garbarini, RRT

As a member of a leadership team conducting an interview of a candidate for a staff respiratory therapist position, I [Ray Braxton] have been known to ask the question: "So tell me the difference between a pressure control (PC) breath versus a pressure support (PS) breath?" After what seems like several minutes the typical response is: "Well, a PC breath is a control breath with a set rate and a PS breath is a spontaneous breath with no set rate." We in the respiratory care profession speak a special language that comes from our formal training and years of experience as respiratory therapists. When we use the word control in explaining a mode of ventilation, we usually infer that set variables such as volume, pressure, flow and/or time are controlled, and usually at a set frequency. On the other hand, when we use the word spontaneous we usually infer that the patient initiates or triggers each breath and has control on how the breath cycles to expiration.

At this point in the interview conversation, I generally give an example of a patient who is on a PC-IMV mode of ventilation with intermittent PS breaths and identical pressure settings. I draw identical pressure-time scalar tracings on a piece of paper representing each breath type asking the applicant to distinguish between which breath is PC versus PS. The following screen shot taken from a Hamilton G5 ventilator depicts this situation.

Can you distinguish between these two breath types from this screen shot taken from a test lung simulation on PC-SIMV mode? As you can see, the pressure and flow scalar tracing are very similar in shape and duration with a set pressure setting of 15 cm H_2O for both PC and PS breaths. In this example the 1st and 3rd breath are PC breaths with a set inspiratory time of 1.2 seconds. With a set frequency of 20 breaths per minute, the timing window (sometimes referred to as "total phase time" or "total cycle time") becomes 3 seconds. The interval between the 1st and 2nd along with the 3rd and 4th breath is approximately 2.5 seconds. Therefore, the 2nd and 4th breaths are patient triggered PS breaths as indicated by the triangle shaped marking below the pressure scalar tracing time line.

The cycle to expiration for the PS breath occurs once the inspiratory flow (not expiratory) drops to some percentage of the initial peak inspiratory flow, or absolute flow rate. So pressure support breaths normally are flow cycled. On the Hamilton ventilators, this flow cycle setting for spontaneous breaths is called the Expiratory Trigger Sensitivity (ETS) setting. In this case, flow reaches the set ETS setting, which is set at 10%. The lesson learned here is that a PC breath cycles to expiration based on a set inspiratory time, and the PS breath cycles to expiration primarily based on the ETS setting. This is the answer that I was seeking with my first question to the applicant. Other terminology examples for the flow cycle setting on other ventilators include "Esens" (PB), "PSVcycle"(Avea), "End Flow Level"(GE), and "Inspiratory Cycle Off" (Servo).

This leads me to my next question for the applicant: "In what clinical situations are adjustments to the ETS setting needed?" This often leads to another period of silence from the applicant. Usually, their response is: "Well, I usually leave it set at its default setting of 25%." The value of setting the ETS appropriately cannot be over-emphasized. There are clinical situations that the patient presents when the RT needs to turn the ETS setting up or down and not just leave it on its initial startup setting. Below is an example of what happens to a PS breath when there is a significant leak in the system, and an ETS setting of 5%. Notice, the 1st and 2nd breaths are PC breaths that cycle to expiration after a set inspiratory time of 1.2 seconds. The 2nd breath is a PS breath with a prolonged inspiratory phase of nearly 3 seconds, which could lead to asynchrony for the patient.

This is a common situation that the RT faces when setting the patient on a mode with PS breaths when there is a leak around an endotracheal tube (ie uncuffed ETT) and/or air leaks from chest tube placement. In this example, a higher ETS setting is required to establish synchrony with the patient's breathing. This situation occurs frequently when providing mechanical ventilator support to a pediatric or neonatal patient. This is a skill that most RTs working with pediatric and/or neonates acquire. Each brand of ventilator also has secondary cycling criteria to terminate a spontaneous/pressure support breath if the flow cycle criteria is not met. Typically, if the pressure support setting is exceeded by 2-3cm H_2O, the breath will cycle off. This is often the case when the patient is actively exhaling prior to the ventilator cycling into expiration, and can be identified by a spike at the end of the pressure-time scalar tracing or waveform (see example below). This is a sign that the flow cycle needs to occur earlier in the breath. Additionally, each ventilator has an absolute limit on inspiratory time for spontaneous breaths. This is 3 seconds for Hamilton ventilators, but it can also be adjusted to shorter times in pediatric and neonatal application, as well as non-invasive application.

Another example of when an adjustment in the ETS setting is needed can be seen when placing a patient with advanced chronic obstructive pulmonary disease (COPD) on PS mode. In the example above right, the patient is grunting himself into expiration on each breath as detected by the pressure spikes at the end of the pressure-time scalar tracing. This imposes work on the patient to breathe during the expiratory phase of the breath, and is an example in which a PS breath may be cycled to expiration by the creation of pressure spike of 2-3 cm H_2O above baseline. In this situation, the ETS setting should be adjusted to a higher % setting until there are no longer pressure spikes detected. This may require increasing ETS to as high as 70% - 80% in some cases of advanced COPD.

In COPD patients with long "emptying"/expiratory times due to long time constants, the ETS/flow cycle criteria often needs to be adjusted to let the breath cycle off at a higher inspiratory flow level. This is because it takes much longer for inspiratory flow to drop. So even if the patient is not actively exhaling or "grunting" to cycle off the breath, adjusting the ETS/flow cycle criteria is often necessary to allow for more expiratory time to reduce air trapping/autopeep.

Most mechanical ventilator manufacturers will incorporate as many as 3 to 5 conditions in which a PSV breath will cycle to expiration. A review of the operator's manual for a specific mechanical ventilator will usually provide this information. It is important to understand precisely how the flow cycle criteria is set for each ventilator. For example, with Hamilton ventilators, the "ETS" is expressed as a percent. So if one increases the ETS setting from 25% to 70%, the PS breath will cycle off sooner as inspiratory flow only has to drop to 70% of the initial inspiratory flow vs down to 25% of the initial flow. A practical way to view adjustment of the flow cycle criteria is that by adjusting this setting you are adjusting the inspiratory time for spontaneous/pressure support breaths.

Adjustments to the ETS may also be essential to successful non-invasive/mask ventilation with a mechanical ventilator in which leaks are routine. In the presence of leaks, it may be necessary to increase the ETS setting to allow the breath to cycle off sooner. Some ventilators, such as the latest Hamilton ventilators, now incorporate automatic leak compensation algorithms which can adapt both the inspiratory flow trigger and expiratory flow termination criteria to compensate for leaks, therefore minimizing the need to make manual adjustments in this scenario.

Today's modern mechanical ventilators generally all come equipped with some level of graphic monitoring. The ability of the RT to interpret the scalar tracings and loops provided and fine-tune the adjustments such as ETS are a part of the art of practicing respiratory care. Hopefully, the previous explanations and examples will be helpful for those who may be faced with a clinical question during an interview such as being asked to provide a more detailed distinction between a PC versus a PS breath.

Product Study: air-Q

The air-Q intubating laryngeal airway is a supraglottic airway device which may overcome some limitations inherent to the classic laryngeal mask airway for tracheal intubation. The authors of a study published in Pediatric Anesthesia reported on a series of cases with patients with anticipated difficult airway in whom the air-Q device was used successfully as a conduit for fiberoptic intubation.*

Background
The laryngeal mask airway has been demonstrated to be effective as a conduit for tracheal intubation in pediatric patients with a difficult airway. Though the LMA has undergone advancements to facilitate tracheal intubation in adults, the authors note that such advancements were not previously available for application to children. The advantages of LMA-assisted tracheal intubation are ease of placement, reliable alignment of the glottic opening, the ability to continuously oxygenate and ventilate the patient, and minimizing disconnection time from the breathing circuit. The air-Q intubating laryngeal airway supraglottic airway device has been designed to overcome the limitations of classic LMA for tracheal intubation. Its advantages include: a shorter, more curved shaft, an easily removable airway adapter, lack of a grill in the ventilating orifice, and the ability to remove the laryngeal airway after tracheal intubation with or without a stabilizing rod. The authors present several cases of patients with anticipated difficult airway in whom the air-Q was successfully used as a conduit for fiberoptic intubation.

I. 2-Year Old With Hurler's Syndrome
A 2-year-old boy with Hurler's syndrome was to undergo ventriculo-peritoneal shunt revision. Two months before the revision, the boy had been difficult to ventilate after inhalation induction. A Cormack and Lehane Grade IV was noted upon direct laryngoscopy. A number 2 classic LMA was placed revealing a C&L II view of the glottis through a fiberoptic bronchoscope, and the patient was successfully intubated with a 4.0 uncuffed TT via the LMA. A new supraglottic revealed a limited oropharyngeal space secondary to mucopolysaccharide deposits resulting in a mouth opening of 12 mm. Intramuscular

ketamine was administered, and IV access established. When positive pressure ventilation was adequate, paralysis was instituted with rocuronium. A size 1.5 air-Q ILA was inserted with a leak pressure of 24 cm H_2O followed by fiberoptic-assisted tracheal intubation with a 4.0 mm ID cuffed TT.

II. 2-Year Old With Large Bilateral Maxillomandibular Dysplastic Mass
A 2-year-old girl with a large bilateral maxillomandibular dysplastic mass presented for excision. CT scans revealed an expanding fibrous mass involving both the maxilla and the mandible. Previous records documented easy mask induction and placement of a 1.5 LMA for the CT scans. The girl's mouth opening was now less than 2 cm. Inhalation induction was performed with sevoflurane in oxygen, and PPV was instituted. IV access was obtained and paralysis was established with rocuronium. An air-Q ILA size 1.5 was placed with a leak pressure of 26 cm H_2O and the patient was intubated with a 4.5 ID cuffed TT over a fiberoptic scope.

III. 6-Year-Old With Treacher-Collins Syndrome
A 6-year-old boy with Treacher-Collins syndrome was to undergo dental extractions. For a previous mandibular distraction surgery, mask ventilation was noted to be easy and an oral fiberoptic intubation was successfully accomplished, although difficult secondary to a large epiglottis. Airway examination revealed a mouth opening of 13 mm with significant micrognathia. Anesthesia was the same as described above for patient II. An air-Q ILA size 1.5 was placed without difficulty, with a leak pressure of 30 cm H_2O and the patient was intubated with a 5.0 ID cuffed TT using a fiberoptic scope.

IV. 7-Year-Old With Goldenhar Syndrome
A 7-year-old boy with Goldenhar syndrome was scheduled for mandibular extraction. Prior history was significant for easy mask ventilation, but limited visualization by direct laryngoscopy and difficult tracheal intubation. Airway examination revealed a limited mouth opening of 15 mm and micrognathia. The patient was sedated with 70% nitrous oxide in oxygen and an IV was placed. Anesthetic induction was achieved with propofol. An air-Q ILA size 2 was placed with a leak pressure of 26 cm H_2O and the patient was intubated with a 5.5 ID cuffed TT and a fiberoptic scope.

V. A 16-Month-Old Girl With Hunter's Syndrome
A 16-month-old girl with Hunter's syndrome presented for magnetic resonance imaging of the brain and spine. At age 10 months she was found to have limited visualization upon direct laryngoscopy. She was a difficult intubation and was intubated with a fiberoptic scope with a 3.5 uncuffed TT through a no. 1.5 LMA for a ventriculo-peritoneal shunt placement. Airway examination revealed a limited oropharyngeal space due to mucopolysaccharide deposits. A size 1 air-Q ILA was placed with

a leak pressure of 28 cm H_2O and the patient was intubated with a 4.0 mm ID cuffed TT using a fiberoptic scope.

Securing the Airway

All patients received 10 mcgÆkg)1 of IV glycopyrrolate to minimize secretions. The air-Q was deflated and inserted using a rotational technique. The cuff of the air-Q ILA was inflated according to the manufacturer's instructions: Size 1 required <3 ml, size 1.5 required <5 ml, and size 2 required 5–10 ml. The authors' goal was to achieve a minimum leak of 20 cm H_2O while staying within the manufacturer's guidelines for cuff inflation. Leak pressures were obtained by auscultation over the anterior neck while observing the ventilator manometer during a positive pressure breath. Subsequently, mechanical ventilation of about 10 mlÆkg) using pressure-limited ventilation was instituted. The airway adapter of the air-Q ILA was removed prior to proceeding with a fiberoptic-assisted intubation. A TT was loaded on to the fiberoptic scope prior to insertion into the trachea. The patients were ventilated through the TT still within the air-Q to verify bilateral breath sounds and end-tidal carbon dioxide. The air-Q ILA was easily removed without the aid of a "pusher" or stabilizing rod after intubation. Removal of the air-Q ILA required removal of the TT adapter, deflation of the air-Q ILA, downward traction on the TT, and distal control of the TT with the forefinger and thumb, while withdrawing the laryngeal airway. All patients were successfully extubated over an airway exchange catheter.

Summary

Classic LMA has some limitations when it is used as a conduit for intubation. The shaft of the LMA can be as long as the TT, making it difficult to maintain control of the TT while removing the LMA. Either a long tracheal tube, a double tracheal tube assembly, or a stabilizing rod is required to overcome the length of the LMA. Shortening the shaft of the LMA or leaving the LMA in place for the duration of surgery have also been suggested to minimize these potential risks. The airway connector of the LMA is not wide enough to allow passage of the cuffed TT pilot balloon. This would result in the pilot balloon "hanging up" within the shaft of the LMA and potentially breaking upon attempted withdrawal of the LMA. When using disposable LMAs, the grill may have to be cut to permit a larger or cuffed TT when compared with its nondisposable counterpart.

The air-Q ILA has several key structural differences from the classic LMA and thus has the potential to overcome the above limitations. Since the shaft of this airway is much shorter and curved, enough of the proximal TT is still above it, allowing for removal of the air-Q without the aid of a stabilizing rod. The air-Q ILA can be easily removed with a specially designed removal stylet to prevent dislodging the TT. In the cases outlined above, the authors were able to remove the air-Q ILA without the use of this stylet to stabilize the TT in the larynx. The airway connector of the air-Q ILA is easily removable, eliminating the potential area where the pilot balloon of the TT can get stuck. The air-Q doesn't have a grill, and pediatric sizes 1, 1.5, 2, and 2.5 can accommodate up to cuffed TT sizes of 4.0, 5.0, 5.5, and 6.0 mm ID. This issue is clinically applicable in patients with a limitation in mouth opening in whom only smaller laryngeal airways may fit, while the placement of a size-appropriate cuffed TT is needed. The authors found the rotational insertion technique of the deflated air-Q ILA to be the most successful. Prior to conducting this case series, they placed several air-Q ILAs in children with normal airways and found this to be easiest. In all patients the TT was inserted into the trachea on the first attempt with no decrease in oxygen saturation. An AEC was placed through the TT prior to extubation as a means to re-intubate if needed. The AEC was removed when the patient exhibited adequate respiratory effort, facial grimacing, and hip flexion. There were no postoperative airway complications in any of the patients.

The air-Q ILA is available in sizes 1, 1.5, 2, 2.5, 3.5, and 4.5 for single use and sizes 2.0, 2.5, 3.5, and 4.5 for reusable use. Sizing of the pediatric air-Q ILA, as for the LMA, is weight-based. A size 1 is designed for patients <5 kg, size 1.5 for 5–10 kg, size 2 for 10–20 kg. In the case series presented here, various cuffed TT sizes can be placed through the same size air-Q ILA as seen with patients I through III, above. The patients demonstrated that a smaller than weight-based size air-Q ILA can be used without compromising ventilation parameters and to allow for tracheal intubation with an appropriately sized cuffed TT. This would not have been possible with an equivalently sized classic LMA. The shaft of the classic LMA does not permit passage of a larger diameter TT or the pilot balloon of a cuffed TT. While the use of the air-Q may not improve the view when used in conjunction with a flexible fiberoptic scope in the presence of blood and secretions, the alignment with the glottis anatomy may allow for increased success in the use of a "light guided" or blind technique for intubation. When intubating neonates, if a continuous ventilation technique is employed, a standard bronchoscope adapter will add length to the shaft of the air-Q ILA, necessitating the use of a stabilizing rod. Once the air-Q ILA airway connector is removed, the bronchoscope adapter will no longer be able to be connected to the shaft.

The authors concluded: "We believe the use of the air-Q ILA may be a well-suited alternative to the classic LMA in children with difficult airways, especially when a cuffed TT is desired. In these patients with restricted mouth opening, this airway offers many advantages over the traditional LMA-assisted intubation… This device may prove to be a valuable tool in the management of a difficult pediatric airway."

Endnote

In a correspondence in a subsequent issue of the journal in which the aforementioned air-Q study appeared, the respondents wrote: "By way of contribution to this debate, we report the successful use of the ILA in two pediatric patients with a predicted difficult airway and discuss solutions to some practical problems we have encountered in our early experiences with this device." Their first patient was ideally suited for a supraglottic device-assisted technique. The size 2.5 device gave a good airway seal at pressures that allowed easy positive pressure ventilation. A stylet helped to overcome a problem particular to pediatrics, where the ETT can be contained entirely within the shaft of an LMA. The stylet effectively lengthens the ETT to sufficiently allow continuous retention of control of the ETT throughout withdrawal of the ILA over the ETT, which is helpful in reducing the risk of accidental extubation. While the note's authors agreed that the ILA could be withdrawn over the ETT without extending the ETT because of the short, hyper-curved style, they noted that this was awkward. Tube hold-up at the ILA exit caused some difficulty. The authors noted that they did not adequately lubricate the lumen of the ILA airway. With better lubrication, they did not have this problem during subsequent intubations through the device. By contrast, in another case, *Continued on page 62…*

Neonatal Resuscitation and Immediate Newborn Assessment and Stimulation for the Prevention of Neonatal Deaths

Anne C.C. Lee, Simon Cousens, Stephen N. Wall, Susan Niermeyer, Gary L. Darmstadt, Waldemar A. Carlo, William J. Keenan, Zulfiqar A. Bhutta, Christopher Gill, Joy E. Lawn.

Abstract

Background: Of 136 million babies born annually, around 10 million require assistance to breathe. Each year 814,000 neonatal deaths result from intrapartum-related events in term babies (previously "birth asphyxia") and 1.03 million from complications of prematurity. No systematic assessment of mortality reduction from tactile stimulation or resuscitation has been published.

Objective: To estimate the mortality effect of immediate newborn assessment and stimulation, and basic resuscitation on neonatal deaths due to term intrapartum-related events or preterm birth, for facility and home births.

Methods: We conducted systematic reviews for studies reporting relevant mortality or morbidity outcomes. Evidence was assessed using GRADE criteria adapted to provide a systematic approach to mortality effect estimates for the Lives Saved Tool (LiST). Meta-analysis was performed if appropriate. For interventions with low quality evidence but strong recommendation for implementation, a Delphi panel was convened to estimate effect size.

Results: We identified 24 studies of neonatal resuscitation reporting mortality outcomes (20 observational, 2 quasi-experimental, 2 cluster randomized controlled trials), but none of immediate newborn assessment and stimulation alone. A meta-analysis of three facility-based studies examined the effect of resuscitation training on intrapartum-related neonatal deaths (RR= 0.70, 95%CI 0.59-0.84); this estimate was used for the effect of facility-based basic neonatal resuscitation (additional to stimulation). The evidence for preterm mortality effect was low quality and thus expert opinion was sought. In community-based studies, resuscitation training was part of packages with multiple concurrent interventions, and/or studies did not distinguish term intrapartum-related from preterm deaths, hence no meta-analysis was conducted. Our Delphi panel of 18 experts estimated that immediate newborn assessment and stimulation would reduce both intrapartum-related and preterm deaths by 10%, facility-based resuscitation would prevent a further 10% of preterm deaths, and community-based resuscitation would prevent further 20% of intrapartum-related and 5% of preterm deaths.

Conclusion: Neonatal resuscitation training in facilities reduces term intrapartum-related deaths by 30%. Yet, coverage of this intervention remains low in countries where most neonatal deaths occur and is a missed opportunity to save lives. Expert opinion supports smaller effects of neonatal resuscitation on preterm mortality in facilities and of basic resuscitation and newborn assessment and stimulation at community level. Further evaluation is required for impact, cost and implementation strategies in various contexts.

Background

Initiation of breathing is critical in the physiologic transition from intra-uterine to extra-uterine life. Between 5-10% of all newborns require assistance to establish breathing at birth, and simple warming, drying, stimulation and resuscitation may reduce neonatal mortality and morbidity. Each year an estimated 814,000 neonatal deaths are related to intrapartum hypoxic events in term infants, previously termed "birth asphyxia," and over one intrapartum million stillbirths occur. Especially in under-resourced settings it may be challenging to distinguish a stillborn from a severely depressed newborn. In addition over one million newborns die from complications of preterm birth, such as respiratory distress syndrome, and these babies also require assistance to breathe at birth.

Neonatal resuscitation is defined as the set of interventions at the time of birth to support the establishment of breathing and
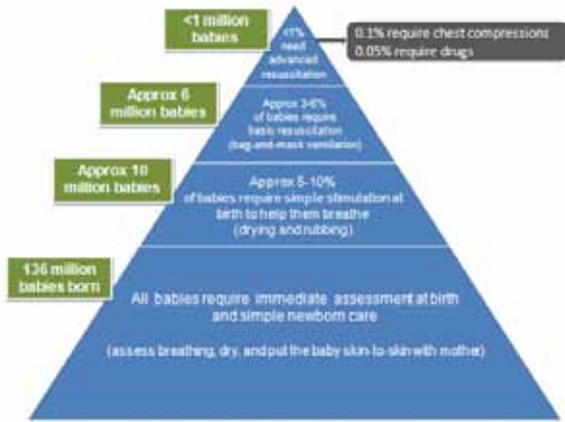
Figure 1. Estimate of annual number of all newborns who require assistance to breathe at birth and varying levels of neonatal resuscitation. Legend: Adapted from [1] using data from [2,3,5,6,20].

circulation. Of 136 million births annually, an estimated 10 million will require some level of intervention. Some non-breathing babies with primary apnea will respond to simple stimulation alone, such as drying and rubbing (Figure 1). Basic resuscitation with a bag-and-mask is required for an estimated 6 million of these babies each year, and is sufficient to resuscitate most neonates with secondary apnea, as their bradycardia primarily results from hypoxemia and respiratory failure. More advanced measures, including endotracheal intubation, chest compressions and medications are required in <1% of births (Figure 1), and most of these babies require ongoing intensive care which is not available in most low income country settings. Supplemental oxygen is not associated with survival benefit in term infants, although the effect may differ in very preterm infants.

While systematic training in resuscitation of the newborn is a cornerstone of modern neonatology, there have been few rigorous evaluations of its effectiveness, partly because the intervention was standard practice before the advent of randomized controlled trials (RCTs), and randomization of individuals or clusters to no treatment would now be considered unethical. However, in low income countries, particularly in South Asia and sub-Saharan Africa, which account for over two-thirds of the world's neonatal deaths, resuscitation is not available for the majority of newborns who are born either at poorly staffed and equipped first-level health facilities, or at home (60 million births annually), where birth attendants may lack skills or may perform practices that delay effective ventilation.

Neonatal resuscitation is receiving increasing attention especially as a missed opportunity for saving lives for births already in facilities, and for improving morbidity outcomes. Increased momentum for scale up in low-middle income countries has resulted from the release of a simplified

resuscitation algorithm and training package led by the American Academy of Pediatrics (http://www.helpingbabiesbreathe.org/), evidence that neonatal resuscitation with room air is effective, and the invention of lower cost, appropriate equipment and training manikins, plus a consortium of implementing partners. In a survey of policymakers and program managers regarding "birth asphyxia," evaluating the effectiveness of neonatal resuscitation, particularly at the community level, emerged as a top research priority. Several recent reviews of neonatal resuscitation in low-middle income settings have concluded that neonatal resuscitation has the potential to save newborn lives; yet, effect estimates of mortality reduction are lacking to guide program planners as to how many lives could be saved by immediate assessment and stimulation, which may be feasible with less skilled workers and no equipment, and the additional effect of basic neonatal resuscitation, including airway positioning and clearing, and bag-mask resuscitation (table 1). The objective of this review is to provide estimates for use in the Lives Saved Tool (LiST), of the effect of immediate newborn assessment and stimulation, and the additional effect of basic neonatal resuscitation, on neonatal mortality from two causes of neonatal death (intrapartum-related deaths in term infants ("birth asphyxia") and complications of preterm birth) and in two contexts (facility and community).

Methods

This review is one of a series of standard reviews to provide consistent and transparent estimates of mortality effect used in the Lives Saved Tool (LiST), a model to assist evidence-based program planning. LiST is described in greater detail elsewhere. In LiST, the estimation of lives saved depends on national estimates of causes of death for mothers, newborns and children under five, and the planned changes in national coverage estimates for given interventions, with a resultant reduction in cause-specific mortality. The sources and methods for each input are being provided in the public domain. The cause of death data is developed by the Child Health Epidemiology Reference Group (CHERG) with the United Nations each year and includes a country review process. Intervention coverage data is based on national coverage estimates, or in the absence of appropriate recent data, the assumptions are described elsewhere. This mortality effect review follows standard methods adapted from GRADE by the CHERG as described previously. We undertook a systematic review of the literature from 1980 until March 2010. The following databases were searched without language restrictions but limited to "human": PubMed, Popline, Cochrane, EMBASE, IMEMR (Index Medicus for the WHO Eastern Mediterranean Region), LILACS (Latin American and Caribbean Health Sciences Literature), and African Index Medicus. The search terms included MeSH terms and combinations of "newborn/neonatal resuscitation," "neonatal mortality," "birth asphyxia," and "asphyxia neonatorum." Snowball searching added literature referenced in key papers. The review for immediate newborn assessment and stimulation was conducted as part of extensive literature reviews of interventions for "birth asphyxia." Efforts were also made to contact investigators and program managers for unpublished data.

Data from studies meeting

Table 1 Definition of Interventions

Immediate assessment and stimulation of the newborn baby

Immediate assessment, warming, drying and tactile stimulation (rubbing with the drying cloth, rubbing the back or flicking the feet) of the newborn at the time of birth. This is not the same as the WHO package of essential newborn care which is more complex and includes immediate breastfeeding, resuscitation, thermal care, eye care, immunization etc.

Basic Newborn Resuscitation

Airway clearing (suctioning if required) head positioning and positive pressure ventilation via bag-and- mask.*

Advanced Newborn Resuscitation (not estimated for LiST)

Basic neonatal resuscitation (as above) *plus* endotracheal intubation, supplemental oxygen, chest compressions, and medications.

*Note: While basic newborn resuscitation includes immediate assessment and stimulation, the effect estimated for the purposes of the LiST tool is the additional effect of basic resuscitation in addition to stimulation as the program implications differ in terms of skills and equipment.

Searches and screening
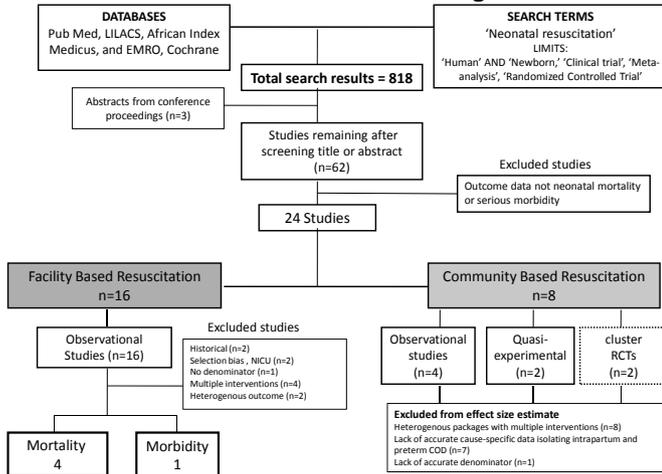
Figure 2 Search, screening and selection of studies reporting effect of neonatal resuscitation on neonatal mortality and morbidity.

the inclusion criteria were extracted using a standard form and re-checked. We abstracted information on study identifiers, context, design and limitations, intervention definitions, and outcomes (table 1). We assessed the quality of each study using the standard approach adapted from GRADE developed by the CHERG. For studies with data missing or requiring clarification, we contacted principal investigators.

We used the PICO format for inclusion/exclusion – Patient, Intervention, Comparison, Outcome. The patient of interest is the newborn baby who is not breathing at birth. We considered the following study designs: randomized controlled trials, observational before-and-after or quasi-experimental. Only studies reporting outcomes for an intervention and a comparison or control group (either historical or concurrent) were included.

We estimate the effects of two interventions: 1) Immediate newborn assessment and stimulation (warming, drying and rubbing the back or flicking soles of the feet). 2) Basic newborn resuscitation, defined as airway clearing (suctioning), head positioning and positive pressure ventilation via bag-and-mask or tube-and-mask (noting that tube-and-mask device is no longer recommended for use) (table 1).

While basic newborn resuscitation includes newborn assessment and stimulation, for the purposes of the LiST model, the estimate is of the additional incremental mortality effect. Advanced resuscitation procedures (including chest compressions, supplemental oxygen, intubation or administration of medications) are very rarely required (Figure 1), unfeasible or unavailable in most low-resource settings, and unlikely to have substantial additional mortality benefit over basic resuscitation in settings without ongoing neonatal intensive care. Thus, the aim of this review was to estimate the impact of basic resuscitation. We do not separately estimate the incremental mortality effect for advanced resuscitation procedures. The effect of breastfeeding, postnatal thermal care practices, and kangaroo mother care for preterm babies, are reviewed elsewhere for LiST and not included here.

A neonatal death was defined as a death in the first 28 days of life, early neonatal death as death in the first 7 days of life, and perinatal death as a stillbirth (≥1000 gms, ≥28 weeks gestation) or death in the first 7 days of life. Studies that reported neonatal mortality, early neonatal mortality, perinatal mortality, "asphyxia"-specific mortality, mortality from complications of preterm birth, or incidence of neonatal encephalopathy were included for assessment.

The definitions used for cause-specific neonatal mortality have changed over time. WHO has previously defined "birth asphyxia" as "the failure to initiate and sustain breathing at birth," indicating the clinical need for neonatal resuscitation, a syndromic state also commonly referred to as neonatal or perinatal respiratory depression. This clinical approach combines two cause-specific mortality outcomes which should be separated for cause of death attribution, notably (1) term babies with intrapartum brain injury and (2) preterm infants who do not breathe at birth. The term "birth asphyxia" is no longer recommended for epidemiological use, especially for cause-of-death attribution, as it combines differing ICD categories with differing prevention strategies. The preferred terminology is "intrapartum-related neonatal death" which refers to term babies with neonatal encephalopathy, or death prior to onset of neonatal

Table 2 Observational studies of neonatal resuscitation training programs in facility settings with mortality outcomes

Author	Setting/ Country	Study Design	Intervention definition	Outcomes: definition	Distinguish Preterm from Intrapartum Deaths	N (Births) A = Baseline B = Endline	Effect Size RR/OR (95%CI)
Zhu XY et al 1997 [3]	Urban Hospital China	Before-and-after study	AAP NRP training at of all delivery room staff at hospital	1) Early Neonatal Mortality (first 7 days): ALL cause	Not stated	A) 1,722; B) 4,751	1) RR 0.34 (0.17-0.67)
Deorari AK et al 2001 [2]	14 University Hospitals, India	Before-and-after study	AAP NRP training of 2 faculty/hospital, subsequent training of DR room nurses and doctors; competency based certification	1) Asphyxia neonatal mortality [Features of fetal hypoxia and 5 min Apgar <6 following complications of pregnancy or delivery]; 2) Hypoxic Ischemic Encephalopathy; 3) Preterm mortality [BW < 1000 g with HMD, IVH or AOP]	Excluded BW < 1000 g, death from HMD/IVH or AOP	A) 7,070; B)25,713	1) RR 0.70 (0.56-0.87) 2) RR 1.68 (1.06-2.67) 3) RR 0.95 (0.74-1.24)
Vakrilova L et al 2005 [44]	All hospitals with delivery rooms in Bulgaria	Before-and-after study	French-Bulgarian Program on Newborn Resuscitation, training in all obstetric wards in country	1) Asphyxia Neonatal Mortality [ICD 9 'perinatal and intrapartum asphyxia'], 2) Early neonatal mortality (first 7 days) 3) Preterm complication [ICD-9 'immaturity related' and 'respiratory distress syndrome']	Excluded death due to preterm complications by ICD-9	A) 67,948; B) 67,647	1) RR 0.83 (0.54-1.27) 2) RR 0.86 (0.74-1.01) 3) RR 1.33 (1.03-1.73)
Carlo, et al 2010 [38]/ Chomba E et al 2008 [39]	18 Urban Low-risk delivery centers, Zambia	Before-and-after study, then RCT	WHO ENC Package, including basic resuscitation with bag-mask,taught by demonstration, clinical practice sessions, and performance evaluations; followed by longer in depth training in NRP including bag-mask ventilation and chest compressions	1) Asphyxia Early Neonatal Mortality (7 d), [not breathing at birth]; 2) Early Neonatal Mortality [first 7 days]; 3) Preterm Mortality [preterm or BW <1500]	Preterm or LBW (< 1500 g) as separate cause of death, though no hierarchy specified for single cause of death	A) 8,148; B) 20,534	1) RR 0.56 (NS) 2) RR 0.60 (0.48-0.76) 3) RR 0.74 (NS)

Table 3 Additional observational studies of neonatal resuscitation training programs in facilities, excluded from meta-analysis

Author	Setting/ Country	Study Design	Intervention definition	Outcomes: definition	Preterm vs. Intrapartum	N (Births) A = Baseline B = Endline	Effect Size RR/OR (95%CI)
Zhu et al* 1993[45]	Health center, Yinshan, China	Before-and-after study	ABCDE protocol of modern resuscitation with labour ward personel	1) Asphyxia Case Fatality	Not Stated	A) Number of resuscitations 184 223	1) RR 0.94
Tholpadi SR et al* 2000 [40]	32 peripheral health centers; Kerala, India	Before-and-after study	AAP NRP Training of village health center physicians, nurses, birth attendants; performance checklist; refresher in 3 months	1) Asphyxia 2) Asphyxia Mortality (definitions not stated)	Not Stated	A) 874; B) 960	1) RR 0.68 (0.15-3.04)
Jeffery HE et al* 2004 [33]	3 Tertiary care, 13 District Hospitals; Macedonia	Before-and-after study	10 month perinatal training program doctors and nurses (Neonatal resuscitation, thermal care, jaundice, respiratory distress syndrome, infection control)	1) PMR 2) Fetal mortality 3) NMR	< 1000 g excluded	A) 68,755 B) 44,263	1) RR 0.72 (0.66-0.78) 2) RR 0.79 (0.71-0.89) 3) RR 0.64 (0.56-0.72)
O'Hare BA et al* 2006 [49]	Teaching Hospital; Kampala, Uganda	Before-and-after study	Team of nurses trained in basic resuscitation to attend all deliveries in 1 month period, performance based evaluation;	1) Mortality of NICU admissions	Preterms excluded	A) 1296; B) 1,046	20.8% in control vs. 17.3% in pilot
Duran R et al* 1998 [42]	Tertiary Care Hospital; Trakya, Turkey	Before-and-after study	NRP courses in Trakya region, Turkey 2003 & 2004	1) "Asphyxia" NICU admissions 2) Duration of asphyxia hospitalization	Not Stated	Not Stated	1) 35 vs 13 NICU admissions for asphyxia 2) 15 to 6 days
Draycott et al* 2006[37]	Maternity Unit; South Meade, UK	Before-and-after study	EOC training course: CTG obstetric emergency drills, and neonatal resuscitation	1) HIE (MacLennan):	Not Stated	A) 8,430 B) 11,030	1) RR 0.50 (0.26-0.95)
Wang H et al* 2008 [41]	17 general, 23 maternal child health hospitals; China	Before-and-after study	Nationwide AAP NRP training, started in 2004 in 20 provinces	1) Asphyxia Mortality [Delivery room death infant 1 min Apgar <7]	Preterms not excluded	A) 51,306; B) 68, 247	1) RR 0.67 (0.34-1.30)
Mufti P et al* 2006[35]	Teaching Hospital, Karachi, Pakistan	Before-and-after study	Training in management of low birthweight, respiratory distress, feeding, neonatal sepsis, and neonatal resuscitation.	1) PMR 2) NMR	Not Stated	A) 2871 B) 4106	1) RR 0.85 (0.69-1.05) 2) RR 0.72 (0.51-1.02)
Boo et al* 2009 [43]	National training in all states Malaysia	Historical/ ecological study	AAP NRP, national training and certification Perinatal Society; written/ practical test for certification; retraining	1) PMR; 2) NMR (all cause)	Not Stated	National annual births over 8 years	Annual NMR reported over 8 years
Sen et al* 2009 [34]	District Hospital, Purulia India	Before-and-after study	Training in neonatal resuscitation, equipping labor room-OR with resuscitation equipment.	1) Labor room death (hospital)	Not Stated	A) 5077 B) 6704	1) RR 0.56 (0.42-0.75)
Opiyo N et al* 2008 [46]	Public Hospital, Nairobi, Kenya	RCT and before-after	Training of delivery room nurses-midwives in adapted UK resuscitation council. Written-clinical competency assessment.	1) NMR (all cause)	Not Stated	A) 4367 B) 4084	NMR 25(pre) vs 26.2 (post-intervention)
Berglund et al* 2010 [36]	Three maternity wards, Ukraine	Before-and-after study	Training maternity staff WHO "Effective Perinatal Care" including emergency obstetric and neonatal care. All maternities equipped for resuscitation	1) Early NMR	Not Stated	A) 1696 B) 2439	No significant effect on ENMR

high quality evidence, but with a strong GRADE recommendation for implementation, we sought expert opinion via a Delphi process. We invited a panel of experts in newborn and public health including multiple disciplines – program management, research and clinical general pediatrics and neonatology. The questionnaire was developed by JL, SW, and ACL, and refined by pilot testing. The questionnaire was sent by email and included background to the Delphi process and asked for estimates of the effect for five scenarios. Respondents were allowed the option of anonymous response. Consensus was defined a priori as an inter-quartile range of responses to a given question of ≤30%.

Results

In the literature review, we identified 818 titles of articles of potential interest (Figure 2), and after initial screening of titles and abstracts, we retrieved 62 papers, reports or conference abstracts for review. We located 24 studies that reported the impact of neonatal resuscitation training on mortality outcomes: 16 studies in facilities, and 8 studies in community settings. Conference abstracts for 3 studies were identified and authors were contacted for further data, and there was one unpublished program report. All studies except one were from low or middle income settings. No studies were identified that examined the effect of newborn assessment and stimulation

encephalopathy, and evidence of intrapartum injury or acute intrapartum events. Preterm neonatal deaths have been defined by the CHERG based on ICD guidelines for as those deaths due to complications of preterm birth, including respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis, or with gestational age <34 weeks, or birth weight <2000 g. We did not examine Apgar score as an outcome since our goal was to establish mortality effect estimates, and Apgar scores are an unreliable indicator of mortality, long term morbidity or cause (influenced by physiologic immaturity, infection, and medications during labour-delivery).

Analyses and summary measures: We conducted meta-analyses for mortality outcomes of observational before-and-after studies of neonatal resuscitation training in facility settings. Statistical analyses were performed using STATA 11. The Mantel-Haenszel pooled risk ratio (RR) or, when there was evidence of heterogeneity (p<0.10), the DerSimonian-Laird pooled risk ratio, was estimated together with a 95% confidence interval (CI). We summarized the overall quality of evidence for each outcome and each data input type using an adapted version of the GRADE protocol table.

Delphi process for establishing expert consensus: For intervention-outcome combinations without moderate or

alone. The details of the studies are given in tables 2, 3 and 6.

The Delphi panel included eighteen experts (90% response rate) representing five WHO regions [Americas (n=6); Southeast Asia (n=4); Eastern Mediterranean (n=2); Africa (n=4); Europe (n=2)], from the following specialties: neonatology (n=7); general pediatrics (n=11) and pediatric infectious disease (n=1). Expert opinion was requested for 5 mortality effects: facility- based basic resuscitation on preterm mortality, community-based basic resuscitation and immediate newborn assessment and stimulation on both intrapartum-related and preterm mortality. Consensus was reached in the first round for all 5 estimates

Evidence for Mortality Impact of Neonatal Resuscitation Training in Facilities: Of 16 observational, facility-based studies of neonatal resuscitation, 14 were before-after studies and 2 were historical reports. Details of each study and the main results are shown in Tables 2 and 3 and the assessment of quality of evidence according to GRADE is shown in table 4.

Intervention descriptions in identified studies: The content and context of the resuscitation training for all facility studies are shown in Tables 2 and 3. Some studies evaluated neonatal resuscitation training as part of a comprehensive perinatal or obstetric care program, and these evaluations were excluded.

Table 4 GRADE assessment of studies of the effect of Neonatal Resuscitation training in facilities on neonatal mortality from Intrapartum-related events (ie. "birth asphyxia")

No of studies	Design	Limitations	Consistency	Generalizability to Population of Interest	Generalizability of intervention of interest	Post-Intervention Events	Control-Baseline Events	Relative Risk (95% CI)
Mortality(Intrapartum-related Neonatal Deaths): Moderate outcome specific mortality								
3 [2,38,44]	Before-and-after	Low quality	No evidence of heterogeneity (P=0.5)	Facility settings (ranging primary to tertiary care level), LIC-MIC	Advanced NRP in 2 studies, WHO Basic ENC in another	360*	185	0.70 (0.59, 0.84)[a]
Mortality(Early Neonatal Deaths): Moderate outcome specific mortality								
3 [3,38,44]	Before-and-after	Low quality	Strong evidence of heterogenity (P=0.002)	Facility settings (ranging primary to tertiary care level), LIC-MIC	Advanced NRP in 2 studies, WHO Basic ENC in another	454*	458	0.62 (0.41, 0.94)[b]
Morbidity(Hypoxic Ischemic Encephalopathy): Low outcome specific morbidity								
1 [2]	Before-and-after	Low quality	NA	Only 1 study, tertiary care hospital	Advanced NRP	128*	21	1.68 (1.06, 2.66)[c]

a) MH pooled RR; b) D & L pooled RR random effect meta-analysis; c) Directly calculated from study results.
*Note numbers of events in post-intervention period are based on longer duration of observation period than baseline.

In the First Breath study, basic neonatal resuscitation was taught in the first phase as part of an essential newborn care package including bag mask ventilation, then followed by a more in-depth training using elements of the American Academy of Pediatrics Neonatal Resuscitation Program, including immediate assessment and stimulation, bag-mask ventilation and chest compressions. Several studies implemented full advanced neonatal resuscitation (American Academy of Pediatrics Neonatal Resuscitation Program, French Bulgarian, ABCDE, or UK resuscitation council training). However, advanced procedures are rarely used (ie chest compressions or medications required in <0.1% of births), the approaches are similar in content, and the additional benefit is likely to be small in low-resource settings. Thus, studies of basic and basic with advanced neonatal resuscitation were combined as long as they had comparable study design and outcome measures. Several training programs required written and/or clinical practical exam to ensure trainee competency (AAP NRP, UK resuscitation council). Refresher training was conducted in some studies to promote skill maintenance, and is shown in Tables 2 and 3 if reported by investigators.

Outcomes reported in identified studies: The case definitions for intrapartum-related neonatal deaths ("birth asphyxia") and preterm mortality varied between studies (Tables 2 and 3). "Asphyxia" mortality was reported in six facility studies, and was considered in three studies to correspond to term intrapartum-related neonatal mortality. Among these three studies which were included in the meta-analysis, the sources of cause-of-death data were hospital records in the Indian study, the National Health Information Centre in the Bulgarian study, and a prospective research tracking system with midwives trained in assigning cause-of-death in Zambia. The Indian and Bulgarian studies used standard ICD rules to assign a single underlying cause of death. The Zambian study did not use a standard hierarchy to assign single cause of death, and some preterm deaths were possibly assigned to asphyxia. Neonatal mortality due to complications of prematurity was reported separately in the same three studies. The Bulgarian study used ICD-9 coding to assign cause of death (Immaturity-related or Respiratory Distress Syndrome). The Indian study also used ICD cause of death rules, however required birthweight <1000 with complications of prematurity. The Zambian study used gestational age or weight cutoff (<1500g or <37 weeks).

Meta analyses performed and Delphi panel estimates: We performed meta analyses to summarize the results of studies of neonatal resuscitation training as an isolated intervention with comparable study design for the following outcomes: mortality from intrapartum-related events (n=3 studies), or all-cause early neonatal mortality (n=3) (given that the majority of deaths from term intrapartum events and early preterm deaths occur in the first week of life).

The quality of individual studies included in the meta-analyses was assessed by adapted WHO GRADE criteria and considered low for cause-specific mortality, although all were set in low-middle income countries and generalizable to the setting of interest. The main limitation was the before-and-after study design, lacking a concurrent control group, and hence the inability to isolate the effect of resuscitation training alone from other changes at the health facilities during the time period, such as improved intrapartum monitoring or post-resuscitation management. Furthermore, the pre-intervention standard of care was not clearly described in several studies and may have differed between facilities, although in all cases presumably included some aspects of immediate newborn assessment and stimulation. The intervention in some cases may have been broader than basic resuscitation alone. An additional limitation of the Zambian study was high rate of loss to follow-up at 7 days (38% pre-intervention and 25% post-intervention). However, this may not have a major effect given that the majority (>70%) of intrapartum-related neonatal deaths occur during the first day of life, and post-hoc imputations of missing data using maternal and infant characteristics suggest larger magnitude reductions in ENMR after training.

We excluded 12 studies from the meta-analysis.
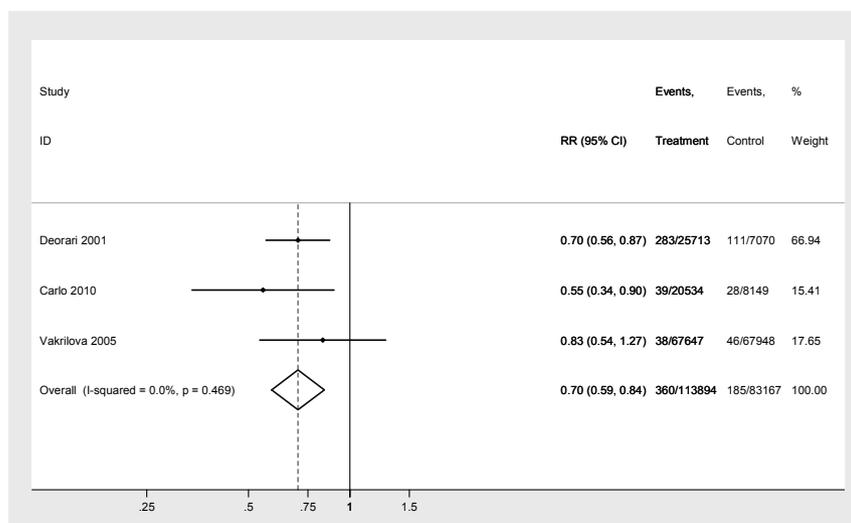
Figure 3. Meta-analysis of before-and-after hospital-based studies examining the effect of additional neonatal resuscitation training on deaths among babies "not breathing at birth".

The Zhu study was excluded as it only reported case fatality ratios for resuscitated newborns, without reporting the total number of births during the observation period. The Tholpadi study was excluded due to the lack of consistent case definitions before and after the intervention. The Draycott, Jeffery, Mufti, Sen, and Berglund studies were comprehensive perinatal training programs that included multiple interventions and did not report intrapartum-related mortality. The Opiyo study was excluded as only all cause-neonatal mortality was reported. The Wang study was excluded as the primary outcome was immediate death among those with Apgar score <7 in the delivery room, which does not capture all intrapartum-related neonatal deaths nor distinguish deaths due to preterm or other complications. The principal investigators of the study were contacted to try to obtain early neonatal mortality data, but this was not available. The Boo study was not included in the meta-analysis as this ecological study spanned 8 years, the coverage of the intervention was unclear and unequally distributed by state, and intrapartum-related outcomes were not reported. The O'Hare and Duran data were excluded as only deaths among those admitted to the Neonatal Intensive Care Unit were reported.

1) Basic neonatal resuscitation effect on intrapartum-related term neonatal deaths ("Birth asphyxia") in facilities: In this meta-analysis of three studies, training in neonatal resuscitation in the facility setting was associated with a 30% reduction in intrapartum-related mortality (RR=0.70, 95% CI 0.59-0.84) (Figure 3). The direction of effect was protective in all studies, and while effect estimates appeared slightly greater in the higher mortality settings (India, asphyxia-specific mortality rate [ASMR] = 15.7/1000; Zambia, ASMR = 3.4/1000) than in Bulgaria, an upper-middle income country, with relatively low mortality (baseline NMR 7.8, ASMR 0.7/1000), there was not strong evidence of heterogeneity of mortality effect between studies (P=0.47). Given the consistency of the data and generalizability to low-middle income countries, the overall grade of evidence for the effect on intrapartum-related mortality was upgraded to moderate.

2) Basic neonatal resuscitation effect on neonatal deaths due to direct complications of preterm birth in facilities: The same three studies reported the impact of resuscitation on preterm mortality. However, the study definitions of preterm mortality were heterogenous between studies (Tables 2 and 3) and in 2 studies a very low birth weight cutoff was used that would have excluded moderately preterm infants who would be most likely to be saved by basic resuscitation without ongoing intensive care. Thus the study data was not pooled in a meta-analysis. Given the strong biologic plausibility (ie. stimulation, thermoregulation, and positive pressure ventilation at birth may prevent hypoxia and hypothermia, particularly in moderate preterm infants), in combination with the low quality of the evidence, further expert opinion was sought. In the Delphi process, basic neonatal resuscitation was estimated to reduce preterm mortality by about 10% in addition to immediate assessment and stimulation (median opinion 10%, Range 4-30%, IQR 10-20%) (table 5).

3) Neonatal resuscitation effect on early neonatal deaths (within 7 days) in facilities: Almost all (98%) intrapartum-related deaths occur in the first week of life, thus, early neonatal mortality may be a useful proxy measure. Three studies were included in a meta-analysis which suggested that neonatal resuscitation training in the facility setting (2 advanced, 1 basic) was associated with a 38% reduction in early neonatal mortality (RR=0.62, 95% CI 0.41-0.94) (Figure 4). There was evidence of heterogeneity between studies (P=0.003) with a smaller effect observed in the Bulgarian study which had a lower baseline early neonatal mortality rate (ENMR) (5.1/1000) than in the Chinese (9.9/1000) and Zambian studies (11.5/1000).

Evidence for mortality impact of neonatal resuscitation in community settings: We identified eight studies of neonatal resuscitation training in community-settings that reported mortality outcomes: two cluster-randomized trials (RCT), two quasi-experimental studies, three observational before-after studies and one study with two components, a before-after study followed by a cluster RCT. A detailed description of the studies and their results is shown in Table 6. Preliminary results were available from one cRCT of TBAs undertaking resuscitation in Bangladesh, however detailed data was not yet available (M Ellis, personal communication).

Intervention descriptions in identified studies: In the community-based studies, basic neonatal resuscitation was typically implemented as part of comprehensive newborn care packages, often including management of low birthweight babies, hypothermia, and neonatal infections. In one cRCT, in half the clusters participatory women's groups were also implemented. Ventilation was provided mouth-to-mouth, or by tube-and-mask or bag-and-mask devices. The providers ranged from traditional birth attendants to community midwives to nurses and physicians. In the First Breath study, bag-mask resuscitation training was a component of the essential newborn case (ENC) package.

Outcome definitions in identified studies: When available, cause-of-death was attributed based on verbal autopsy. In most cases, "birth asphyxia" was based primarily on the clinical symptom of "not breathing at birth" and did not exclude preterm infants with respiratory depression; although the First Breath study excluded infants weighing <1500 g and the Lunesp study provided preterm as a separate cause of death.

Study quality and Delphi panel estimates: The individual study quality for cause-specific mortality

Table 5 LiST estimates for the effectiveness of immediate stimulation, and of basic neonatal resuscitation on cause-specific neonatal mortality

Cause of death to act on	Newborn assessment and stimulation	Basic resuscitation in the community	Basic resuscitation in facility
		Effect (additional to assessment and stimulation)	Effect (additional to assessment and stimulation)
Intrapartum-related neonatal deaths	DELPHI Median 10% (IQR: 5-15%) (Range: 0-25%)	DELPHI Median 20% (IQR: 15-25%) (Range: 10-50%)	META-ANALYSIS (Figure 2) 30% (95% CI: 16 - 41%)
Neonatal deaths due to complications of preterm birth	DELPHI Median 5% (IQR: 5-10%) (Range: 0-20%)	DELPHI Median 5% (IQR: 5-10%) (Range: 1-40%)	DELPHI Median 10% (IQR:10-20%) (4-30%)

Delphi Expert Opinion estimates based on median answer from Panel of 18 members representing the following.
1) WHO Regions: Americas (n=6); Southeast Asia (n=4); Eastern Mediterranean (n=2); Africa (n=4); Europe (n=2).
2) Specialties: Neonatology (n=7); General Pediatrics (n=11); Pediatric Infectious Disease (n=1).

Table 6 Observational, quasi-experimental, and cluster randomized trials of community-based neonatal resuscitation

Author	Country	Study design	Intervention definition	Simultaneous Interventions	Intervention Coverage	Outcomes: Definition	Preterm vs. Intrapartum Death	N (Births) A = control B = comparison	Effect Size RR/OR (95% CI)
Pratinidhi et al, 1985 [50]	Pune, India	Before-and-after	CHW training in basic resuscitation with mouth to mouth	Management of low birth weight, preterm, feeding, illness, cord cutting, feeding, nutrition;	80% of home births received CHW care; 75% of births at home	1) NMR; 2) PMR	Not stated	A) 1444; B) 1546	1) RR 0.75 2) RR 0.98
Daga SR et al, 1991 [51]	Maharashtra, India	Before-and-after, no control	TBA training in basic resuscitation with mouth-to-mouth breathing	Management of low birth weight, hypothermia; transport and referral of high risk babies to hospital	TBAs attended 90% of deliveries	1) NMR; 2) PMR; 3) SBR	Not stated	A) 321; B) 660	1) RR 0.59 (0.32-1.09); 2) RR 0.39 (0.21-0.69); 3) RR 0.49 (0.16, 1.50)
Kumar R et a; 1998 [55]	Haryana, India	Quasi-experimental	Advanced TBA training modern resuscitation with bag mask ventilation and mucus extractor	NS	TBAs delivered 92% of babies at home;	1) Asphyxia mortality (Verbal Autopsy); 2) PMR	Combined "not breathing"	A) 964; B) 884	1) RR 0.30 (0.11-0.01) 2) RR 0.82 (0.56-1.19)
Bang AT et al 2005 [5,72]	Gadichiroli, India	Quasi-experimental	1) 1996-1999: CHW+TBA attend deliveries together, basic resuscitation with tube-mask; 2) 1999-2003: Bag mask. Refresher training every 2 months.	Community treatment of suspected neonatal sepsis, essential newborn care	VHWs attended 84% of deliveries	1) Asphyxia mortality (Verbal autopsy) 2) NMR 3) PMR 4) SBR 5) ENMR	Combined "not breathing" [Failure to breathe at 1, 5 min]	Before-after comparison A) 763 (95-6); B) 5510 (96-03) QE comparison A)1108 B) 979	1) RR 0.35 (0.15-0.78)ᵃ 2) RR 0.41 (0.26-0.66)ᵇ 3) RR 0.50 (0.35-0.71)ᵇ 4) RR 0.58 (0.36-0.93)ᵇ 5) RR 0.44 (0.27-0.73)ᵇ
Ariawan I, et al 2006 [54]	Cirebon, Indonesia	Before-and-after, no control	Community mid-wife training in resuscitation with tube-mask, refresher training 3, 6, 9 month and VCD refresher video; training in "post-resuscitation" care	Not stated	60% of asphyxia cases managed by midwives; uncertain coverage rate	1) Asphyxia mortality (Verbal autopsy); 2) NMR; 3) SBR	Not stated	A) est 44,000; B) est 44,000	1) RR 0.39 (0.31-0.48) 2) RR 0.60 (0.53-0.68) 3) RR 0.39 (0.31-0.48)
Carlo W et al 2010 [52]	Argentina, DR Congo, Guatemala, India, Pakistan, Zambia	Before-and-after ENC; cluster RCT for NRP training	Training of community birth attendants (TBAs, nurses, midwives, and physicians) in WHO Essential Newborn Care, including basic resuscitation with bag-mask ventilation	Clean delivery, thermal protection, breastfeeding, kangaroo care	78% of births attended by community birth attendant after ENC training	1) PMR 2) SBR 3) ENMR	BW < 1500 g excluded	A) 22,626; B) 35,017	1) RR 0.85 (0.70-1.02) 2) RR 0.69 (0.54-0.88) 3) RR 0.99 (0.81-1.22)
Gill C et al 2011 [53]	Zambia	Cluster RCT	TBA Training in modified neonatal resuscitation program (NRP) w/ facemask; competence assessments with refresher trainings every 3-4 mos.	Thermal care, Facilitated referral for presumptive neonatal sepsis (amoxicillin and referral)	Undetermined	1) NMR 2) Day 1 mortality 3) Asphyxia NMR (Verbal autopsy) 4)PMR	Single cause assigned by VA "asphyxia" or "preterm"	A) 1920 B) 1517	1) aRR 0.55, (0.33-0.90) 2) aRR 0.40, (0.19-.83) 3) aRR 0.37 (0.17-0.81) 4) aRR 0.72 (0.51-1.00)
Azad K et al 2011 [73]	Bangladesh	Cluster RCT, factorial design	Intervention arm: TBATraining neonatal resuscitation with bag-valve mask, with subsequent retraining; Control: TBA Training in mouth-to-mouth resuscitation	Intervention and control: Clean delivery, danger signs, emergency preparedness, facility referral. Women's participatory groups in half of clusters	Intervention Coverage: 22% of home deliveries attended by trained TBA; Control 19% by trained TBA	1) ENMR	Not stated	A) 13195 B) 12519	1) 0.95 (0.75-1.21)

a Before-after comparison period 1995-6 versus 1996-2003.
b Calculated from data presented in paper for year 3 of intervention (1997-1998) comparing experimental vs. control areas [72].

effect ranged from very low to moderate; the interventions implemented and case definitions used were heterogeneous. The cluster-randomized component of the First Breath study was excluded as the comparison was between two different training programs of neonatal resuscitation, both including ventilation with bag-and-mask; thus only the before-after essential newborn care training data was considered here. The Lunesp cRCT was rated as moderate quality for the purpose of this review, given the concurrent interventions and hence difficulty separating the effect of resuscitation from sepsis management. Only preliminary results from the Bangladesh cRCT were available, the level of evidence may be considered moderate for this review given the lack of cause-specific mortality data and low coverage of the intervention (~20% of deliveries). Two studies were quasi-experimental with non-random allocation of the intervention and considered to provide low to moderate quality evidence. Four other studies were before-and-after studies, providing very low to low quality evidence by GRADE criteria.

Because of substantial heterogeneity in the interventions implemented, the inability to isolate the effect of resuscitation training in community newborn care packages, differences in study design, and the lack of consistent outcomes definitions separating neonatal deaths due to term-intrapartum events vs. preterm birth, no meta-analysis was performed using the community data and the data is summarized.

1) Basic neonatal resuscitation effect on all cause mortality in community based studies: Five studies reported the intervention package effect on all cause perinatal mortality. Three studies reported a 28-61% reduction in PMR, whereas three studies failed to demonstrate a significant effect (RR 0.98, CI not reported; RR 0.82, 95% CI 0.56-1.19; RR 0.85, 95% CI 0.70-1.02). In the First Breath study, however, a sub-analysis of deliveries attended by birth attendants reported a reduction in PMR after vs. before training (RR 0.81, 95% CI 0.68-0.97). Four studies reported reductions in all cause neonatal mortality ranging from 25-59% and one study failed to demonstrate a significant effect (RR 0.59, 95% CI 0.32-1.09). Early neonatal mortality was reduced 42% in the Lunesp cRCT (aRR 0.58, 95% CI 0.38-0.89); however no effect on ENMR was observed in the First Breath before-after ENC comparison (RR0.99, 95% CI 0.81-1.22), most likely due to the large reported reduction of stillbirths, although interpretation may be complicated by misclassification between stillbirths and early neonatal deaths, which is an issue even in high resource settings and is common where routine heart rate assessment at birth is limited. In the Bangladesh cRCT, there was no significant effect on ENMR of bag-mask training of TBAs compared to mouth-to-mouth resuscitation (RR 0.95, 95% CI 0.75-1.21).

2) Basic neonatal resuscitation effect on intrapartum-related neonatal deaths in community-based studies: "Asphyxia" specific mortality was reported for four studies, with the effect ranging

Figure 4 Meta-analysis of before-and-after hospital-based studies of neonatal resuscitation training on early neonatal mortality (all cause).

2) Neonatal deaths due to direct complications of preterm birth: The median opinion was for a 10% reduction (Range 0-20%, IQR 5-10%) in preterm deaths following immediate newborn assessment and stimulation alone.

Mortality effect, combining stimulation and basic resuscitation: The total effect of basic resuscitation is estimated as the effect of newborn assessment and stimulation, and the additional effect of basic resuscitation on the remaining deaths, after subtracting the lives saved from initial newborn assessment and stimulation (table 5). In the meta-analysis, the additional effect of basic resuscitation included studies where training with bag-and-mask was implemented on top of existing basic newborn care. In the Delphi, the effect of basic resuscitation was incremental to newborn assessment and stimulation.

For example, if there are 1000 intrapartum related deaths in the absence of any care, introducing newborn assessment and stimulation for all children would be expected to prevent 10% of these deaths (=100), leaving 900 deaths still occurring. Adding basic resuscitation in the community to newborn assessment and stimulation would prevent 20% of these remaining deaths (=180). Thus, the total number of deaths prevented would be 280 (=28%). In the LiST software, assessment and stimulation is included with skilled attendance for facility birth and the basic resuscitation is a separate additional option.

Summary of the results and the quality of evidence: The LiST mortality effects for the two interventions (immediate newborn assessment and stimulation, and basic neonatal resuscitation) on the two causal categories of neonatal death (term intrapartum-related and preterm birth complications) are summarized in table 7, along with evaluations of quality of evidence, or expert opinion, and limitations of the data. The overall level of evidence for facility based neonatal resuscitation impact on term intrapartum related mortality was based on a meta-analysis of 3 studies and was rated as moderate, while all the remaining estimates were based on Delphi expert consensus and the quality of the evidence was rated very low.

Discussion
Despite the wide acceptance of neonatal resuscitation as a standard of care, there is limited evidence of its impact on neonatal outcomes, in part due to the ethical challenges of undertaking individually randomized RCTs. To our knowledge, this is the first systematic review, meta-analysis and expert panel convened to provide estimates of the reduction in neonatal mortality that could be achieved through neonatal resuscitation training. Immediate assessment and stimulation of the newborn is more feasible without equipment or skilled workers. Our expert panel estimated that this simple action could reduce both term intrapartum-related (ie "birth asphyxia") and preterm mortality by 10%. Our meta-analysis suggests that neonatal resuscitation training in facilities was associated with an additional 30% reduction in intrapartum-related neonatal mortality. Studies have not consistently assessed the effects on preterm deaths, and there is no high or moderate quality

from 61-70% reduction. However, the definition used in three studies was "not breathing at birth" and hence included deaths in preterm infants; only one study distinguished preterm deaths. Sepsis management with antibiotics was a co-intervention in 2 studies and study designs were heterogeneous (1 cRCT, 2 quasi-experimental, 1 before-after), thus the data was not pooled. A Delphi expert process was conducted (table 5). Basic neonatal resuscitation was estimated to reduce term intrapartum-related mortality in the community by 20%, in addition to assessment and stimulation (median opinion 20%, Range 10-50%, IQR 15-25%).

3) Basic neonatal resuscitation effect on neonatal deaths due to preterm birth complications in community-based studies: No studies were identified that met criteria for intervention and outcome definitions. The Lunesp study reported no significant reduction in mortality attributed to preterm birth. Given the biologic plausibility, expert opinion was also sought. The Delphi process estimated a 5% reduction, in addition to assessment and stimulation (Range 1-40%, IQR 5-10%) in neonatal deaths due to neonatal resuscitation with positive pressure ventilation in the community (table 5).

4) Basic neonatal resuscitation effect on stillbirths in community-based studies: In the First Breath study, the stillbirth rate was reduced by 31% after the intervention, and in the SEARCH study, the fresh stillbirth rate was 32% lower during the period of bag-mask compared to tube-mask resuscitation (p<0.09). In the Lunesp study, there was no significant effect of the intervention on stillbirth rate.

Evidence for impact of immediate newborn assessment and stimulation: We identified no studies which reported mortality outcomes for newborn assessment and stimulation alone in the community, or in facilities; therefore, an expert Delphi process was undertaken.

1) Intrapartum-related neonatal deaths: The median opinion was for a 10% reduction (Range 0-25%, IQR 5-15%) in term intrapartum-related deaths with immediate newborn assessment and stimulation alone.

Table 7 Cause specific mortality effects and GRADE estimate for the effect of newborn resuscitation

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Effect on intrapartum-related neonatal deaths ("birth asphyxia")

Cause specific effect
Immediate newborn assessment, drying, and stimulation 10% (Range 0-25%, IQR 5-15%)
Basic neonatal resuscitation (facility) 30% (95% CI: 16 - 41%)
Basic neonatal resuscitation (community) 20 % (Range 10-50%, IQR 15-25%)
(*note that the resuscitation effect is in addition to immediate assessment, drying, and stimulation)
Quality of input evidence:
Basic neonatal resuscitation (facility) - moderate (3 low quality before-and-after studies, upgraded for consistency)
Immediate newborn assessment, drying, and stimulation - very low (based on Delphi)
Basic neonatal resuscitation (community) - very low (based on Delphi)
Proximity of the data to cause specific mortality effect:
Moderate (cause specific mortality but lack of consistency in cause-of-death definitions)
Limitations of the evidence:
There is a lack of rigorous evaluation particularly for the effect of immediate newborn assessment, drying, and stimulation. Data are compromised by misclassification of live births and intrapartum stillbirths and by inconsistencies in cause-of-death attribution between term intrapartum-related neonatal deaths and preterm complications especially if a clinical case definition of "not breathing at birth" ("birth asphyxia") is applied which includes both categories.
Possible adverse effects:
Babies who survive despite severe brain injury may have long term impairments. There is a dearth of data on long term outcomes from low and middle income settings.

Effect on neonatal deaths due to preterm direct complications

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Cause specific effect
Immediate newborn assessment, drying, and stimulation 10% (Range 0-20%, IQR 5-15%)
Basic neonatal resuscitation (facility) 10% (Range 4-30%, IQR 10-20%)
Basic neonatal resuscitation (community) 5% (Range 1-40%, IQR5-10%)
(*note that the resuscitation effect is in addition to immediate assessment, drying, and stimulation)
Quality of input evidence:
Very low (all based on Delphi)
Limitations of the evidence:
As discussed above.
Possible adverse effects:
As discussed above.

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evidence addressing this; expert opinion estimated a 10% reduction in prematurity-related neonatal deaths following resuscitation in health facilities. Current evidence for neonatal resuscitation in community settings is heterogeneous, and experts estimated a 20% reduction in term intrapartum-related deaths and 5% reduction in deaths attributed to preterm birth for community-based resuscitation either with a midwife alone at home or a TBA.

Simple immediate newborn assessment and warming, drying and tactile stimulation is the first step of neonatal resuscitation and was estimated by experts to result in a small (10%) reduction in intrapartum-related ("birth asphyxia") and preterm deaths. In resource limited settings, these simple initial steps are feasible to be performed by a family member or primary healthcare provider with minimal skills – for example, rubbing the baby dry with a cloth– and might save lives, but this is expected to have limited effect. Observational studies suggest that between 6-42% of newborns who do not breathe at birth require ventilation, indicating that the majority of non-breathing babies may respond to simple steps alone. Although the anticipated mortality impact is low, the cost is also likely to be low as no equipment is required.

Our meta-analyses evaluating the impact of facility-based neonatal resuscitation training included low quality before-after studies, but at least comparable in intervention and outcome definitions for intrapartum-related and early neonatal mortality. Consistent effect sizes were observed for intrapartum-related mortality and all cause early neonatal mortality. The China NRP study was excluded but it is notable that the reduction in labour room mortality for term babies (33%) was of similar magnitude. It is disappointing that the majority of the 16 facility studies identified did not meet inclusion criteria. However, given mortality effect consistency across the studies and generalizability to low-middle income countries, applying adapted GRADE criteria the evidence level was moderate (table 7). For all included studies, the comparison groups involved some pre-training management of the non-breathing baby, thus,

these estimates reflect the impact of additional training for resuscitation, incremental to immediate newborn assessment and stimulation. Implementing basic neonatal resuscitation in a setting where no simple immediate newborn care is in place, such as peripheral maternity clinics, may have a greater effect. On the other hand, some of the effect may have been due to improved post-resuscitation care in two of the studies. While some data was available on the impact of facility-based resuscitation on preterm mortality, the data was too heterogeneous to pool. However, there is strong biologic plausibility that resuscitation may reduce mortality in moderate-late preterms who require minimal assistance with positive-pressure ventilation to initiate breathing, without requiring ongoing assisted ventilation; experts estimated a10% effect at facility level.

The impact of resuscitation training may be greater in higher mortality settings where obstetric care is more limited. In Bulgaria, an upper-middle income country where the baseline intrapartum-related mortality was relatively low, the estimated effect was smaller (16%) than in higher mortality settings such as Zambia and India, where neonatal resuscitation training was associated with a 30-43% reduction in intrapartum-related mortality. In settings with high coverage of high quality intrapartum management, the majority of term infants who die from intrapartum-related causes may be severely asphyxiated infants who require interventions beyond neonatal resuscitation alone, such as ongoing ventilation and therapeutic hypothermia.

The evidence for basic resuscitation in community settings was too heterogeneous to combine: study designs varied substantially, resuscitation training was one of numerous interventions in newborn care packages, and the outcome measure of cause-specific mortality differed across studies, often reflecting reduction in other causes of death such as preterm birth and infections. Significant reductions in all-cause neonatal or perinatal mortality were observed in 4 studies, ranging from 25-61%, and reported "asphyxia" specific mortality was reduced in four studies, ranging from 61-70%. In the multi-center "First Breath" study, although no overall impact on PMR was observed, there was a significant 19% PMR reduction for deliveries with trained birth attendants, and a reduction in intrapartum-related morbidity (prevalence of 5 minute Apgar scores <4 and abnormal neurologic exams at 7 days). On the other hand, preliminary results from a cRCT in Bangladesh failed to demonstrate a reduction in ENMR with the additional training of TBAs in bag-mask resuscitation beyond immediate care and mouth-to-mouth resuscitation. Although it was not possible to derive a cause-specific mortality estimate from existing evidence, our expert panel agreed on the presence of an effect (20% for intrapartum-related mortality, 5% for preterm mortality), albeit

slightly smaller than for facility based resuscitation, reflecting the additional challenges in implementation in such contexts, with a single provider and variable cadres. There is a need for consistency in future studies with respect to intervention content, study design, outcome measurement and definitions in order to more precisely evaluate the potential impact of resuscitation training at community level.

Important programmatic considerations for resuscitation training in resource limited settings include the benefit of teaching advanced procedures, provider competency, and skill maintenance. Two of the studies in our meta-analysis included some aspects of advanced neonatal resuscitation; however, advanced procedures are more complex to teach (ie chest compressions, intubation, or medications) and are required for ~2% of all babies who do not breathe at birth, and fewer than 1% of all babies born. Basic neonatal resuscitation is sufficient for most babies who would be saved by resuscitation in low-middle income settings, and the additional benefit of advanced procedures is likely to be low. For the purposes of this LiST estimate, the effect of facility based neonatal resuscitation was assumed to be achievable with basic neonatal resuscitation, which is the clear priority for rapid scale up in facilities in low and middle income countries, given feasibility, skills required, and equipment costs. Furthermore, training programs should emphasize routine assessment of provider knowledge, competency and skill maintenance. Provider knowledge and performance skills to conduct resuscitation decline significantly over time. Regular refresher training programs, practice drills, and DVD videos of resuscitation are methods of ensuring skill maintenance and program effectiveness.

A reduction in stillbirth rate has been observed in 2 community-based studies, after training programs including bag-mask resuscitation. A live newborn with severe neonatal depression is difficult to distinguish from a stillborn, and there is the potential for misclassification in low-resource settings where newborns are not typically assessed for signs of life at birth (particularly heart rate). In addition to reducing misclassification, training in neonatal assessment and resuscitation may also increase survival in apparently stillborn infants (Apgar score assessed as 0 at 1 minute). Among apparently stillbirth infants who were resuscitated, case fatality ranges between 16-65% in high income settings, with major intensive care support, and long term outcomes that are significantly worse than for resuscitated babies who did have a heart rate detected. These findings emphasize the need to accurately count stillbirths and assess long term outcomes to capture the full impact of obstetric and immediate newborn care interventions.

Consistent case definitions are required for comparable population-level surveillance of disease burden and for evaluation of intervention effectiveness. A survey of policy makers revealed that "confusing terminology" and "lack of valid measurement indicators at the community level" were key barriers to obtaining the necessary information to make policy decisions. Recent advances have been made in case definitions and verbal autopsy hierarchies to distinguish intrapartum-related events in term or almost term babies from preterm babies, although the issue of distinguishing growth restricted infants remains a challenge and is especially important in South Asia. Consistent use of such verbal autopsy tools, and more importantly the hierarchies, is critical. This review emphasizes the need to minimize misclassification of live births as stillbirths,

and to apply standardized definitions for intrapartum-related neonatal deaths, as opposed to clinical definitions such as "birth asphyxia." Definitions and measurement varied across studies and between facility and community/home-based studies. Even in facility settings, the few studies that reported preterm mortality used inconsistent birth weight and gestational age cut-offs. There is a marked lack of data regarding effect of resuscitation on preterm babies. The long-term developmental outcomes following resuscitation also require further research. Particularly in low-middle resource settings, where health systems and families have limited resources to care for survivors with chronic disability, there is a dearth of comparable long term developmental outcome data (ACL, personal communication for CHERG/GBD neonatal encephalopathy estimates group).

This review has important implications for the scale up of neonatal resuscitation. The immediate opportunity is for facility based resuscitation. Even in facilities, equipment is lacking and few providers are trained in neonatal resuscitation. In 6 African national service provision assessments (DHS Macro), between 2-12% of delivery staff had been trained in neonatal resuscitation and fewer than one quarter of hospitals had newborn bag-masks available. Given these challenges, achieving high coverage with basic neonatal resuscitation should be prioritized, as advanced resuscitation is infrequently required and may have limited additional mortality impact in low-resource settings. Establishing resuscitation training for pre-service education of midwives, doctors and nurses who provide newborn care is a crucial step. Recent advances in simpler training and robust, low cost equipment hold great promise for rapid scale up at much lower cost. Furthermore, for the 60 million births a year outside facilities, while implementing basic neonatal resuscitation at the community level is controversial, there may be a role in some high-mortality settings where most births occur at home, skilled attendance is not achievable in the foreseeable future, alternative cadres already attend the majority of deliveries, and the case load per attendant is high enough to justify the training, equipment inputs and skill maintenance.

Conclusions
There is evidence from facility-based studies in low and middle-income countries that neonatal resuscitation training reduces neonatal mortality from intrapartum-related events (ie. "birth asphyxia") by 30%, potentially saving 93,700 each year just by addressing missed opportunities for current facility births, and up to 192,000 babies at 90% coverage, only considering the effect on intrapartum-related neonatal deaths. In order to achieve maximal reduction in intrapartum-related neonatal deaths, preterm birth and intrapartum stillbirths, effective obstetric care remains the most important intervention and this should be complemented with immediate newborn care and resuscitation. There is increasing investment in obstetric care, yet to be matched by effective implementation, scale-up, and sustainability of immediate newborn care and basic neonatal resuscitation.

In the community, immediate simple care at birth is feasible, although estimated by experts to be low impact (10% on preterm and on intrapartum related neonatal deaths). Community-based neonatal resuscitation may reduce all-cause neonatal and perinatal mortality, but data is heterogeneous to presently estimate an effect size from the evidence. Future studies should attempt to address limitations identified here particularly in terms of intervention definitions, design, comparison groups,

outcome definitions and misclassification of stillbirths and neonatal deaths.

While the quality of evidence for stimulation at birth and for neonatal resuscitation is low, partly because they are considered standard of care, there is sufficient and consistent evidence of impact. Yet such basic care remains a rarity especially for the world's 60 million home births. Simplified training programs, and robust, low cost equipment are now available. Every baby born alive has the right to breathe at birth and to solutions helping those who do not breathe – the question remains if this right will be systematically advanced in policies and programs or will be left to chance depending on where a baby is born.

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is known about the markers of the stem cells in the interfollicular epidermis or the composition of the stem cell niche. Bulge stem cell markers do not routinely label interfollicular epidermal cells. In humans, the in vitro colony-forming ability of interfollicular keratinocytes correlates to the expression level beta-l (b1) integrin. Clusters of cells highly positive for bl integrin are found in specific locations in relationships to the epidermal-dermal junction in the interfollicular epidermis.

Skin stem cells represent the potential for new skin growth. Under normal circumstances they proliferate into mature skin cells and start producing keratin. As we age there are less and less active stem cells, leading to delayed repair of skin injuries. Therefore, activation or "waken up process" of our own skin stem cells will improve their wound healing properties and substance of the skin itself.

Stem cell markers and fetal wound healing

Roh and Lyle[3] identified bl integrin as the first marker to be over-expressed in epidermal stem cells. Keratin 15 (K15) expression was found to be highly specific for stem cells in the human hair bulge.[4]

In our studies[5] we successfully evaluated activity of epidermal stem cells based on the expression of b1 integrin and cytokeratines 15 and 19. We expect to see more markers of epidermal stem cells as the area is being researched extensively.

Unlike adult, fetal tissue has the ability to rapidly heal skin wounds without a scar. A number of differences between fetal and adult wound healing have been identified.[6] Fetal tissue is in a sterile environment while adult tissue is contaminated. In fetal skin, there is rapid re-epithelialization and the skin is less differentiated. Fetal skin has more hyaluronic acid and nonsulfated glycosaminoglycans. In fetal wounds there is less inflammation compared with adults. In fetal stroma there is more fibronectin, more fibroblast migration and a higher proportion of collagen type III resulting in less scaring than in adults.

Stem cells may also play a significant role in scarless fetal wound healing. It is well known that levels of functional epidermal stem cells decreases with aging in human skin.[7] Similar to neonatal mouse skin, human fetal skin also shows confluent basal epidermal expression of the K15 stem cell marker. These results agree with our findings on the increased stem cell markers in the skin/functional epidermal stem cell layer of adult mice exposed to p199 (ABG Lab, LLC, Great Neck, NY), a protein derived from the Wharton jelly of the umbilical cord and known to activate epidermal stem cells. We, therefore, agree with Roh and Lyle.[3]

Conclusion

The number and location of stem cells within skin may be a contributing factor in fetal scarless wound healing and decreased healing in older adults. As evidence indicates, scarless wound healing appears to be intrinsic to fetal skin and independent of the intrauterine environment. Differences in stem cells between fetal and adults skin in the context of wound healing has not been extensively studied, however recent work suggests this is an important area for further investigation.

References

1 Barrandon Y and Gren H. Three clonal types of keratinocyte with different capacities for multiplication. Proc. Nati. Acad. Sci. USA (Cell Biology). 1987;84: 2302-2306.
2 Lajtha LG. Stem cell concepts. Differentiation. 1979;14(1-2):23-34.
3 Roh C, Lyle S. Cutaneous stem cells and wound healing Pediatr Res 2006;59 (4 Pt 2): 100R-3R.
4 Lyle S, Christofidou-Solomjdou M, Liu Y, Elder DE, Albelda S, Cotsarlis G. The C8/144B monoclonal antibody recognizes cytokeratin 15 and defines the location of human hair follicles stem cells. J Cell Sci 1998;111:3179-3188.
5 Petrikovsky B. Stem cells as a target for mesotherapy. Inject Meth in Cosmet. 2010;3:88-91.
6 Bullard KM, Longaker MT, Lorenz P. Fetal wound healing: current biology. World J Surg 2003;2:7:54-61.
7 Zouboulis CC. Acne and sebaceous gland function. Clin Dermatol 2004;22:360-366.

Boris M. Petrikovsky, MD, PhD is a member of this journal's Editorial Advisory Board. He is Director, Prenatal Diagnostic Unit Services, New York Downtown Hospital. Dr Petrikovsky is a partner in ABG Lab, LLC, which produces P199. Jeffrey Karsdon, MD is a Neonatologist with New York Downtown Hospital.

Convective Burn from Use of Hairdryer for Heel Warming Prior to the Heel Prick Test – a case report

Robbie Ray, Yvette Godwin, Ashley Shepherd

Abstract

Background: Blood sampling through heel lancing is the most common invasive painful procedure performed on newborn infants.

Case Presentation: We report the case of a five day old infant who sustained burns to the left foot and leg after the mother's hairdryer was used by the midwife to warm the baby's heel prior to capillary blood sampling (CBS) with an automated device.

Conclusion: Heel warming is not recommended for routine CBS although it is often practiced. If pre-warming is to be practiced, standardised devices should be used rather than improvised techniques. This will reduce the risk of injury to these infants.

Background

Capillary blood sampling (CBS) is routinely offered to all newborn infants born in the United Kingdom to identify babies who may have rare but serious conditions for example phenylketonuria, congenital hypothyroidism, or cystic fibrosis. CBS uses dried spots of blood obtained by heel prick and collected on filter paper. Current blood spot sampling guidelines suggest that additional warming of the foot is not required before heel puncture but that the heel should be warm.[1] Although the heel prick procedure is relatively easy to complete, a recent study has highlighted great variability in the technique among midwives.[2] Problems with CBS still exist including pain for the baby,[3] anxiety for the parents[4] and complications from mild bruising.[5] The case reported below describes the injuries sustained by a five day old infant after heel heating.

Case Presentation

A five day old baby presented with burns to the left foot and leg after having a heel prick test performed. A community midwife had visited the parents' home four hours earlier and to facilitate blood sampling, had used the mother's hairdryer to warm the baby's foot. The hairdryer was set on a high setting and was held about six inches from the baby's foot for less than one minute. The baby became distressed as soon as the heel prick was

administered, and it was an hour after the procedure when the baby was finally consoled that the mother noticed erythema and blistering over the baby's foot and leg.

On examination the baby had serous blistering over all the toes suggesting a superficial partial thickness burn (Figure 1). Swelling and erythema extended from the leg to the knee and the infant was clearly distressed and obviously in pain from the injury.

During the next 48 hours there was concern regarding the possible progression of the depth of the burn hence the infant was admitted for observation and wound dressing. The blisters were deroofed and conservative treatment with dressings was pursued. At three weeks post injury, there was complete closure of the burns wounds. A final review, in outpatient's clinic, showed minor maturing scars on the pulps of the 2nd-5th toes. No long-term consequence of these minor scars, or scar contracture was anticipated and the patient was discharged.

Blood sampling through heel lancing is the most commonly performed invasive painful procedure in the newborn.[6] A literature review was performed using Medline and Cinahl databases for papers published between 1992 and 2011 with the search terms – heel prick, capillary blood sampling and warming in multiple combinations.

It is acknowledged that the heel prick procedure can be uncomfortable for the child[7] so it is imperative to perform the procedure as efficiently as possible with the minimum of trauma to the infant. Analgesia in the form of breast feeding, non-nutritive sucking and a dose of oral sucrose or glucose is recommended.[8,9] Automated devices which allow for a standard safe penetration of the vascular bed have been recommended for the heel prick procedure.[10] Warming of the heel prior to incision is based on the supposition that an increase in skin temperature causes an increase in blood flow which should provide a larger volume of blood to sample. However, evidence from videophometric microscopy analysis has shown that capillary blood flow is unaffected over the range of temperature that is increased by heel warming.[11] Furthermore, randomised control trials have shown that there is no increase in the volume of blood expressed or reduction in complications such as pain or bruising when the heel is warmed.[12,13]

Prior to incision, warming of the heel can be performed if the foot is clearly cold using a specifically prepared gel filled heel warmer (Rapidaid[14]). These warmers are activated by

Figure 1. Photograph taken on admission to hospital.

manipulation of a trigger disc which heats the gel to 40°C via an exothermic reaction and then secured in place with tape. Alternatively the infant's heel can be heated using water warmed to 42°C which must be checked by the midwife prior to heating.[10,12,13] There are currently no reports in the literature of using hairdryers to warm the heel. The inquiry held after this specific case has resulted in national guidance being issued to midwives to avoid unknown heating sources for pre-warming of infants' feet.

One previous paper[15] and a report from the New Zealand health commission refer to burns caused by heel warming. [16] These injuries were sustained when a midwife used a nappy soaked in hot water and a cup of water boiled from a kettle respectively. This case study is the first report of injuries to be sustained from a hairdryer burn.

CBS is an important public health screening measure that allows health professionals to detect potentially harmful conditions and treat them at an early stage. For some conditions management can be initiated which will greatly reduce the deleterious effects and complications caused to the child. For example if started early, treatment for infants diagnosed with phenylketonuria is highly effective at preventing development of serious mental disability. [17] The UK newborn screening program centre, funded by the Department of Health does not advocate routine heel warming in their most recent guidelines[1,17] and the literature does not support the need for heel warming before the heel prick test.[12,13] Intense heat or prolonged exposure to a heat source would have been required to cause a partial thickness burn in glaberous skin, as found on the sole of the foot in this case study infant. Therefore, if the heel is very cold and does have to be warmed, safe methods such as a standardized heel warmer should be used so that reliable temperatures can be reached every time and the baby is not at risk of burns.[12] However, further research is clearly needed to asses the usefulness of heel warming in these infants and the most effective way to do this.

Conclusions
The heel prick procedure used by midwives today is similar to that followed when the heel prick test was first introduced despite research findings which contradict many of the steps.[18] The techniques used to obtain a sufficient sample are variable and one possible reason for this is that the procedure is taught by midwife mentors who tend to teach their own preferred method[2] rather than following the most recent research based guidelines.[1] Due to the problems discussed here and the new

findings reported in this case study, perhaps the time has come for the heel prick test to be an accredited skill requiring a certificate of competence.

References
1 UK Newborn Screening Programme Centre: Standards and guidelines for newborn blood spot screening. Department of Health, London; 2008.
2 Cavanagh C, Coppinger C, Franck : A survey of newborn blood screening practices. British Journal of Midwifery 2005, 13:160-164.
3 Sheeran M: Pain in infants: a literature review. Journal of Neonatal Nursing 1997, 3:13-18.
4 Meehan RM: Heel sticks in neonates for capillary blood sampling. Neonatal Network 1998, 17:17-24.
5 Fleischman AR: Clinical considerations for infant heel blood sampling. Neonatal Intensive Care 1992, 5(1):62-68.
6 Shah VS, Taddio A, Bennet S, Speidel BD: Neonatal pain response to heel stick vs venepuncture for routine blood sampling. Archives of Disease in Childhood Fetal and Neonatal Edition 1997, 77:F143-F144.
7 McIntosh N, Van Veen L, Brameyer H: The pain of heel prick and its measurement in preterm infants. Pain 1993, 52(1):71-4.
8 Frank L, Gilbert R: Reducing the pain during blood sampling in infants. Clinical Evidence 2003, 9:419-435.
9 Shah PS: Breastfeeding or breast milk for procedural pain in neonates. Cochrane Database of Systematic Reviews 2006, 3:CD004950.
10 Shepherd AJ, Glenesk A, Niven CA, Mackenzie J: A Scottish study of heelprick blood sampling in newborn babies. Midwifery 2006, 22(2):158-68.
11 Norman M, Herin P, Fagrell B: An evaluation of skin capillary blood flow determinations in neonatesusing a computerized videophotometric method. Microvasc Res 1992, 43(3):276-84.
12 Janes M, Pinelli J, Landry S, Downey S, Paes B: Comparison of capillary blood sampling using an automated incision device with and without warming the heel. J Perinatol 2002, 22(2):154-8.
13 Barker DP, Willetts B, Cappendijk VC, Rutter N: Capillary blood sampling: should the heel be warmed? Archives in Disease and Childhood Fetal Neonatal Ed 1996, 74(2):F139-40.
14 Rapidaid medical products. [http://www.rapidaid.com/products/ productdetails_hw.php].
15 Hassan Z, Shah M: Scald injury from the Guthrie test: should the heel be warmed? Archives in Disease and Childhood Fetal Neonatal Ed 2005, 90(6): F533-4.
16 Health and Disability Commissioner. Case 00HDC06573 [http://www.hdc.org.nz/decisions–case notes/case-notes/midwife-accidentally-caused-scaldwhen- warming-baby's-heel-for-guthrie-test-(00hdc06573)], Accessed April 2011.
17 UK Newborn Screening Programme Centre: Newborn blood spot screening in the UK. Health Professionals Handbook, Department of Health, London; 2005.
18 Shepherd AJ, Glenesk A, Niven CA: What influence does experience play in heel prick blood sampling? Journal of Neonatal Nursing 2006, 12(3):97-102. Pre-publication history The pre-publication history for this paper can be accessed here: http://www.biomedcentral.com/1471-2431/11/30/prepubdoi:10.1186/1471-2431-11-30 Cite this article as: Ray et al.: Convective burn from use of hairdryer for heel warming prior to the heel prick test - a case report. BMC Pediatrics 2011 11:30.

Nutrition of Preterm Infants in Relation to Bronchopulmonary Dysplasia

Andreas Wemhöner, Daniel Ortner, Edda Tschirch, Alexander Strasak, Mario Rüdiger

Abstract

Background: The pathogenesis of bronchopulmonary dysplasia (BPD) is multifactorial. In addition to prenatal inflammation, postnatal malnutrition also affects lung development.

Methods: A retrospective study was performed to analyze during the first two weeks of life the total, enteral and parenteral nutrition of premature infants (<31 weeks, birth weight ≤1500 g) born between 08/04 and 12/06.

Results: Ninety-five premature infants were analyzed: 26 with BPD (27 ±1 weeks) and 69 without BPD (28 ±1 weeks). There was no statistical significant difference in the total intake of fluids, calories, glucose or protein and weight gain per day in both groups. The risk of developing BPD was slightly increased in infants with cumulative caloric intake below the minimal requirement of 1230 kcal/kg and a cumulative protein intake below 43.5 g/kg. Furthermore, the risk of developing BPD was significantly higher when infants had a cumulative fluid intake above the recommended 1840 ml/kg. In infants who developed BPD, the enteral nutrition was significantly lower than in non-BPD infants [456 ml/kg (IQR 744, 235) vs. 685 (IQR 987, 511)]. Infants who did not develop BPD reached 50% of total enteral feeding significantly faster [9.6 days vs 11.5].

Conclusions: Preterm infants developing BPD received less enteral feeding, even though it was well compensated by the parenteral nutrient supply. Data suggest that a critical minimal amount of enteral feeding is required to prevent development of BPD; however, a large prospective clinical study is needed to prove this assumption.

Background

Bronchopulmonary dysplasia (BPD) is a chronic pulmonary disease that affects preterm infants. In the past, BPD was mainly caused by ventilatory injury and affected about 30% of preterm infants with birth weights below 1000 grams.[1] Gentler ventilation techniques, antenatal steroids and surfactant treatment have reduced the incidence of lung injury. Despite this progress, the incidence of BPD is not decreasing, but the picture of BPD is changing. The so called "new BPD" is a lung development problem that involves impairment of alveolarization which results in large, simplified alveolar structures, dysmorphic capillary configuration and variable interstitial cellularity and/or fibroproliferation.[2]

Several factors are considered responsible for altering lung development and may subsequently support the development of BPD. In addition to prenatal inflammation, nutrition plays an important role in normal lung development and maturation.[2,3] Nutrition has a direct effect on the developing lung because it can modulate lung structure. General under-nutrition in humans leads to lung emphysema.[4,5] In rats, caloric restriction reduces the alveolar number by 55% and the alveolar surface area by 25%.[6] Seventy two hours after re-feeding, however, rat lungs are re-modeled with normal alveolar numbers and surface areas.[7]

Sufficient nutrition is often difficult to achieve in preterm infants. Due to various problems associated with immaturity, extremely preterm infants receive only minimal enteral nutrition during the first weeks of life and require supplemental parenteral nutrition. However, there is an ongoing debate concerning the required amount of protein, carbohydrates and calories.[8] A sufficient amount of protein and calories seems to be necessary for organ growth; thus, a low protein or caloric intake could impair lung development, resulting in BPD.

The present study was performed to test the hypothesis that nutrition intake during the first 2 weeks of life is lower in infants who subsequently develop BPD. Furthermore, the effects of protein, calorie and carbohydrate intake and the percentage of enteral nutrition during the first two weeks on the subsequent development of BPD were studied. The charts for all preterm infants under 31 weeks and below 1500 g who were born in our unit during a 17-month period were analyzed.

Methods

The observational cohort study was performed in the neonatal intensive care unit (NICU) of a tertiary centre at the Department of Pediatrics, Neonatology at the University Hospital Innsbruck, Austria. The medical ethics committee of the Medical University Innsbruck approved the study. Data were obtained from all preterm infants born between August 2004 and December 2006.

Table 1. Perinatal data

Perinatal data for infants in BPD and non-BPD (NBPD) group.

	BPD	NBPD
Patients (number)	26	69
Gestational age (weeks)	27 ±1*	28 ±1
Birth weight (gram)	965 ±255*	1170 ±246
Length (cm)	35 ±3.2*	37 ±2.5
Head circumference (cm)	24.7 ±2.1*	26 ±1.6
Apgar score at 5 minutes	7.8 ±1	7.9 ±1
Female infants	12 (46%)	38 (55%)
Singletons	16 (61%)	50 (72%)
Caesarean section	25 (96%)	67 (97%)
Small for gestational age	3 (11%)	5 (7%)
Completed courses of antenatal steroids	25 (96%)	65 (94%)

*p<0.02 vs. NBPD

Data are mean ± standard deviation or number and percentage (in parentheses)

Table 2. Body composition

Data for the study population at the 14th day of life and at 36 weeks post-conception.

	Day 14		36 Weeks	
	BPD	NBPD	BPD	NBPD
Weight (grams)	1015 ± 254*	1190 ± 241	1883 ± 286*	2038 ± 286
Length (cm)	36.8 ± 3.3*	38.5 ± 2.6	42 ± 2*	43 ± 2
Head circumference (cm)	25 ± 2*	26.7 ± 1.7	30 ± 1.5*	31.4 ± 1.5

*p<0.01 vs. NBPD

Data are mean ± standard deviation

All infants with birth weights below 1500 g and gestational ages below 31 weeks who were treated in the NICU during that period were included in the study. Infants were excluded from the analysis for the following reasons: death within the first week of life, transfer to another hospital and missing data.

The following demographic variables were obtained for all preterm infants born during the study period: birth weight, gestational age, mode of delivery, singleton pregnancy, 5 minute APGAR score and completed courses of antenatal steroids given.

The main outcome parameters were the cumulative amount of protein, calorie, carbohydrate and enteral feeding intake at 14 days of life. Parameters of total nutrition were obtained daily, and parameters of neonatal growth (weight, head circumference and length) were obtained daily up to day 14 and were then obtained at day 28 and 36 weeks postmenstrual age.

The following morbidity parameters were collected: Respiratory Distress Syndrome (RDS) incidence, surfactant application after intubation, surfactant application and the presence of an open ductus arteriosus as determined by echocardiography. The following discharge parameters were obtained: body weight and length, head circumference and length of stay in hospital.

Table 3. Nutrient intake

Total nutrient intake during the first two weeks of life.

	BPD	NBPD
Total fluid [ml/kg]	1864 (1792, 1929)	1860 (1813, 1904)
Total calories [kcal/kg]	1089 (966, 1190)	1154 (1081, 1221)
Total protein [g/kg]	46 (41, 49)	45 (41, 49)
Total carbohydrates [g/kg]	100 (187, 103)	102 (96, 108)

Data are median and interquartile range (in parentheses)
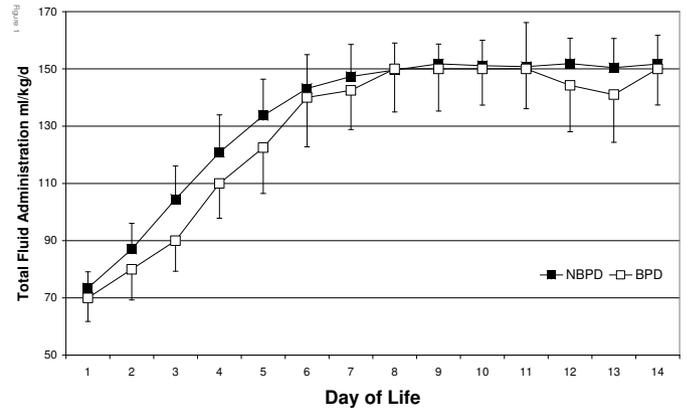
Figure 1. Amount of daily fluid intake during the first two weeks of life. Data are the means and standard deviations for infants from the NBPD (open square) and BPD (black square) groups.

Definition of bronchopulmonary dysplasia: The aim of the study was to compare nutritional data during the first 14 days of life in infants who later developed BPD with data of non-BPD infants. BPD was defined as treatment with oxygen >21% for at least 28 days on 36 week postmenstrual age or discharge to home, whichever comes first as described elsewhere.[9]

Enteral nutritional regime: During the study period, the feeding regime was not changed. Preterm infants were fed according to a local protocol that was adapted by the attending neonatologist to meet the actual requirements of the individual patient.[10,11] According to NICU routine, oral feeding is started with either 0.5 [birth weight (b.w.) ≤750 g] or 1 ml (b.w. >751 g) mother milk or donor breast milk as soon as possible after birth. Subsequently, the daily feeding volume was increased by about 10 ml/kg body weight. The volume was neither increased nor decreased if the attending staff noticed "feeding intolerance". Preterm infants were either fed with their mother's milk or donor breast milk. Milk fortification was usually performed if a feeding volume of more than 100 ml/kg*d was achieved.

Parenteral nutritional regime: Enteral nutrition was supplemented with parenteral nutrition if needed. Actual requirements were calculated daily with software that calculates fluid, calories, protein and glucose requirements for enteral and parenteral nutrition and lipids for parenteral application. The required parenteral nutrition was gradually tapered as enteral feeding volumes increased and was generally stopped if a feeding
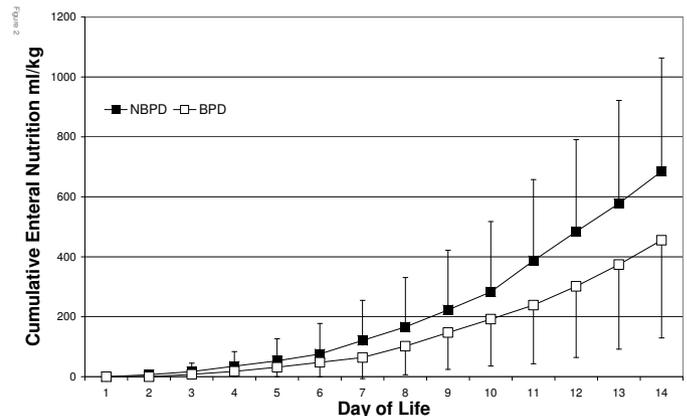

Figure 2. Cumulative amount of enteral feeding during the first two weeks of life. Data are the means and standard deviations for infants from the NBPD (open square) and BPD groups (black square).
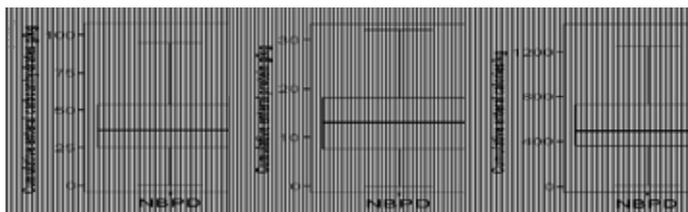
Figure 3. Cumulative enteral management during the first two weeks of life is shown for the NBPD and BPD groups. Cumulative enteral carbohydrates, protein and calories (* p<0.01, vs. control).

volume of 130 to 140 ml/kg of fortified milk was achieved.[12] The protocol for parenteral nutrition started with a total of 70-80 ml/kg/d fluid on the first day of life.[13] The fluid intake was increased by 10-20 ml/kg/day until 150 ml/kg/d was achieved. Protein administration was started during the first day of life with 1 g/kg/day and was increased by 0.5 g/kg per day until 3 g/kg is achieved. On the third day, intravenous lipid administration was started with 0.5 to 1 g/kg/d and was advanced in increments of 0.5 to 1 g/kg/d until 3 g/kg/d was achieved.

It is assumed that a "minimal nutritional requirement" is needed for undisturbed growth and that problems occur only below that critical threshold. Therefore, minimal requirements during the first two weeks were calculated according to recent recommendations[13,14] protein 43.5 g/kg, calories 1110-1210 kcal/kg and carbohydrates 187-213 g/kg. Because volume overload is associated with the subsequent development of BPD, a "maximal" total fluid intake during the first two weeks of life was calculated at 1620-1800 ml/kg. The relative risk of developing BPD was calculated if the minimal requirements were not achieved.

Data analysis: Continuous data, which is normally distributed, is presented as mean/SD; for skewed data, medians with interquartile ranges are shown. Statistical analyses of outcome were conducted in order to compare data for BPD and non-BPD infants. Univariate comparisons of proteins, calories, carbohydrates and total fluid were performed using the non-parametric Mann-Whitney U-Test. All reported p-values are two-sided with a level of significance set at 0.05. All analyses were performed using SPSS 15.0 (Chicago, IL).

Results

Perinatal data of the study group: All together, 100 infants were born and treated during the study period. Five infants were excluded from the analysis because of death (n = 2) within the first week of life or transfer to another hospital (n = 3). The incidence of BPD in the study population was 27%. The perinatal data for BPD and non-BPD infants are shown in table 1. As expected, infants who developed BPD had a lower gestational age and birth weight (p<0.02). These infants also had lower average weight, length and head circumference at the 14th day of life and at a postmenstrual age of 36 weeks (p<0.02 table 2) but the weight gain per day was not different.

Cumulative nutrition management: The difference in total fluid intake during the first two weeks was not statistically significant between infants with and without subsequent BPD (table 3). As shown in figure 1, the increase in fluid administration was similar in both groups. However, all infants who received more than the "maximal total fluid intake" of 1840 ml/kg developed BPD (relative risk in comparison to infants without BPD: p=<0.01 RR 4.00, 95% CI 2.6, 6.2).

The difference in the total caloric intake during the first two weeks of life was not statistically significant between infants with and without subsequent BPD (table 3). The risk of developing BPD was slightly (but not significantly) higher if the caloric intake during the first two weeks of life was below a minimal requirement of 1230 kcal/kg (RR 1.92, 95% CI 0.6, 5.7).

The total intake of amino acids during the first two weeks of life was not significantly different between the two groups (table 3); however, there were large variations between infants. Again, the risk of developing BPD was (not significantly) higher if the protein intake was below the minimal requirement of 43.5 g/kg (RR 1.2, 95% CI 0.6, 2.4). Finally, the intake of carbohydrates during the first two weeks of life was not significantly different between the two groups (table 3).

Enteral nutrition: As shown in figure 2, the two groups differed with respect to the amount of enteral feeding. Infants who did not develop BPD received significantly more enteral feeding during the first two weeks of life when compared with infants who developed BPD (p<0.04) (Figure 3a). Whereas 50% of enteral feeding was achieved at a median of 9.6 days in infants who did not develop BPD, a median of 11.5 days was required to achieve this level of feeding in infants who developed BPD (p<0.01). In sum, the enteral intake of carbohydrates (figure 3a), proteins (figure 3b) and calories (figure 3c) during the first two weeks of life was lower (p<0.01) in infants who developed BPD.

Clinical outcome and other aspects of preterm morbidity: Analysis of data on postnatal respiratory morbidity revealed that significantly more infants received surfactant in the BPD group (80 vs. 52%, p<0.01), whereas the incidence of RDS was similar in both groups (100 vs. 94%). There was a higher rate of ROP in the BPD group (57 vs 21%, p=0.001) and IVH (30 vs 7% p=0.004). Furthermore, the incidence of a persistent ductus arteriosus (42%), need for treatment ductus arteriosus (38%) and NEC >stage II (0%) were the same in both groups.

Finally, the length of stay in the hospital was significantly longer for infants with BPD than for infants who did not develop BPD (96 vs. 60 days, p<0.01), respectively.

Discussion

The present study tested the hypothesis that infants who develop BPD have lower caloric or protein intake during the first two weeks of life than infants without BPD. However, data from the current study do not support this assumption; the total intake of fluids, calories, amino acids, carbohydrates and weight gain per day was similar in infants with and without BPD. However, infants who developed BPD had a significantly lower amount of enteral nutrition during the first two weeks of life. Furthermore, the present study supports previous reports of the importance of fluid restriction during the first weeks of life to prevent the development of BPD.[15,16] Whereas the median fluid intake was similar in both groups of the present study, infants who received more than the recommended amount of fluid had a significantly higher risk of developing BPD. In contrast to other studies[17,18] we did not find any significant differences in calories and fat intake in the first 14 days of life. The reasons therefore might be a greater number of patients and a longer observational period in those studies.

Data from the present study are of great clinical interest because the impact of nutrition on BPD development has

been discussed for a long time. Sosenko et al hypothesized that general under-nutrition, specifically insufficient protein intake, may increase the vulnerability of a preterm infant to oxidant-induced lung injury and the development of "old" BPD.[19] Furthermore, nutrition plays an important role in lung growth and development. The "new BPD" is characterized by a rarefaction of alveolar structures, which could be partially explained by insufficient protein or caloric intake during the postnatal period. According to the present study, though, not all infants who developed BPD had low caloric intake. If intake of calories or protein was below the minimal requirement, infants were more likely to develop BPD. However, the values did not reach statistical significance due to the small number of patients in this study.

One of the major findings of the present study is the lower enteral intake during the first two weeks in infants who developed BPD. Infants with a greater illness severity may be at a higher risk of BPD, and may also have a greater magnitude of feeding intolerance or a reluctance on the part of the clinician to aggressively increase enteral feeds. It could be assumed that parenteral nutrition alone is insufficient to meet the nutritional needs of preterm infants.[20,21] Furthermore, enteral nutrition could also have some beneficial effects for lung development. However, previous studies on enteral nutrition did not find a similar association between low enteral intake and subsequent development of BPD.[22] While this study is of clinical interest, some limitations should be discussed. First of all, the data were obtained retrospectively. It was the aim of the study to show whether infants who develop BPD received fewer calories and protein despite the very strict guidelines on nutrition in our neonatal intensive care unit. Thus, it was of interest to see a large variation between infants. A second limitation is the small number of infants, which may have caused type II errors. Over a long study period of more than two years, changes in management are likely and, thus, interpretation of the data would be more difficult. However, the present study provides a sound base for a prospective study on this subject.

Conclusions

In conclusion, the present study shows that infants who developed BPD received less enteral feeding during the first two weeks of life, which was well compensated by the parenteral nutrient supply. It seems that a critical amount of protein and caloric intake is required to prevent the development of BPD; however, a large prospective randomized trial is needed to prove this assumption.

References

1 Stevenson DK, Wright LL, Lemons JA, Oh W, Korones SB, Papile LA et al.: Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1993 through December 1994. Am J Obstet Gynecol 1998, 179: 1632-1639.
2 Coalson JJ: Pathology of new bronchopulmonary dysplasia. Semin Neonatol 2003, 8: 73-81.
3 Jobe AH: Let's feed the preterm lung. J Pediatr (Rio J) 2006, 82: 165-166.
4 Coxson HO, Chan IH, Mayo JR, Hlynsky J, Nakano Y, Birmingham CL: Early emphysema in patients with anorexia nervosa. Am J Respir Crit Care Med 2004, 170: 748-752.
5 Massaro D, Massaro GD: Hunger disease and pulmonary alveoli. Am J Respir Crit Care Med 2004, 170: 723-724.
6 Massaro GD, Radaeva S, Clerch LB, Massaro D: Lung alveoli: endogenous programmed destruction and regeneration. Am J Physiol Lung Cell Mol Physiol 2002, 283: L305-L309.
7 Massaro D, Massaro GD, Baras A, Hoffman EP, Clerch LB: Calorie-related rapid onset of alveolar loss, regeneration, and changes in mouse lung gene expression. Am J Physiol Lung Cell Mol Physiol 2004, 286: L896-L906.
8 Atkinson SA: Special nutritional needs of infants for prevention of and recovery from bronchopulmonary dysplasia. J Nutr 2001, 131: 942S-946S.
9 Jobe A, Bancalari E: Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001, 163: 1723-1729.
10 Kuzma-O'Reilly B, Duenas ML, Greecher C, Kimberlin L, Mujsce D, Miller D et al.: Evaluation, development, and implementation of potentially better practices in neonatal intensive care nutrition. Pediatrics 2003, 111: e461-e470.
11 Pauls J, Bauer K, Versmold H: Postnatal body weight curves for infants below 1000 g birth weight receiving early enteral and parenteral nutrition. Eur J Pediatr 1998, 157: 416-421.
12 Caple J, Armentrout D, Huseby V, Halbardier B, Garcia JG, Sparks JW et al.: Randomized, controlled trial of slow versus rapid feeding volume advancement in preterm infants. Pediatrics 2004, 114: 1597-1600.
13 Biniwale MA, Ehrenkranz RA: The role of nutrition in the prevention and management of bronchopulmonary dysplasia. Semin Perinatol 2006, 30: 200-208.
14 Thureen PJ: Early aggressive nutrition in very preterm infants. Nestle Nutr Workshop Ser Pediatr Program 2007, 59: 193-204.
15 Oh W, Poindexter BB, Perritt R, Lemons JA, Bauer CR, Ehrenkranz RA et al.: Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. J Pediatr 2005, 147: 786-790.
16 Mataloun MM, Leone CR, Mascaretti RS, Dohlnikoff M, Rebello CM: Effect of postnatal malnutrition on hyperoxia-induced newborn lung development. Braz J Med Biol Res 2009, 42: 606-613.
17 Akram KM, Kuzma-O'Reilly B, Brodsky NL, Bhandari V: Site-specific characteristics of infants developing bronchopulmonary dysplasia. J Perinatol 2006, 26: 428-435.
18 Kurzner SI, Garg M, Bautista DB, Bader D, Merritt RJ, Warburton D et al.: Growth failure in infants with bronchopulmonary dysplasia: nutrition and elevated resting metabolic expenditure. Pediatrics 1988, 81: 379-384.
19 Frank L, Sosenko IR: Undernutrition as a major contributing factor in the pathogenesis of bronchopulmonary dysplasia. Am Rev Respir Dis 1988, 138: 725-729.
20 Cooke RW: Factors associated with chronic lung disease in preterm infants. Arch Dis Child 1991, 66: 776-779.
21 Hammerman C, Aramburo MJ: Decreased lipid intake reduces morbidity in sick premature neonates. J Pediatr 1988, 113: 1083-1088.
22 Ehrenkranz RA: Early, aggressive nutritional management for very low birth weight infants: what is the evidence? Semin Perinatol 2007, 31: 48-55.

Temporal Trends in Neonatal Outcomes Following Iatrogenic Preterm Delivery

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Abstract

Background: Preterm birth rates have increased substantially in the recent years mostly due to obstetric intervention. We studied the effects of increasing iatrogenic preterm birth on temporal trends in perinatal mortality and serious neonatal morbidity in the United States.

Methods: We used data on singleton and twin births in the United States, 1995-2005 (n=36,399,333), to examine trends in stillbirths, neonatal deaths, and serious neonatal morbidity (5-minute Apgar ≤3, assisted ventilation ≥30min and neonatal seizures). Preterm birth subtypes were identified using an algorithm that categorized live births <37 weeks into iatrogenic preterm births, births following premature rupture of membranes and spontaneous preterm births. Temporal changes were quantified using odds ratios (OR) and 95% confidence intervals (CI).

Results: Among singletons, preterm birth increased from 7.3 to 8.8 per 100 live births from 1995 to 2005, while iatrogenic preterm birth increased from 2.2 to 3.7 per 100 live births. Stillbirth rates declined from 3.4 to 3.0 per 1,000 total births from 1995-96 to 2004-05, and neonatal mortality rates declined from 2.4 to 2.1 per 1,000 live births. Temporal declines in neonatal mortality/morbidity were most pronounced at 34-36 weeks gestation and larger among iatrogenic preterm births (OR=0.75, CI 0.73-0.77) than among spontaneous preterm births (OR=0.82, CI 0.80-0.84); P<0.001. Similar patterns were observed among twins, with some notable differences.

Conclusion: Increases in iatrogenic preterm birth have been accompanied by declines in perinatal mortality. The temporal decline in neonatal mortality/serious neonatal morbidity has been larger among iatrogenic preterm births as compared with spontaneous preterm births.

Background

Preterm birth is the leading cause of neonatal mortality and morbidity and preterm infants are more likely to experience neurodevelopmental delay and childhood disability. Thus, the recent increase in preterm birth that has been observed in many industrialized countries is acause for concern. For instance, in the United States, the rate of preterm birth increased by 20% from 10.6% in 1990 to 12.7% in 2007[1,2] whereas in Canada the rate of preterm birth increased by 18% from 6.6% in 1990 to 7.8% in 2007.[3,4]

Preterm birth can result from many maternal and fetal causes. Three major clinical subtypes of preterm birth can be identified, namely, iatrogenic (medically indicated) preterm birth, spontaneous preterm birth, and preterm birth following premature rupture of membranes. In North America, the recent increases in preterm birth occurred predominantly due to increases in iatrogenic preterm birth at late preterm gestation (34-36 weeks).[5,6] Other factors in the increase in preterm birth have included changes in maternal characteristics (such as increases in older maternal age)[7-10] and in the frequency of multiple births.[11,12]

Infants born following medically indicated preterm birth are at a two-fold higher risk of neonatal mortality as compared with infants born following spontaneous preterm birth.[13-15] If the risks of adverse birth outcomes among the different preterm birth subtypes have remained unchanged, a temporal increase in preterm neonatal mortality could be expected given the recent increase in iatrogenic preterm births. On the other hand, the recent increases in medically indicated preterm birth have followed improvements in fetal surveillance, obstetric care and neonatal care. This could have resulted in differential reductions in neonatal mortality and serious neonatal morbidity among infants born following iatrogenic preterm birth (as compared with those born following spontaneous preterm birth).

Our goal was to estimate temporal trends in iatrogenic and spontaneous preterm birth and to quantify trends in stillbirth, neonatal mortality and serious neonatal morbidity among the different preterm birth subtypes. We hypothesized that, over the past decade, there have been larger declines in neonatal mortality and serious neonatal morbidity among preterm infants born following obstetric intervention, as compared with infants born following spontaneous preterm labor.

Methods

We used population-based data on singleton and twin births in the United States, 1995-2005, from the National Centre for Health Statistics (NCHS). Information in the NCHS period linked

birth and death files, and fetal death files was abstracted from birth certificates of liveborn infants and from fetal and infant death certificates.[16,17] These data files provided gestational age estimates based on menstrual dates and also the clinical estimate of gestation.[18] The menstrual estimate of gestational age was estimated by the NCHS based on the date of the last normal menstrual period, with the day imputed if missing. The clinical estimate of gestation was that provided by the health care provider, without specification of the source (ie, whether based on clinical examination, ultrasound, etc). For this study we used the latter, more accurate clinical estimate of gestation at birth.[19-21] We excluded infants born before 24 weeks of gestation, and those weighing less than 500 grams in order to avoid potential bias due to variable birth registration at the borderline of viability,[22-24] as attitudes toward such registration may have changed over time. We further excluded infants with a missing clinical estimate of gestational age, a gestational age >45 weeks, or missing data on birth weight or mode of delivery. We excluded an additional 10.9% of births in 2004-05 due to missing data on rupture of membranes; 5 these missing data was related to the introduction of the new birth certificate by some states in 2004-05. Sensitivity analyses were carried out to account for this limitation. Preterm birth was defined as live birth before 37 completed weeks of gestation, and classified into 3 subtypes using a previously published algorithm.[6,15] Since the NCHS files do not contain direct information on preterm birth subtypes, this algorithm used information on premature rupture of membranes, labor induction, etc, to assign the preterm birth subtype in the following sequence [6,15]: 1) preterm birth following premature rupture of membranes for over 12 hours (PROM); 2) iatrogenic preterm birth (preterm birth following labor induction or caesarean delivery without PROM or conditions indicating prior onset of labor); 3) spontaneous preterm birth (all other births). In the absence of labour induction, preterm birth following cesarean delivery that occurred after the onset of labor (indicated by mention of complications such as precipitous labor, prolonged labor, cephalopelvic disproportion or dysfunctional labour) was assigned to the spontaneous preterm birth category.

Neonatal death was defined as death of an infant that occurred within the first 28 days after birth and serious neonatal morbidity was defined as any of the following conditions: a 5- minute Apgar score ≤3, assisted ventilation ≥30 minutes and neonatal seizures. A composite measure including neonatal death or any of the serious neonatal morbidity listed above was used to estimate the overall rate of adverse neonatal outcomes. We examined potential differences in maternal characteristics between 1995-96 and 2004-05, with respect to age, race (non-Hispanic white, non-Hispanic black, Hispanic, other), marital status (married or common-law vs. other), education (<12 years vs 12 years or more), smoking during pregnancy (yes/no) and prior live births (yes/no). We also examined infants' 6 gender, gestational age distributions among stillbirths and neonatal deaths, and the birth prevalence of congenital anomalies.

Temporal trends were quantified by contrasting neonatal mortality and neonatal mortality/serious neonatal morbidity between 1995-96 and 2004-05 using odds ratios and 95% confidence intervals (CI). Temporal changes were further examined within gestational age categories 24-27, 28-31, 32-33, and 34-36 weeks. Odds ratios were reported separately for singletons and twins. Differences in the magnitude of the temporal decline in neonatal mortality or neonatal mortality/

serious neonatal morbidity between subtypes of preterm birth (eg, between the odds ratios expressing the temporal declines in neonatal mortality among preterm birth following iatrogenic delivery vs spontaneous preterm birth) were assessed using a test for heterogeneity of the odds ratios.[25] We also carried out supplementary analyses to assess if our results were affected by the exclusion of infants with congenital anomalies since temporal increases in prenatal diagnosis and pregnancy termination may have influenced neonatal mortality trends. Sensitivity analyses were also carried out to examine if the exclusion of states which introduced a new birth certificate form in 2004 or 2005 affected our results. Finally, supplementary analyses were carried out to examine if there were temporal difference in outcomes among subgroups such as older mothers (≥35 years). Data used in this study were publicly accessible from the National Centre for Health Statistics. All analyses were performed using SAS statistical package version 9.1.3 (SAS Institute Inc., Cary, NC).

Results

Maternal characteristics changed during the study period: women who delivered in 2004-05 were older, more educated and smoked less during pregnancy compared with women who delivered in 1995-96 (Table 1). The proportion of births to mothers of Hispanic origin, unmarried mothers and mothers with no prior live births increased, while the frequency of congenital anomalies decreased. The rates of stillbirth and neonatal mortality decreased in all gestational age categories among both singletons and twins (Table 1). The largest declines in stillbirth and neonatal mortality rates occurred at late preterm and term gestational ages.

The overall rate of preterm birth increased from 8.4 per 100 live births in 1995 to 10.5 per 100 live births in 2005. Late preterm births (34-36 weeks), which increased from 5.3 per 100 live births in 1995 to 6.7 per 100 live births in 2005, were responsible for most of the increase. Preterm birth rates increased from 7.3 in 1995 to 8.8 per 100 live births in 2005 among singletons (odds ratio=1.22, 95%CI:1.21-1.23) and from 52.3 to 62.0 per 100 live births among twins (odds ratio=1.49, 95%CI:1.46-1.52).

The increase in the singleton preterm birth rate was predominantly due to an increase in iatrogenic preterm birth from 2.2 in 1995 to 3.7 per 100 live births in 2005 (odds ratio=1.77, 95%CI:1.76-1.79; Figure 1). The rate of spontaneous preterm birth among singletons was 4.1 per 100 live births in 1995 and 4.2 per 100 live births in 2005, while the rate of PROM preterm birth was 1.0 per 100 live births in 1995 and 0.9 per 100 live births in 2005. Among twins, the iatrogenic preterm birth rate increased from 24.9 to 39.8 per 100 live births from 1995 to 2005 (odds ratio=2.07, 95%CI:2.03-2.11), while the spontaneous preterm birth rate declined from 21.7 to 16.9 per 100 live births over the same period (odds ratio=0.70, 95%CI:0.69-0.72; Figure 1). Rates of preterm birth following PROM were 5.7 in 1995 and 5.4 per 100 live births in 2005 (Figure 1).[8]

Neonatal mortality rates declined from 2.5 to 1.9 per 100 preterm live births between 1995-96 and 2004-05 among singletons born following iatrogenic preterm delivery and from 1.6 to 1.2 per 100 preterm live births among singletons born spontaneously. The magnitude of the decline in neonatal mortality following iatrogenic preterm birth (odds ratio=0.75, 95%CI:0.71- 0.78) was not significantly greater than the decline following spontaneous preterm birth (odds ratio=0.78, 95%CI:0.74-0.81; P value for

difference in odds ratios=0.21). There was no significant change in neonatal mortality rates among live births following preterm rupture of membranes between 1995-96 and 2004-05 (odds ratio=0.95, 95%CI:0.88-1.02). The difference in temporal trends in neonatal mortality between infants born after PROM and those born following iatrogenic and spontaneous preterm birth was significant (P value<0.001 for both contrasts). In general, larger reductions in neonatal mortality were observed at late preterm gestation (34-36 weeks) compared to earlier gestational ages (24-27, 38-31 and 32-33 weeks (Table 2).

Among twins, neonatal mortality rates between 1995-96 and 2004-05 declined significantly among all 3 preterm birth subtypes. The magnitude of the decline in neonatal mortality among the 3 preterm birth subtypes was similar (P>0.05 for all 3 contrasts). The observed declines in neonatal mortality within each preterm birth subtype were largest among live births at 34-36 weeks gestation (Table 2).

Composite neonatal mortality or serious neonatal morbidity showed a different pattern of change between 1995-96 and 2004-05 (Table 3). The reduction in neonatal mortality/serious neonatal morbidity among singletons was greater among infants born following iatrogenic preterm birth compared with those born following spontaneous preterm birth (odds ratio=0.75, 95%CI:0.73-0.77 vs 0.82, 95%CI:0.80-0.84; P value for difference in odds ratios<0.001).[9] Neonatal mortality/serious neonatal morbidity rates among preterm live births following PROM increased significantly from 1995-96 to 2004-05 and this change was significantly different from the temporal changes in the 2 other subtypes of preterm birth (P value<0.001 for both contrasts, Table 3). The reductions in neonatal mortality/serious neonatal morbidity in the iatrogenic and spontaneous preterm birth groups were observed at early preterm gestation as well as at late preterm gestation; among live births following preterm PROM, the temporal increase in neonatal mortality/morbidity was observed in the 34-36 week group (Table 3).

Among twins, neonatal mortality/serious neonatal morbidity rates declined significantly following iatrogenic preterm birth and spontaneous preterm birth, while neonatal mortality/serious neonatal morbidity rates among preterm births following PROM did not change significantly (Table 3). The neonatal mortality/ serious neonatal morbidity decrease among iatrogenic preterm births was larger in magnitude than that among spontaneous preterm births (odds ratios=0.84, 95%CI:0.81-0.88 vs. 0.92, 95%CI:0.87-0.97; P value for difference in odds ratios=0.01). Significant reductions in neonatal mortality/morbidity among twin live births following iatrogenic preterm birth were observed at 24-27, 28-31 and 34-36 weeks but not among those born at 32-33 weeks. Among twins born following spontaneous preterm birth, neonatal mortality/serious neonatal morbidity was significantly reduced at 24-27 and 28-31 weeks but not at 32-33 and 34-36 weeks, while among twins born following PROM, neonatal mortality/morbidity was not significantly reduced in any gestational age group (Table 3).

Supplementary analyses showed that trends in neonatal mortality/serious neonatal morbidity remained unchanged even after the exclusion of infants with congenital anomalies from the analysis. There was a significantly larger temporal decline in neonatal mortality/serious neonatal morbidity following iatrogenic preterm birth (odds ratio=0.80, 95%CI:0.78-0.82) than 10 following spontaneous preterm birth (odds ratio=0.92,

95% CI:0.90-0.95; P value for difference in odds ratios<0.001). Similar results were also obtained when analysis was restricted to the US states that did not introduce the new birth certificate form in 2004 or 2005. Preterm birth rates were similar between states that did and did not introduce a new birth certificate (10.7 and 10.5 per 100 live births, respectively). Supplementary analyses carried out among older mothers (≥35 years) showed that between 1995-96 and 2004-05, neonatal mortality/serious neonatal morbidity among singletons born preterm following iatrogenic delivery, declined from 10.3 to 7.4 per 100 live births, odds ratio=0.69 (95%CI: 0.64-0.75); among preterm infants born spontaneously the composite outcome increased from 6.5 to 7.1 per 100 live births, odds ratio=1.10 (95%CI: 1.03- 1.18). Neonatal mortality/serious neonatal morbidity rates remained relatively stable among infants born following PROM (12.7 and 13.2 per 100 live births), odds ratio=1.05 (95%CI: 0.95- 1.16).

Discussion
We have shown that the temporal increase in preterm birth in the United States between 1995 and 2005 was primarily due to an increase in iatrogenic preterm birth at late preterm gestation among both singletons and twins. This increase in medically indicated preterm birth coincided with reductions in stillbirth rates and neonatal mortality rates. Also, infants born following medically indicated preterm birth showed larger reductions in neonatal mortality and serious neonatal morbidity rates when compared with infants born following spontaneous preterm birth. Neonatal mortality/serious neonatal morbidity rates among infants born following preterm PROM showed a temporal increase among singletons and no significant change among twins.

Our study and previous studies[6,13,14] show that medically indicated preterm birth is the primary cause of the recent increase in preterm birth. This is particularly evident among twins, among whom increases in medically indicated preterm birth have resulted in declines in spontaneous preterm birth. Nevertheless, the various factors responsible for the overall increases in preterm birth (eg, obstetric intervention, older maternal age and multi-fetal pregnancy) are not mutually exclusive. For instance, population increases in older maternal age lead to increases in medically indicated preterm birth because older maternal age is a risk factor for fetal growth restriction, perinatal mortality and serious neonatal morbidity.[26-28]

The reasons for the observed differences in neonatal mortality and serious neonatal morbidity reductions observed among the iatrogenic and spontaneous preterm birth groups probably relate to changes in obstetric surveillance and management. High risk pregnancies with suspected fetal compromise are more carefully monitored currently, with early delivery intervention if the benefits of delivery are deemed to outweigh the risks of preterm birth and expectant management. Given the temporal advances in neonatal care, this effect would be expected mainly at late preterm gestation, when the preterm birth poses less risk to the newborn as compared to earlier gestation. Correspondingly, our findings showed the largest decline in neonatal mortality/serious neonatal morbidity among iatrogenic preterm births which occurred at late preterm gestation. Closer fetal surveillance may also improve outcomes by ensuring that prophylactic antenatal corticosteroid therapy is used, unlike in cases of spontaneous preterm birth where the unexpected onset of labor may preclude such prophylaxis. Maternal transport

to a higher level perinatal care facility for labor induction or caesarean delivery may have also contributed to the temporal improvement in neonatal outcomes following iatrogenic delivery. In addition, iatrogenic preterm birth may be carried out for less severe indications in recent years as compared with past years, as the improvements in neonatal care allow for intact survival of preterm infants, especially at late preterm gestation. Although audits of indications for preterm birth show that medically indicated preterm birth is mostly unavoidable and carried out typically for severe or unstable medical/obstetric conditions such as severe preeclampsia or fetal compromise, a small proportion of iatrogenic preterm births may be without a clear medical indication.[29-30] Finally, increases in prenatal diagnosis and pregnancy termination during the study period may have contributed to the differences in trends in neonatal mortality/ serious neonatal morbidity following spontaneous and iatrogenic delivery. However, the differences in temporal trends in neonatal mortality/serious neonatal morbidity by preterm birth subtype persisted even after exclusion of infants with congenital anomalies, rendering this explanation unlikely.

The lack of a temporal improvement in neonatal mortality and in neonatal mortality/serious neonatal morbidity among infants born after preterm premature rupture of membranes over 12 hours is concerning. Such infants constitute approximately 1% of singleton live births and approximately 5% of twin live births. Neonatal mortality rates in this preterm category are currently high and the absence of a temporal decline in neonatal mortality/ serious neonatal morbidity suggests that this subgroup has not benefitted from recent improvements in obstetric and neonatal care. Research needs to be directed at improving management options for this condition.

The differential temporal reductions in neonatal mortality/ serious neonatal morbidity among the iatrogenic and spontaneous preterm subgroups were not evident in contrasts of neonatal mortality. Although reductions in neonatal mortality were somewhat larger among infants born after iatrogenic preterm birth compared with those born following spontaneous preterm birth (odds ratio 0.75 vs. 0.78), this difference was not statistically significant. One possible reason for this may be the lesser frequency of neonatal mortality ie, the lack of a significant difference could have arisen due to a lesser study power.

The limitations of our study include a potential misclassification of preterm birth subtypes. Some cases of spontaneous preterm labor or PROM who were delivered by caesarean for indications such as fetal compromise may have been misclassified as iatrogenic in our study. This problem arose because our data source did not include details regarding the onset of labor. However, the misclassification introduced because of this is likely small as studies from other more clinically focused databases (which include information on labor onset) have shown similar proportions of iatrogenic and spontaneous preterm births. For instance, a study from British Columbia, Canada,[30] showed that 43% of preterm births in 2005 occurred following preterm labor induction or cesarean delivery in the absence of labor (compared with 42% in 2004-05 in this study). The categorization of preterm birth has been the source of some debate in the past.[31,32] Although each subtype of preterm birth may have a different implication for preventive efforts, [33] etiologic pathways are complex and in many instances overlap.[31,34] Another limitation arises because we were not able to utilize data on neonatal morbidity from those states that

introduced the new birth certificate forms in 2004 and 2005 due to the incompatibility of definitions for assisted ventilation. However, sensitivity analyses showed that this had a minor impact on our findings. In addition, newborns from states that introduced the new birth certificate during 2004-05 had similar characteristics as compared with infants born in the other states. Disease specific information, such as occurrence of intraventricular hemorrhage, necrotizing entrerocolitis or respiratory distress syndrome, was not available in the US data. Instead, we used a composite outcome including neonatal mortality or severe neonatal morbidity, the latter being approximated by Apgar score at 5 minutes ≤3, prolonged ventilation, and neonatal seizures. This composite outcome was chosen to identify neonates who died or those at a high risk of infant death or disability. This composite outcome has been used in previous studies[35] and is strongly associated with adverse outcomes in longterm follow-up studies.[36,37] Data from California, which did not report the clinical estimate of gestation, was excluded from our study (13% of births). This represents a limitation of our study but is balanced by the use of an accurate estimate of gestational age.

Conclusion

In summary, our study shows that recent increases in obstetric intervention in the United States have resulted in larger declines in rates of neonatal mortality and serious neonatal morbidity among infants born following iatrogenic preterm birth as compared with infants born following spontaneous preterm birth. On the other hand, neonatal mortality/serious neonatal morbidity rates among infants born following PROM showed a temporal increase among singletons and no significant change among twins. Whereas our findings on iatrogenic preterm birth are encouraging, they highlight the need for improving outcomes among preterm infants born following preterm premature rupture of membranes. More research is needed to identify the underlying maternal and fetal conditions that lead to preterm delivery in order to develop targeted interventions to prevent adverse neonatal outcomes resulting from preterm birth.

References

1 Hamilton BE, Martin JA, Ventura SJ. Births: Preliminary data for 2007. National vital statistics reports. Hyattsville, MD: National Center for Health Statistics. Released March 18, 2009; vol. 57; no. 12.
2 Martin JA, Kirmeyer S, Osterman M, Shepherd RA. Born a Bit Too Early: Recent Trends in Late Preterm Births. NCHS Data Brief 2009 Nov; 24:1-8.
3 Health Canada. Canadian Perinatal Health Report, 2000. Ottawa: Minister of Public Works and Government Services Canada, 2000; 2000.
4 Births 2007. Statistics Canada. Minister of Industry. Ottawa 2009; Catalogue No. 84F0210X.
5 Joseph KS, Demissie K, Kramer MS. Trends in obstetric intervention, stillbirth and preterm birth. Semin Perinatol. 2002;26:250-9.
6 Ananth CV, Joseph KS, Oyelese Y, Demissie K, Vintzileos AM. Trends in preterm birth and perinatal mortality among singletons: United States, 1989 through 2000. Obstet Gynecol. 2005; 105(5):1084-91.
7 Tough SC, Newburn-Cook C, Johnston DW, Svenson LW, Rose S, Belik J. Delayed childbearing and its impact on population rate changes in lower birth weight, multiple birth, and preterm delivery. Pediatrics. 2002; 109(3):399-403. 17
8 Martin JA, Hamilton BE, Sutton PD, Ventura SJ. Births; Final

data for 2006. National Vital Statistics Reports. Hyattsville, MD: National Centre for Health Statistics; 2009. Report No.: 7, vol 57.

9   Fell DB, Joseph KS, Dodds L, Allen AC, Jangaard K, Van den HM. Changes in maternal characteristics in Nova Scotia, Canada from 1988 to 2001. Can J Public Health. 2005; 96(3): 234-8.

10 Health Canada. Canadian Perinatal Health Report, 2008 Edition. Ottawa, Catalogue No HP10-12/2008E; 2008.

11 Blondel B, Kaminski M. Trends in the occurrence, determinants, and consequences of multiple births. Semin Perinatol. 2002; 26(4):239-49.

12 Blickstein I, Keith LG. Aging, twinning, and perinatal outcomes. Fertil Steril 2003; 79(3):661-2.

13 Barros FC, Velez MP. Temporal trends of preterm birth subtypes and neonatal outcomes. Obstet Gynecol. 2006;107(5):1035-41.

14 Norman JE, Morris C, Chalmers J. The effect of changing patterns of obstetric care in Scotland (1980-2004) on rates of preterm birth and its neonatal consequences: perinatal database study. PLoS Med. 2009;6(9):e1000153.

15 Chen A, Feresu SA, Barsoom MJ. Heterogeneity of preterm birth subtypes in relation to neonatal death. Obstet Gynecol. 2009;114(3):516-22. 18

16 Department of Health and Human Services, Centre for Disease Control and Prevention, National Centre for Health Statistics, Division of Vital Statistics. Public Use Data File Documentation, 1995 Period Linked Birth/Infant Death Data Set. http://www.cdc.gov/nchs/data_access/Vitalstatsonline. htm; Accessed April 2011

17 Department of Health and Human Services, Centre for Disease Control and Prevention, National Centre for Health Statistics, Division of Vital Statistics. Public Use Data File Documentation, 2005 Period Linked Birth/Infant Death Data Set. http://www.cdc.gov/nchs/data_access/Vitalstatsonline. htm; Accessed April 2011

18 Wier ML, Pearl M, Kharrazi M. Gestational age estimation on United States livebirth certificates: a historical overview. Paediatr Perinat Epidemiol. 2007; 21 Suppl 2:4-12.

19 Joseph KS, Huang L, Liu S, Ananth CV, Allen AC, Sauve R, et al. Reconciling the high rates of preterm and postterm birth in the United States. Obstet Gynecol. 2007; 109(4):813-22.

20 Mustafa G, David RJ. Comparative accuracy of clinical estimate versus menstrual gestational age in computerized birth certificates. Public Health Rep. 2001; 116(1):15-21.

21 Ananth CV. Menstrual versus clinical estimate of gestational age dating in the United States: temporal trends and variability in indices of perinatal outcomes. Paediatr Perinat Epidemiol. 2007; 21 Suppl 2:22 -30.

22 Sepkowitz S. International rankings of infant mortality and the United States' vital statistics natality data collecting system–failure and success. Int J Epidemiol. 1995; 24(3):583-8. 19

23 Sachs BP, Fretts RC, Gardner R, Hellerstein S, Wampler NS, Wise PH. The impact of extreme prematurity and congenital anomalies on the interpretation of international comparisons of infant mortality. Obstet Gynecol. 1995; 85(6):941-6.

24 Kramer MS, Platt RW, Yang H, Haglund B, Cnattingius S, Bergsjo P. Registration artifacts in international comparisons of infant mortality. Paediatr Perinat Epidemiol. 2002; 16(1):16-22.

25 Breslow NE, Day NE. Statistical methods in cancer research: Vol. I - The analysis of case-control studies. Lyon: IARC; 1980: Scientific Publ. No 32.

26 Joseph KS, Allen AC, Dodds L, Turner LA, Scott H, Liston R. The perinatal effects of delayed childbearing. Obstet Gynecol. 2005; 105:1410-1418.

27 Aldous MB, Edmonson MB. Maternal age at first childbirth and risk of low birth weight and preterm delivery in Washington State. JAMA. 1993; 270:2574-2577.

28 Jolly M, Sebire N, Harris J, Robinson S, Regan L. The risks associated with pregnancy in women aged 35 years or older. Hum Reprod. 2000; 15:2433-2437.

29 Holland MG, Refuerzo JS, Ramin SM, Saade GR, Blackwell SC. Late preterm birth: how often is it avoidable? Am J Obstet Gynecol. 2009; 201(4):404.

30 Joseph KS, Barker S, Dale S, Lee L, McMaster R, Miyazaki L. Preterm birth in British Columbia. British Columbia Perinatal Health Program. Vancouver. March 2008.

31 Savitz DA, Dole N, Herring AH, Kaczor D, Murphy J, Siega-Riz AM et al. Should spontaneous and medically indicated preterm births be separated for studying aetiology? Peadiatric and Perinatal Epidemiology. 2005; 19, 97-105.

32 Berkowitz GS, Blackmore-Prince C, Lapinski RH, Savitz DA. Risk factors for preterm birth subtypes. Epidemiology. 1998; 9:279-285.

33 Joseph KS. Theory of obstetrics: An epidemiologic framework for justifying medically indicated early delivery. BMC Pregnancy and Childbirth. 2007; 7:4

34 Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Maternal-Fetal and Neonatal Medicine. 2006; 199(12): 773-782.

35 Joseph KS, Fahey J, Platt RW, Liston RM, Lee SK, Sauve R, Liu S, Allen AC, Kramer M. An outcome-based approach for the creation of fetal growth standards: Do singletons and twins need separate standards? Am J Epid. 2009; 169(5): 616-624.

36 Mellits ED, Holden KR Freeman JM. Neonatal seizures. II. A multivariate analysis of factors associated with outcome. Pediatrics. 1982; 70(2):177-185 21

37 Eilenberg JH, Nelson KB. Cluster of perinatal events identifying infants at high risk for death or disability. J Pediatr. 1988; 113(3):546-552 22

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the authors of the correspondence encountered no difficulty passing the 3.5 cuffed endotracheal tube past the distal aperture of the size 1 ILA. The only problem encountered was an inability to pass the pilot balloon through the ILA lumen. This was handled by cutting off the pilot balloon. Using a 4.0 uncuffed endotracheal tube would have obviated this problem. They noted that the technique of inverting a stylet designed for a larger ETT worked very well but didn't routinely recommend it because of the theoretical risk of having the end of the stylet advance too far into the endotracheal tube such that it becomes difficult to remove. The correspondents noted: "In summary, we have used a novel supraglottic airway device, the air-Q ILA, as a conduit for fiberoptic intubation in two difficult intubation scenarios." The correspondents are: Kawshala Peiris, Mike Traynor and Simon Whyte, with BC Children's Hospital, Vancouver.

Thrombocytopenia in Neonates and the Risk of Intraventricular Hemorrhage: a retrospective cohort study

Jeannette S. von Lindern, Tjitske van den Bruele, Enrico Lopriore, Frans J. Walther

Abstract

Background: The overall prevalence of thrombocytopenia in neonates admitted to neonatal intensive care units ranges from 22 to 35%. There are only a few small studies that outline the relationship between the severity of thrombocytopenia and the risk of bleeding. This makes it difficult to form an evidence-based threshold for platelet transfusions in neonatal patients. The aim of this study was to determine the prevalence of thrombocytopenia in a tertiary neonatal intensive care unit and to study the relation between thrombocytopenia and the risk of intraventricular hemorrhage (IVH).

Methods: We performed a retrospective cohort study of all patients with thrombocytopenia admitted to our neonatal tertiary care nursery between January 2006 and December 2008. Patients were divided into 4 groups according to the severity of thrombocytopenia: mild (100-149 × 10⁹/L), moderate (50-99 × 10⁹/L), severe (30-49 × 10⁹/L) or very severe (< 30 × 10⁹/L). The primary outcome was IVH ≥ grade 2. Pearson's chi-squared and Fischer's exact tests were used for categorical data. ANOVA, logistic regression analysis and multivariate linear regression were used for comparisons between groups and for confounding factors.

Results: The prevalence of thrombocytopenia was 27% (422/1569). Risk of IVH ≥ grade 2 was 12% (48/411) in neonates with versus 5% (40/844) in neonates without thrombocytopenia (p<0.01). After multivariate linear regression analysis, risk of IVH ≥ grade 2 in the subgroups of thrombocytopenic infants was not significantly different (p=0.3). After logistic regression analysis the difference in mortality rate in neonates with and without thrombocytopenia was not significant (p=0.4). Similarly, we found no difference in mortality rate in the subgroups of neonates with thrombocytopenia (p=0.7).

Conclusion: Although IVH ≥ grade 2 occurs more often in neonates with thrombocytopenia, this relation is independent

of the severity of thrombocytopenia. Prospective studies should be conducted to assess the true risk of hemorrhage depending on underlying conditions. Randomized controlled trials are urgently needed to determine a safe lower threshold for platelet transfusions.

Background

The overall prevalence of thrombocytopenia in neonates ranges from 1 to 5%[1-3] and is reported to be much higher in neonates admitted to neonatal intensive care units, ranging from 22 to 35%.[1-6] From 22 weeks' gestation onwards, the platelet count reaches and maintains a level above 150 × 10⁹/L, thereby defining thrombocytopenia in the newborn as a platelet count below 150 × 10⁹/L.[1,2] Many neonatal and maternal conditions are associated with thrombocytopenia, of which septicemia and prematurity are the most common.[2,6] In thrombocytopenia the major concern is an increased risk of bleeding.

In 1882 Bizzozzero was the first to describe the role of platelets in coagulation and thrombosis.[7] Since then, only a few small studies investigating the relationship between the severity of thrombocytopenia and the risk of bleeding in newborns have been reported.[4,8,9] Likewise, the number of clinical trials examining thrombocytopenia and the effects on bleeding in adults is limited.[10-13] The lack of studies makes it difficult to form an evidence-based threshold for platelet transfusions in neonatal patients.

The aim of this study was to analyze and describe all cases with thrombocytopenia admitted to our neonatal nursery during a 3-year period and study a possible relationship between the risk of intraventricular hemorrhage (IVH) and the severity of thrombocytopenia. We studied the prevalence and risk factors of thrombocytopenia in relation to the risk of IVH and mortality.

Methods

Patients: We retrospectively collected data from all neonates admitted between January 2006 and December 2008 to the neonatal department of the Leiden University Medical Center, a tertiary neonatal care center in The Netherlands. In the Netherlands no ethical approval is required for this type of research as no new intervention or treatment is studied. Nor is any randomization needed. All collected data was anonymized. We identified all thrombocytopenic newborns by extracting data from our dedicated patient-database, medical files, laboratory system and electronic blood banking records. We excluded neonates with only one platelet count

measurement below 150×10^9/l. We considered these isolated counts as clotted samples, platelet clumping, laboratory error or one-time only measurements with immediate normalization. Thrombocytopenia was defined as a platelet count below 150×10^9/L. The included neonates with thrombocytopenia were divided into 4 groups, based on their lowest platelet count during their stay in our unit, and classified as mild (platelet count 100-149 $\times 10^9$/L), moderate (platelet count 50-99 $\times 10^9$/L), severe (platelet count 30-49 $\times 10^9$/L) or very severe (platelet count < 30 $\times 10^9$/L), according to standard classification.[1,2,6,14-17]

We recorded the presence of IVH detected by cranial ultrasound and classified according to Volpe.[18] IVH grade 2, grade 3 or grade 4 (ie periventricular hemorrhagic infarction (PVHI)) were recorded.

Cranial ultrasounds were performed according to local protocol depending on gestational age and degree of illness.

Data for demographic as well as clinical conditions of all infants were collected, including gender, gestational age at birth, birth weight, small for gestational age, chromosomal disorders, perinatal asphyxia, necrotizing enterocolitis, sepsis/meningitis, hemorrhage, thrombosis, central catheters, polycythemia, rhesus hemolytic disease, exchange transfusion, neonatal allo-immune thrombocytopenia and the number of blood product transfusions (platelets, erythrocytes, fresh frozen plasma). Small for gestational age was defined as a birth weight <3rd percentile for the corresponding gestational age.[19] Chromosomal disorders were defined as congenital anomalies related to thrombocytopenia, such as trisomy 18 and 21. Perinatal asphyxia was defined as a five minute Apgar score <5, a decelerative heart rate on a cardiotocogram and/or an arterial umbilical cord pH below 7.0. Hypotension was defined as a mean blood pressure below the 3rd percentile for gestational age and requiring inotropic support. Sepsis was defined as a positive blood culture in a neonate with clinical signs of infection. Necrotizing enterocolitis was scored based on Bell staging criteria.[20] Polycythemia was defined as a venous hematocrit ≥65% in symptomatic infants or ≥70% with or without symptoms. A thrombus could be catheter related, in a major blood vessel or intracardial, detected with ultrasound. The primary outcome measure was IVH ≥ grade 2. The secondary outcomes were total number of platelet transfusions and mortality.

In our hospital a platelet transfusion for neonates is a concentrated single donor product in plasma and is leukocyte depleted. The dose is a median of 20×10^9 platelets per kg. The product is irradiated with 25 Gy for all infants with a gestational age below 32 weeks and/or a birth weight below 1500 grams and/or for neonates that previously underwent an intra-uterine transfusion. Guidelines for platelet transfusions in our department were as follows: 1) platelet count $<30 \times 10^9$/L and stable, 2) platelet count $<50 \times 10^9$/L and unstable, and/or birth weight <1000 g, and/or previous major bleeding, and/or after exchange transfusion, and/or before planned surgery and/or rapid decrease of platelets, or 3) platelet count $<100 \times 10^9$/L in neonates with active bleeding and/or at start of exchange transfusion.[17]

Statistics: Data analyses were performed using Statistical Package for Social Sciences (SPSS), version 16.0 (SPSS, Inc., Chicago, Illinois, USA). For every separate variable the Pearson's chi-squared test was used. If the chi-squared-test could not be used (frequency of an event was <5) the Fisher's exact test was used. Comparisons between group means were analyzed using the one way ANOVA test (with a 95% confidence-interval). Logistic regression was performed to evaluate the confounders between the infants with and without thrombocytopenia. Factors considered potential confounders were variables with a significant difference in thrombocytopenia. Multivariate linear regression was used to compare for confounders in the subgroups of thrombocytopenic neonates, because of the small number in some of the subgroups of thrombocytopenic neonates. A p-value smaller than 0.05 was considered to be significant.

Results

Total patient population: A total of 1,727 neonates were admitted to our neonatal nursery during the 3-year study period. Thrombocytopenia was detected in 580 neonates, of which 158 were excluded because of only one platelet count below 150×10^9/L. The prevalence of thrombocytopenia was 27% (422/1569). Neonates with thrombocytopenia were divided into four groups according to their lowest platelet count; 122 (29%) mild, 164 (39%) moderate, 67 (16%) severe and 69 (16%) with very severe thrombocytopenia. The distribution of included and excluded neonates is shown in Figure 1. An overview of the baseline characteristics of all included neonates with (n=422) and without (n=1147) thrombocytopenia is presented in Table 1. Except for gender, single or multiple births and chromosomal disorders, every characteristic was significantly different.

Primary and secondary outcome in total patient population: Cranial ultrasound was performed in 97% (411/422) of neonates with thrombocytopenia and in 74% (844/1147) of infants without thrombocytopenia. The rate of IVH ≥ grade 2 in neonates with and without thrombocytopenia was 12% (48/411) and 5% (40/844), respectively (p<0.01). After multiple regression analysis, with all significantly different variables, the correlation between IVH and thrombocytopenia was still statistically significant (p=0.045); gestational age remained an independent significant risk factor for IVH (p<0.01). Mortality rate in neonates with and without thrombocytopenia, respectively 9% (39/422) vs. 3% (32/1147), was not significantly different after multiple regression analysis (p=0.4).

Thrombocytopenic patient population: Thrombocytopenia was detected at a mean of 2 days after birth (range 0-56 days). In the group of thrombocytopenic neonates (n=422), 27 died before thrombocytopenia had resolved and in 32 neonates laboratory testing was discontinued before a platelet count above 150×10^9/L was recorded during follow-up. In these 32 infants platelet counts were not measured because of already increasing platelet counts with a value above 120×10^9/L. In the remaining 363 neonates, the mean duration of thrombocytopenia was 9 days (range 0-112 days). We found a significant positive correlation between severity of thrombocytopenia and the time to recovery. Duration of thrombocytopenia in the mild, moderate, severe and very severe group was 5, 8, 10 and 16 days, respectively (p<0.01).

Mean gestational age at birth was 32.5 (range 24 to 42) weeks. Of all thrombocytopenic neonates, 75% (316/422) were preterm (<37 weeks). Patient characteristics divided into subgroups according to severity of thrombocytopenia are shown in Table 2. After linear regression analysis, severity of thrombocytopenia remained associated with sepsis (p<0.01) and thrombi (p<0.01). In 66% of the 105 thrombocytopenic neonates with sepsis, the low platelet count was already present before the child became

ill, whereas in 15% thrombocytopenia developed after the onset of sepsis.

Primary and secondary outcome in thrombocytopenic patient population: In the majority (87%) of neonates with an IVH ≥ grade 2 the hemorrhage occurred within the first 3 days of life. In 23% of the 48 neonates (11/48) with an IVH, the hemorrhage was discovered on the same day as the thrombocytopenia. In 20 (42%) neonates the hemorrhage was discovered after and in 16 (33%) before the thrombocytopenia even existed. In 1 neonate we could not trace the timing of the hemorrhage.

Among the 122 neonates who received a platelet transfusion 17 had an IVH ≥ grade 2. Two (13%) of these infants developed an IVH during thrombocytopenia despite platelet transfusions (one IVH grade 2, one IVH grade 3).

The primary and secondary outcome in the 4 subgroups of neonates with thrombocytopenia is presented in Table 3. Risk of hemorrhage was 10% (12/117), 14% (22/160), 6% (4/66) and 15% (10/68). We found no significant association between bleeding and severity of thrombocytopenia (p=0.3). After logistic regression analysis, the severity of thrombocytopenia was not a significant risk factor for IVH.

Logistic regression analysis showed no significant relation between mortality and the severity of thrombocytopenia (p=0.7). In 5 patients treatment was withdrawn because of poor neurological prognosis due to major hemorrhage (IVH grade 3 or PVHI) in combination with respiratory and/or cardiac insufficiency.

Of all included neonates with thrombocytopenia 29% (122/422) received a platelet transfusion (Table 3). The median number of platelet transfusions in the mild, moderate, severe and very severe groups was 0, 1, 1 and 3, respectively. The 9 neonates in the moderate thrombocytopenia group ($50\text{-}99 \times 10^9/L$) were transfused because of a rapid drop in platelet count in combination with sepsis (n=4), IVH ≥grade 2 (n=3) or adrenal hemorrhage (n=1). In most cases the infants with severe thrombocytopenia ($30\text{-}49 \times 10^9/L$) received a platelet transfusion before or during an intervention (such as a lumbar puncture or exchange transfusion), because of active bleeding or if they were clinically unstable. The rest of the newborns were transfused when the platelet count was below $30 \times 10^9/L$. Only 4 neonates with very severe thrombocytopenia did not receive a platelet transfusion. Three of them had a gestational age of 37 and the fourth one of 31 weeks. All four were clinically stable, 2 had polycythemia and 2 had Rhesus hemolytic disease. None of them had IVH.

Discussion

This study shows that although thrombocytopenic neonates are a high risk group (more unstable, and sicker than non-thrombocytopenic neonates), the severity of thrombocytopenia is not related to IVH or mortality. In 33% of the thrombocytopenic neonates with IVH grade 2 or more, IVH occurred before the thrombocytopenia even existed. Our data confirm that risk of IVH in neonates is a complex mechanism related to a wide variety of factors, of which low platelet counts is only one.

Prevalence of thrombocytopenia: The overall prevalence of thrombocytopenia found in this study (27%) is in accordance with the rates reported in the literature for tertiary care

centers (22-35%).[1-6] The prevalence of severe ($<50 \times 10^9/L$) thrombocytopenia (8%) was also similar to other studies (2-25%).[1-3] Our findings confirm that thrombocytopenia in neonates is associated with a wide variety of factors, including prematurity and low birth weight, small for gestational age, sepsis, hypotension, necrotizing enterocolitis, asphyxia, thrombi and exchange transfusions.[1,4,14,21]

Platelet transfusion: We found a positive correlation between the severity of thrombocytopenia, the duration of thrombocytopenia and with the total number of platelet transfusions. In the subgroup of infants with severe thrombocytopenia, platelet transfusion resulted in a good, but less sustained rise in platelet count (data not shown). A few studies have suggested that a fast drop in platelet count after transfusion is caused by ongoing platelet consumption instead of platelet underproduction.[21]

The reason for platelet transfusions in more than half of the cases was an existing thrombocytopenia. Despite the platelet transfusions, 13% (2/17) developed an IVH (≥ grade 2), independent of the severity of thrombocytopenia. In newborns that required more transfusions (data not shown) no increased risk for IVH was seen, comparable to other studies.[9,16,21] Therefore the jury is still out on the protective value of platelet transfusions.[1,4,6,9,22]

Risk of hemorrhage: We found no significant relationship between hemorrhage and severity of thrombocytopenia. This suggests that bleeding in neonates depends on more variables than a platelet count alone. In approximately one-third of the thrombocytopenic neonates the IVH was discovered before the thrombocytopenia existed and this raises the question whether IVH can be explained as a cause or an effect of thrombocytopenia.[22-24] Hemorrhage is probably due to pre-existing fragility in vessel wall structure (especially in premature neonates) and damaged blood vessels, amongst others by cytokines and/or a co-existing coagulopathy.[9,22]

Our results are important in the discussion whether thrombocytopenia is one of the major causes of IVH in neonates. Major IVH has a large impact on neurological development and mortality. However, the risk for an IVH cannot be predicted based on a platelet count alone. We also looked at other bleedings of importance in the thrombocytopenic neonates, such as pulmonary- or gastrointestinal bleedings, but the number of these hemorrhages was too small to analyze. Other variables such as gestational age, birth weight and underlying illness are of equal importance and should be taken into account. Several studies have searched for other factors that may influence the development of hemorrhage in thrombocytopenic neonates. Deficiencies, immaturity or increased consumption of other blood products, such as thrombopoietin, coagulation factors, megakaryocyte progenitor cells, cytokines and mean platelet volume, have been reported.[3,25]

One of the current major issues in transfusion medicine is the appropriate trigger for platelet transfusion. Different triggers are being used for platelet transfusion. While some centers transfuse all neonates with platelet counts below $50 \times 10^9/L$, other centers use lower thresholds such as <30 or $<20 \times 10^9/L$.[1,2,13,17,26] There is an apparent evolvement amongst neonatologists towards more liberal platelet transfusion practices, even in the absence of evidence based data.[27] This study does not demonstrate a

difference in IVH between neonates with a platelet count below 50×10^9/L or below 30×10^9/L (nor between <150, <100 or lower for that matter), questioning the different transfusion thresholds. Whether platelet transfusions have a protective value in neonates with a platelet count below 20×10^9/L is still not known.

Conclusion

In this study, we found no relationship between the severity of thrombocytopenia and IVH, suggesting that the etiology of IVH in neonates is a complex multifactorial process. However, our findings should be interpreted with care due to limitations associated with the retrospective nature of the study and the relatively small sample sizes of some variables in the subgroups. Prospective studies should be conducted to assess the true risk of hemorrhage depending on underlying conditions. Randomized controlled trials are urgently needed to determine a safe lower threshold for platelet transfusions.

References

1 Roberts I, Stanworth S, Murray NA: Thrombocytopenia in the neonate. Blood Rev 2008, 22:173-186.

2 Sola-Visner M, Saxonhouse MA, Brown RE: Neonatal thrombocytopenia: what we do and don't know. Early Hum Dev 2008, 84:499-506.

3 Sola MC, Rimsza LM: Mechanisms underlying thrombocytopenia in the neonatal intensive care unit. Acta Paediatr Suppl 2002, 91:66-73.

4 Christensen RD: Advances and controversies in neonatal ICU platelet transfusion practice. Adv Pediatr 2008, 55:255-269.

5 Del Vecchio A, Sola MC, Theriaque DW, Hutson AD, Kao KJ, Wright D, et al: Platelet transfusions in the neonatal intensive care unit:factors predicting which patients will require multiple transfusions. Transfusion 2001, 41:803-808.

6 Roberts I, Murray NA: Neonatal thrombocytopenia. Semin Fetal Neonatal Med 2008, 13:256-264.

7 Bizzozero J: Über einen neuen formbestandteil des blutes und dessen rolle bei der thrombose und blutgerinnung. Virchow's Arch Path Anat Physiol Klin Med 1882, 90:261-332.

8 Andrew M, Castle V, Saigal S, Carter C, Kelton JG: Clinical impact of neonatal thrombocytopenia. J Pediatr 1987, 110:457-464.

9 Andrew M, Vegh P, Caco C, Kirpalani H, Jefferies A, Ohlsson A, et al: A randomized, controlled trial of platelet transfusions in thrombocytopenic premature infants. J Pediatr 1993, 123:285-291.

10 Guidelines for the use of platelet transfusions. Br J Haematol 2003, 122:10-23.

11 Delaney M, Meyer E, Cserti-Gazdewich C, Haspel RL, Lin Y, Morris A, et al: A systematic assessment of the quality of reporting for platelet transfusion studies. Transfusion 2010, 50:2135-2144.

12 Strauss R, Wehler M, Mehler K, Kreutzer D, Koebnick C, Hahn EG: Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. Crit Care Med 2002, 30:1765-1771.

13 Slichter SJ, Kaufman RM, Assmann SF, McCullough J, Triulzi DJ, Strauss RG, et al: Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med 2010, 362:600-613.

14 Het Kwaliteitsinstituut voor de Gezondheidszorg CBO: CBO-richtlijn bloedtransfusies. Alphen aan den Rijn, Van Zuiden Communications B.V 2004, 247-257.

15 Murray NA, Howarth LJ, McCloy MP, Letsky EA, Roberts IA: Platelet transfusion in the management of severe thrombocytopenia in neonatal intensive care unit patients. Transfus Med 2002, 12:35-41.

16 Sola MC: Evaluation and treatment of severe and prolonged thrombocytopenia in neonates. Clin Perinatol 2004, 31:1-14.

17 von Lindern JS, Brand A: The use of blood products in perinatal medicine. Semin Fetal Neonatal Med 2008, 13:272-281.

18 Volpe JJ: Neurology of the newborn. 5 edition. Philadelphia: Saunders Elsevier; 2008.

19 Kloosterman GJ: [Intrauterine growth and intrauterine growth curves]. Ned Tijdschr Verloskd Gynaecol 1969, 69:349-365.

20 Neu J: Necrotizing enterocolitis: the search for a unifying pathogenic theory leading to prevention. Pediatr Clin North Am 1996, 43:409-432.

21 Bonifacio L, Petrova A, Nanjundaswamy S, Mehta R: Thrombocytopenia related neonatal outcome in preterms. Indian J Pediatr 2007, 74:269-274.

22 Stanworth SJ, Bennett C: How to tackle bleeding and thrombosis in the newborn. Early Hum Dev 2008, 84:507-513.

23 Baer VL, Lambert DK, Henry E, Christensen RD: Severe Thrombocytopenia in the NICU. Pediatrics 2009, 124:e1095-e1100.

24 Stanworth SJ, Clarke P, Watts T, Ballard S, Choo L, Morris T, et al: Prospective, Observational Study of Outcomes in Neonates With Severe Thrombocytopenia. Pediatrics 2009, 124(5):e826-34.

25 Sola-Visner M, Sallmon H, Brown R: New insights into the mechanisms of nonimmune thrombocytopenia in neonates. Semin Perinatol 2009, 33:43-51.

26 New HV, Stanworth SJ, Engelfriet CP, Reesink HW, McQuilten ZK, Savoia HF, et al: Neonatal transfusions. Vox Sang 2009, 96:62-85.

27 Josephson CD, Su LL, Christensen RD, Hillyer CD, Castillejo MI, Emory MR, et al: Platelet transfusion practices among neonatologists in the United States and Canada: results of a survey. Pediatrics 2009, 123:278-285.
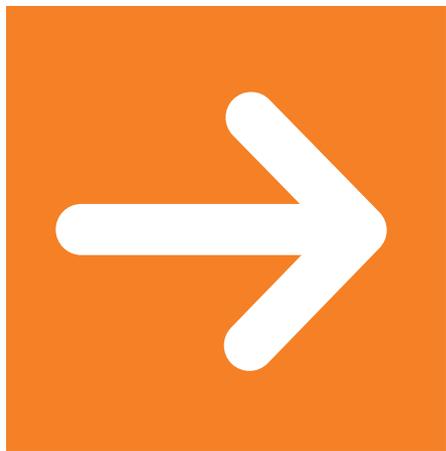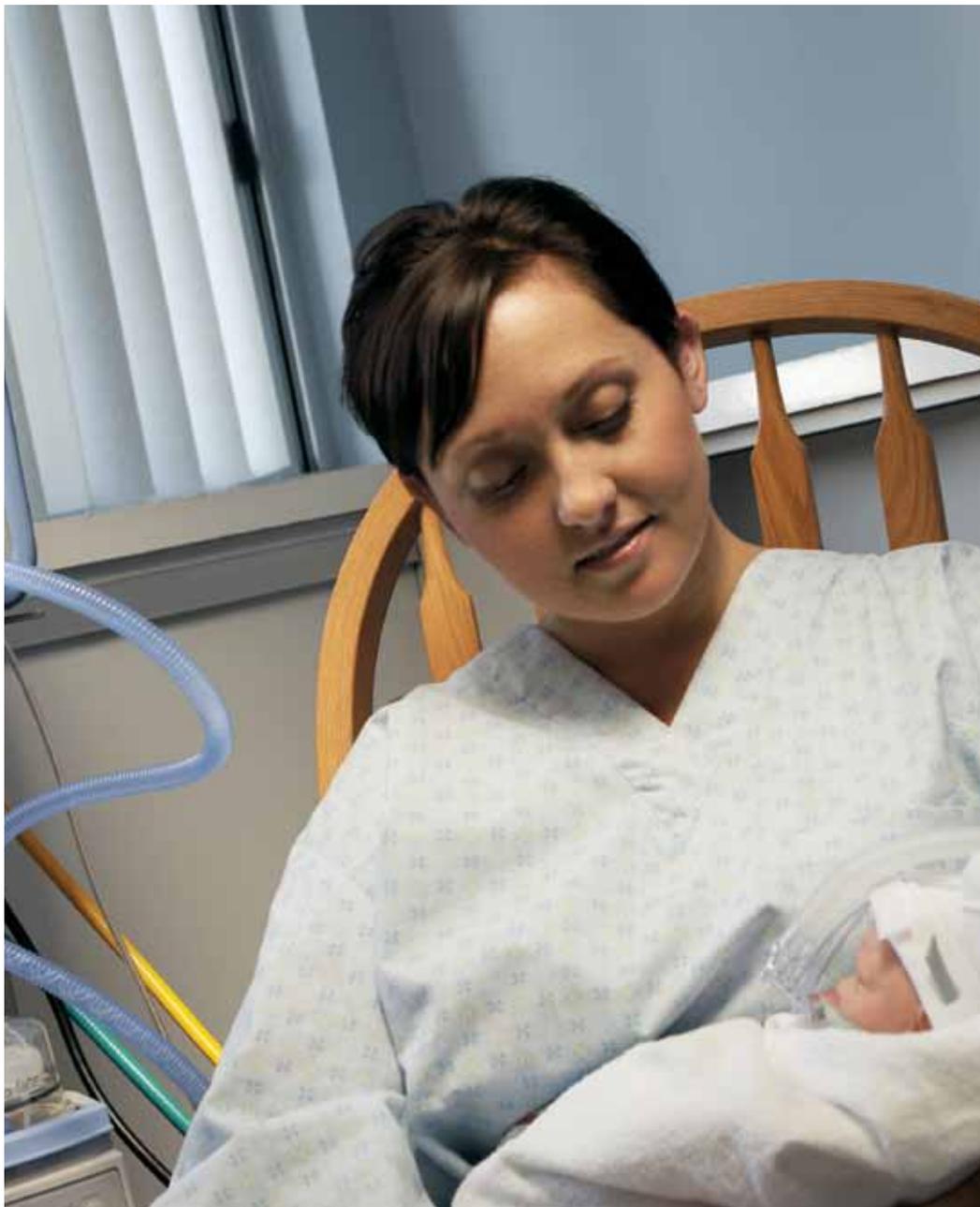
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