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You Decide

We’ve discussed ethical issues at some length in these pages. Two recent studies have brought forth more empirical evidence about neonatal resuscitation decision-making. The journal Pediatrics reports on a study at McGill University meant to reveal if newborns are dealt with according to different standards than older patients when it comes to resuscitation. Anonymous questionnaires describing eight incompetent patients with potential neurologic sequelae who required resuscitation were sent to groups of physicians and students. Survival and morbidity rates were delineated for a preterm infant, a full term infant and a two-month-old infant with identical outcomes. Respondents were asked whether resuscitation was in each patient’s best interest and whether they would comply with the families’ wishes if resuscitation was refused for a seven-month-old infant, and an 80-year-old patient who were significantly impaired. Almost all the respondents stated that it was in the best interests of the two-month-old infant and the seven-year-old child to be resuscitated, followed by the 50-year-old patient and the term infant (87%), the two patients with 5% chance of survival (76% and 80%), the premature infant (69%), and finally the 80-year-old patient (32%). Approximately one fifth of the respondents who thought that it was in a patient’s best interests to be resuscitated would nevertheless accept the family’s refusal of resuscitation for all scenarios except the 80-year-old patient (72% acceptance) and the preterm infant (54% acceptance). The authors concluded that whether resuscitation is considered in a patient’s best interests is not closely related to survival rates or disability. Newborn infants and particularly preterm infants were systematically devalued, in comparison with older patients whose outcomes are the same or worse. Accepting a family’s refusal of resuscitation, even among respondents who thought that resuscitation was in the patient’s best interest, was much more common for the newborns.

Important decisions about neonatal care accrue to both healthcare providers and the spokespersons for the infants: the parents. A topically-related study, published in J Paediatr Child Health, examined evidence suggesting that NICU parents with a baby born at the threshold of viability do not always receive sufficient counseling during an emergency admission and therefore aren’t well-informed to accept withdrawal of treatment or quality of life decisions. The authors noted that prospective parents aren’t educated earlier in pregnancy about extreme premature delivery, and that crucial information and counseling explaining neonatal issues is only offered to laboring women during their emergency admission. As a result, according to the authors, most of these parents have difficulty understanding the risks and benefits of their baby’s treatment and therefore rely heavily on the perinatal physician to take responsibility for the initial treatment. The abstract noted, “This lack of understanding often leaves parents disadvantaged, as many are left unprepared to participate objectively in quality of life decisions.” Since morbidity figures remain relatively high for premature babies, with one in five survivors at risk of a long-term disability, some parents will be confronted by the ethical decision of whether or not to continue treatment, and this may not be apparent until days after treatment has been established. Research has also shown that parents do want increased involvement in the decision-making process regarding their child’s treatment. The study concluded that parents should be provided with information earlier in pregnancy to familiarize themselves with quality of life issues which they may encounter as the NICU parents of an extremely premature infant. For more on these studies see: 1. Pediatrics. 2008 May;121(5):963-9, The best-interest standard is not applied for neonatal resuscitation decisions, Janvier A, Leblanc I, Barrington KJ, Department of Pediatrics, McGill University, Montreal, Quebec H3A 1A1, Canada; 2. J Paediatr Child Health. 2008 May;44(5):392-4, Ethical issues for parents of extremely premature infants, Schroeder J., Centre for Human Bioethics, Monash University, Victoria, Australia. jisch1@bigpond.com.
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LETTERS

YEA
I applaud Ms. Julia Pippa for her article, “A Message to a Multiple Birth Mother” in the March/April 2008 issue of Neonatal Intensive Care. She addressed issues that need to be faced and yet are sadly ignored by the prospective parents and their physicians. Thank you, Julia Pippa, for an excellent commentary. —Leslie Chadwick, RN

NAY
Please excuse my direct response; however, it is as clear as the author’s name—can we say: burn out? This is obviously written by a person who has passed the point of return for compassion, understanding the now and present, the need to make some lemonade with a lemon situation. Can we say there is a higher power in the positive approach with a family under great demand; is that not the whole idea “the family”? Just sign me another old NICU RN, and lovin’ it. The angels I care for everyday surely will greet me at heaven’s gate someday, right behind, of course, their parents, grandparents, family and friends. —Dorothy Foster, RN, Vanderbilt Childrens Hospital, Nashville, TN

EDITOR’S NOTE: HURRAY
We think we know what we think, until the thing we have opinions about affects us personally. My best friend J.C.O. gave birth by c-section to preemie twins at seven months, seven weeks and four days, on the night of the summer solstice. The twins were IVF babies, mom’s fourth attempt. The birth, at St. John’s Hospital in Santa Monica, CA, was an emergency c-section, with mom manifesting hypertension, symptoms of diabetes, and toxemia. Mom’s preeclampsia was missed by her physician. A close call. The boy and girl, Haplin and Lucy, weighed in at three pounds, 7 ounces each, with apgar scores of 8-9 and 7-8, respectively. Both babies had bilirubinemia, and on day 10, Hap had a meconium blockage for which he had to be transferred to surgery from St. John’s to Cedar’s Sinai. As I write, both babes are back at St. John’s eight-bed Level II NICU. Hap seems fine, Lucy has apnea and some bradycardia. The mom’s blood pressure remains too high, and her liver function is being monitored. I’ll keep you posted. J.C.O. will offer her experience in our next issue. —Les Plesko, Editor

NEWS

NOT TOO YOUNG TO TOUCH
VLBW babies benefit from skin to skin contact with their parents, according to researchers at McGill University, though NICUs don’t encourage it. Their study is the first to look at babies born between 28 and 31 weeks. The researchers carried out heel prick tests on babies who were being actively cuddled, skin to skin, and measured facial expressions, heart rate and blood oxygen levels to assess the amount of pain suffered. Pain scores after 90 seconds were much lower than for those who were not cuddled. The study suggests that, even for the very youngest premature babies, skin to skin contact can reduce the stress response.

OVERDOSE
Seventeen babies in a Corpus Christi, TX, NICU received overdoses of heparin, CNN reported. One of the babies died. Nursing staff at the hospital discovered the problem
two days after the medication was believed to have been first administered, according to published reports, and the hospital said it took corrective measures afterwards. Twelve of the 16 other babies remained in stable condition in the neonatal intensive care unit subsequent to the overdosing, three were discharged, and one remained critical.

NOT AT RISK
Having a cesarean does not necessarily raise the risk of a stillbirth in a subsequent pregnancy, according to researchers at the University of Calgary. The study suggests a mother’s obesity may instead be the key factor. Researchers said obesity had been consistently linked to both c-sections and stillbirths, but it had proved difficult to tease out its independent effect. The study examined 157,029 second births, and took potentially confounding factors, such as maternal weight, into consideration. Among women who had previously had a caesarean, the stillbirth rate was 2.1 per 1,000, compared with 1.6 per 1,000 in women who had no such history, not a statistically significant difference. The researchers admitted that they were not able to completely account for maternal weight, but had done so far more than previous research.

TWICE AS NICE
Doctors at Texas Children’s Hospital have removed a fetus from a mother’s womb, removed a tumor from a fetus, then put the fetus back. In effect, MSNBC reported, the baby was born twice, with a ten-week gap between the “surgery” birth and the second delivery. An ultrasound in the 23rd week revealed a tumor in the fetus’s tailbone, as large as the fetus itself. Texas Children’s Hospital is one of only three hospitals in the world that specialize in such conditions. The surgery was described as “tricky.” Surgeons opened the mom’s abdomen and brought her uterus entirely outside her body, in a way that didn’t disturb the placenta. The surgeons pulled out 80% of the baby’s body, leaving the head and upper body in the womb. They had to work quickly to stop her from going into cardiac arrest, and then to close up the uterus to keep the amniotic fluid from leaking out.

NO PAST
A woman has conceived Britain’s first baby guaranteed to be free from hereditary breast cancer, according to a report by Sarah-Kate Templeton published in The Sunday Times of London. Doctors screened out an inherited gene that would have left the baby with a greater than 50% chance of developing the cancer. The woman had her embryos screened because her husband had tested positive for the gene, and her sister, mother, grandmother and cousin have all had the cancer. The couple produced 11 embryos, of which five were found to be free from the gene. Two of these were implanted in the woman’s womb and she is now pregnant. By screening out embryos carrying the BRCA-1 gene, the couple will eliminate the hereditary disease from their lineage. About 5% of the 44,000 cases of breast cancer diagnosed in Britain each year are estimated to be caused by the BRCA-1 and BRCA-2 genes. Doctors say thousands of cases of breast cancer could be avoided by screening embryos using the technique, called preimplantation diagnosis (PGD). The woman and her husband had to go through IVF even though they are fertile, in order to create embryos that could be screened. Tests on the 11 embryos were conducted by removing just one cell when they were three days old. Six of the embryos carried the breast cancer gene. Two embryos that were free of the gene were then implanted, resulting in a single pregnancy. The couple have also been able to freeze two healthy embryos for future use.

“CUT” COSTS
Some mothers are being turned down for insurance because they had C-sections, the rationale being that having the operation once increases the odds that it’ll have to be done again, and insurers don’t want to pay for it. The number of such disqualifications is likely to increase because the pool of people seeking individual health insurance, now about 18 million, has been growing steadily, as has the Caesarean rate, which is at an all-time high of 31.1%. As a result, said a spokesperson for the International Caesarean Awareness Network, “Obstetricians are rendering large numbers of women uninsurable by overusing this surgery.” Adding to the problem, hospitals often refuse the option of a second normal birth because it carries a risk of uterine rupture. Insurers’ rules on prior c-sections vary by company and state, with some companies treating the surgery like a pre-existing condition. In one case, the insurer informed the mom that it would only insure her if it could exclude paying for another cesarean for three years. In some states, mothers facing this dilemma can get coverage from state-sponsored policies, but premiums are 140% of standard rates. While some insurers don’t treat cesareans as a preexisting condition, they do factor in associated factors like high blood pressure or diabetes. Adding insult to injury, a denial by one insurer often red-flags other insurers, making it virtually impossible to get coverage elsewhere. Reported in the New York Times.

SHOW ME THE MONEY
The 550,000 preemies born each year in the US run up about $26 billion in annual costs, mostly related to care in NICUs. That represents about half of all the money hospitals spend on newborns. Factor in the cost of treating all of the possible lifelong disabilities and the years of lost productivity for the caregivers, and the real tab may top $50 billion, according to one estimate. Insurers pay out 15 times as much for babies born prematurely in their first year of life as for full-term babies, at an average cost of about $41,000 per child. For the earliest of the preemies, who are born in fewer than 28 weeks and spend up to three months in the hospital, the total tab may be approaching a million dollars. One family with a preemie reported a two-month hospital stay at $400,000, not including certain surgeries and procedures. Subsequently, nursing costs were added to the tab. The family reported getting up to 12 bills per day. According to a recent report, hospitals want NICUs because they are profit centers, like cardiac units, and healthcare companies want to stock NICUs with devices and drugs. Meanwhile, there is much debate about early intervention. Critics note that a third of preemies suffer from severe disabilities such as cerebral palsy, chronic lung disease, and blindness. A 2006 report from the Nuffield Council on Bioethics, an independent British group, recommended that preemies struggling for their lives after 22 weeks of gestation should not be given intensive care. In the meantime, an anti-abortion group, the “ProLife” Alliance, suggested lowering the viability threshold to 20 weeks. However, the NICHD said, “extending intensive care to the most immature infants would entail considerable suffering, resource use, and cost in order to benefit only a small proportion of infants.” Most healthcare economists seem to agree that spending on preemies offers a high rate of return for all but the earliest-stage infant, and is more cost-effective than, say, coronary bypass surgery. In any case, NICUs are likely to flourish because of the aforementioned revenue potential for hospitals. For example, Children’s National Hospital set a goal of 4% profit margins overall, but NICU profits can be double that. Last November the hospital unveiled a $75 million tower that features various
specialty units to treat heart and brain problems of preemies. Its expansion plans include a second NICU that will open next year.

NEUROLOGIC IMPAIRMENT
Early Human Development, June 17, 2008, presented “Changes in physiological and behavioral pain indicators over time in preterm and term infants at risk for neurologic impairment.” Authors Gibbins et al with Sunnybrook Health Sciences Center and The Hospital for Sick Children in Toronto sought to compare physiological and behavioral pain responses of infants at three levels of NI risk during the NICU neonatal period and at 6 months. The researchers studied 149 preterm and term infants at high, moderate, and mild risk for NI from 3 Canadian tertiary level NICUs. Infants were observed during 3 standardized phases of a heel lance: baseline, stick, and return-to-baseline. At 6 months, infants were observed during the same three phases during an intramuscular immunization injection. Physiological and behavioral responses were continuously recorded. NICU infants exhibited significant response to heel sticks, including brow bulge, eye squeeze, nasolabial furrow and open lips between sessions, with less facial actions demonstrated at six months. There were significantly lower mean and minimum heart rate and higher minimum and maximum oxygen saturation at six months. The authors concluded that behavioral and physiological infant pain responses were generally diminished at 6 months of age compared to those in the neonatal period, with some differences between NI risk groups in cry responses.

BPD AND IVH
The Journal of Perinatology presented in its June 19 issue, “Association of BPD and IVH with early neutrophil and white counts in VLBW neonates with gestational age <32 weeks.” Authors Palta, Sadek-Badawi and Carlton with the University of Wisconsin-Madison investigated associations between early low neutrophil count from routine blood samples, WBC, pregnancy complications and neonatal outcomes for very low birth weight infants (VLBW 1500 g) with gestational age <32 weeks. Information was abstracted on all infants admitted to level III neonatal intensive care units in Wisconsin 2003 to 2004. A total of 1,002 VLBW neonates (78%) had differential and corrected total white counts within 2½ h of birth. Low neutrophil count (<1000 per mul) was strongly associated with low WBC, pregnancy complications and antenatal steroids. Low neutrophil count predicted bronchopulmonary dysplasia severity level (odds ratio, OR: 1.7, 95% confidence interval, CI: 1.1 to 2.7) and intraventricular hemorrhage grade (OR: 2.2, 95% CI: 1.3 to 3.8). The authors concluded that early neutrophil counts may have multiple causes interfering with their routine use as an inflammatory marker. Nonetheless, low neutrophil count has consistent independent associations with outcomes.

FAS
A retrospective study in Queensland reviewed the records of indigenous women whose infants were diagnosed with Fetal Alcohol Syndrome to obtain information that could assist in the identification of women who require alcohol interventions. The study, “Pregnancy characteristics of women giving birth to children with fetal alcohol syndrome in Far North Queensland,” by Katherine Coyne, et al, aimed to review the pregnancy records of women whose infants were subsequently diagnosed with FAS by the Paediatric Outreach Service (POS) of the Cairns Base Hospital, and to determine how such women might be identified prospectively in pregnancy and offered intervention to reduce alcohol consumption. Results of a twelve-year records search revealed that mothers of babies with FAS were older, of higher parity, smoked more cigarettes, attended fewer antenatal visits and experienced more antenatal and delivery complications than mothers of controls. The average gestational age at booking was not statistically significant between the two groups. There was a significant difference between the two groups in self-reported alcohol consumption both before and during pregnancy and in numbers of women who decreased alcohol consumption once the diagnosis of pregnancy was known to them.

LBW
Just over 8% of infants born in the US in 2005 had low birthweights, the highest percentage since 1968, according to the 2008 Kids Count report compiled by the Annie E. Casey Foundation. The report collected data measuring 10 indicators of child wellness, including low birthweight, infant mortality and births among teenagers. It found no change in infant mortality and a decrease in the teen birth rate. Composite rankings for all 10 indicators placed Connecticut, Massachusetts, Minnesota, New Hampshire and Utah at the top of the ranking, while Alabama, Louisiana, Mississippi, New Mexico and South Carolina were ranked lowest. Mississippi had the highest percentage of low-birthweight infants at 11.8%, while Alaska, Oregon and Washington state had the lowest at 6.1%. About 13.6% of black infants were born with low birthweights, compared with 7.3% for whites and 6.9% for Hispanics. The increase in low-birthweight infants can be attributed in part to an increase in multiple births due to fertility treatments, although low birthweights also increased among single-infant deliveries. The report also noted that teen birth rate decreased by 17% from 48 births per 1,000 in 2000 to 40 births per 1,000 in 2005. The teen birth rate decreased in 47 states, while North Dakota, Wyoming and Washington, DC reported an increase. Reported by nationalpartnership.org, © 2008 The Advisory Board Company.

OVER THERE
Toronto’s Globe and Mail examined the dangerous journeys pregnant women in parts of rural southern Afghanistan are taking to obtain prenatal care. Afghanistan has one of the highest infant and maternal mortality rates in the world, with about 24,000 women dying annually after childbirth. While there are reports that healthcare services have improved since the putative overthrow of the Taliban regime, many women living in so-called “restive” regions say the situation has worsened. Afghan officials say they have bolstered midwife training and eased access to female healthcare providers, but the lack of security is said to be a problem in many areas, with four districts in Kandahar having no health clinics. Some women in rural areas do not visit a hospital or clinic throughout their entire pregnancies. Untrained midwives often assist with home births, and complications such as bleeding and hypertension often result in death for either the pregnant woman or infant. Some medical personnel have been driven out or killed. In Kandahar City, however, pregnant women have access to no-cost deliveries and medicines, with programs sponsored by the Canadian government and UNICEF. Information provided by nationalpartnership.org, The Advisory Board Company, Medical News Today.

TAKING A SHOT
TV personality Ricki Lake took a shot at ACOG and the AMA after she was criticized for promoting at-home birthing, according to a report by the Associated Press. Lake’s documentary, “The Business of Being Born,” looks at the current maternity care system and at-home childbirth, and the film
shows Lake's own home birth. After ACOG weighed in against home deliveries, specifically citing Lake, she said she was being singled out and targeted. In an interview in the International Herald Tribune, Lake said, "I'm all about choice. This is not unlike the abortion issue. I am pro-choice when it comes to childbirth and choices in childbirth. Home birth was around long before hospitals were taking over, and I just think women need to know (the information) so that they can make the best choice for them." Lake added that she never said there's no need for doctors or technology, but that "we also need to value the process of giving birth normally."

SIDE EFFECTS
Women who have an STD or urinary tract infection just before or during early pregnancy are four times more likely to have babies with gastroschisis, according to a study by the University of Utah published by the British Medical Journal. While the researchers noted that their results were preliminary and needed further study, they also noted the concurrent increase in gastroschisis and STDs. The causes and mechanisms of gastroschisis are not known, but researchers suspect environmental and maternal factors may be related to the birth defect. The age of the mom also appears significant, with women under 20 eleven times more likely to have babies with gastroschisis than women over 25. Researchers compared data on mothers of 505 babies with gastroschisis and a control group of 4,924. Women who reported having both an STD and UTI were four times more likely to have a child with gastroschisis.

A LEG UP
Australian surgeons saved the leg of an unborn baby by operating when her mother was just 22 weeks pregnant. The surgery was carried out after the fetus developed Amniotic Band Syndrome. Melbourne's Monash Medical Centre used lasers to cut away the tissue from the left leg, but left the right leg as the bands were too deeply embedded. The baby was born in January and is now doing well after plastic surgery. Doctors believe the girl will eventually be able to walk on both feet. Doctors noted that diagnosis for this syndrome is not always made before birth and therefore surgery of this type is not that common. During a previous operation, doctors had pierced the mother's abdomen with a 2mm thick telescopic needle to allow them to apply a laser to cut the band above the baby's left foot. But the right leg was so badly affected, with the band having cut through to the bone, that the surgeon decided to leave the already swollen and infected foot alone.

MISSING LINK
Scientists may have identified a biological explanation for the link between cesarean-section delivery and risk of allergy and asthma in childhood. Researchers at the University of California San Francisco looked into the effect of c-section versus vaginal delivery in newborns to determine whether cesarean-section was associated with reduced regulatory T-cell function. In a previous study, they demonstrated an association between cesarean section and increased neonatal secretion of IL-13. In this study, the researchers measured the expression and function of specific regulatory T-cells in the cord blood of 50 newborns born by c-section, and 68 delivered vaginally, with at least one parent who had allergies or asthma. They found that babies born by cesarean section showed a reduction in the suppressive function of their regulatory T-cells, with a trend for lower level of TGF-fo, a cytokine secreted by tregs, and higher levels of IL-4 and IL-13 among children born by c-section as compared to children born by vaginal delivery. The researchers said this suggests that the mode of delivery may be an important factor influencing immune system development in the neonate.

IT'S THE GERMS
Bacteria may be a contributing factor to SIDS, according to researchers at Great Ormond Street Hospital in London. They found Staphylococcus aureus and E. coli in nearly half of all babies who died suddenly and without explanation over a decade at a London hospital. The researchers cautioned, however, that the causal link might be inconclusive, because the higher level of bacteria may be indicative of another condition that killed the babies, or may even have been coincidental. The researchers used autopsy samples from 470 infants who died suddenly between 1996 and 2005 and found dangerous bacteria in 181 babies, or nearly half of the 365 whose deaths were unexplained. There were similar bacteria in about a quarter of the babies who died of known causes, excluding those who died of bacterial infections. Most of the bacteria were detected in the babies' lungs and spleens. The researchers cautioned that the bacteria might simply aggravate other risk factors for SIDS. Reported by the Associated Press.

STATIN STOPPER
Taking cholesterol-lowering statins may help minimize the risk of an emergency caesarean, according to researchers at the University of Liverpool, who also suggested that high cholesterol levels may weaken contractions enough during labor to rule out a natural delivery. The study of 4,000 pregnancies found overweight women were far more likely to need an emergency c-section because of a slow labor. Laboratory tests on samples of muscle tissue taken from the uteruses of overweight women confirmed that its ability to contract was compromised, and analysis suggested that this might be due to reduced flow of calcium into the muscle cells. In the past, doctors have avoided recommending statins in pregnancy because a woman's cholesterol level tends to rise naturally when she is pregnant, suggesting cholesterol may be needed by the developing fetus.

ANOTHER WAY
An alternative method for obstetric care has led to lower neonatal intensive care unit admission rates, higher uncomplicated vaginal birth rates, and a lower mean Adverse Outcome Index (AOI) score, according to a new study from the University of Pennsylvania School of Medicine. The alternative method is known as Active Management of Risk in Pregnancy at Term. AMOR-IPAT uses risk-based preventative labor induction to ensure that each pregnant woman enters labor at a gestational age that maximizes her chance for vaginal delivery," said lead researcher, James M. Nicholson, MD, Assistant Professor of Family Medicine and Community Health at Penn. Unlike previous retrospective studies of labor induction, this study attempted to minimize confounding factors by using a randomized prospective design. The study included 270 women who were recruited when they were between 32 and 37½ weeks into their pregnancy. Women who remained undelivered at 37 weeks 4 days of gestation were randomized to either AMOR-IPAT or usual care. Three facilities within the University of Pennsylvania Health System recruited women, including the Hospital of the University of Pennsylvania Obstetrics Clinic, the Pennsylvania Hospital Obstetrics Clinic, and Penn Family Care. Risk factors for the AMOR-IPAT exposed group were identified and categorized as either interfering with placental growth or accelerating fetal growth. Each of these factors is associated
with a published odds ratio for cesarean delivery, which, in turn, is used to determine the optimal time of delivery. If a woman in the exposed group did not experience spontaneous labor as she approached the end of this time frame, preventative labor induction was scheduled. In the AMOR-IPAT group, the greater the number and severity of risk factors, the earlier preventative labor induction was offered within the term period (38 – 41 weeks of gestation). The findings of this study suggest that the AMOR-IPAT approach to obstetric risk lead to healthier babies and better birth outcomes for mothers. In addition, the results challenge the current belief that a greater use of labor induction necessarily leads to higher rates of cesarean delivery. In order to further explore the potential benefits of the AMOR-IPAT method of care, further research involving larger randomized clinical trials in more diverse populations is needed.

ANTIRETROVIRAL THERAPY

A brief paper in Retrovirology, published by Biomed Central: Early vs Deferred Highly Active Antiretroviral Therapy in HIV Infected Infants: A European Collaborative Cohort Study, reports the following: Background: Without antiretroviral therapy (ART), approximately 20% of HIV-1 vertically infected infants develop severe disease manifestations before the age of 1 year and surrogate markers poorly predict infants at higher risk of rapid disease progression. Several small prospective and retrospective studies in developed countries have suggested that ART initiated early in life could prevent this rapid clinical and immunologic deterioration.2-6

Because of the small number of HIV-infected infants delivered in industrialized countries where mother to child transmission prophylaxis is widely applied, a prospective study of early versus delayed ART is currently not feasible. Implementation of early ART has varied across countries and over time since 1996 in Europe. The objective of this collaborative study was to compare the outcome of infants who received ART early in life with the outcome of those with deferred treatment.

Materials and methods: Children born between 01/09/96 and 31/12/2004 to mothers with known HIV infection at birth, who received neonatal prophylaxis, and diagnosed with HIV before age 3 months were eligible. The children who were identified as HIV-infected at the same time or after being diagnosed with AIDS, and children who develop AIDS before the age of 3 months were excluded. Thirteen prospective and retrospective cohorts from 11 European countries participated, enrolling a total of 210 eligible infants. Data including general demographics and pregnancy data, details of prophylaxis and ART in early life, CDC events and death, immunological and virological measurements since birth, were collected and pooled. The risk of AIDS/death was estimated by Kaplan-Meier survival analysis, and compared between the groups of infant treated or not treated before 3 months of age. Cox regression was used to estimate hazard ratios.

Results: Among the 210 children, 21 developed AIDS and 3 died. The exposure to treatment was heterogeneous among cohorts. Overall ART and Highly active ART were initiated in 59% and 48% of the infants before 3 months of age and in 87% and 76% by one year, respectively.

Treatment was initiated before the age of 3 months in 124 infants. There was no significant difference in demographic, pregnancy and delivery characteristics between the two groups. Moreover the proportion of infants with early treatment did not vary significantly over time. As shown in figure 1, we found that the risk of developing AIDS/death at one year was 1.6% in infants treated before the age of 3 months compared to 11.7% in infants who started treatment later (p<0.001). At 5 years the risks were 4.6% and 21.5% respectively. Deferred treatment was associated with a five-fold higher risk of AIDS as compared with treatment before 3 months of age (crude hazard ratio = 5.0; 95% CI: 2.0-12.6). Adjustment for ethnicity, birth weight, breast feeding, number and class of neonatal prophylaxis, number and class of drug in first treatment did not substantially affect the hazard ratio.

Conclusion: The preliminary results of this retrospective collaborative study suggest a significant association between ART started before the age of 3 months and a lower subsequent incidence of AIDS/death in infancy.

References


The article was authored by Goetghebuer and 21 co-authors from throughout Europe and the UK.
HYDROCEPHALUS
BioMed Central reports a study published by Cerebrospinal Fluid Research © 2007 Heep et al; licensee BioMed Central Ltd, High Pressure Hydrocephalus in Neonates is Associated With Increased CSF Concentrations of Interleukin-18 and Interferon Gamma.

Background: High pressure hydrocephalus (HC) is associated with micro-glial activation and subsequent white matter damage. In addition to high pressure and ischemia, chronic inflammation may be pathophysiologically involved. In a rat model for HC (HTx rat, based on aqueduct stenosis), anti-inflammatory treatment reduces micro-glial scarring (Miller, 2006 CSFR). In human HC, immuno-regulatory processes involved in white matter damage are still largely undefined. Under various pathological conditions, increased CSF interleukin-18 (IL-18; expressed in microglial cells) and interferon gamma (IFNγ; expressed in natural killer cells affecting oligodendrocytes) concentrations relate with white matter damage. We hypothesize that CSF IL-18 and IFNγ concentrations are increased in neonatal high pressure HC, irrespective of underlying etiology.

Materials and methods: In 45 neonates with congenital high pressure HC (n = 30) CSF IL-18 and IFNγ concentrations were determined (ELISA). HC neonates were grouped according to etiology. Group 1: HC in spina bifida aperta (n = 20), group 2: triventricular non-hemorrhagic HC (n = 4), group 3: post hemorrhagic HC after fetal intracerebral hemorrhage (n = 6). Low risk neonates who underwent lumbar puncture for exclusion of meningitis (and appeared negative) served as controls (n = 15).

Results: In the three groups of HC neonates, IL-18 concentrations were significantly higher than in controls [medians and range: controls: 12.5 (12.5–158) pg/ml; group 1: 80 (23–232) pg/ml; group 2: 66 (55–236) pg/ml; group 3: 223 (103–406) pg/ml (each group vs. controls, p < 0.01)]. Similarly, IFNγ concentrations were significantly higher in CSF of the 3 HC groups [controls: 8 (8–22) pg/ml; group 1: 35 (12–139) pg/ml; group 2: 22 (15–28) pg/mL; group 3: 22 (17–56) pg/mL (each group vs. controls, p < 0.01; between the groups, NS)].

Conclusion: Irrespective of underlying aetiology, neonatal high pressure HC is associated with increased CSF IL-18 and IFNγ concentrations. The increased CSF concentrations reflect their pathophysiological involvement in inflammatory white matter damage. We hypothesize that early anti-inflammatory treatment could ameliorate cerebral white matter damage in human neonatal HC.

NO TURKEY
Bloomberg News reports that SIDS may be caused by imbalances in serotonin, according to a study in mice. Cristina Alesci writes that mice genetically modified to produce low levels of the brain signaling protein suffered drops in heart rate and other symptoms of SIDS, and many of the animals died at an early age, a study by Italian scientists found. Depleted levels of serotonin in the animals’ brains, which control heartbeat and breathing, may have caused sudden death, researchers said. The experiment may give researchers an animal model to test the effect of drugs on serotonin system dysfunctions in the brain and help pinpoint biological risks for crib death in humans. The mouse study builds on previous evidence of serotonin’s role in SIDS. Two years ago scientists at Children’s Hospital Boston and Harvard linked serotonin to SIDS by performing autopsies on 31 SIDS babies. Their analysis showed abnormalities in the SIDS infants’ brainstem, which uses serotonin to tell the body how to react to environmental changes. In the latest study, investigators genetically modified mice to create a serotonin system imbalance. After being exposed to slight external temperature changes, the rodents suddenly died because their bodies could not adjust.

OVERHEARD
From the website, overheardinnewyork.com (“overheard in the office” section), which publishes overheard conversations in New York City and elsewhere—Pediatrician, to screaming addicted newborn: Oh, you poor thing, are you jonesin’ for some crack? —NICU, Jacksonville, FL.

PRODUCTS
READY, SET...
Discovery Laboratories, Inc recently held a teleconference on June 18, 2008 with the FDA to discuss Discovery Labs’ approach to addressing key remaining items identified in its Approvable Letter to potentially gain US marketing approval of SURFAXIN (lucinactant) for the prevention of RDS in premature infants. Discovery Labs received clarification on its proposals and, although timeline assessment is continuing, believes that it could submit its formal response to the Approvable Letter this month. Discovery Labs also believes that this response may be designated by the FDA as a Class 1 resubmission with a target review period of 60 days. Prior to receiving the Approvable Letter, Discovery Labs had made notable progress towards gaining FDA approval of SURFAXIN, including agreeing with the FDA on the form of the SURFAXIN package insert and successfully concluding a pre-approval inspection of Discovery Labs’ manufacturing operations. The Approvable Letter did not require any additional clinical trials to gain SURFAXIN approval. Subsequently, Discovery Labs submitted a pre-meeting information package to the FDA that outlined Discovery Labs’ proposals for responding to select items identified in the Approvable Letter. The purpose of the meeting was to clarify and reach agreement with the FDA on the remaining steps necessary to achieve SURFAXIN approval, prior to filing a formal response to the Approvable Letter. Importantly, the meeting confirmed Discovery Labs’ approach to finalizing SURFAXIN drug product specifications. With the exception of two items, Discovery Labs could prepare its responses using readily available data. The FDA has requested that Discovery Labs provide additional preclinical data and related information for two items. One of the two items requires additional SURFAXIN biological activity test data. These additional data will be correlated with results of previously conducted preclinical studies and also will be used to justify the acceptance criteria for this biological activity test. The other item involves justifying the proposed specifications for certain lipid-related impurities in the individual active pharmaceutical ingredients (APIs) that comprise SURFAXIN. Discovery Labs’ approach to justifying the levels of these lipid-related API impurities was based, in part, on their being present in the human lung at levels equal to or greater than that in SURFAXIN. The FDA has requested additional information about the levels of these lipid-related API impurities in the neonatal lung. Discovery Labs believes that it will be able to develop this information based on existing scientific literature. Discovery
Labs presently anticipates completing the activities related to finalizing these two items in order to submit its formal response to the Approvable Letter this month.

**LOOK IT UP**

ARUP Consult is a first of its kind, no-cost resource for healthcare professionals, nurses, clinical decision makers and physicians in any diagnostic capacity. It supplements the diagnostic process of common and esoteric diseases or conditions by supplying current lab test suggestions and interpretations of more than 1,500 lab tests, more than 50 algorithms, links to PubMed, recommendations congruent with national guidelines and concise diagnostic advice. Through updates occurring bi-monthly, its information stays current with ever-evolving lab tests and discoveries, providing healthcare professionals accurate diagnostic knowledge at the point of care. ARUP Laboratories (a wholly-owned entity of the University of Utah) has produced ARUP Consult—a comprehensive laboratory test selection support tool to provide physicians with instant, up-to-date access for test ordering information. Since its introduction, ARUP Consult content and functionality has been updated every eight weeks. ARUP’s goal was to put reliable and up-to-date laboratory testing and interpretation information in the hands of physicians at or very near the point of patient care. ARUP gives clinicians a single source of medical content necessary for diagnostic decision making. It can be accessed from any locale. Algorithms provide physicians with a visual, systematic process for diagnosing and monitoring a disease state, thus eliminating a shotgun approach to testing. Content is organized by disease categories, which allows the physician to diagnostically process the patient’s symptoms and to differentiate among other possible diseases, and determine the appropriate laboratory tests to request for evaluating the patient. The site provides linked references to key journal articles, national guidelines, and other web sites. This resource is available at no charge; registration is not required and anyone with Web access can utilize the guide. ARUP combines several types of reference tools in one location and provides a laboratory tests available guide, diagnostic testing guide—detailed algorithms which serve as testing roadmaps for complex diseases and conditions, a disease states summary—a succinct, bulleted summary of various disease states along with diagnostic guidance, and a reference locator. The content is compiled and drafted by experts drawn from the University of Utah's Department of Pathology and ARUP Laboratories’ medical directors as well as a current practicing clinician. ARUP offers varied browsing and searching options. To see ARUP, go to www.arupconsult.com.

**PREMIER PERFORMANCE**

Children’s Medical Ventures (ChMV), a subsidiary of Respironics, Inc, announced that it has received a Premier Performance Award, presented by the Premier Healthcare Alliance’s Purchasing Partners unit. ChMV is one of 54 of more than 800 Premier contracted suppliers to receive the Performance Award, which recognizes the efforts of contracted suppliers to meet or exceed Premier members’ service expectations. Awards are based on satisfaction and performance data that is collected and scored over four successive calendar quarters. Feedback is provided during regular supplier business line reviews. Organizations scoring 80% or higher earn the award. The Premier Healthcare Alliance serves more than 2,000 US hospitals and 50,000 other healthcare sites. Children’s Medical Ventures, a subsidiary of Respironics, offers a wide range of clinical and educational products supporting developmentally appropriate care for infants. Contact childmed.com.

**WARMING AND WATCHING**

GE announced new products for neonatal care. Presented at AWHONN this year was an optional device to the Giraffe family of products and Panda Warmers, the uninterruptible power supply (UPS), an accessory that mounts safely and securely to any new or installed Giraffe product. Whether moving between care areas or between bed places, the UPS feature offers uninterrupted power to the bed and display for continuous monitoring of the baby’s condition and bed controls. The UPS feature also allows thermally supported, cordless mobility and peace of mind during periods of power uncertainty. Using battery backup, the UPS for Giraffe and Panda achieves security for any of the Giraffe or Panda family of products by keeping the baby warm and stable without the need to reset patient settings during weather-related power surges and outages, or line voltage fluctuations. Two other maternal-infant care devices presented at AWHONN were the Corometrics 250cx, a new model that provides more comprehensive perinatal monitoring of mothers and fetuses as they progress through the birthing process from prenatal evaluations to postpartum assessments. The optional Exergen TAT-5000 Maternal Temporal Scanner allows clinicians to obtain maternal temperature using a non-invasive infrared technology that detects heat through the skin’s surface via an external scanner.

GE Healthcare received a 2008 Medical Design Excellence Award for the Panda Warmer with integrated infant resuscitation for labor and delivery. The most recognizable feature of the new warmer is the innovative recessed heater that completely eliminates the traditional, often awkward, overhead design. This design improves clinician and parent access to the infant, removing overhead obstacles while providing uniform heat across the entire mattress. Optional resuscitation equipment also provides critical care to newborns if needed. The integrated resuscitation system that was designed with the American Academy of Pediatrics’ (AAP) latest Neonatal Resuscitation Program Guidelines (NRP) in mind. The resuscitation system requires minimal setup time and can help standardize resuscitation protocols across the perinatal care area. The Hands Free Alarm silence allows a clinician to silence alarms with a wave of their hand; clinicians can stay gloved during procedures and no longer need to call for help just to silence an alarm.

GE also announced an innovative clinical education program, designed specifically for physicians, midwives, nurses, residents and students in obstetrics, to enhance their knowledge of fetal heart rate monitoring. GE’s Electronic Fetal Heart Rate Monitoring Interpretation and Management education program, developed in partnership with Frank Miller, MD, FACOG and David Miller, MD, FACOG, both leading experts in the field of fetal monitoring, emphasizes the importance of using standardized NICHD terminology to describe, communicate and interpret abnormal fetal heart rate tracings. Until recently there has been no agreement on standard definitions and nomenclature for interpreting fetal heart rate patterns. In GE’s education program, language and terminology is standardized, facilitating communication, thus helping to reduce errors and improve patient safety. The e-learning program can be accessed from any computer with an internet connection, meaning, courses are available 24 hours a day, seven days a week. GE’s Fetal Heart Rate Monitoring Interpretation and Management
RF Technologies has been providing wireless RFID security systems to healthcare since 1987 and has an install base of over 10,000 healthcare facilities. Contact rft.com.

SPOTLIGHT ON VENTILATION

IMPROVED

The Bunnell Life Pulse High Frequency Ventilator provides improved oxygenation and ventilation of infants at lower mean and peak pressures than other high frequency or conventional ventilators. Jet pulse technology, passive exhalation, and a wide range of I:E ratios are the keys to achieving the lowest therapeutic pressures. The Life Pulse is easy to use with only three control settings: PIP, Rate (BPM), I-Time. All other functions are controlled automatically. Bunnell's LifePort adapter has eliminated the need to reintubate with a special endotracheal tube and the new WhisperJet inspiratory valve has significantly reduced noise levels. For a free trial contact Bunnell Incorporated at (800) 800-4358 or khekking@bunl.com.

DO IT AT HOME

BiPAP AVAPS is Respironics' newest noninvasive ventilator for use in the home, and features AVAPS (Average Volume Assured Pressure Support) technology. The AVAPS algorithm guarantees an average tidal volume by automatically adapting pressure support to meet the patient's needs on a breath-by-breath basis. The algorithm achieves this by estimating the patient's tidal volume over several breaths and calculating the change in pressure needed to achieve the target tidal volume. AVAPS slowly increases or decreases the IPAP pressure to achieve the proper pressure support. Additional features include BiPAP technology, Digital AutoTrak Sensitivity, SmartCard for use with Encore Pro and integrated alarms. Contact bipapavaps.respironics.com.

IN AGREEMENT

Hamilton Medical, Inc has signed an agreement with Premier, one of the largest group purchasing organizations in the United States. Hamilton Medical’s three-year agreement offers all Premier members access to contracts for Hamilton Medical’s complete ventilation line. Owned by not-for-profit hospitals, Premier operates one of the leading healthcare purchasing networks and the nation’s most comprehensive repository of hospital clinical and financial information. A subsidiary operates one of the nation’s largest policy-holder owned, hospital professional liability risk-retention groups. Premier is working with the United Kingdom’s National Health Service North West and the Centers for Medicare & Medicaid Services to improve hospital performance. Headquartered in San Diego, Premier has offices in Charlotte, NC, Philadelphia and Washington. For more information, visit premiereinc.com. For more about Hamilton Medical, visit hamilton-medical.com.
The management of critically ill immature neonates who are admitted to the NICU requires a multidisciplinary team approach to provide optimal care from the day of birth until hospital discharge. These babies are of extremely low birth weight and physically immature with substantially higher potential for medication errors occurring in the NICU setting unless a chain of command is in place to prevent them.

Introduction
The National Coordinating Council for Medication Error Reporting and Prevention defines a medication error as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer.” In recent years news media have highlighted the medication errors in premature infants resulting in mortality and morbidity. According to the Institute of Medicine (IOM), preventable adverse events are the leading cause of death and disability with medication errors occurring more frequently than what has been reported. At least 40,000 and perhaps 90,000 Americans die each year as a result of medication errors. Most errors occur due to the use of abbreviations, miscalculations, misinterpretations, miscommunication, or misidentification of the patient, resulting in inadvertent administration of medications. In a recent report, incidental drug mix up, overdose and drug reaction was responsible for harm to about 1 out of 15 hospitalized children. As part of its National Patient Safety Goal, the Joint Commission and Accreditation of Health Organization (JCAHO) has issued guidelines that include prevention of medication errors to ensure the safety of hospitalized patients.

Methods
Lincoln Medical and Mental Health Center is a Health and Hospital Corporation (HHC) affiliated acute health care facility in New York City serving the underserved urban population. In the NICU, the provision of services by the medical, nursing and paramedical staff follow the JCAHO National Patient Safety Goals. Neonatologists, pediatric residents and nurses provide round-the-clock in-house coverage to provide optimal care to the patients. In addition to other national safety goals, prevention of medication errors is a top priority. We reviewed the pediatric departmental QI minutes on incident/occurrence reports, pharmacy and therapeutic committee reports, risk management cases in reference to medication errors, medication error reports and adverse drug reactions for the past ten years from January 1997 to December 2007.

Time line of medication usage, preparation and documentation from 1997-2007:

- 1997-2005: The NICU staff used to prepare medications and fluids in the unit, working closely with the pharmacist and the nurses.
- 2005-2006: The NICU went on-line for ordering fluids and medications. The medications and fluids were prepared in the pharmacy and provided to the unit. All potentially dangerous medications were removed from the unit.
- 2006-2007: On-line orders and preparation of hyperalimentation fluids and electrolytes occurred before 11 am everyday depending on an infant's needs. The entire process was entirely supervised by the neonatal attending and the final preparation was evaluated by the pharmacist.
- Present: We do not prepare any medications or fluids in the unit except ampicillin which is biodegradable and must be used within one hour of preparation. For practical purposes everything is ordered on-line, reviewed by the attending and prepared and checked by the pharmacists in the pharmacy before the medicine is delivered to the Pyxis system for nurses to pick up the order and administer the medicine to the patient.
When medications are ordered, the following procedure is followed:

- The patient’s weight, gestation age and medical condition are known.
- The dose, preparation and method of administration is checked in the NEOFAX available to the staff in each room in the unit. NEOFAX is specially meant for neonatal medications in regard to dose, route, preparation, length of administration and adverse effects.
- The resident must check with the attending physician prior to writing the order.
- The attending physician must check the resident order for accuracy.
- All orders are reviewed and prepared by the pharmacists in the pharmacy.
- The NICU nurses must check the doctor’s order and pick up the medicine in the PYXIS. If they have any concern about the order they discuss it with the attending and the pharmacist.
- Before any drug is given it must be checked by two nurses and by the medical doctor if it is a dangerous drug.
- The nurses have to identify the infant by checking the wristband and medical record number before any medication is given.
- If any drug is left over after use, it must be labeled with the drug name, date of opening and the expiration.

Any adverse drug reaction is reported to the Chief of Neonatology who initiates a drug reaction report and submits it to the departmental pediatric QI committee.

**Results**

From January 01, 1997 to December 31, 2007, we did not have any medication errors that resulted in any issues reportable to the departmental QI committee. However, an occasional dosage error was identified by our nurses or pharmacists and was corrected before the medication was delivered to the patient for a “good catch.”

These instances are:

- 2005: Two occurrences reports: March: Trimentin IV was ordered by MD as 190 g instead of 190 mg. The nurse identified the error and gave only 190 mg. November: Reglan 0.1 mg PO was ordered by MD and given to the infant by NICU nurse but she failed to document it on the patient record.
- 2006: One occurrence report: October: Reglan ordered PO, but an IV preparation of Reglan was found in the patient bin by a nurse. The nurse picked up the pharmacy error and it was corrected before the medication was given to the infant.
- 2007: None reported
- 2008: One occurrence report: A pulmonary surfactant (Curosurf) was given to premature infant via trachea, the first dose was correct and the second dose should have been ½ the first dose, but mistakenly a full dose was given. No adverse reaction noted. All the staff was counseled and the pharmacy made aware of this incident.

**Discussion**

Patients in the NICU are at high risk for medication errors. The chain of command ensures that the NICU staff has sufficient information about the patient and their medications. It also enforces close supervision and communication among the staff. It is important to safeguard the patient from medication errors. A recent report focused on a trigger tool developed to evaluate adverse events reported that adverse events were higher if the patient was less than 28 weeks of gestation and weighed less than 1500 grams. Fifty percent of adverse events were preventable. We reviewed medication errors that occurred before we went on-line and thereafter. Some minor adjustments were discussed with the pharmacist to suit the infant’s needs. We had a daily dialogue with the pharmacist, particularly on hyperalimentation composition. Because of our multidisciplinary team approach in the NICU and the cooperation of the pharmacy department, we have not had any medication errors either before or after we went on-line that have caused serious harm to our patients.

Table 1. JCAHO Hospital National Safety Goals for 2007

<table>
<thead>
<tr>
<th>Goal</th>
<th>Description</th>
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<tbody>
<tr>
<td>Goal 1</td>
<td>Improve the accuracy of patient identification.</td>
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<tr>
<td>Goal 2</td>
<td>Improve the effectiveness of communication among caregivers.</td>
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<tr>
<td>Goal 3</td>
<td>Improve the safety of using medications.</td>
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<tr>
<td>3B</td>
<td>Standardize and limit the number of drug concentrations used by the organization.</td>
</tr>
<tr>
<td>3C</td>
<td>Identify and, at a minimum, annually review the list of look-alike and sound-alike drugs used by the organization, and take actions to prevent errors involving the interchange of these drugs.</td>
</tr>
<tr>
<td>Goal 4</td>
<td>Reduce the risk of health care-associated infections.</td>
</tr>
<tr>
<td>Goal 5</td>
<td>Reduce the risk of patient harm resulting from falls.</td>
</tr>
<tr>
<td>Goal 6</td>
<td>Encourage patient’s active involvement in their own care as a patient safety strategy.</td>
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<tr>
<td>Goal 7</td>
<td>The organization identifies safety risks inherent in its patient population.</td>
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</table>

In our Chain of Command: (Fig. 1)

- Each infant admitted to the NICU is assigned to a senior resident and an attending neonatologist who will be responsible for providing care.
- During shift changes, sign-outs are done between residents, attending neonatologists and nurses. Each patient’s condition and therapeutic management are discussed in detail at the bedside.
- No verbal order is carried out unless it has been ordered on-line or in emergency in person.
- Abbreviations, acronyms and symbols are not used.
- Medications are not mixed in the unit and all drug and intravenous fluid preparations are prepared in the pharmacy by the pharmacists. The only medication we mix in the unit is ampicillin.
- The pharmacists review all orders, and if they have any concern they call the unit immediately.
- A list of potentially dangerous drugs used in the NICU is posted in the unit and the staff is aware of the listed medications, such as heparin, digoxin, prostin, indocin, propranolol, sedatives, opiates, pancuronium, inotropics, potassium chloride, and sodium bicarbonate.

When medications are ordered, the following procedure is followed:

- The patient’s weight, gestation age and medical condition are known.
- The dose, preparation and method of administration is checked in the NEOFAX available to the staff in each room in the unit. NEOFAX is specially meant for neonatal medications in regard to dose, route, preparation, length of administration and adverse effects.
- The resident must check with the attending physician prior to writing the order.
- The attending physician must check the resident order for accuracy.
- All orders are reviewed and prepared by the pharmacists in the pharmacy.
- The NICU nurses must check the doctor’s order and pick up the medicine in the PYXIS. If they have any concern about the order they discuss it with the attending and the pharmacist.
- Before any drug is given it must be checked by two nurses and by the medical doctor if it is a dangerous drug.
- The nurses have to identify the infant by checking the wristband and medical record number before any medication is given.
- If any drug is left over after use, it must be labeled with the drug name, date of opening and the expiration.
patients in the past decade. The neonatologist supervises the residency staff and closely works with the NICU nurses and is responsible for enforcing patient safety goals. Their daily, 24-hour presence in the hospital makes a significant difference in preventing medication errors and addressing other safety issues.

Conclusions
The “chain of command” and national safety goal standards are being followed in the NICU. Everyone who works in the unit is fully aware of the critical nature of our patients and their special needs. Medications, which are calculated in micrograms, milligrams, grams and milliliters, are carefully ordered, prepared and administered with checkpoints at every step so that we can avoid medication errors in the NICU.

References
The practice of medicine is an ever changing process with new techniques and protocols appearing daily that change the way we practice. In addition, new concepts continue to emerge that change not only the way we treat patients but the way we think, perform research and teach residents and students. Evidence based medicine (EBM) is one of these new concepts that is well into its second decade of being emphasized in clinical practice. The current technological advances in the computer industry and Internet have enabled rapid access to the medical literature to enable nearly seamless incorporation of medical evidence into clinical practice. Student, residents and physicians have continuous access to literature, texts and reviews through hospital based and public sites of information that enables a critical review of the literature for almost any clinical scenario. However, in spite of its acceptance into the medical community and the practice of medicine, it remains to be universally accepted into the curriculum of our medical schools.

Evidence based medicine is defined as the coordination of the best research evidence with clinical expertise and patient values.1 Although recently coined as a term in 1992, the origins of evidence based medicine can be traced back to 1910 with the publication of the Flexner Report that suggested basing medical education on scientific research to ensure that clinical practice would be grounded in factual scientific information.2 Prior to that time, medical decisions were based primarily on pathophysiology, clinical judgment and clinical experience of the provider. Although evidence based medicine does not replace these essential clinical tools, it incorporates them into the current medical literature to improve patient outcomes.

The source of this information should incorporate the medical literature, expert reviews, committee opinions and continuing medical education. The best time to teach evidence based medicine to physicians is in medical school as residents do not gain the same comfort with evaluating and application of the medical literature as do students.3

It has been suggested that the ideal evidence based medicine curriculum should incorporate five critical concepts.4 These concepts include what type of information is important to patient care; formulating clinically relevant questions; focused literature search; critical appraisal of the medical literature; and application of the evidence to the clinical circumstances. In achieving these goals, the curriculum should include courses in public health, epidemiology, biostatistics, internet and computer technology and library media use.1 Although such a curriculum may be a separate course in either the clinical or preclinical years, ideally it should be integrated extending from the preclinical through the clinical years of medical school education. During the preclinical years, students should practice researching the medical literature, formulating clinical questions and applying their knowledge to problem based sessions. In the clinical years, preceptors of students can require students to research clinical problems using a literature search to assess the literature and then discuss its relevance and integration into their patient care.5

A recent review of the curriculum in 12 osteopathic medical schools noted only four programs that offered evidence based medical training as part of their curriculum.5 Of the remaining eight schools that were surveyed, seven of the eight indicated that they planned to add evidence based medicine into their curriculum. These four institutions that currently incorporated EBM varied in the time devoted to this training, the year in which it was taught, faculty involved in training and assessment tools. Only one of the four schools incorporated EBM in both clinical and preclinical years with two schools only teaching EBM in the preclinical and one only in the clinical years. Three of the schools used problem based learning to assess the skills obtained.

For this editorial, we reviewed the curriculum of the current residents and students in our training program to determine if their medical school curriculum incorporated EBM into their training. Our training program incorporates both US, osteopathic and international medical graduates representing a varied background of medical education. Fifty percent of the osteopathic residents noted training in EBM in their medical schools while 40% of the residents from US medical schools noted similar training. None of the international medical graduates noted EBM training in their medical school programs. In all of the medical schools noted to have training in EBM, half ...
Case Report
This is a 2,910 grams female infant born at 38 2/7 weeks gestation by NSVD to 29 years old gravida one woman, with Apgar scores of 7 and 9 at 1 and 5 minutes respectively. Maternal prenatal history was significant for diet controlled gestational diabetes. There was thick meconium and fetal tachycardia with no maternal fever prior to delivery. Maternal genital culture for group B streptococcus was negative.

Baby had mild respiratory distress needing nasal CPAP with FiO2 of 0.4 initially. Baby's blood gases remained stable. She was gradually weaned off the O2 support and CPAP by 5th day with resolution of the tachypnea. CXR showed normal lungs and heart.

Baby remained tachycardic intermittently with heart rate increasing to 180's and stable blood pressure. She had grade 2/6 systolic murmur with no heave or signs of congestive cardiac failure. Her EKG revealed excessive right ventricular forces with sinus tachycardia. Her echocardiogram showed normal ventricular function and mild pulmonary hypertension. The baby also developed a maculo-papular rash all over the body on 7th day. Due to the presence of rash and tachycardia, diagnosis of viral infection was considered. Enterovirus PCR was negative. The rash started to resolve on its own but tachycardia persisted rising up to 250. Brain natriuretic peptide level was 19pg/ml (normal). Thyroid function tests showed TSH 0.015 µIU/ml; Free T4 3.5ng/dl, total T4 25.8µg/dl and Free T3: 10.4pg/ml. Low TSH with the high level of T4 was suggestive of neonatal thyrotoxicosis. Further questioning of the mother revealed that she had palpitations, tremors and profuse sweating, which she had attributed to pregnancy. Maternal lab results revealed TSH < 0.007µIU/ml, thyroid stimulating Immunoglobulin (TSI) 233% of the baseline and thyroid peroxidase antibody <10 U/ml (normal). Thyroglobulin was 59.3 (elevated), thyroglobulin Ab was <20 (normal) and Free T4 was 5.38ng/dl; confirming the diagnosis of thyrotoxicosis in the mother. Goiter was not present in baby or mother. Thus maternal thyrotoxicosis was diagnosed because of neonatal tachycardia as the only manifestation of neonatal thyrotoxicosis.

The baby was started on antithyroid medication Propylthiouracil and Propranolol to control the heart rate. The dose was titrated according to changes in the free T4. The baby started to improve clinically with the resting heart rate returning to 140's to 150's and the T4 value returned to normal. On further follow up, with stabilization of heat rate and monitoring of thyroid function tests (TFTs), Propranolol was discontinued initially and at 36 days of age Propylthiouracil was stopped. Baby remained asymptomatic with normal heart rate and TFTs remained stable.

Introduction
Congenital hyperthyroidism is less frequent than congenital hypothyroidism but its impact on growth and development can be as dramatic.1 Grave’s disease is present in approximately 0.2% of pregnancies; neonatal hyperthyroidism seems to occur in only 1% - 2% of neonates born to mothers with Graves’ disease. If left untreated it can be associated with a mortality rate up to 25%.2,3,4,5 We report a case of neonatal thyrotoxicosis presenting with tachycardia as the only manifestation and with initially unknown maternal thyrotoxicosis.

Discussion
Hyperthyroidism in neonates has been described for almost a century with first description by Oschner and Thompson in 19106 and by White7 in 1912. Almost five decades later in 1961 McKenzie8 demonstrated the transplacental passage of thyroid stimulating immunoglobulin producing neonatal thyrotoxicosis in the setting of maternal Grave’s disease which was confirmed by Nutt et al9 and by Dirmakis et al10 in 1974 and 1975, respectively.2

The most common cause of hyperthyroidism in the newborn is transplacental passage of thyroid stimulating immunoglobulins (TSI) from the mother with Graves’ disease, or more rarely, Hashimoto’s thyroiditis. TSI activates the TSH receptor and stimulates the fetal thyroid gland. Neonatal thyrotoxicosis secondary to TSI is a transient disorder, limited by the clearance of maternal antibody from the baby’s circulation. The fetal...
concentration of TSI is low at the 15th week and increases progressively to reach maternal level at 30th week.1,2,11

Other causes of persistent congenital hyperthyroidism are also described. These patients are often members of families where this condition seems to have an autosomal dominant inheritance pattern.1,2,11 In 1991 Yoshimoto12 reported the first non-immune hyperthyroidism because of an activating mutation of the gene encoding the alpha subunit of the stimulatory g-protein in a patient with Mc-Cune-Albright syndrome.13 In 1995 Kopp14 et al described the mutation of the gene for Thyrotropin (TSH) receptor.2

Fetuses and neonates are susceptible to thyrotoxicosis if maternal circulating TSI levels are 5 times the upper limit of normal. However fetal and neonatal hyperthyroidism may appear with much lower maternal level. It is important to remember, that TSI may continue to be produced even after ablation of the thyroid gland with surgery or radioiodine.15

The clinical diagnosis of mild to moderate Grave’s disease in pregnancy can be difficult because pregnant women often exhibit signs of hyperdynamic circulation similar to hyperthyroidism. Almost all women with Grave’s disease will have a goiter. Dermopathy and ophthalmopathy are rare.

In the fetus the diagnosis of fetal thyrotoxicosis is suspected if fetal heart rate rises above 160 beats per minute and/or fetal growth retardation with history of maternal Grave’s disease.16 Premature birth is frequent. Other clinical features in the fetus are non-immune hydrops probably due to cardiac failure, and intrauterine death. Cordocentesis or amniocentesis has been recommended for definitive diagnosis.2 In the absence of maternal treatment with antithyroid drugs (ATD), hyperthyroidism develops in the fetus during the 2nd half of pregnancy.17 Ultrasonography with color Doppler can show increased vascularization of the thyroid and fetal goiter (best sign of fetal thyroid dysfunction).2 Fetal free T4 level correlates with maternal free T4 and fetal euthyroidism can be achieved by maintaining maternal free T4 in the upper normal level during ATD treatment.

Neonatal Grave’s disease affects both sexes equally and the clinical signs appear after several days of birth if the mother received any ATD. The symptoms usually start to appear by the 10th day of life1 when ATD levels start to decrease because TSI has a longer half life than the ATD. Clinical signs can vary in severity. Most infants have a goiter. Central nervous system symptoms are jitteriness, irritability and restlessness. Eye signs include periorbital edema, exophthalmos and lid retraction. Cardiovascular signs are tachycardia and arrhythmia that can progress to cardiac failure. Systemic hypertension and persistent pulmonary hypertension may be present.18 Symptoms due to hypermetabolism such as increased appetite, weight loss, diarrhea, sweating and flushing can be present. Other signs include persistent acrocyanosis, voracious appetite, hepatosplenomegaly, lymphadenopathy, jaundice, cholestasis, thrombocytopenia causing bruising and petechiae, thymic enlargement, hyperviscosity, advanced bone age, craniosynostosis and microcephaly.1,2,11,15,16

If the newborn has clinical signs of hyperthyroidism confirmation should be done by determination of plasma levels of free T4, free T3 and TSH. The levels should be determined taking into account the reference ranges for thyroid hormone in the neonatal period.1 When the diagnosis of hyperthyroidism is confirmed, its autoimmune origin should be established by determining levels of TSI.1,2,3

After confirming the diagnosis of neonatal hyperthyroidism treatment is usually started with an antithyroid medication. An antithyroid drug, either Propylthiouracil (PTU, 5-10 mg/kg per day) or Methimazole (0.5 to 1.0 mg/kg per day), should be administered every eight hours.

β-blockers ameliorate rapidly many of the symptoms, including palpitations, tachycardia, tremulousness, anxiety, and heat intolerance. A β-blocker, such as Propranolol, Atenolol, Alpenolol or Metoprolol is an important adjunct in controlling neuromuscular and cardiovascular hyperactivity. Propranolol is highly lipid-soluble, allowing it to become sufficiently concentrated in tissues to inhibit Monodeiodinase activity. This effect of Propranolol is slow, occurring over 7 to 10 days, and contributes little to the therapeutic effect of the drug.20

Iodine, in the form of one drop (8 mg) of Lugol’s solution (126 mg iodine/ml) every eight hours orally or SSKI (potassium iodide) one to two drops daily, can be given to inhibit thyroid hormone release. Glucocorticoids can also be given in extremely ill infants. In addition to their anti-inflammatory actions, glucocorticoids inhibit thyroid hormone secretion and decrease peripheral conversion of T4 to triiodothyronine (T3). Digoxin may be helpful if congestive heart failure is present.

Once improvement is evident, treatment should be gradually decreased and then discontinued. This may require frequent monitoring of thyroid function tests. The duration of neonatal hyperthyroidism secondary to maternal Graves’ disease depends on the persistence of the maternal TSI in the newborn blood and usually remits after 8 to 20 weeks. Virtually all neonates are euthyroid by 48th week.11,18

References

Medical Student Education…continued from page 24 received it as part of a biostatistics/epidemiology course and half in addition to biostatistics and epidemiology. All courses were in the preclinical years.

Medical school curricula have been mostly unchanged for years not reflecting the current state of medicine. This is reflected in the inadequate training in evidence based medicine. Such training should incorporate numerous courses including epidemiology, biostatistics, ethics, internet technology and media use and should be integrated into both the preclinical and clinical years. In addition, the educators involved should reflect the magnitude of this task with both clinical and non-clinical faculty. During the preclinical years, courses in EBM should teach the basics of theory and practice with problem based scenarios. During their clinical rotations, medical students should learn to develop clinically relevant questions, perform a focused literature search with critical appraisal of the literature and application to the clinical question and patient care. Appropriate testing should incorporate problem based assessment and oral examination to ensure adequate acquisition of such skills. Until such training is incorporated into medical schools, the gap will continue to widen between the state of medicine and the state of medical education.

References
Tradition and concern about the fragility of premature infants (especially extremely low birth weight infants) has governed the policies and procedures for feeding in the Neonatal Intensive Care Unit (NICU). Predetermined goals for volume and caloric intake as well as weight gain have supported traditional, structured feeding regimes using rigid schedules and gavage feeds as mainstays. Only in recent years have researchers begun to look at more interactive, infant driven feeding regimes. Most of these studies have focused on transition time from total gavage feeds to bottle feeding in the premature population. In most studies target volumes, caloric intake and scheduled feeding times have been kept as part of the feeding regime. Few studies allowed premature infants to self-regulate feeding times and/or volumes.

Cues to determine feeding start times have occasionally been given some attention. Satiation cues have received even less focus. Negative cues and feeding regimes have not been studied. See table 1 for a list of various cues. Non-nutritive sucking prior to feeds has been used to shorten transition times.

Allowing premature infants with gestational or corrected ages as early as 33 weeks to determine their own feeding times and intake, without gavage feeding, while encouraging breast feeding, is quite different from traditional approaches to feeding these infants. It requires healthcare staff to embrace a different belief system regarding feeding of preterm infants.

Neurodevelopmental maturity is an individualized process for infants. Using this information a prospective quasi-randomized study in our NICU provided the evidence needed to use Cue-Based Feeding as a standard of care for well and convalescing premature infants between 33-36 weeks gestation. Length of hospital stay for cue-based feeding infants was significantly shorter. Weight gain was unaffected and breast feeding numbers were similar in both control and cue-based feeding groups.

Fewer adverse events such as apnea and bradycardia were recorded for cue-based infants. Gavage feeds were stopped when infants started this feeding regime. For complete study results refer to the article: Puckett B, Grover K, Holt T, Sankaran K. 2008, Cue Based Feeding a Prospective Trial, American Journal of Perinatology (in press).

This study provided the template to implement this feeding regime successfully. It has now been used in our NICU for five years.

Nursing staff receive orientation about this feeding regime when they begin work in NICU. The cues outlined for implementation of this regime are listed in Table 1.

Initial bottle/breast feeding is offered occasionally to premature infants at a minimum corrected age of 32 weeks in our unit based on their clinical status and readiness as assessed by the healthcare team. Eligibility for cue-based feeding includes any premature infant with a gestational or corrected age of 33-36 weeks who is receiving all nutrition orally. Within that age group the infant must have shown some signs to the nursing staff that they can breast/bottle feed part of a feed while maintaining homeostasis. Other signs of readiness are: waking before feeding time, eagerness when bottle/breast feeding, consistently taking part of the feed by bottle/breast. When these signs are evident, gavage feeds are stopped and the infant is allowed to cue-base feed.

There is a transition time following the implementation of cue-based feeding for some infants before consistent weight gain is seen. The typical transition time is one to three days. During this time, for bottle-fed infants who have fluids and calories calculated daily, a slight decrease in intake may be seen. Weight loss is not dramatic; less than 5% over this time, often with the infant at a plateau. Other infants immediately increase their intake above that which they had previously been ordered to receive. Some infants show a pattern of feeding that may include small frequent feedings initially; typically they transition to a feeding frequency between feeds of 3-5 hours.

Occasionally, infants ingest lower volumes in the first twenty-four hours of cue-based feeding and/or need to be awakened...
frequently at 5 hours to feed. As long as they will bottle/breast feed when awakened, have normal blood sugar levels and an acceptable number of wet diapers, cue-based feeding is continued on a trial basis. Their readiness for continuing cue-based feeding is then reassessed at daily medical/nursing management rounds using eagerness of feeding, gestational age, temperature control, presence of jaundice, frequency of apneas and/or bradycardias, etc to determine if cue-based feeding should be continued. Very rarely cue-based feeding is stopped temporarily; the infant is again given a set volume for intake as well as gavage feeds on a prn basis. The most common decision regarding the infant is to be patient during this transition phase.

In an attempt to make the assessment of readiness and initial start of cue-based feeding a more objective decision and therefore even a more successful intervention, we are going to implement a scoring process similar to that outlined in the article: Ludwig, SM, Waitzman KA, 2007, Changing Feeding Documentation to Reflect Infant-Driven Feeding Practice, Newborn & Infant Nursing Reviews, Elsevier, 7(3), Sept p155-160 Gastrointestinal Issue.1 It is hoped that this simple objective scoring system will help both professional and family caregivers to select the most appropriate timing for the successful implementation of cue-based feeding. We feel this will empower nurses to advocate for the infant regardless of their nursing experience.

A word of caution is noteworthy when considering the implementation of cue-based feeding in late preterm infants during the first week of life. Although this can be a very successful feeding regime for this group of infants, close monitoring of bilirubin levels is necessary to ensure that any evidence of lowered intake is not reflected in rising bilirubin levels requiring aggressive therapy.

A second finding we have occasionally noticed with infants using this feeding regime is that they may not be able to handle both cue-based feeding and transitioning from isolettes to bassinette at the same time. We have found that allowing infants to cue-base feed until a steady weight gain is seen, coupled with a slowed weaning of isolette temperature ensures a more successful transition to bassinette care. These observations are most often seen with those infants who require transition time relating to intake and consistent weight gain.

As concluded in the research article, premature infants respond well to a cue-based feeding regime. We continue to discharge infants from the NICU at 35+ weeks corrected age with a well established “demand” schedule for parents to continue at home. This feeding regime may allow for infants to return to community hospitals at earlier gestational ages than feeding regimes requiring gavage feeding.

On occasion NICU nurses and physicians still need to be reminded to base decisions on the neurodevelopmental behavior of the infant rather than absolute weight, gestational age or resolved but complex medical issues that continue to be interpreted as fragility of the infant in question.

### Reference

1 Changing Feeding Documentation to Reflect Infant-Driven Feeding Practice, Newborn & Infant Nursing Reviews, Elsevier, 7(3), Sept p155-160 Gastrointestinal Issue. Abstract: Nipple feeding is a complex task for most preterm or high-risk infants. It requires a skilled and observant caregiver to assist the infant in a pleasurable feeding experience that maximizes intake and minimizes stress. This article presents the traditional progression, method, and documentation routinely used in nurseries, as well as an infant-driven approach to feeding that is beginning to surface in nurseries. The article will review the goals for successful nipple feeding and present the Infant-Driven Feeding Scales to be used as an assessment, a guide for intervention, and a means for documentation of nipple feedings. The scale encompasses infant feeding readiness and quality of nippling, as well as caregiver techniques. The article includes parent use of the scale, as well as a case review using the Infant-Driven Feeding Scales.

### Table 1. Feeding Cues for Preterm Infants in an Infant Driven Feeding Regime

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<td>Falls Asleep</td>
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<tr>
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Introduction
Deliberate action to improve evidence-based healthcare practices through provision of consistently reliable quality care is a recognized challenge of the healthcare industry. Leaders of this movement include the Institute of Medicine (IOM), the Institute for Healthcare Improvement (IHI) and the Joint Commission (TJC). The IHI, specifically, recognizes the need to create processes that enable clinicians to reliably provide evidence-based best practices to reduce error and improve outcomes (Cherouney et al. 2005). “Measurement is at the core of quality improvement” (Martin et al. 2007). Consequently, initiatives that strive to impact quality care delivery must be monitored for their return on investment.

Background
Despite major technological and scientific advances, preterm infants have a significantly greater risk than their term counterparts for a variety of medical and psychological morbidities such as chronic lung disease, intraventricular hemorrhage, learning disabilities, neurosensory deficits and behavioral problems (Aylward 2005, Bhutta et al. 2002, Hack 2006, Hack et al. 2005). In addition to immaturity and infection, emerging evidence suggests that environmental factors such as noise, bright lights, frequent handling and painful procedures contribute to poorer outcomes for the critically ill preterm infant (Philbin 2000, Symington and Pinelli 2006, Symington and Pinelli 2002).

Developmentally Supportive Care
Developmentally supportive, family-centered care is a practice strategy employed in the neonatal intensive care unit (NICU) that recognizes the physical, psychological and emotional vulnerabilities of infants and families. This care model aims to minimize the deleterious effects of the intensive care experience on the developing infant. Developmental care has been shown to decrease the length of hospital stay and hospital costs, improve weight gain and time to full enteral feeds as well as improve neurodevelopmental scores at 9 to 12 months of age (Jacobs et al. 2002, Symington and Pinelli 2006, Symington and Pinelli 2002).

Despite these documented benefits, there has been inconsistent adoption and implementation of developmental care practices.

The Wee Care Program
The Wee Care Program (Children’s Medical Ventures, Norwell, MA, USA) focuses on process improvement in the NICU specifically as it relates to developmentally supportive care practices. Synthesizing the current body of evidence-based research and utilizing adult teaching principles presented by clinically active neonatal professionals, this program facilitates the integration of developmentally supportive, family-centered care into the NICU culture. The program consists of a pre- and post-program site assessment, two leadership workshops (held before and after the educational component), the education component, and then three clinical practice follow-up visits to assess progress, practice integration and measure outcomes.

The Wee Care Program site assessment evaluates the unit’s developmental care practices across four domains that research has identified as critical to developmental care practice: the admission process, the physical environment, caregiving-handling-positioning and family participation in the NICU before and after the program. Data compiled provides a comparative reference point to Wee Care sites interested in benchmarking against other Wee Care facilities as well as documenting individual unit progress. The site assessment tool was developed by William G. Cvetnic, MD, in collaboration with other Wee Care clinical consultants and has demonstrated inter-rater reliability. The measurable parameters were assigned scores of increasing value. These values correlated with idealized developmental care practices. This tool was the first of its kind and attempted to quantify developmentally supportive family-centered care practices in the NICU. To date, 60 NICUs across the United States have participated in the Wee Care Program. A convenience sample of Wee Care site data was evaluated and presented at the 48th Annual Meeting of the European Society for Paediatric Research. [The convenience sample was comprised of Wee Care sites whose data was accessible via electronic records. Paper data was incomplete and thereby excluded from the analysis.] The data revealed a statistically significant improvement in overall post program scores (p = 9 x 10^-5). Data was then separated across the four domains and continued to demonstrate statistical significance.

Mary Coughlin, RN, MS, NNP

Mary Coughlin is Global Clinical Services Manager, Children’s Medical Ventures.
Every high-risk newborn deserves a head start towards a healthy life.

At Children’s Medical Ventures, we create quality care, process improvement and consulting programs to promote the healthy development of infants at risk. Drawing on evidence-based research and utilizing adult teaching principles presented by clinically active neonatal professionals, we challenge your clinicians and NICU staff to meet the highest standards of developmental care in support of these special babies. Call us today to learn more about our Wee Care process improvement program or for a free catalog detailing our comprehensive education and e-Learning offerings.

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Future Direction
As global healthcare leaders acknowledge the importance of evidence-based quality care delivery in improving patient outcomes and reducing healthcare costs, organizations are challenged with operationalizing methodologies that will achieve this aim (NAS 1999, Whitfield et al. 2001, Nolan et al. 2004). Children's Medical Ventures' Wee Care Program responds to this quality care movement and provides administrators and clinicians with practical, evidence-based, staff-wide education couched in a process improvement model to yield measurable, sustainable practice change in the NICU (Turnage Carrier 2000, Hendricks-Munoz et al. 2002, Altimier et al. 2004).

References
Introduction
Aniridia is a rare disorder characterized by unilateral or bilateral absence of the iris. This condition can be sporadic or hereditary and rarely occurs in its pure form. Usual presentation is with a rudimentary stump of iris. We report case of a newborn with bilateral aniridia with particular emphasis on its clinical significance and parent education. We present this case along with a brief review of the relevant literature.

Case Report
A full term appropriate for gestational age infant was delivered vaginally at 39 weeks of gestation with assisted vacuum delivery. Maternal prenatal screens were negative and her clinical follow up was unremarkable. The infant had Apgar scores of 9 and 9 at 1 and 5 minutes respectively. Infant's birth weight (2450gms), head circumference (33cm), chest circumference (31cm), abdominal circumference (27cm) and length (47cm) were all appropriate for gestational age. The initial eye examination was not complete since the infant received eye prophylaxis in the delivery room.

On the day of discharge a thorough physical examination was performed and an ophthalmologic evaluation revealed normal sized eyes, no external anomalies and dilated pupils with sluggish response to light and accommodation. Red reflex was present in both eyes with bilateral non-visualization of the iris (Fig 1 & 2). A tentative diagnosis of a bilateral aniridia was made and due to its association with other conditions the following consultations were obtained. An ophthalmology consult confirmed the diagnosis of incomplete bilateral aniridia with minimal retinal hemorrhage. Genetic consultation recommended a chromosomal study with high resolution 11P and 2P. Parental evaluation and genetic history was negative. Renal ultrasound of the infant was negative. Genetic inheritance could not be established. Chromosomal arrangements were reported as normal with 46XX. Pediatric Neurology consultation recommended a brain ultrasound to rule out any neurological associations which were normal.

Discussion
Aniridia is an uncommon anomaly of the newborns. The reported incidence is approximately 1.8/100,000 live births. Three phenotypes are recognized:
- Autosomal dominant aniridia is most common and is present in approximately 85% of all cases. It is not associated with any other systemic manifestations.
- Congenital sporadic aniridia is found in association with Wilms' tumor (nephroblastoma), genitourinary anomalies and mental retardation (Miller's syndrome). It has been labeled as WAGR syndrome (for Wilms’ tumor, aniridia, genitourinary anomalies, retardation) which is linked with partial deletion of the short arm of chromosome 11 (11p13). WAGR syndrome accounts for approximately 13% of all aniridias.
- Autosomal recessive aniridia is seen in approximately 2% of all cases and is associated with cerebellar ataxia and mental retardation (Gillespie’s syndrome).

Different theories have been developed to explain the pathogenesis of aniridia. Some researchers consider it a subtype of coloboma. Others believe in mesodermal and neuroectodermal theories of its development as there are associations between some types of aniridia with hypoplastic discs and absence of iris musculature. The arrest of the neuroectodermal tissue is the most striking histopathological feature of this condition. With histological examination, a small stump of iris that lacks iris musculature may be observed. The iris remnant appears continuous with the trabecular meshwork. Glaucoma develops in about 50% of patients who have aniridia. It is rare in newborns and is usually seen after the second decade of life, as anatomical changes occur in the angle secondary to contracture of peripheral iris strands. These iris strands bridge the space between the iris stump and trabecular meshwork, and the progressive contracture of the iris strands creates an angle-closure glaucoma. In addition, goniodysgenesis is noted in some cases. Glaucoma in Miller's syndrome may develop secondary
to angle anomalies, which include dysgenesis of the trabecular meshwork and Schlemm's canal.\(^6\)

The clinical manifestations of aniridia include photophobia related to the extent of iris involvement. Pendular nystagmus, decreased vision, amblyopia, and strabismus are seen secondary to foveal and optic nerve head hypoplasia. Bilateral ptosis also may occur in aniridia.\(^2\)\(^4\) With gonioscopy, the iris appears as a rudimentary stump with fibers that bridge the angle. This rudimentary iris leaflet appears to be pulled forward by iris strands, which results in posterior synechiae formation and subsequent angle-closure glaucoma.\(^6\) In addition to the anterior segment changes, findings in the posterior segment may include foveal and optic nerve head hypoplasia and choroidal coloboma. Lenticular changes include cataract, ectopia lentis, microphakia, and persistent pupillary membranes. Microcornea and corneal opacifications also have been observed in aniridic patients.\(^7\) The corneal opacification is often associated with a fine, vascular network and pannus formation.\(^8\)

Wilms’ tumor (nephroblastoma) is found in association with aniridia in Miller’s syndrome. Approximately 25–33% of patients who have sporadic aniridia develop Wilms’ tumor. In addition to Wilms’ tumor, severe mental retardation, genitourinary anomalies, craniofacial dysmorphism, and hemihypertrophy can occur.\(^9\) In Gillespie’s syndrome, mental retardation and cerebellar ataxia are seen.\(^3\)

Management is based on the symptomatology and includes treatment of glaucoma and other vision defects. By 20 years of age, most aniridic patients eventually fail pharmacological therapy and require surgery for adequate intra-ocular pressure control.\(^8\) A prophylactic modified goniotomy has been advocated to prevent this secondary glaucoma in certain young patients with aniridia.\(^6\)\(^10\)

**Conclusions**

Aniridia is a rare ophthalmologic congenital anomaly seen in newborns. A thorough newborn physical examination including eyes using ophthalmoscope for inspecting cornea, papillary reaction, iris and the red reflex should be routine. Early diagnosis of this condition will help to educate parents and a good follow-up by a pediatric ophthalmologist can prevent major vision disorders and associated medical conditions. In addition these infants should be referred to early childhood developmental center and also to lighthouse those who specialize in training of infants and education of parents to prevent further vision disorders.

**References**

Introduction
Jaundice is a yellowish discoloration of the whites of the eyes, skin and mucous membranes caused by deposition of bile salts (bilirubin) in these tissues. Increased bilirubin in neonates and premature infants, if left untreated can cause mental retardation and death. In jaundice of newborns this occurs when total bilirubin values are greater than 12 mg/dL. This condition is known as hyperbilirubinemia. Jaundice is common in 25-50% of all full term neonates and there is an increased occurrence in premature babies, that is infants born after a gestation period of less than 37 weeks. It is important to determine if this condition is due to physiologic conditions which is normal, or an underlying pathologic condition, which is abnormal and requires immediate intervention.

Pathology
Bilirubin is a bi-product of red cell breakdown. The total bilirubin is metabolized into two biproducts, carbon monoxide and unconjugated bilirubin. Once released into the bloodstream, the unconjugated bilirubin is transported to the liver for conversion. The unconjugated bilirubin enters the liver and undergoes a series of reactions with glucose and oxygen. The converted conjugated form of bilirubin is then removed from the neonate or infant.

Contributory factors to hyperbilirubinemia in neonates and premature infants are poor liver function due to liver development, increased red cell volume and reduced oxygen or glucose levels due to delayed lung development. The result can be an increased level of bilirubin in the bloodstream. And since unconjugated bilirubin is not water soluble but is very soluble in fat, the excess bilirubin is deposited in the fatty tissues, mucous membranes and especially brain tissue.

Discussion
With the increasing number of cases of hyperbilirubinemia in neonates and premature infants, the American Academy of Pediatrics and JCAHO guidelines recommend transcutaneous monitoring of all neonates and premature infants for hyperbilirubinemia. They require any monitoring value that exceeds 12 mg/dL to be verified by an accepted clinical chemistry method. Running a complete ABG panel with metabolites enables the healthcare provider to determine the root cause of hyperbilirubinemia and immediately map the best course of treatment by not only assessing the bilirubin level but also by assessing the glucose, PO2 and O2 saturation.

Recommendation
The cobas b 221 blood gas system correlates with accepted clinical chemistry methods for bilirubin testing and can provide a much larger clinical picture from just one blood draw reducing blood loss and improving patient care and outcomes at the point of care.

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Kangaroo Mother Care Diminishes Pain From Heel Lance in Very Preterm Neonates: A Crossover Trial

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Abstract

Background: Skin-to-skin contact, or kangaroo mother care (KMC) has been shown to be efficacious in diminishing pain response to heel lance in full term and moderately preterm neonates. The purpose of this study was to determine if KMC would also be efficacious in very preterm neonates.

Methods: Preterm neonates (n=61) between 28 0/7 and 31 6/7 weeks gestational age in three Level III NICUs in Canada comprised the sample. A single-blind randomized crossover design was employed. In the experimental condition, the infant was held in KMC for 15 minutes prior to and throughout heel lance procedure. In the control condition, the infant was in prone position swaddled in a blanket in the incubator. The primary outcome was the Premature Infant Pain Profile (PIPP), which is comprised of three facial actions, maximum heart rate, minimum oxygen saturation levels from baseline in 30-second blocks from heel lance. The secondary outcome was time to recover, defined as heart rate return to baseline. Continuous video, heart rate and oxygen saturation monitoring were recorded with event markers during the procedure and were subsequently analyzed. Repeated measures analysis-of-variance was employed to generate results.

Results: PIPP scores at 90 seconds post lance were significantly lower in the KMC condition (8.871 (95%CI 7.852-9.889) versus 10.677 (95%CI 9.563-11.792) p <.001) and non-significant mean differences ranging from 1.2 to 1.8. favoring KMC condition at 30, 60 and 120 seconds. Time to recovery was significantly shorter, by a minute (123 seconds (95%CI 103-142) versus 193 seconds (95%CI 158-227). Facial actions were highly significantly lower across all points in time reaching a two-fold difference by 120 seconds post-lance and heart rate was significantly lower across the first 90 seconds in the KMC condition.

Conclusions: Very preterm neonates appear to have endogenous mechanisms elicited through skin-to-skin maternal contact that decrease pain response, but not as powerfully as in older preterm neonates. The shorter recovery time in KMC is clinically important in helping maintain homeostasis.

Background

Doing no harm to very preterm neonates is particularly challenging. By virtue of being born too early, before 32 weeks gestational age, the very preterm neonate spends the first several weeks of life in the Neonatal Intensive Care Unit (NICU) where numerous noxious procedures are part of routine care. The most common painful procedures are heel lance and intravenous line insertions but topical anesthetics have not been found to be effective in very preterm neonates. Sucrose has been repeatedly shown to be effective but frequently repeated doses of sucrose in the very preterm neonate, while effective, may not be safe especially in younger infants. Parenteral analgesics either have negative sequellae or have not been tested for pain in this population. Behavioral methods of pain control such as non-nutritive sucking, simulated rocking, facilitated tucking, positioning have been tested with nonnutritive sucking having a significant effect, even in very preterm neonates. However, reports that mothers find loss of parental role and the pain the infant experiences as being the most stressful aspects of having a child in the intensive care setting lead us to explore means of involving mothers to provide comfort during painful events. Breast feeding was found to be effective, but thus far has only been reported to be used for pain control in full-term neonates. However, reports that mothers find loss of parental role and the pain the infant experiences as being the most stressful aspects of having a child in the intensive care setting lead us to explore means of involving mothers to provide comfort during painful events. Breast feeding was found to be effective, but thus far has only been reported to be used for pain control in full-term neonates. Breastfeeding is difficult to establish for very preterm neonates. Results from one study indicate that it may be the contact of breast feeding, as opposed to the breast milk, that is efficacious and this has been supported by results of studies that found breast milk per se not to have pain reducing properties. Thus for the very preterm group,
skin-to-skin maternal contact, or Kangaroo Mother Care (KMC), would appear to be a method which could decrease pain response. Furthermore, it would provide mothers an opportunity to comfort their infant during painful procedures in a technologically invasive environment.

Skin-to-skin contact by the mother, referred to as Kangaroo Mother Care (KMC), has been shown to be efficacious in reducing pain in three previous studies. The first randomized controlled trial was conducted with full-term neonates with results of significant decrease in crying and heart rate acceleration. The first study of KMC in preterm neonates, with restricted age of 32-36 weeks gestational age, had significant decreases in scores of a multidimensional scale that also included behavioral and physiological components. A second study on KMC with preterm neonates included neonates as young as 30 weeks gestational age and it too found decreases in scores of a multidimensional scale that also included behavioral and physiological components. A third study compared KMC to usual incubator care with results of significant decrease in crying and heart rate acceleration. The first study of KMC in preterm neonates, with restricted age of 32-36 weeks gestational age, had significant decreases in scores of a multidimensional scale that also included behavioral and physiological components.

Based on results of animal literature, it had been suggested that infants younger than 32 weeks gestational age may not have the endogenous mechanisms that could be evoked to decrease pain compared to infants above that age. Although mechanisms underlying the efficacy of non-nutritive sucking or sweet taste have been debated as endorphin release or some other mechanism such as serotonin release, it seems clear that some endogenous mechanism triggered by these non-pharmacological strategies is responsible for the analgesic effect in very preterm neonates. This study aimed to test if, like non-nutritive sucking and sucrose, kangaroo maternal care could also be effective in decreasing pain response to routine heel lance in infants less than 32 weeks gestational age.

### Methods/Recruitment

The protocol and consent forms were reviewed by the constituted institutional research ethics review board of each participating centre, namely, the Montreal Children's Hospital, the IWK Health Centre, and Hôpital Ste. Justine. These committees approved the incubator-control condition without sucrose following discussion with staff of the participating units where sucrose was not considered standard care in younger preterm neonates due to perceived safety concerns. The study took place in three level III units, all of which admitted both inborn infants as well as transfers. All supported KMC but did not systematically promote it and none had standard of care policies at the time of the study. Ventilated infants were rarely allowed into KMC and staff comfort with smaller infants varied.

Mothers and their preterm neonates were eligible for participation in the study if the infants met the following criteria: were born between 28 0/7 and 31 6/7 completed weeks post menstrual age (pma) determined by ultrasound at 16 weeks, had informed parental consent, had Apgar scores >6 at 5 minutes, were within 10 days of birth, were breathing unassisted, did not have any major congenital anomalies, had not suffered Grade III or IV intra-ventricular hemorrhage or subsequent periventricular leukomalacia, had not undergone surgery, and were not receiving paralytic, analgesic, or sedative medications within 48 hours. Mothers had to be willing and able to hold their infant in the KMC position for the study. The protocol was explained to the mother who was told about the two conditions lasting 15 minutes of undisturbed time in order for the infants to be in a true baseline state. For practical purposes, if the infant was to be discharged before needing two sessions of blood work, mothers were not approached to participate in the study. Using data from an earlier maternal kangaroo care study using our primary outcome with a mean difference of two points and a standard deviation of 4.5 points, sample size for a power of 0.9 and significance level set to .05, was 55. (PowerSample Size).

### Procedure

Employing a single-blind crossover design each infant was to undergo heel lancing for blood procurement for clinical purposes in either KMC position or usual incubator situation within 4 days of each other. Due to the infrequency of blood sampling which was determined by clinical considerations, we allowed a wider window of postnatal age such that there was a minimum of 24 hours and a maximum of 14 days between conditions. Ordering of conditions was determined randomly by a computer-generated program in the study centre and assignment was accessed on the website by the site research nurse after consent was obtained. In the KMC condition, the diaper-clad infant was held upright, at an angle of approximately 60o, between the mother’s breasts, providing maximal skin-to-skin contact between baby and mother. A blanket and then the mother's clothing were placed over the infant’s back and tucked under each side of the mother. The baby remained in this condition at least 15 minutes prior to heel lancing procedure. Fifteen minutes is shorter than in our earlier study with older preterm neonates, and this time...
was determined according to acceptance by the staff for whom KMC was not routine. We had also noted that physiological stability and deep sleep typically occur within a minute of being placed in KMC. We asked that the mother keep her hands clasped behind the infants’ back throughout the procedure and refrain from touching the infant’s head with her face (to keep observers blind). The mother was allowed to speak to her infant since there was no audio recording during the procedure. In the control condition, the baby was placed in the incubator in a prone position, swaddled with a blanket (with heel accessible), for at least 15 minutes prior to the heel lancing procedure. Prone position was selected since it controlled for the frontal pressure component of KMC, allowing us to test the maternal proximity component, as well as the fact that it is recommended for preterm neonates.46,47

The heel lancing procedure includes five phases. One minute of baseline was collected at the end of the 15 minutes in the assigned condition, that is following 15 minutes of KMC or in incubator. The heel warming phase lasted 1 minute. The heel was then swabbed and lanced with a spring loaded lancet (Tenderfoot). The instant of lancing was the point at which changes from baseline was determined and was analyzed in 30 second blocks from that instant. An adhesive bandage was applied to the site immediately after all blood was procured. This was the point that indicated the end of the blood sampling procedure. Return to baseline was calculated as time from adhesive bandage application until baseline HR was achieved. There was continuous video, but not audio, recording and pulse oximeter monitoring the heart rate and transcutaneous oxygen saturation of the infant throughout the session, both of which always occurred in the morning after the infant was fed. The continuous data were analyzed in allocated blocks of time and averaged for each phase of the procedure.

**Measures**

The primary outcome was the Premature Infant Pain Profile (PIPP).48-50 The PIPP is a composite measure of pain including physiological (heart rate, transcutaneous oxygen saturation), and behavioral (facial action) indicators and includes weights for younger gestational age and sleep state. Physiological scores are calculated based on changes in maximum heart rate and minimum oxygen saturation changes from baseline. The scores are totaled so that with the seven components scores can range from 0-21, and a difference of two points between conditions can be considered clinically important. The PIPP has been tested for reliability, construct validity and clinical utility, all with results indicating excellent psychometrics.49-51 One of the strengths of the PIPP is that it accounts for infant contextual variables known to influence pain response, specifically behavioral state at baseline and gestational age. Since in earlier studies KMC put almost all infants into quiet sleep, this poses a problem. According to PIPP protocol, we measured baseline state after the infant had been in the condition. There are additional pain score points if an infant is in quiet sleep, which would decrease any differences between conditions if KMC indeed put infants into quiet state, that is, there are additional pain score points given if infant is in quiet sleep during baseline. A second problem in using the PIPP in this study is that all the infants were in the same age range, so there would be no variance in the age factor of the PIPP. Therefore we also analyzed the individual components of the PIPP, ie facial actions, heart rate, and oxygen saturation, in order to compensate for the background factors of behavioral state and gestational age.

Heart rate was collected using four ECG leads connected to a data acquisition system (Compumedics E-series) with a sampling rate of 100 Hz averaged on a beat-to-beat basis. Transcutaneous oxygen saturation was collected via infrared oximeter (Massimo Radical placed on a hand or the unaffected foot of the infant and connected to the data acquisition system. The physiological data were analyzed using the software in the system (Compumedics E-series Profusion PSG II) that allowed minimum, maximum, mean, and standard deviation to be calculated. Artifacts were removed according to protocol in our laboratory which deleted sections in which HR was below range for 4 or more consecutive beats before analyzing. The three facial actions (brow bulge, eye squeeze and naso-labial furrow) of the PIPP were continuously recorded by a digital video camera Panasonic KS162 that allows for close range, high quality facial images. This camera was wired into the physiological data acquisition system, with the research nurse striking keys on the computer and flashing color coded cards into the camera to mark phases of heel lancing procedure. Since both physiological and video data were fed into the same data acquisition system, the time stamps were synchronous. The camera was in close up focus on the infant’s face with very little surrounding area, no sound, with minimal color, and turned to an angle in the kangaroo condition as to mimic the prone position in order to decrease possibility of unblinding by research assistants who scored the tapes. Research assistants, who were blinded to the purpose of the study by being told that the study was about infant facial actions, coded facial actions in the laboratory of the PI (CJ). The three facial actions were scored according to the Neonatal Facial Coding System12-15 that provides a detailed, anatomically based, and objective description of newborn reactions to the heel lance. The selected facial actions were scored on a second-to-second basis. The video-recordings were viewed in real time on Windows Media Player which allowed viewing of the Panasonic AG-1970 default screen with clock to the 4th decimal place. Each recording session was scored three times, once for each of the facial actions, using a laptop computer with software developed in the lab based on BASIC software that records the scores and
allows for information on artifacts to be included. A final score based on percentage of time the facial action was present was calculated each 30 second time block throughout each phase of the procedure. The neurobehavioral state component was determined according to Prechtl's categories of quiet sleep or quiet awake or active sleep or active awake,65,67 during the baseline. Gestational age was taken from the chart, based on ultrasound at 16 weeks.

Severity of illness, as a potentially confounding variable, was scored using the Score for Neonatal Acute Physiologic Version II (SNAP-II68) for the 12-hour period after birth and in the 12 hour period prior to each study session. The elements of this score can be found in the medical record and include hemodynamic, respiratory, hematological, metabolic, electrolytic, and neurologic parameters. The score has predictive validity for perinatal mortality.

Results
Across the three sites, there were 236 infants admitted during the data collection period (April 2003-December 2005). (Figure 1.) Of those 125 meeting the selection criteria, 114 were approached, and 77 accepted to participate, giving a refusal rate of 32 percent. The main reasons for refusal were that mothers: felt too stressed to participate, did not want anything extra done to their infant, and did not want to see the baby in pain. One mother withdrew when attempting KMC for the study because she felt “too nervous.” Physiological and behavioral data were completed for both KMC and control sessions on 64 infants, however data were incomplete (face obscured, EKG lead detaching) on three. The primary reason that infants were lost to the study was that the infant was discharged from the unit or did not require bloodwork within the time frame of the study. The 61 infants remaining in the study were a mean age of 30.5 weeks (SD 7 days), at birth weighed 1421 gm (SD 490 gms), had 5-minute Apgar scores of 8.2 (SD 1.3), and SNAP-PE-II score of 10.08 (SD 10.9). There were significant differences in weight and age between the two sessions (Table 1). Order of condition, postnatal age, or weight had no effect on the pain response. Since gestational age and SNAP scores were not correlated with any outcomes (r < .15) they were not included in the analyses as covariates. Means for outcomes between sites and order of condition were almost identical and thus neither of these factors were included in analyses. A repeated measures analysis of variance with condition (KMC vs incubator) as the repeated factor was conducted for each 30 second period following heel lance through 2 minutes when the majority (83%) of the heel lance procedures had been completed. Thirty-one infants underwent KMC before the incubator condition. Although the blood sampling procedure was 17 seconds shorter in KMC than incubator (153 vs 170 seconds), this was not significant. Average baseline heart rate was within 1 beat per minute and oxygen saturation levels within 0.2% between conditions. Behavioral state was different at baseline with 60% of infants in quiet sleep in KMC condition versus 30% in incubator condition ($\chi^2 (3) = 50.9, p < .0001$).

Mean pain scores (PIPP) (see Figure 2) were not significantly lower, in the KMC condition at 30 and 60 seconds post-heal lance. By 90 seconds post-heel lance, the difference between conditions was significant (KMC 8.871 (95%CI 7.852-9.889) versus Incubator 10.677 (95%CI 9.563-11.792) p < .001). The difference continued to 120 seconds, although fell short of significance (8.855 (95%CI 7.447-10.262) versus 10.210 (95%CI 9.030-11.389) p = .145). The time to return to baseline heart rate following the application of the adhesive bandage signifying the end of blood sampling was significantly different, 123 seconds (95%CI 103-142) for the KMC condition and 193 seconds for incubator condition (95% CI 158-227) (F (61,1) = 13.6, p < .0000).

In examining the average physiological indicators and facial actions of the PIPP, facial actions were significantly lower in the KMC condition than the incubator condition (See Figure 3) throughout the phases, reaching a two-fold difference by 120 seconds, and average heart rate was significantly lower at 30, 60, and 90 seconds post-heal lance and (See Figure 4). Average oxygen saturation levels were significantly higher at 60 and 90 seconds post-heal lance (See Figure 5). The physiological...
Figure 5. Oxygen Saturation Between Condition Across Heel Lance Procedure

![Oxygen Saturation Between Condition Across Heel Lance Procedure](image)

* p < .05

differences were calculated on average value, dissimilar to how calculated in the PIPP.

**Discussion and Conclusions**

Maternal contact in the skin-to-skin paradigm of KMC decreases pain response in preterm neonates between 28-32 weeks gestational age who are undergoing a heel lance for blood procurement, although the magnitude of the difference is less than 2 points on the 21-point outcome measure, found in our report of infants 32-36 weeks. The differences between incubator and KMC were approximately between 1.1 and 1.8 in the first three 30 second blocks of time, out of a total possible score of 21. While the levels reached statistical significance for some of the phases, and the mean individual components of the PIPP reached statistical differences, the magnitude of the effect was smaller than estimated, based on our earlier study of 32-36 weeks gestational age infants. The effect of KMC was not immediate following the heel lance, as in the study with the older preterm neonates, but was evident further into the heel lance procedure, not until 90 seconds post lance. This delay in older preterm neonates, but was evident further into the heel lance procedure, not until 90 seconds post lance. Perhaps more importantly, was the significantly quicker time to recovery. Of clinical interest on procedural pain in very preterm neonates are response, that is the degree to which they respond, and recovery, how quickly they return to pre-procedure state. The ability to recover quickly is a sign of ability to maintain homeostasis, a major task that the very preterm neonate must accomplish in order to grow and develop. Facilitation of homeostasis maintenance through KMC has been reported regarding temperature, state, oxygen saturation levels, and growth, but not in the context of the additional stress of pain. The results of this study indicate that maternal contact can facilitate not only a diminished response, but a quicker recovery in infants between 28 and 32 weeks gestational age.

There are some explanations other than maternal contact for the results. It was impossible to blind the person conducting the heel lance procedure, so that they may have been gentler during that condition. Anecdotally however, they preferred the incubator condition since conducting the procedure in KMC meant the person procuring the blood sample had to bend over towards the infant or be seated on a stool next to mother and infant, not standing next to incubator. Additionally the mother would be observing and some staff were not comfortable with that. When the infant was in KMC, gravity may have helped the blood flow and made the procurement faster, although the 17 second difference was not significant.

Infants in this study were not intubated or even requiring supplemental oxygen, according to the protocols of the units at the time the study began. Now, some intubated infants are permitted to be in KMC and it would be interesting to see if KMC is efficacious for procedural pain in a similar age group, but intubated population. One study on KMC in neonates less than 28 weeks showed that those infants could not maintain temperature in KMC, and until other studies contradict that, studying KMC for pain control in infants less than 28 weeks may not be indicated at this time.

Kangaroo Mother Care for pain management in preterm neonates is obviously cost-effective and has now been shown to be effective in infants from 28 weeks through term. Mothers should be offered KMC as NICU policy, not only to be close to their infant, but also to provide comfort. It is not known if KMC is commonly included as a non-pharmacologic intervention for procedural pain in NICUs but based on results here as well as earlier studies with older preterm neonates, it would be recommended, alone or in conjunction with other strategies such as sweet solutions.

Very preterm neonates between 28-32 weeks gestational age can benefit from KMC to decrease pain from heel lance procedures.

**References**


Kernicterus by Glucose-6-phosphate Dehydrogenase Deficiency: A Case Report and Review of the Literature

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Abstract
Introduction: Glucose-6-phosphate dehydrogenase deficiency is an X-linked recessive disease that causes acute or chronic hemolytic anemia and potentially leads to severe jaundice in response to oxidative agents. This deficiency is the most common human innate error of metabolism, affecting more than 400 million people worldwide.

Case presentation: Here, we present the first documented case of kernicterus in Panama, in a glucose-6-phosphate dehydrogenase-deficient newborn clothed in naphthalene-impregnated garments, resulting in reduced psychomotor development, neurosensory hypoacousia, absence of speech and poor reflex of the pupil to light.

Conclusion: Mutational analysis revealed the glucose-6-phosphate dehydrogenase Mediterranean polymorphic variant, which explained the development of kernicterus after exposition of naphthalene. As the use of naphthalene in stored clothes is a common practice, glucose-6-phosphate dehydrogenase testing in neonatal screening could prevent severe clinical consequences.

Introduction
Glucose-6-phosphate dehydrogenase (G6PD) is a housekeeping enzyme that catalyzes the first step in the pentose phosphate pathway, providing reducing power in the form of nicotinamide adenine dinucleotide phosphate (NADPH). This metabolic pathway is the only source of NADPH in erythrocytes and is therefore the mechanism by which the cell damage caused by oxidative stress is avoided.1,2

Individuals deficient in G6PD are usually asymptomatic; however, in some cases exposure to chemicals (for example, naphthalene) and drugs (including sulfamides, antipyretics, nitrofurane, primaquine and chloroquine) can induce massive intravascular hemolysis. Among the clinical forms of this enzymatic deficiency are jaundice, acute hemolytic anemia and chronic nonspherocytic hemolytic anemia. A more severe consequence of neonatal hyperbilirubinemia is kernicterus, a neurological syndrome caused by the deposition of bilirubin in the brain tissues, which results in severe consequences and even death.2-4

G6PD deficiency is an X-linked recessive disease and is the most common human innate error of metabolism, affecting more than 400 million people worldwide.5 The G6PD gene is highly polymorphic and more than 140 mutations have been described. In the Mediterranean, Middle East, India, China and Southeast Asia, the distribution of multiple alleles account for the total prevalence. There are no reports concerning the prevalence of this enzymatic deficiency in Panama; however, our preliminary studies indicate a high prevalence of G6PD deficiency in this country (unpublished data).

Here we present a kernicterus case in a G6PD-deficient newborn resulting in severe neurological damage.

Case presentation
Clinical history
A 4-day-old boy was admitted to the Hospital del Niño in Panama. He was the first child of a healthy young woman from a normal vaginal birth at term. He had an Apgar score of 9 at 1 minute and 9 at 5 minutes, a birth weight of 3.5 kg, body length of 53 cm and a 35 cm cephalic circumference. The newborn was hospitalized when clinical examination revealed 4+ jaundice, hypoacllary, hypoxemia and generalized tonic-clonic seizures, requiring management with anticonvulsives, phototherapy and exchange transfusion. A history of use of naphthalene-impregnated clothes was recorded. Analysis of clinical symptoms and laboratory tests diagnosed the proband with kernicterus by G6PD deficiency. Despite clinical management, after 5 years the patient presented with reduced psychomotor development, neurosensory hypoacousia, absence of speech and poor reflex of the pupil to light.
Laboratory data
Upon admission the patient presented total bilirubin values of 42.6 mg/dl (41.8 mg/dl from indirect bilirubin), 11.8 g/dl hemoglobin, 8% reticulocytes, O (Rh+) and B (Rh+) blood types for child and mother, respectively, and negative direct Coombs. G6PD testing was reported as deficient, and the quantification of the serum levels of this enzyme was 0.278 U/gHb (normal value range 4.6 to 13.5 U/gHb). Cranial magnetic resonance imaging demonstrated hyperintense basal ganglia lesions on T2-weighted images (Figure 1).

Mutational analysis
Determination of the G6PD polymorphic variant was achieved by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) as described elsewhere. Genomic DNA from the patient and one heterozygote G6PD Mediterranean variant control were obtained from heparinized peripheral blood with the salting out method described by Miller et al. We used 100 ng of DNA to amplify the region flanking nucleotide 563 containing the polymorphism. Amplified products were then digested with the restriction enzyme Mbo II and the digestion mix was electrophoresed in 10% polyacrylamide gel. Analysis showed the G6PD Mediterranean polymorphic variant genotype (Figure 2), which explained the G6PD deficiency phenotype.

Conclusion
G6PD deficiency is an X-linked recessive disease and is the most common human innate error of metabolism, affecting more than 400 million people worldwide. At the Hospital del Niño of Panama, we have observed a high prevalence of G6PD deficiency in our patients; however, there are no reports concerning the prevalence of this enzymatic deficiency in this country.

Here we presented the first documented case of kernicterus in Panama in a G6PD-deficient newborn. The proband presented with hyperbilirubinemia (total bilirubin of 42.6 mg/dl) and was treated with phototherapy and two exchange transfusions.

G6PD deficiency testing was positive explaining the symptoms and clinical signs. Mutational analysis demonstrated the G6PD Mediterranean polymorphic variant genotype (Figure 2).

The use of naphthalene-impregnated clothes prior to the episodes of seizure explained the development of severe jaundice that led to kernicterus. As the use of naphthalene in stored clothes is a common practice, so testing for G6PD as part of neonatal screening could prevent this severe clinical consequence.

References
Abstract

Background: There is currently an unprecedented expressed need and demand for estimates of maternal mortality in developing countries. This has been stimulated in part by the creation of a Millennium Development Goal that will be judged partly on the basis of reductions in maternal mortality by 2015.

Methods: Since the launch of the Safe Motherhood Initiative in 1987, new opportunities for data capture have arisen and new methods have been developed, tested and used. This paper provides a pragmatic overview of these methods and the optimal measurement strategies for different developing country contexts.

Results: There are significant recent advances in the measurement of maternal mortality, yet also room for further improvement, particularly in assessing the magnitude and direction of biases and their implications for different data uses. Some of the innovations in measurement provide efficient mechanisms for gathering the requisite primary data at a reasonably low cost. No method, however, has zero costs. Investment is needed in measurement strategies for maternal mortality suited to the needs and resources of a country, and which also strengthen the technical capacity to generate and use credible estimates.

Conclusions: Ownership of information is necessary for it to be acted upon: what you count is what you do. Difficulties with measurement must not be allowed to discourage efforts to reduce maternal mortality. Countries must be encouraged and enabled to count maternal deaths and act.

Background

In 2000, 189 countries signed-up to improve maternal health as one of the eight Millennium Development Goals (MDGs). Progress towards this MDG-5 can be measured using a wide variety of indicators.1 Government and donor commitments to maternal health can be monitored using financial indicators and policy approvals. Investment in maternal health programmes can be tracked by measuring inputs (such as midwifery training), outputs (such as the number of midwives posted) and processes (such as the uptake of skilled delivery care).2 These indicators are necessary for planning, implementing and monitoring initiatives to improve maternal health. However, there is also a need to show progress in terms of impact: reduced mortality, complications and disabilities, and improved health. In general, however, it is easier to track the inputs and outputs of a program than its impact.3

For developing countries without routine registration and medical certification of cause of death, measuring who dies and the cause of death is particularly difficult, and maternal mortality is no exception.4 Currently, two-thirds of countries do not have the means to fully count or register their populations. Long-term efforts are needed to strengthen country capacities for comprehensive routine reporting of births and deaths. In the interim, measurement scientists have devised a range of alternative approaches that can help many countries without comprehensive vital statistics to generate estimates of mortality for various population sub-groups and causes. These alternatives approaches have evolved considerably over the last half century.5 Some are predominantly empirical approaches which rely on capturing new data on deaths, and others predominantly analytical, adjusting or modelling existing data on deaths and other related variables. Advances in the measurement of child mortality have been more marked than for adult mortality,6 although techniques for some cause-specific adult causes, such as HIV/AIDS,7 have improved in the last two decades.

Maternal mortality, a subset of adult female deaths, has also benefited from new or enhanced approaches for use in resource-
of resources affects the suitability of different options. In this and accuracy of the information required, and the availability or too expensive to measure. Third, to respond to the heightened measurement stagnation:9 that maternal mortality is too difficult or too expensive to measure. To measure maternal mortality is often an iterative process, which involves making trade-offs between all of the considerations in Table 2.

So what are these opportunities and options? Figure 1 introduces the alternatives schematically, and highlights the basic distinction between empirical approaches, the primary focus of this paper, and analytical approaches, which are discussed briefly later. Here we are also distinguishing between the primary mechanism or platform (measurement opportunity) for gathering the data, and the method (measurement option) used to identify maternal deaths and derive estimates of mortality. Figure 1 proposes five major data-gathering opportunities: (1) death registration; (2) health facilities; (3) decennial censuses; (4) surveys; and (5) surveillance. In addition, there are composite approaches which draw upon various combinations of these five to identify all deaths of women of reproductive age and then ascertain the maternal cases and circumstances. These are referred to collectively as Reproductive Age Mortality Studies (RAMOS).17,18 The five primary opportunities can be broadly grouped into routine or special sources. Generally speaking, routine opportunities yield a narrower range of information about maternal deaths than special studies but, with the exception of censuses, are continuously available and able to provide data for small geographical units. Moreover, as they form part of the wider information system, their use to measure maternal mortality involves minimal extra costs. The drawbacks, however, relate primarily to availability, reliability, completeness and coverage. Special studies, on the other hand, require more of the resources flagged in Table 2, but have the potential to produce detailed additional information on the circumstances of deaths. Their drawbacks relate primarily to margins of uncertainty due to both sampling and non sampling errors, timeliness and predictability.

Figure 1 also shows that for some data-capture opportunities, such as surveys, there are a number of alternative methods or options that can be used within them to identify maternal deaths. For example, surveys provide an opportunity to apply methods which seek deaths reported in the household or among sisters, or deaths reported through respondents using sampling at service sites (SSS),19 such as antenatal care. Additional file 1 acts as a reference resource, providing details on the characteristics of each option for measuring maternal mortality, as well as their strengths and limitations, and further supporting references.20 There are also a number of web-based resources which provide

Table 1. Principal definitions and measures of maternal mortality

<table>
<thead>
<tr>
<th>Definition</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy-related death</td>
<td>The death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death. This is a time-of-death definition.</td>
</tr>
<tr>
<td>Maternal death</td>
<td>The death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes. This definition requires cause-of-death information in order to exclude incidental causes.</td>
</tr>
<tr>
<td>Maternal mortality ratio (MMR):</td>
<td>Number of maternal deaths during a given time period per 100,000 live births during the same time period.</td>
</tr>
<tr>
<td>Maternal mortality rate:</td>
<td>Number of maternal deaths in a given time period per 100,000 women of reproductive age, or woman-years of risk exposure, in the same time period.</td>
</tr>
<tr>
<td>Lifetime risk of maternal death:</td>
<td>The probability of maternal death across a woman's reproductive life, usually expressed in terms of odds.</td>
</tr>
<tr>
<td>Proportion of maternal deaths among female deaths (PMDF):</td>
<td>Maternal deaths as a proportion of all female deaths of reproductive age, usually defined as 15-49, in a given time period.</td>
</tr>
</tbody>
</table>

Table 2. Two key issues to clarify prior to measuring maternal mortality

<table>
<thead>
<tr>
<th>Why is the estimate needed?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>To generate a broad estimate of the magnitude of the problem</td>
<td></td>
</tr>
<tr>
<td>To identify detailed causes, differentials and determinants</td>
<td></td>
</tr>
<tr>
<td>To identify differences in levels within a country</td>
<td></td>
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<tr>
<td>To permit cross-country comparisons</td>
<td></td>
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<tr>
<td>To enable regular monitoring of progress</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>What resources are available?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Existing data sources or data-collection opportunities, for example routine civil registration, large multi-purpose surveys</td>
<td></td>
</tr>
<tr>
<td>Human resources, for example technical skills to design a survey, or to manage, analyse and interpret data</td>
<td></td>
</tr>
<tr>
<td>Field budget, for example funds available for new data collection</td>
<td></td>
</tr>
<tr>
<td>Time available, for example estimate needed immediately, in 1-2 years time, or longer</td>
<td></td>
</tr>
</tbody>
</table>

Methods

Laying-out the opportunities and options

We focus in this paper primarily on measuring the magnitude and trends in maternal mortality at national and major sub-national levels; Table 1 defines the key terms and indicators we use. We do not address approaches whose main purpose is to identify or improve interventions to prevent maternal deaths, such as quality of care audits or confidential enquiries.11 Similarly, we do not discuss the various approaches and indicators which may act as proxy measures of maternal mortality, but which also provide essential information for monitoring programs, such as the UN process indicators12 and Unmet Obstetric Need;13 these are reviewed in several recent papers.14-16 Opportunities for measuring maternal mortality, as for other mortality outcomes, can be categorized according to cost, complexity, time involved, desired precision of the estimates or comparability over time. The intended utility of the estimates affects the required scope and accuracy of the information required, and the availability of resources affects the suitability of different options. In this paper we focus on a practical, non-specialist perspective to understanding the alternatives. Table 2 shows the two overriding questions that must be asked from the outset, and which lead to further practical considerations. The final choice of options to

poor countries.8 While none of these is ideal compared with the gold standard of complete death registration, they do enable many countries to begin to establish the magnitude of the problem within their own borders. This article aims to raise awareness of the alternatives among all who commission and act upon information on maternal mortality. We summarize the main opportunities and options for generating empirical estimates, describe their evolution and evaluation, and propose optimal measurement strategies for different country contexts. It is timely to emphasize these opportunities for a number of reasons, and not just because one of the two indicators for MDG-5 is maternal mortality. First, to further help empower countries to measure maternal mortality and “own” their national estimates. Second, to challenge the prevailing view of measurement stagnation:9 that maternal mortality is too difficult or too expensive to measure. Third, to respond to the heightened need for health outcome data owing to results-based financing of maternity services in developing countries.10

Table 1. Principal definitions and measures of maternal mortality
additional details on specific options, now including a site dedicated to maternal mortality measurement.21

Two other useful differences between opportunities for data capture are, firstly, whether deaths are identified actively or passively and, secondly, whether the starting point is all deaths, reproductive-aged female deaths, pregnancy-related deaths or maternal deaths (see Table 1 for definitions). Active identification enumerates cases in the population through direct interviews in the context of a census, survey or surveillance. Passive approaches, such as civil registration or health facility statistics, rely on deaths already captured by an existing system but go on to extract the maternal or pregnancy-related fraction. As a composite approach, RAMOS involves both active and passive identification of deaths. The distinction between active and passive is important in terms of completeness of reporting, with the latter more prone to omission of deaths and to bias because certain population subgroups are underrepresented.

The techniques for differentiating maternal from non-maternal deaths fall broadly into those with involvement from health professionals (medical certification or health facility data) versus those based on lay reports. With the involvement of health professionals the key distinction is between the presence or absence of diagnostic procedures, such as post-mortem, operative or laboratory results. With lay reports, maternal deaths are identified through time-of-death questions (yielding pregnancy-related mortality) or a verbal autopsy. The latter is a structured interview and/or narrative account administered to caregivers or family members of the deceased to identify signs and symptoms and thus determine probable cause(s) of death.

Alongside empirical measurement, there are three main analytical approaches which have been developed specifically for maternal mortality (Figure 1). Birth and Death Record Linkage identifies maternal deaths by using existing records of births (including stillbirths if available) and deaths obtained from routine civil registration or demographic surveillance. Records of births and reproductive-age female deaths are compared, and those which can be linked are deemed to be pregnancy-related deaths. Capture-recapture22 or Dual (records) Methods use statistical methods to correct for underreporting from two sources of maternal deaths.23 Finally, statistical models have been used to estimate levels of maternal mortality for countries without any reliable national-level empirical data. United Nations24 models use statistical regression and the proportion of maternal deaths among deaths of women of reproductive age to derive estimates of maternal mortality.

Evolution and evaluation of opportunities and options
The five main empirical opportunities and related options for measuring maternal mortality (Figure 1) have evolved over last 20 years in response to the demand generated initially by the Safe Motherhood Initiative and sustained by the advent of MDG-5. In developing countries, heightened interest in data on maternal mortality began in the mid-1980s with a series of special studies, as discussed in a report by the WHO.25 These revealed the serious underreporting in routine statistics and gave early insights into the challenges of capturing maternal deaths, particularly where the vast majority occurs without contact with the health system. Since then, considerably more experience has accumulated on these challenges and the published literature has been very explicit about them;26,27 some would argue overly so.9
The principal challenges are two-fold: first, to obtain sufficient or reliable detail, in official records or relatives’ reports, to differentiate maternal from non-maternal causes; and, second, due to the comparative rarity of the event on a population basis, extremely large samples or complete enumeration are required to produce stable estimates. However, while facing similar difficulties to all-cause and cause-specific adult mortality, the maternal sub-group also has some positive features which make ascertainment easier and likely to be more complete. In most settings, pregnancy is a memorable event, and death related to pregnancy among otherwise healthy young women even more so. These deaths also cluster around the time of labor and delivery and in the following 24 hours, in other words at a time when the woman’s pregnancy status is well recalled by reporting relatives.28

Paying increased attention to the challenges of measuring maternal mortality has yielded benefits, both to the issue of maternal death itself and to the methods and empirical data available. For example, since national estimates for maternal mortality were first released in 1996 by WHO and UNICEF,24 the proportion of countries lacking usable data, and so dependent on modelled figures, has declined from almost half in 1990 to just over one-third in 2005.29 This growth in alternative measurement opportunities and options highlights the important contribution made by the Demographic and Health Surveys as a major platform for applying the Direct Sisterhood Method.30

The different options for estimating maternal mortality have different strengths and weaknesses. There is unfortunately no standard metric for valuing the advantages and disadvantages of measurement options. Rather comparisons need to be made based on broad categories and propensities for certain qualities. Inevitably, there are trade-offs to be made, for example between practical considerations, such as cost, time and statistical capacity, and scientific criteria of precision, reliability, comparability and validity. Many of the resource issues stem from the large sample sizes or complete enumeration needed, mentioned earlier, and this places practical and scientific considerations in direct competition. Moreover, the decision about size is not solely a statistical matter, but also influenced by the purpose of the resulting estimates, and hence the degree of certainty needed. There have been few publications on the comparative costs and benefits of different measurement opportunities and options. Generally speaking, routine and continuous systems, such as civil registration or demographic surveillance, are more cost-effective than special studies but require long-term commitment and attention to quality. Censuses are major undertakings, both in terms of human and financial resources, but the marginal cost of adding questions on maternal mortality is small.31

From a scientific perspective, the validity and reliability of measurement options are of primary concern. There is, however, a conundrum with evaluating any new method for maternal mortality for use in low-income countries: the lack of existing estimates from a gold-standard source, namely, complete and accurate death registration. As a consequence, many so-called validation studies are, strictly speaking, comparative assessments of two or more alternatives, ideally applied to the same geographical area, population and time period. For example, recent work in Bangladesh compared pregnancy-related deaths in the household with deaths among sisters, and found extremely similar estimates of maternal mortality but with wide confidence intervals.8 There are very few comprehensive appraisals of the magnitude of bias and uncertainty for the main opportunities and options for measuring maternal mortality. This gap needs to be addressed as a research and development priority, linking-up with similar efforts for other outcomes. One appraisal, of the Direct Sisterhood Method used by the DHS,32 found relative errors in the maternal mortality estimates averaging at 15% across 14 countries. Another form of appraisal has been published for the census as a means of measuring maternal mortality.33 Although there are no sampling errors in such complete enumerations, non-sampling errors resulted in the need to upwardly adjust the numbers of adult female deaths, maternal deaths and, indeed, births in all but one of the five countries included in the assessment. In terms of health facility statistics, these will always be biased where some maternal deaths still occur in the community, but the direction of the error in estimates is hard to assess and quantify. For example, where facilities have a disproportionate fraction of high-risk deliveries, then the estimate may be much higher than that for the population as a whole and, conversely, where many deaths do not reach care, the facility figure will be an underestimate of the true population level. Moreover, this bias is often further aggravated by the omission of maternal deaths occurring on non-obstetric wards.

All opportunities and options for measuring maternal mortality in fact face the same two sources of error: identifying adult female deaths and/or determining whether such deaths are maternal or pregnancy-related. There are several demographic techniques for assessing and adjusting identification of adult female deaths, although they cannot be used with sample surveys. Distinguishing whether deaths are pregnancy-related on the basis of time of death is widely regarded as valid in comparison with medical certification of death,34 although differentiating specific sub-causes of maternal death is more problematic. The recently developed standardized verbal autopsy tool developed by WHO represents a significant advance but will itself require validation.34 Recent work with a computer-based algorithm35 for assigning deaths from verbal autopsies which was applied in Burkina Faso showed that the Direct Sisterhood Method questions on time-of-death relative to pregnancy status differed by less than 10% from symptom-based questions in detecting pregnancy-related deaths.

Country strategies for measuring maternal mortality
In this final section of the paper, we turn to the need for measurement strategies to generate estimates of levels and trends in maternal mortality, suited to specific contexts or developmental phases of a country. The phases are defined primarily on the basis of the status of the civil registration system and cause of death ascertainment, with complete and accurate coverage regarded as the optimum in the fourth and final phase. Even at this state of development, it is still relevant for other complementary measurement opportunities and options to be used, since no single approach can adequately meet all of the needs for information on maternal mortality.

There is considerable overlap in strategies between phases. We emphasize the importance of taking advantage of add-on opportunities provided via the decennial census and large multi-purpose surveys, since the incremental costs of obtaining data on maternal mortality from these sources is marginal. However, these are not very timely; usually every decade for the census and every 4-5 years for large multi-purpose surveys, and often delayed in their implementation as well as the analysis
and release of findings. For the four given states of the civil registration system, other measurement opportunities are proposed on the basis of the likely resources available and the completeness and accuracy of health facility statistics. A practical guide on how to select between the different options for measuring maternal mortality and for the specific phases is now available as a web-based resource.21

There are two further key requirements in developing countries for any measurement strategy to yield the reliable, timely and comparable data on maternal mortality required by decision-makers. First, the data must be processed, analysed, interpreted and communicated. This analysis should include estimation of uncertainty surrounding the maternal mortality indicators, as well as the use of various adjustment techniques to correct for under- or over-reporting of deaths or births. More developmental work is needed to refine some of these techniques, and to help reconcile and understand variation in estimates from different sources. Secondly, all measurement strategies depend on the skills and capacity of personnel in-country to undertake competently all stages from design through to communication, sometimes with external technical support. There is an urgent need to strengthen this skills base for all aspects of health information systems in developing countries.36

Conclusions
There is currently an unprecedented expressed need and demand for estimates of maternal mortality in developing countries. This has been stimulated in part by the creation of an MDG that will be judged partly on the basis of reductions in maternal mortality by 2015. The proposed shift towards results-based financing of maternal, neonatal and child health programs by donors is now adding further incentives to improve data on this and other outcome indicators.37 There are significant challenges to meeting these needs and demands which we would be foolish to ignore. Many of these are, however, very similar to the issues faced and, to a degree, overcome by other specific health problems, such as HIV/AIDS. The limitations of civil registration and routine health information systems in many countries are serious, but only by making maximum use of the data which are adequate and by investing in a continuous process of improvement will these be realized as the optimal sources.38 Universal counting of maternal deaths should be the goal.39 This aspiration does not, however, mean an indefinite wait for high quality data on maternal mortality.

Since the launch of the Safe Motherhood Initiative in 1987, new opportunities for data capture have arisen and new methods have been developed, tested and used. No approach, however, can be perfect, and there is certainly still much room for improvement, especially assessing the magnitude and direction of biases and their implications for different data uses. Some of the innovations in measuring maternal mortality provide efficient mechanisms for gathering the requisite primary data at a reasonably low cost. No method, however, has zero costs. Investment is needed in measurement strategies for maternal mortality suited to the needs and resources of a country, and which also strengthen technical capacity to generate and use credible estimates. Ownership of information is necessary for it to be acted upon: what you count is what you do.39 Difficulties with measurement must not be allowed to discourage efforts to reduce maternal mortality. Countries must be encouraged and enabled to count maternal deaths and act.

References
The LifePulse is pressure-limited and time cycled with adjustable PIP and rate. Inspiratory time (I-time) is kept as short as possible (0.02 sec.). Exhalation is passive. The LifePulse delivers small tidal volumes (VT) at rapid rates via a special ET tube adapter with built-in jet nozzle. Connecting this adapter to a patient’s endotracheal or tracheotomy tube enables tandem use of CMV. Gas flow is feedback-controlled by matching monitored PIP with set PIP. Monitored servo-controlled driving pressure (Servo Pressure) is used to detect changes in lung compliance and resistance and mishaps such as accidental extubation, pneumothorax, bronchospasm, etc.

**Ventilation Controls**

Pressure amplitude (PIP-PEEP) produces VT and controls PaCO₂. VT = 1 mL/kg body mass is about half the size of anatomic dead space. The LifePulse high velocity inspirations penetrate through the dead space instead of pushing the resident deadspace gas ahead of fresh gas as we do when we breathe normally. Exhaled gas cycles out in a counter-current helical flow pattern around the gas jetting in, which facilitates mucociliary clearance in the airways. PIP may be set as high as that used during CMV. However, because inspirations are so fast and brief, PIP falls quickly as HFV breaths penetrate down the airways, and peak alveolar pressure is much lower than peak airway pressure.

The LifePulse uses passive exhalation. Thus, airway pressure at end-exhalation, PEEP, is constant throughout the lungs, as long as rate is set slow enough to avoid gas trapping. Rate is usually set 10 times faster than CMV rates, in proportion to patient size and lung time constants (lung compliance x airway resistance). Keeping I-time constant at its shortest value (0.02 sec.) allows exhalation time (E-time) to be proportionally longer at lower LifePulse rates, which aids in the treatment of larger patients and infants with restricted or obstructed airways.

At 240 bpm (4 Hz) for example, I:E = 1:12. Smaller patients may be treated at rates up to 660 bpm (11 Hz) where I:E = 1:3.5. Lowering rate may require raising PIP to maintain PaCO₂, because LifePulse VT is independent of rate. But, LifePulse VTs are still ~10 times smaller than CMV VTs because of the 0.02 sec. I-time.

**Oxygenation Controls:**

CMV settings control oxygenation. CMV at 2-5 bpm facilitates alveolar recruitment with its larger VTs. PEEP is the primary determinant of mean airway pressure (MAP) and lung volume. Optimal PEEP may be found using CMV breaths and pulse oximetry. MAP on CMV prior to starting the LifePulse is reproduced at start-up by raising PEEP 1-2 cm H₂O initially. Patients are then stabilized with CMV = 5 bpm and FIO₂ adjusted to produce appropriate SaO₂. CMV is then switched to CPAP mode, and PEEP is increased until SaO₂ is restabilized. Thus, CMV breaths are only used intermittently.

This approach produces an HFV version of “lung protective ventilation,” where alveoli are opened, kept open with appropriate PEEP (usually in the range of 8 - 10 cm H₂O), and ventilated as gently as possible. Gas for the patient’s spontaneous breathing is provided by the CMV in CPAP mode.

**Gas Trapping Considerations:**

Gas trapping occurs when tidal volumes have insufficient time to exit the lungs. Thus, larger CMV tidal volumes represent a greater threat of gas trapping compared to much smaller HFV breaths. CMV rate should therefore be reduced before HFV rate whenever there are indications of gas trapping, such as hyperinflation on chest x-ray or when the LifePulse monitored PEEP exceeds CMV set PEEP. If hyperinflation persists once the CMV is in CPAP mode, decrease the LifePulse rate in 60 bpm increments to improve the I:E ratio and lengthen the exhalation time.

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This paper was provided by Bunnell.
Tidal volumes necessary to produce adequate ventilation at high rates are very small, and lung compliance is often poor in very low birth weight infants, so gas trapping is unlikely to occur with the LifePulse. However, the maximum rate of 660 bpm is rarely used even in preemies weighing less than 1000 grams. Most LifePulse users limit rate to 540 bpm (9 Hz) where I:E = 1:4.5. The minimum I-time of 0.02 sec. usually works best for all patients at all rates.

**Applications**

While some clinicians use the LifePulse for premature infants with uncomplicated RDS, it is most often used to rescue infants and children with lung injury. PIE is the most common indication for the LifePulse, because it automatically improves ventilation/perfusion matching and facilitates healing by reducing mechanical ventilation of the most affected areas of the injured lungs.

PIE is characterized by inflamed airways with high airway resistance that creates gas trapping, pulmonary overdistension, and alveolar disruption when other forms of mechanical ventilation are used. Since high airway resistance deters high velocity inspirations, resolution of PIE is much more likely using the LifePulse.

Other airleaks, meconium aspiration and other pneumonias (especially those accompanied by excessive secretions), congenital diaphragmatic hernia, and PPHN are other common applications of the LifePulse in NICUs, while trauma and severe pneumonia are typical applications in PICUs. Some institutions also use the LifePulse during and after pediatric cardiac surgery (eg, Fontan procedure), especially when complicated by respiratory failure.

A pilot study using the LifePulse was recently initiated for “evolving” chronic lung disease in prematurely born infants at 1 to 3 weeks of age. Strategy for these patients is low LifePulse rate (240 bpm), no CMV breaths, and moderate PEEP (~8 cm H₂O). [Note: PEEP is needed to keep airways as well as alveoli open. Reducing PEEP to lessen gas trapping may make matters worse by allowing small airways to collapse during exhalation.] Previous randomized controlled trials support use of the LifePulse for uncomplicated RDS, RDS complicated by PIE, and PPHN.

**Complications**

Hyperventilation with the LifePulse is associated with increased incidence of cystic periventricular leukomalacia in premature infants with RDS. A single center study revealed such increased adverse effects when the LifePulse was used with low PEEP (5 cm H₂O) where hyperventilation and inadequate oxygenation occurred during the first 24 hours of life. (Inadequate PEEP leads to using higher PIP to generate more MAP, which causes hyperventilation.)

**Servo Pressure**

Servo Pressure auto-regulates gas flow to the patient to keep monitored PIP = set PIP. The following examples are typical of what automatically set upper and lower Servo Pressure alarms indicate.

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- Accumulating secretions at the end of the ET tube (ie, patient needs suctioning)
- Tension pneumothorax
- Right mainstem intubation

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- ICD-9 00.12 may trigger contractual payment mechanisms

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\textsuperscript{a} HCPCS, Healthcare Common Procedure Coding System. 
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