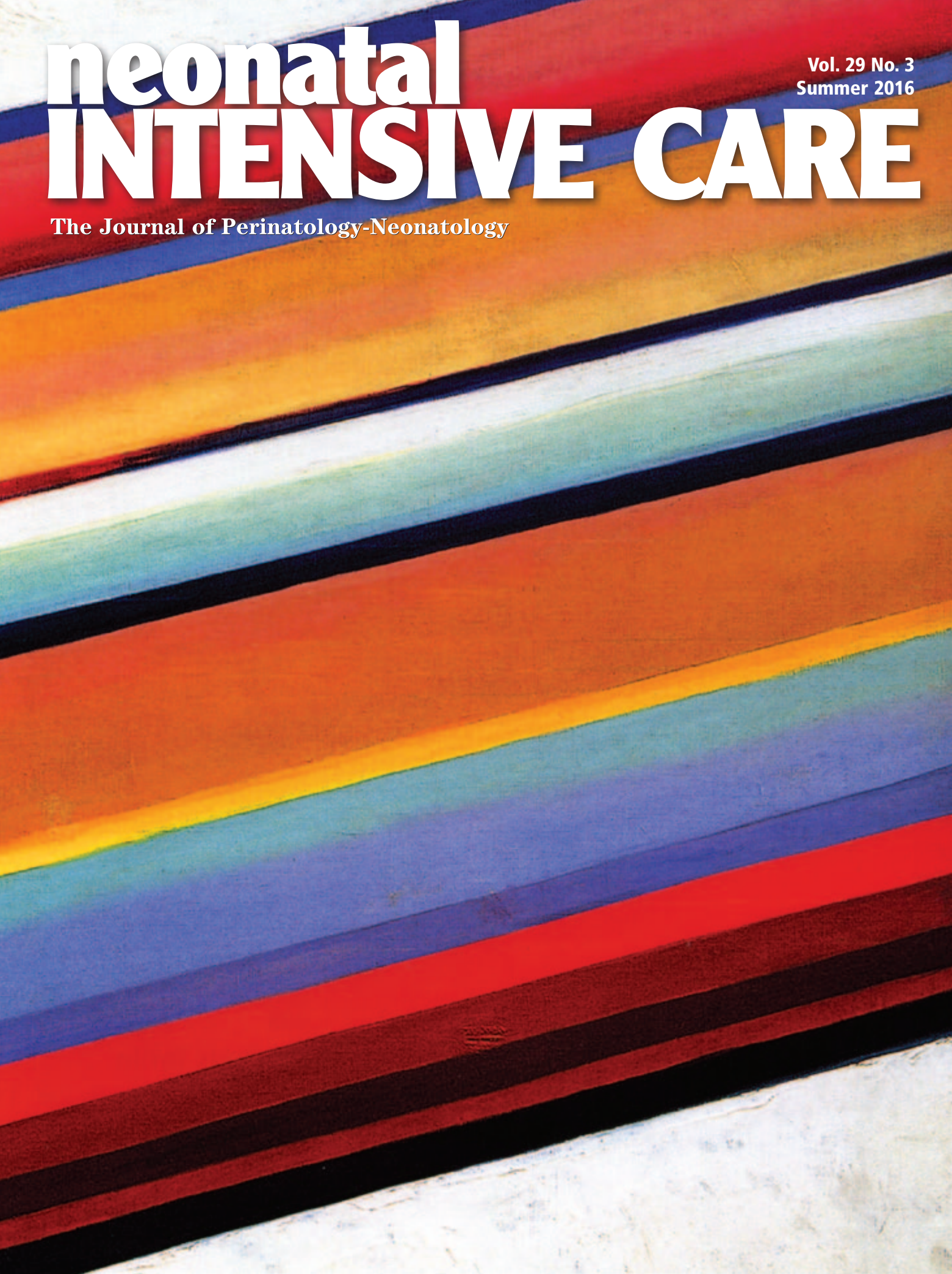
Vol. 29 No. 3
Summer 2016

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology



Advanced care for newborns with critical or special care needs

Stanford Children's Health

Lucile Packard Children's Hospital Stanford

Our neonatology team has a strong tradition of providing innovative, high-quality care for newborns, from world-leading research and advanced simulated training to expert treatments and follow-up care. We care for the smallest and sickest newborns, many of whom need complex therapies, in our 40-bed Level IV NICU. One of 14 academic nurseries participating in NICHD, our success is driven by our team's dedication to providing nurturing care, advancing scientific knowledge and training the next generation of neonatologists.

Stanford | MEDICINE

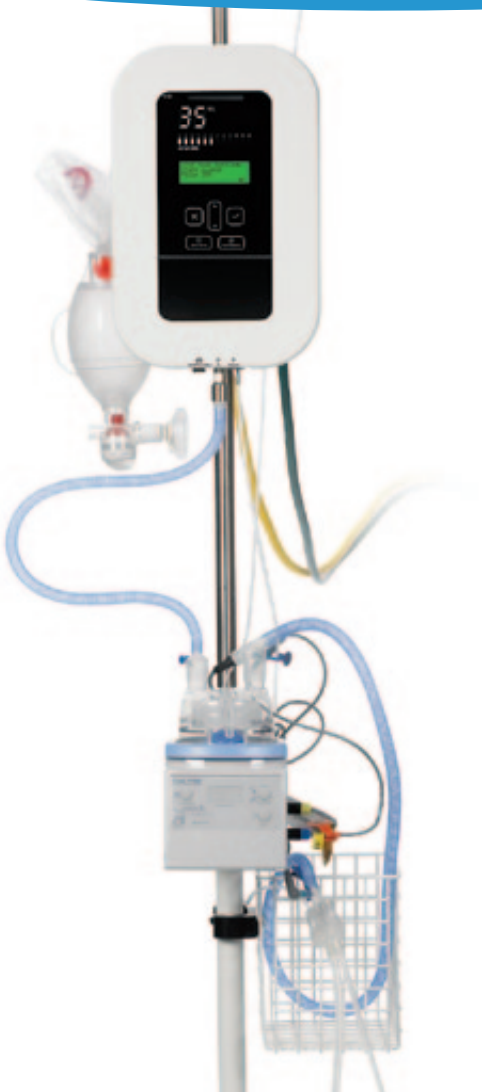
Learn more at neonatology.stanfordchildrens.org

NeoPAP® infant respiratory support system

Simple design
Easy to use
Effective delivery

NeoPAP's innovative design is literally a breeze...

- CPAP, high flow and resuscitation modes are built into one easy to use device, improving workflow efficiency and reducing costs.
- Baby-Trak® leak compensation and sophisticated alarms give you peace of mind and the ability to focus on the specialized needs of your RDS patients.
- The unique bonnet and patient-friendly interface support developmental care and may help reduce costly skin damage.



See what NeoPAP can do for your NICU...
Learn more at www.circadiance.com
or contact us at info@circadiance.com

Circadiance® Pediatric Care

888-825-9640 www.circadiance.com

101463 REV 1

neonatal INTENSIVE CARE

Vol. 29 No. 3
Summer 2016

Table of Contents

DEPARTMENTS

ARTICLES

Editorial Advisory Board

Human milk makes all the difference

The American Academy of Pediatrics' (AAP) policy recommends the use of human milk for all preterm infants, whether mother's own milk (MOM) or pasteurized donor human milk when mother's own milk is unavailable.[1]

Only Prolacta Bioscience, the leader in the science of human milk, provides:

- A full line of human milk-based nutrition for premature infants
- Human milk products that undergo the most rigorous testing and screening in the industry

1. American Academy of Pediatrics. Breastfeeding and the Use of Human Milk. Section on Breastfeeding. [originally published online February 27, 2012]. Pediatrics. DOI: 10.1542/peds.2011-3552

PremieLact™ Prolact HM™
Standardized Donor Milk Products

Prolact CR™
Human Milk Caloric Fortifier

Prolact+H²MF®
Human Milk-Based Human Milk Fortifier Products

Prolact RTF™
Human Milk-Based Premature Infant Formula

To provide your preterm patient with a 100% human milk-based diet, call:
1-888-PROLACT (1-888-776-5228)
www.prolacta.com

Prolacta® BIOSCIENCE
Advancing the Science of Human Milk

News

☐ Summer 2016

One Device Better Than Two

Masimo announced that its SET Measure-through Motion and Low Perfusion pulse oximetry has now been integrated into ACUTRONIC Medical System AG's fabian HFO Neonatal Critical Care Ventilator for improved patient outcomes. The fabian HFO, the world's first dedicated Neonatal Ventilator to offer Masimo SET pulse oximetry, provides continuous display of newborn oxygenation status. Instead of using two separate devices to collect ventilation and oxygenation patient data, clinicians now simply attach the pulse oximetry sensor via USB interface to the fabian HFO to display oxygenation, perfusion index and pulse rate values on the ventilator's color touchscreen. This combined technology platform is expected to optimize patient assessments and improve workflow, allowing clinicians to spend more valuable time tending to patients. Masimo said its SET pulse oximetry has been shown to virtually eliminate false alarms and increase a clinician's ability to detect life-threatening events, helping to substantially contribute to improved patient outcomes and patient safety. The clinical accuracy of Masimo SET pulse oximetry has also been shown to help clinicians significantly reduce retinopathy of prematurity (ROP), screen for critical congenital heart disease in newborns, reduce oxygen overdose and medical errors, and save lives in post-surgical floors, recovery, labor and delivery rooms, and ICUs.

Birth Tool Found in a Dream

A tool to help babies stuck in the birth canal is earning rave reviews from the World Health Organization. Jorge Odón, an Argentine car mechanic, came up with the idea from a dream after watching a YouTube video about extracting a lost cork from a wine bottle. Odón built his first prototype in his kitchen, using a glass jar for a womb, his daughter's doll for the trapped baby, and a fabric bag and sleeve sewn by his wife as his lifesaving device. A US medical technology company has just licensed it for production. With the Odón Device, an attendant slips a plastic bag inside a lubricated plastic sleeve around the head, inflates it to grip the head and pulls the bag until the baby emerges. Doctors say it has enormous potential to save babies in poor countries, and perhaps to reduce cesarean section births in rich ones. About 10 percent of the 137 million births worldwide each year have potentially serious complications. About 5.6 million babies are stillborn or die quickly, and about 260,000 women die in childbirth. Obstructed labor, which can occur when a baby's head is too large or an exhausted mother's contractions stop, is a major factor. The current options in those cases are forceps — large, rounded pliers — or suction cups attached to the baby's scalp. In untrained hands, either can cause hemorrhages, crush the baby's head or twist its spine. Although more testing is planned on the Odón Device, doctors said it appeared to be safe for midwives with minimal training to use. Along the way, it has won research grants from the United States Agency for International Development and from Grand Challenges Canada. The device will be manufactured by Becton, Dickinson and Company, or BD, of Franklin Lakes, NJ, which is better known for making syringes. The WHO will now oversee tests on 100 more women in normal labor in China, India and South Africa, and then on 170 women in obstructed labor. Information is from an article that appeared in the New York Times. Copyright The New York Times.

Saintly Donation

Marques Colston is noted for creating noise with his amazing catches across the middle of the football field, but the New Orleans Saints wide receiver is quietly helping New Orleans neonates hang on to something more important than a football—their lives. Colston donated about $100,000 to Children's Hospital to fund the purchase of a NeoRay Digital Imaging System for the hospital's Neonatal Intensive Care Unit. The highly portable X-ray system is specially designed for use with newborns. It may be easily moved from incubator to incubator and allows for a drastic reduction in radiation exposure; a critical need in the early days of life. Children's Hospital is a 247-bed, not-for-profit regional medical center offering pediatric care to children from birth to 21 years. Children's Hospital recorded 200,834 patient

neonatal INTENSIVE CARE

ISSN 1062-2454
Published five times each year by

Goldstein and Associates, Inc.

10940 Wilshire Blvd., Suite 600
Los Angeles CA 90024
Phone: 310-443-4109
Fax: 310-443-4110
E-mail: s.gold4@verizon.net
Web: www.nicmag.ca

Publisher/Editor in Chief
Steve Goldstein

Managing Editor
Christopher Hiscox

Senior Editor
Vincent Terrier

News Editor
Chris Campbell

Associate Editor
Jordana Hammeke, Susan Goldstein

Circulation, Coverage, Advertising Rates: Complete details regarding circulation, coverage, advertising rates, space sizes, and similar information are available to prospective advertisers. Closing date is 45 days preceding date of issue.

Change of Address: Notices should be sent promptly to Circulation Department. Provide old mailing label as well as new address; include zip code or postal code. Allow two months for change.

Editorial Contributions may be sent by e-mail and will be handled with reasonable care: however, publishers assume no responsibility for safety of art work, photographs, or manuscripts. Every precaution is taken to ensure accuracy, but the publishers cannot accept responsibility for the correctness or accuracy of information supplied herein or for any opinion expressed. Editorial closing date is the first day of the month preceding month of issue.

In term and near-term neonates with hypoxic respiratory failure (HRF)...

When do you stop the cascade?

Early intervention with INOMAX® (nitric oxide) for inhalation upon confirmation of pulmonary hypertension may help:

- Avoid higher levels of supplemental oxygen
- Improve oxygenation[1]
- Potentially prevent the progression of HRF[2]

Learn more at www.inomax.com

Indication

INOMAX® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems.

Important Safety Information

- INOMAX is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.
- Abrupt discontinuation of INOMAX may lead to increasing pulmonary artery pressure and worsening oxygenation even in neonates with no apparent response to nitric oxide for inhalation.
- Methemoglobinemia and NO_2 levels are dose dependent. Nitric oxide donor compounds may have an additive effect with INOMAX on the risk of developing methemoglobinemia. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.
- In patients with pre-existing left ventricular dysfunction, INOMAX may increase pulmonary capillary wedge pressure leading to pulmonary edema.
- Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOMAX administration.
- Use only with an INOmax DS_{IR}®, INOmax® DS, or INOvent® operated by trained personnel.

Please see Brief Summary of Prescribing Information on adjacent page.

References: 1. INOMAX [package insert]. Hampton, NJ: Ikaria, Inc.; 2013. **2.** González A, Fabres J, D'Apremont I, et al. Randomized controlled trial of early compared with delayed use of inhaled nitric oxide in newborns with a moderate respiratory failure and pulmonary hypertension. *J Perinatol*. 2010;30(6):420-424.

Mallinckrodt Pharmaceuticals

INOmax® (nitric oxide) FOR INHALATION

Stop the cascade

INOMAX® (nitric oxide) for inhalation
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Treatment of Hypoxic Respiratory Failure
INOMAX® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

The safety and effectiveness of INOMAX have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies.

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOMAX administration.

CONTRAINDICATIONS
INOMAX is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

WARNINGS AND PRECAUTIONS

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation
Wean from INOMAX. Abrupt discontinuation of INOMAX may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOMAX therapy immediately.

Hypoxemia from Methemoglobinemia
Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOMAX; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOMAX to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOMAX, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide
Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues. If the concentration of NO_2 in the breathing circuit exceeds 0.5 ppm, decrease the dose of INOMAX.

If there is an unexpected change in NO_2 concentration, when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of INOMAX and/or FiO_2 should be adjusted as appropriate.

Heart Failure
Patients with left ventricular dysfunction treated with INOMAX may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOMAX while providing symptomatic care.

ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOMAX doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOMAX, a result adequate to exclude INOMAX mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOMAX and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOMAX and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOMAX than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

OVERDOSAGE
Overdosage with INOMAX will be manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOMAX.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

DRUG INTERACTIONS
No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. INOMAX has been administered with dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Although there are no study data to evaluate the possibility, nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOMAX on the risk of developing methemoglobinemia. An association between prilocaine and an increased risk of methemoglobinemia, particularly in infants, has specifically been described in a literature case report. This risk is present whether the drugs are administered as oral, parenteral, or topical formulations.

visits in 2012, with children coming from all 64 parishes in Louisiana, 37 states and 6 foreign countries. In all, 60,557 children received care from the hospital in 2012.

Costs Vary in NY Hospitals

Just how expensive is your hospital? In New York, the answer may lie in a trove of hospital cost data newly posted online by the State Health Department. As part of an effort to make health care pricing more transparent, the state is naming hospitals and listing their median charges and costs for 1,400 conditions and procedures from 2009 to 2011. In 2011, prices ranged from the $8 bill at Benedictine Hospital in Kingston, NY, for treating a case of gastritis (cost: $2), to a $2.8 million charge for a blood disorder case at University Hospital of Brooklyn that cost it $918,462. Hospital trade groups, who opposed the release of the database, say the figures will only confuse consumers, who rarely pay the sticker price for hospital care, especially if they have insurance. The hospitals also argue that cost figures, though based on reports to the government by the hospitals themselves, cannot be reliably compared because the state did not edit them for deaths, transfers and aberrations. Among the most common hospital admissions each year are cases of childbirth and the routine medical care of healthy newborns. There, too, the database shows extreme and unpredictable variations in cost, markups and charges. AO Fox again seems like a bargain, the rare hospital that charged less, on average, for its 140 vaginal deliveries with minor severity than its reported median cost—$1,998 versus $2,603. At Westchester Medical Center in Valhalla, on the other hand, 183 deliveries coded the same way cost $6,692 and were charged at $22,413, among the most expensive such cases in the state. Maimonides Medical Center in Brooklyn spent $1,675 per case of newborn care and charged $5,400, while at Montefiore Medical Center in the Bronx, the cost was $2,586 and the price $10,950. Information is from an article that appeared in the New York Times. Copyright The New York Times.

Study Goes Nuts

Pregnant women who eat more peanuts and tree nuts during pregnancy might be less likely to bear nut-allergic children, a new study suggests. Pregnant women who eat more peanuts and tree nuts during pregnancy might be less likely to bear nut-allergic children, a new study suggests. The research, published in the journal JAMA Pediatrics, supports the current consensus among medical professionals that delaying the introduction of nuts, milk, fish, shellfish, eggs and other highly allergenic foods in young children doesn't prevent the development of food allergies, said Michael C. Young, associate clinical professor of pediatrics at Harvard Medical School, and a senior author of the study. The findings inversely link a pregnant mother's consumption of peanuts or tree nuts with the onset of nut allergies in her child. The more nuts the mother ate while pregnant, or within a year before or after pregnancy, the lower the risk that the child would go on to develop nut allergies, Dr Young said. The study doesn't demonstrate a causal relationship between a pregnant mother's diet and the onset of nut allergies in her offspring, he said. The researchers stopped short of advising pregnant women to eat more nuts. Further, interventional studies—in which researchers would separate participating pregnant women into groups and prescribe their diets, rather than simply track their consumption—are required before they can make such a recommendation. Researchers analyzed data from 8,205 children born between Jan 1, 1990 and Dec 31, 1994 to mothers who had reported their diets at or around the time of pregnancy. Of the children they tracked, 140 had developed a peanut or tree nut allergy by 2009. All self-reported cases of physician-diagnosed nut allergies were reviewed independently by two pediatricians, according to the study. The prevalence of childhood peanut allergy in the US has become an "epidemic" in recent years, Dr Young said. The rate of 1.4% in 2010 is more than triple the rate of 0.4% in 1997, according to the study. Information is from an article that appeared in the Connect by Lindsay Gellman. Copyright Connect.

Home Births Linked to Complications

The small but rapidly increasing number of women who choose to give birth at home may want to consider new research indicating that home births are linked to increased neonatal complications, including seizures. Researchers from Oregon Health & Science University and University of California at San Francisco, which studied babies born in 2008, found that home birth nearly doubled the risk for Apgar scores of four or lower on a 10-point scale; seven is considered normal. The scores evaluate newborns based on appearance, pulse, grimace, activity and respiration. Although educated and married white women over

age 35 were most likely to choose home birth, the researchers controlled for age, race, gestational age at birth, among other factors. The home birth mothers in the study were less likely than others to experience induced labor or an assisted delivery, and researchers found that home births attended by certified nurse-midwives yielded complication rates not much different from hospital births. Nurse-midwives presided over more than a quarter of these home births.

Reality of Resuscitation Times

A new study suggests many newborns are not being managed within resuscitation guidelines and that the recommended intervals may be too short. The study—through a team of researchers in Dublin, Ireland, including at the Department of Neonatology, National Maternity Hospital—said that most newborns in the study "were not managed within the time frame recommended in resuscitation guidelines. The recommended 30- and 60-second intervals may be too short." Researchers were looking to determine whether resuscitation teams were able to adhere to the recommended algorithm for newborn resuscitation. Video recordings were made of delivery room resuscitations of 194 high-risk neonates (gestational age 27-34 weeks; mean, 29 weeks) at 2 hospitals. Staff in these hospitals were trained to follow the NRP algorithms in the delivery room and were experienced in neonatal resuscitation. Interventions in newborn resuscitation, known as "initial steps," involve placing the newborn who requires assistance on a radiant warmer, then towel-drying or placing the newborn's body in a polyethylene bag; positioning the airway (and clearing the airway if needed); assessing the infant's respiratory effort and heart rate; and stimulating the infant to breathe, if necessary. These steps are intended to be accomplished by 30 seconds of age, and the clock starts ticking at the time of birth, not the time that the infant is placed on a radiant warmer. According to the study, called Timing of Interventions in the Delivery Room: Does Reality Compare With Neonatal Resuscitation Guidelines, "the median time taken to perform all tasks was greater than that recommended in the guidelines."

'Terms' of Endearment

Concerned by trends to induce labor or schedule cesarean deliveries earlier than 39 weeks gestation for a single fetus, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine has issued four new definitions of 'term' deliveries to clarify matters for women and doctors. The new definitions are based on the duration of pregnancy calculated from the first day of a woman's last menstrual period, a known date of conception, or an ultrasound measurement of the fetus during the first 13 weeks of pregnancy: early term, between 37 weeks, 0 days and 38 weeks, 6 days; full term, between 39 weeks, 0 days and 40 weeks, 6 days; late term, between 41 weeks, 0 days and 41 weeks, 6 days; post term, 42 weeks, 0 days and beyond. The college hopes this terminology change makes it clear to both patients and doctors that newborn outcomes are not uniform even after 37 weeks. The college advocates patience: observing mother and fetus weekly, and allowing nature to take its course when there is no reason to intervene. If it is important to schedule a C-section or to induce labor in an otherwise healthy pregnancy, "after 39 weeks is appropriate," the college said.

Risk of Infections Elevated

A study suggests increased infections could be created with longer duration PICC placement. According to study author Dr Aaron M Milstone of Johns Hopkins University, peripherally inserted central catheters (PICCs) are often used in the neonatal intensive care unit (NICU) to aid in the delivery of medications and nutrients to neonates. However, PICCs can also be the culprit of central line associated blood stream infections (CLABSIs). Dr Milstone said the multicenter, retrospective cohort study looked at the temporal relationship between PICC insertion and development of CLABSI. Through this analysis, researchers found an elevated risk of CLABSI when PICC placement went beyond 7 days as opposed to shorter durations. This increase in risk persisted for 2 weeks after placement, and then remained elevated, but stable for the duration of the PICC. While Gram-positive infections were the most common etiology of CLABSIs in PICCs, an increase in Gram-negative infections was noted when PICC duration exceeded 50 days. This study's multicenter design limited consistency in data collection and reporting across included institutions. This research suggests ongoing attention to necessity of PICCs, and to further quality improvement measures to decrease occurrence of CLABSIs. Given the noted incidence of CLABSIs with PICC dwelling time, the judicious placement and removal of PICCs could be warranted to prevent infections.

Later Not Necessarily Better

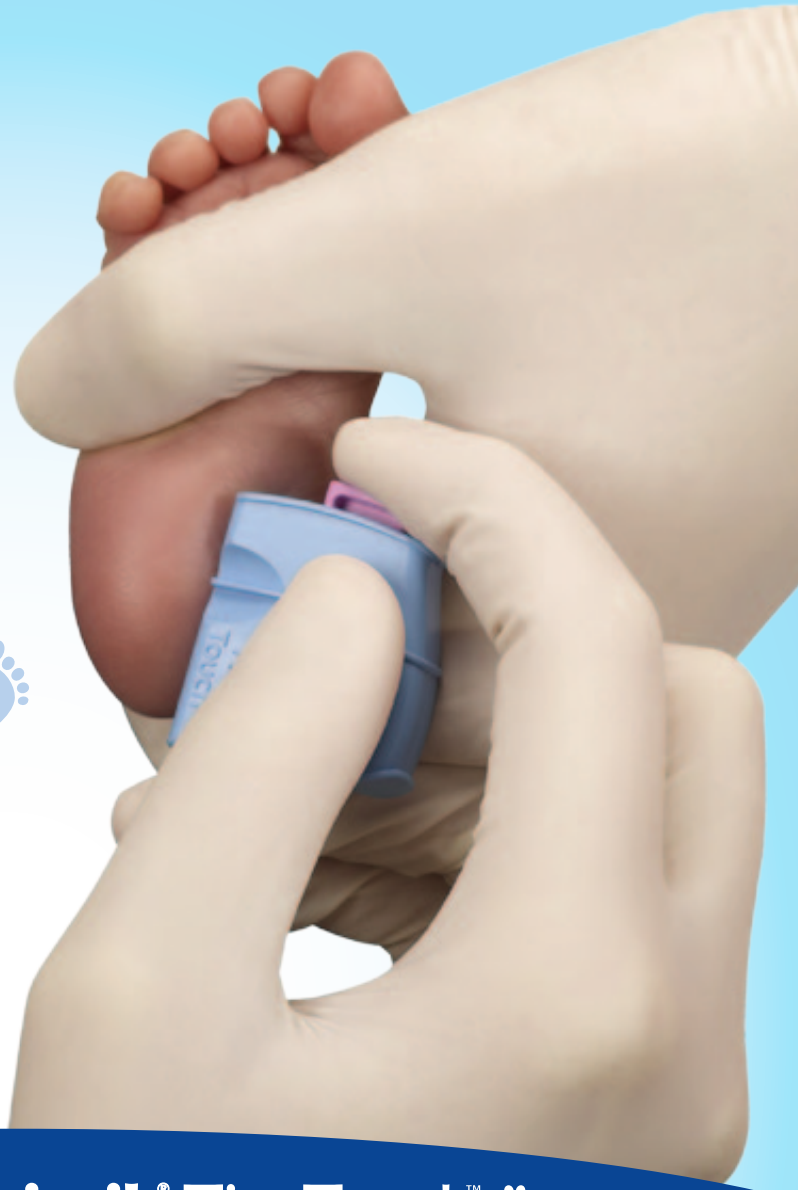
A study suggests that a shift in practice away from elective late preterm delivery to early term deliveries has shown little impact on neonatal outcomes such as intensive care length of stay, neonatal morbidity, or mortality in a population with major congenital heart disease. Researchers at Columbia University Medical Center and Morgan Stanley Children's Hospital, both in New York, sought to evaluate the effect of a change in delivery practice that was introduced following the 2009 publication of a study showing improved outcomes in infants delivered after 39 weeks. Medical records were reviewed for infants with critical congenital heart disease and compared outcomes in 878 infants born at a single tertiary center during 2004-2008 to outcomes in 124 infants born in 2010, after the change in practice had been implemented. There was a significant increase in the mean gestational age (37.8 weeks vs. 38.4 weeks, respectively; P less than .01) and in mean birth weight (2,975 grams vs 3,134 grams; P less than .01). However there were no significant differences between 2004-2008 and 2010 data in 5-minute APGAR scores (8.5 vs. 8.6; P = .11), median length of stay (14 days [1-197] vs. 16 days [1-144]; P = .18) and neonatal mortality (6% vs. 11%; P = .07), according to data presented at the International Society of Ultrasound in Obstetrics and Gynecology world congress. Information is from an article that appeared in the News Digital Network. Copyright News Digital Network.

Neonatal Webcam Gets Thumbs Up

Parents are praising a webcam system for letting them monitor their babies' progress at the Anya Marie Jackson Neonatal Intensive Care Unit at Aspirus Wausau Hospital. The webcam system, called NICVIEW, includes cameras in each room of the intensive care unit that can be positioned over each baby. Families are given secure, encrypted login information that they can pass along to friends and family members who can log in any time to monitor a baby's progress. There is no charge for the service. With this new system, parents, friends or family members can log in from a computer, a tablet or a smartphone and see the baby and what's happening inside the NICU. The NICVIEW system cost $51,990 and funding was made possible through the 2013 Aspirus Women's Golf Classic. Nearly 300 golfers, caddies and volunteers partnered with Aspirus and

Complete the request below to receive **FREE SAMPLES**

Discover A KINDER INCISION



Unistik TinyTouch

Leading National Brand

Introducing Unistik® TinyTouch™

Because Tiny Feet Deserve a Tiny Touch

Tiny feet can offer big challenges when it comes to neonatal capillary testing. Unistik TinyTouch is designed to deliver a precise and kinder incision during neonatal blood sampling, for happier babies and healthcare workers.

FREE SAMPLE REQUEST

YES! I'm interested in trying Unistik TinyTouch Heel Incision Device for free! To receive samples and literature please fax this sheet back to 770-977-2866, call 1-800-421-6936 or email samples@owenmumfordinc.com!

NAME:		
TITLE:		
FACILITY NAME:		
ADDRESS:		
CITY:	**STATE:**	**ZIP:**
PHONE:	**EMAIL:**	

Please allow 8-10 weeks for delivery of samples. While supplies last. No purchase necessary.

NICSPRING/OMI/0516/1/US

OWEN MUMFORD
Making a World of Difference

UnistikTinyTouch.com
1-800-421-6936

Unistik® TinyTouch™ is available in Preemie and Full Term sizes.

nearly 100 businesses and community members to help make the purchase possible.

Exercise Could Affect Babies' Brains

A study of expectant mothers and their newborns says physically active pregnant women increase the development of their unborn child's brain. Researchers at the University of Montreal in Canada recruited a group of local women who were in their first trimester of pregnancy. The women were randomized either to begin an exercise program, commencing in their second trimester, or to remain sedentary. The women in the exercise group were asked to work out for at least 20 minutes, three times a week, at a moderate intensity, equivalent to about a six or so on a scale of exertion from one to 10. Most of the women walked or jogged. Every month, for the remainder of each woman's pregnancy, she would visit the university's exercise lab, so researchers could monitor her fitness. All of the volunteers, including those in the non-exercise group, also maintained daily activity logs. After about six months and following the dictates of nature, the women gave birth. All had healthy boys or girls—which the scientists gently requested that the mothers almost immediately bring in for testing. Within 12 days of birth, in fact, each of the newborns accompanied his or her mother to the lab. There, each baby was fitted with an adorable little cap containing electrodes that monitor electrical activity in the brain, settled in his or her mother's lap, and soothed to sleep. Researchers then started a sound loop featuring a variety of low, soft sounds that recurred frequently, interspersed occasionally with more jarring, unfamiliar noises, while the baby's brain activity was recorded. The study found brainwave activity soared in response to the novel sounds among the children born to mothers who had remained sedentary during pregnancy. But it was noticeably blunted in the babies whose mothers had exercised. Information is from an article that appeared in the New York Times. Copyright The New York Times.

Drinking Study Upsets Group

A Danish study on the behavioral outcomes of children whose mothers consumed alcohol during pregnancy is being called potentially harmful by Fetal Alcohol Syndrome (FAS) experts because of the media coverage it has generated. "It's deeply concerning," said Dr Kenneth Lyons Jones, who is president of MotherToBaby, a service of the international non-profit Organization of Teratology Information Specialists, and professor of pediatrics at the University of California, San Diego. The research causing such concern among experts over misinterpretation is a series of studies out of the University of Copenhagen. "The take-home message of this study should in no way be to encourage drinking in pregnancy as a means to better mental health for children," Dr Jones said. Janni Niclasen, a psychologist, surveyed approximately 37,000 Danish women who reported on drinking habits during pregnancy. The study results showed that women who drank as much as one glass of wine per week had children with better emotional and behavioral outcomes by age seven compared to children of mothers who claimed to not drink at all. However, the author also points out that mothers who reported drinking tended to be more educated and have other potentially healthier characteristics overall. In addition, the author points out that the timing of the alcohol exposure during the surveyed pregnancies, which can play an important role in how the fetus is affected, was ignored. According to a statement from MotherToBaby, the study does not show that drinking caused mothers to have children with fewer behavioral concerns — rather that mothers who reported drinking were very different from mothers who did not in multiple ways. These differences in family and home environment, along with the way that alcohol exposure and child health were measured could easily mask any associations with low-level alcohol.

Helpful Bacteria Can Also Harm

Cells that allow helpful bacteria to safely colonize the intestines of newborn infants also suppress their immune systems to make them more vulnerable to infections, according to new research in Nature. The study could prompt a major shift in how medicine views the threat of neonatal infections and how researchers go about looking for new strategies to stop it, said scientists at Cincinnati Children's Hospital Medical Center who conducted the research. Leading up to this study, the prevailing view has been that newborn infants are susceptible to infection because their immune system cells are immature or underdeveloped. The study suggests this is caused by active immune suppression during this developmental period, as opposed to the immaturity of immune cells. The suppressive cells in this case are CD71+ precursors of mature red blood cells. The researchers found CD71+ precursor cells are enriched in newborn mice (and in human umbilical cord blood) to prevent an over reactive immune response as infants adapt to their new microbe-filled world. CD71+ cells express an enzyme called arginase-2 that is essential to suppress immune cells. Researchers said this process plays a vital role in infants' developing intestines by preventing an onslaught of inflammation in response to colonizing bacteria that help digestion and related functions. Researchers used a series of laboratory tests in human blood cells and mouse models to show temporary immune suppression in newborns extends beyond the intestines to also affect other parts of the body.

Breakthrough in Neonatal Diabetes

Researchers at University of Exeter Medical School in Britain say they have discovered two new genetic causes of neonatal diabetes, a rare disease that affects approximately 1 in 100,000 births. Neonatal diabetes is caused by a change in a gene which affects insulin production. This means that levels of blood glucose (sugar) in the body rises dangerously high. The team discovered that mutations in two specific genes which are important for development of the pancreas can cause the disease. The study focused on 147 young people with neonatal diabetes. Following a systematic screen, 110 patients received a genetic diagnosis. For the remaining 37 patients, mutations in genes important for human pancreatic development were screened. Mutations were found in 11 patients, four of which were in one of two genes not previously known to cause neonatal diabetes—NKX2-2 and MNX1. The genetic discovery is critical to the advancement of knowledge on how insulin-producing beta cells are formed in the pancreas. This could one day lead to a cure for neonatal diabetes, said the paper published in the journal Cell Metabolism.

Hospital Doesn't Drink Decaf

Caffeine has been shown to help reduce the risk of neurological (brain) damage in premature infants, help infants come off ventilators (breathing machines) sooner, as well as help infants who have stopped breathing (apnea), according to research from the Cone Health Women's Hospital in North Carolina. The team of pharmacists at Women's Hospital has researched and published a report providing the range of caffeine levels that are appropriate for each condition. It found different levels and forms of caffeine must be administered for each situation. This

research provides the neonatal care team with a base line to help individualize the caffeine dosage each infant needs to receive the optimal benefits. This is just one research study done in collaboration with the Neonatal Pharmacotherapy Education Program. The goal is to advance the neonatal care that premature infants and full-term infants who have experienced certain complications at birth receive at Women's Hospital. At Women's Hospital, the dosing of antibiotics is individualized from the first dose because several studies performed by the neonatal pharmacists and physicians at Women's Hospital showed that the dosing guidelines from dosing handbooks were not reliable at achieving blood levels needed for effective treatment, while also avoiding damage to the kidneys and ears. Instead, blood levels of the antibiotic are drawn twice after the first dose, and the pharmacists use special calculations to make sure the most effective and safe levels are achieved to help infants get better and home to their families as quickly as possible.

Distance From Hospital a Risk

Infants with hypoplastic left heart syndrome (HLHS) born far from a hospital providing neonatal cardiac surgery for the condition have increased neonatal mortality, with most deaths occurring before surgery, according to a new study. Researchers led by Texas Children's Hospital and Baylor College of Medicine (BCM), published online in the journal, Circulation, also concluded that efforts to improve prenatal diagnosis of HLHS and subsequent delivery near a large volume cardiac surgical center may significantly improve neonatal HLHS survival. HLHS occurs when the fetus's left side of the heart does not develop normally, and is present in approximately 1 in 6,000 live births.

Of the more than 3.4 million births during the study period, 463 infants with HLHS were assessed. Mothers delivering farther from a cardiac surgical center were less educated and more often lived in a poverty-stricken area. Additionally, 39 percent of newborns studied were prenatally diagnosed with HLHS and delivered significantly closer to a cardiac surgical center. Forty percent of newborns with HLHS died that were born more than 90 minutes from a cardiac surgical center, compared to 21 percent of those born within 10 minutes of a surgical center. The percentage of patients that died after the first surgery for HLHS was two to four times higher in low volume surgical centers than in the highest volume centers. Overall, in the latest years of the study, newborns with a prenatal diagnosis, born less than 10 minutes from a cardiac surgical center, and cared for at a large volume cardiac surgical center, had a neonatal mortality of 6 percent. For those born in the same era without a prenatal diagnosis, more than10 miles from a cardiac surgical center, and cared for at a low volume cardiac surgical center, 28-day mortality was 29 percent.

Plan Set for Infant Mortality

The health department of India has developed a plan to reduce infant mortality in the country by implementing certain clinical guidelines and quality standards that are expected to change the manner in which neonatal care is practised in major hospitals. The department teamed with Access International, a not-for-profit organization that works with governments and provides research and training inputs to improve health care service delivery and processes. Four working groups, including pediatricians, neonatologists, obstetricians, and infection-control

experts from major tertiary care hospitals in the country, have been working on the basic premise—based on a study by the Indian Academy of Pediatrics (IAP)—that the major causes of infant deaths in the area of Kerala were prematurity (34.6 percent), congenital anomalies (28 percent), sepsis (9.3 percent), and birth asphyxia (8 percent). The IAP study had reported that 75 percent of the infant deaths occurred during the neonatal period, and that of the total neonatal deaths, 59 percent of the deaths occurred during the first week of life. The groups have now formulated 13 quality statements relating to antenatal, intra-partum and neonatal interventions, the practice of which is expected to make a significant dent in neonatal mortality. The majority of deliveries in the area continue to take place in the private sector, and any quality improvement program aimed at bringing down the IMR would have to include the private sector, the IAP has pointed out.

Hospital Adds Cooling in Transport

Texas Children's Hospital is now the only pediatric hospital in Texas to offer active and regulated whole body cooling for infants who are oxygen-deprived at birth during ambulance transport to the hospital's level IV neonatal intensive care unit (NICU). Previously, oxygen-deprived infants would be passively cooled prior to and during transport, where all heat sources were turned off, meaning many infants would be under-cooled or overcooled. Whole body cooling treatments are administered within six hours of birth, last for 72 hours and bring a baby's temperature down to 33.5 degrees Celsius (92.3 Fahrenheit) to allow brain cells that would have otherwise died or been severely damaged, to survive. Texas Children's Newborn Center, together with the hospital's new Pavilion for Women, houses the nation's largest NICU and is one of only two hospitals in the greater Houston area to offer whole body cooling treatments and the only pediatric hospital in Texas to offer safe and regulated active whole body cooling during ambulance transport using specialized cooling equipment.

Computer Hears Babies Cry

Researchers at Brown University and Women and Infants Hospital in Providence have devised a computer program to help analyze a baby's cries. They hope to soon make it available to researchers world-wide looking to analyze crying patterns that can't always be detected by the human ear. The computer program breaks down cries into 12.5-millisecond frames and measures the pitch and volume, among other parameters. In total, it can evaluate 80 different parameters, which could help detect risk for conditions affecting a newborn baby's health. Because a cry is controlled by cranial nerves, it can be a window into the brain. While researchers haven't reached the stage where they can link cry characteristics with specific conditions, they've found that, on a group level, an infant's nervous system and therefore cry can be affected by prenatal exposure to alcohol, birth injuries, and even related to later diagnoses of autism. Researchers aren't at the stage where cries can pinpoint specific illness, although that is the ultimate goal. Today, a baby's cry can be tapped for information on pain and the nervous system. Information is from an article that appeared in the Wall Street Journal. Copyright the Wall Street Journal.

Wrong Route Error in the NICU: Protecting Patients and Practitioners

Kim Flanagan, MSN, CRNP

Introduction

Most nurses do not envision their career ending in a horrific incident involving the harm or death of one of their patients. In fact, most of us live in fear over whether that day could ever come asking "What if that happened to me?"

It is the challenging work of the clinician to provide excellent care for their patients while minimizing risk and potential harm, particularly during hospitalization. While the patient and their families are the obvious victims in these situations, there is also another victim: the clinician. In high acuity settings, such as the NICU, these errors pose an even greater threat to the vulnerable neonatal patient and caregiver. Though many excellent strategies have been implemented to mitigate the risk of these errors, they still occur in alarming numbers. This article will review these strategies and look at the next layer of interventions to protect our patients, families and care providers from the devastating consequences of wrong route errors.

Medication errors

Medical errors occur in the United States every day, according to the Institute of Medicine's 1999 report "To ERR is Human," it is estimated that anywhere from 44,000 to 98,000 people die in hospitals every year as a result of preventable medical mistakes costing 17 to 29 billion dollars annually.[1] Many of these errors are from medication errors: according the FDA over 30,000 medication errors have been reported since 1992 but, since these reports are not mandated, the actual estimate is thought to be much higher.[2]

Nursing practice includes medication management as governed by the 7 "Rights": right medicine, right dose, right time, right patient and right route, right reason and right documentation.[3] A medication error usually occurs when there is a breach in one of these rights.[4] A wrong route error, also known as medical misconnection, is when a "seemingly apparent incompatible system that, when inadvertently connected, can result in life threatening events in the clinical arena."[5] An example of a wrong route error is when a nurse unintentionally places an enteral feed into an IV catheter. While not as prevalent in the literature, tubing misconnections are suspected of being underreported and when they do occur, they tend to impose grave consequences. As of 2009, "nine cases of tubing misconnections have been reported to the Joint Commission Sentinel Event Database. These events resulted in 8 deaths and 1 permanent loss of function," including two infants.[6]

Second Victim Syndrome

Most errors occur from intelligent well-meaning clinicians involved in "complex clinical conditions, poorly designed processes and inadequate communication patterns."[7]

Clearly the victim in these situations is the patient and their families. However, due to the severe emotional, personal and professional anguish suffered by the healthcare provider it is evident that the "second victim" is the clinician. Dr Albert Wu first identified second victim syndrome in 2000.[8] According to one literature review, the prevalence of second victim syndrome varied in prevalence from 10.4 to up to 43.3%.[9]

Over the past 15 years, support for the healthcare professional dealing with the consequences of these situations has improved greatly. Hospitals are no longer hiding from these mistakes, but instead encouraging reporting and education thanks to government and regulatory agencies like the A.S.P.E.N, the FDA and ISMP.[10] Some institutions now have support systems in place to help caregivers get help to heal from the shame and suffering of having to live with the harm they have unintentionally caused. Patients and clinicians benefit from the honest, open discussion and root cause analysis done to prevent mistakes from being repeated.

Much time and effort has also been put into mitigating the risk of these types of errors from a variety of regulatory agencies such as Joint Commission, Vermont Oxford Network, Institute for Safe Medication Practices, and the World Health Organization.[11] Interventions such as tracking, bar coding, line reconciliation, computerized physician order entry, labeling changes and patient and provider education have made great strides in improving the situation. Despite these efforts, according to the WHO: "misconnections errors still occur with significant frequency with deadly consequences." More can be done to protect both our patients and our nurses, particularly in the Neonatal Intensive Care Unit.

Risk in the NICU

According to the NANN position statement on Medication Safety, medication administration is at increased risk for

Kim Flanagan, MSN, CRNP has worked as a NICU nurse and Neonatal Nurse Practitioner for 20 years. She currently serves as the Clinical NICU Specialist for Medela, Inc. In this role, she works with NICUs across the country to maximize their use of human milk in the neonatal population to improve patient outcomes, patient safety and best practices.

adversity related to three factors: "vulnerable nature of NICU patients, the complexity of the medications used, and the challenges of the NICU environment."[12] Examples of this include small size, non-verbal status, weight and physical immaturity.[13,14] Not only are these patients at greater risk for experiencing a medication error but, because of their fragile condition, they are more likely to have a worse outcome as a result.[15] The high acuity setting with its low lighting and array of tubing leaves a fatigued and over worked nurse at greater risk for harming a patient. An example of the risk associated with the NICU population is the Luer-lock or Luer-slip fit syringes which are able to fit into both IV connectors and enteral tubing. In addition feeding and medications are often infused on similar (if not the same) syringe pumps. Similar to the adult world, efforts have been made to allay these risks. Yet the incidence of medication errors are reported to be as high as 57% and occur eight times as often than in the adult population.[16] Clearly, additional interventions are needed to improve patient safety.

Design change as protection for Infant and Nurse

One of the earliest medical misconnections documented in the literature was from 1972 when milk was inadvertently administered thru an IV.[17] In 1996 the Joint Commission created a Sentinel Event Policy to assist healthcare facilities in taking steps to improve safety.[18] That same year, the Association for the Advancement of Medical Instrumentation (AAMI) implemented a standard to make enteral connectors incompatible with IV Luer-lock connectors. However, because it was a voluntary step, manufacturers never developed the alternative designs and once they did they were not mandated thus were never universally adopted.[19] Ten years later in 2006, Sentinel Event Issue 36 was released. In it, the Joint Commission acknowledged the risks which could lead to patient safety issues, such as look-alike multi-purpose tubing, which continued to be a problem despite best efforts.[20] The Joint Commission has urged manufactures to implement design change for products that make them unique to their function. An example of this would be enteral feeding tubes and syringes that can no longer be used for anything other than enteral feeding by nature of their design. This is called force function. Enteral feeding equipment will be the first of many product design changes that will finally be brought into the market. More importantly, the same design will be shared by multiple manufactures with the goal of national standardization. As a result, hospitals will receive many benefits such as not having to change tubes when patients are transported and form institution to institution. Future areas planned for change include: connectors for flow of gases, limb cuffs, urological access, neuraxial access.[21]

But as we know from history, voluntary adoption of these products may lead to limited use. Finally, one state has no longer made this a voluntary option. In July 2016 the adoption of the force function design for enteral feeding, called ENFit, will become a legal requirement for all hospitals in the state of California. Thus putting into effect what A.S.P.E.N and the Joint Commission has long recommended: the physical inability for a nurse to connect enteral feeding into intravenous line (or any connection other than enteral) regardless of how busy she is or how complex the clinical environment. The effort to create a product design that allows a physical impediment to prevent a medical misconnection has been in the works for over 10 years. Researchers agree that human factors are the most frequent cause contributing to medical errors.[22] Having products and equipment that have force function inherent in their design only brings us closer to our common goal: a culture of safety.

Conclusion

Medical mistakes happen with frightening frequency in the United States. In the NICU our patients and clinicians are at even higher risk of an adverse event. Many of our medical institutions, government and regulatory agencies have worked very hard and continue to discuss and implement strategies to decrease the risk factor that contribute to these devastating outcomes. Patient safety is a complex, multidisciplinary effort with no "one fix" solution. We have come a long way in making improvements in the area of medication safety. But we are now at the next stage when manufacturers are contributing solutions to decrease these horrific events. As hard and costly as change can be, we as care providers and administrators are now ethically obligated to utilize this next layer of protection from misconnection errors, not only for our patients, but also for the people on the front lines of patient care who treat them every day.

References

1 Institute of Medicine. (1999). To err is human: Building a safer health system (L.T. Kohn, J. M. Corrigan, & M. S. Donaldson, Eds.). Washington, DC: The National Academies Press.

2 http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143553.htm

3 Smeulers, M., Verweij, L., Maaskant, J. M., de Boer, M., Krediet, C. T. P., Nieveen van Dijkum, E. J. M., & Vermeulen, H. (2015). Quality Indicators for Safe Medication Preparation and Administration: A Systematic Review. PLoS ONE, 10(4), e0122695. http://doi.org/10.1371/journal.pone.0122695

4 Wakefield DS, Wakefield BJ, Borders T, Uden-Holman T, Blegen M, Vaughn T. Understanding and comparing differences in reported medication administration error rates. AmJMedQual. 1999; 14(2):73–80. PMID: 10337117

5 The Joint Commission: Tubing misconnections—A persistent and potentially deadly occurrence, Sentinel Event Alert, Issue 36, Apr. 3, 2006.

6 Guenter, P.A., et al.:Enteral Feeding Misconnections: A Consortium Position Statement. The Joint Commission Journal on Quality and Patient Safety 34: 285-92, May 2008.

7 Kumar S. Fatal Care: Survive in the U.S. Health System. Minneapolis, MN: IGI Press; 2008. ISBN: 9780977712113. Wu AW. Medical error: the second victim. The doctor who makes the mistake needs help too. BMJ. 2000;320:726-727

8 Wu AW. Medical error: the second victim. The doctor who makes the mistake needs help too. BMJ. 2000;320:726-727

9 Seys D, Wu AW, Van Gerven E, Vleugels A, Euwema M, Panella M, Scott SD, Conway J, Sermeus W, Vanhaecht K. Eval. Healthcare professionals as second victims after adverse events: a systematic review.Health Prof. 2013 Jun; 36(2):135-62. Epub 2012 Sep 12.

10 Stavroudis TA1, Shore AD, Morlock L, Hicks RW, Bundy D, Miller MR.NICUmedication errors: identifying a risk profile for medication errors in the neonatal intensive care unit. J Perinatol. 2010 Jul;30(7):459-68. doi: 10.1038/jp.2009.186. Epub 2009 Dec 31

11 http://www.who.int/patientsafety/solutions/patientsafety/PS-Solution7.pdf

12 National Association of Neonatal Nurses. Medication Safety in the Neonatal Intensive Care Unit: Position Statement #3060. NANN Board of Directors. June 2014.

13 Kozer E, Scolnik D, Keays T, Shi K, Luk T, Koren G. Large errors in the dosing of medications for children. N Engl J Med 2002; 346: 1175
14 Gray JE, Goldmann DA. Medication errors in the neonatal intensive care unit: special patients, unique issues. Arch Dis Child Fetal Neonatal Ed 2004; 89: 472–473.
15 Sharek, P. J., Horbar, J. D., Mason, W., Bisarya, H., Thurm, C., Suresh, G.,Classen, D. (2006). Adverse events in the neonatal intensive care unit:Development, testing, and findings of a NICU-focused trigger tool to identify harm in North American NICUs. Pediatrics, 118(4), 1332–1340
16 Kugelman, A., Inbar-Sanado, E., Shinwell, E. S., Makhoul, I. R., Leshem, M.,Zangen, S., Bader, D. (2008). Iatrogenesis in neonatal intensive careunits: Observational and interventional, prospective, multicenter study. Pediatrics, 122(3), 550–555.
17 Guenter, P.A., et al.:Enteral Feeding Misconnections: A Consortium PositionStatement. He Joint Commission Journal on Quality and Patient Safety 34: 285-92, May 2008.
18 http://www.jointcommission.org/Sentinel_Event_Policy_and_Procedures
19 American National Standards Institute (ANSI)/Association for the Advancement of Medical Instrumentation (AAMI): Enteral Feeding Set Adapters and Connectors. Arlington, VA: ANSI/AAMI, 1996.
20 http://www.jointcommission.org/SentinelEvents/SentinelEventAlert/sea_36.htm
21 https://www.ismp.org/newsletters/acutecare/articles/20100715.asp
22 Stavroudis, T. A., Miller, M. R., & Lehmann, C. U. (2008). Medication errors in neonates. Clinics in Perinatology, 35(1), 141–161.

Nutrition Guidelines for an Exclusive Human Milk Diet

Andi Markell RD, LD

The Nutrition Advisory Committee (NAC) comprises five neonatal dietitians from around the U.S. who have experience using an "Exclusive Human Milk Diet" (EHMD). The NAC, which is sponsored by Prolacta Bioscience, was created to provide clinical expertise, research, insights, and guidance on premature infant nutrition. They also serve as a resource to fellow clinicians for education and support around the growing use of an EHMD for extremely premature infants with a commitment to sharing ideas and evidence-based practices.

An EHMD is a diet composed of all human milk; the base of the feed is mom's own milk, banked human milk or both. The fortification is a human milk based human milk fortifier, and, if needed, a modular made of human milk. There is a strong body of research linking an EHMD with a decrease in necrotizing entercolitis. Through the practice of using an EHMD, we are now realizing even more potential benefits from such a diet.

The "Nutritional Advisory Committee NICU Enteral Guidelines for the use of an Exclusive Human Milk Diet for Babies ≤1250g" was one of the first ways the committee wanted to share best practices with other clinicians. The goal was to create a resource that anyone could benefit from, whether they had experience using an exclusive human milk diet or just beginning the process of implementing one. This guideline has a foundation of well-known references in combination with the unique input from the NAC members — a compilation of best-practices from six dietitians in six NICUs. The end result is a guideline with tangible information to help in the daily nutritional management of premature infants in the NICU.

2016 NICU Enteral Guideline
Exclusive Human Milk Diet (EHMD) for ≤ 1250 g babies

Calorie/Protein Goals	• 110-130 kcal/kg, 3.5-4.5 g/kg of protein[1] • Calories and protein should be based on nutritional assessment
Initiation of Feeds	• Initiate feeds on day of birth or as soon as possible[1,2] • Use Mom's own Milk (MOM) or Banked Breast Milk (BBM)[3]
Advancement of Feeds	• Feeding Protocol recommended[1,2] • 10-35 mL/kg advancement[1]
Initiation of Fortification	• Initiate fortification before 100 mL/kg[1] Prolact+4 H²MF® for lower volume fortification - Example 40-60 mL/kg Prolact+6 H²MF® for higher volume fortification - Example 80-100 mL/kg • Avoid fortification and advancement on the same day • Wait to make changes in fortification until tolerance shown
Fortification Goals	• Fortification goals to meet protein and caloric goals ≥ 170 mL/kg: MOM/BBM with Prolact+4 H²MF® ≥ 145 mL/kg: MOM/BBM with Prolact+6 H²MF® ≥ 125 mL/kg: MOM/BBM with Prolact+8 H²MF® < 125 mL/kg: MOM/BBM with Prolact+10 H²MF® • Further increase in concentration may be needed to meet growth goals • Do not add non-human milk-based modulars to EHMD • Prolact CR® Prolact CR® can be mixed as 4 mL Prolact CR with 96 mL of MOM/BBM
Vitamins & Iron	• 1 mL MVI without Fe • Fe 2-3 mg/kg[1] • Consider splitting dose twice a day for tolerance
Growth Goals	• Weight: 15-20 g/kg[4] • Length: ≤ 0.9 cm/wk[4] • OFC: ≤ 0.9 cm/wk[4]
Transition off EHMD	• Consider using an EHMD until 34 weeks post menstrual age Consider transition off Prolact+ H²MF® over three days Example of Feeding Transition: Day one: 6 of 8 feeds as Prolact+ H²MF® Day two: 4 of 8 feeds as Prolact+ H²MF® Day three: 2 of 8 feeds as Prolact+ H²MF® Day four: Transition complete

1. Koletzko B, Poindexter B, Uauy R, eds. In: Koletzko B, ed. Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. Basel, Switzerland: Karger; 2014. World Review of Nutrition and Dietetics. Vol 110.
2. Kleinman, Ronald E., and Frank R. Greer. "Pediatric Nutrition." AAP Books (2013).
3. Eidelman, Arthur I., et al. "Breastfeeding and the use of human milk." Pediatrics 129.3 (2012): e827-e841.
4. Groh-Wargo, Sharon, Melody Thompson, and Janice Hovasi Cox. Academy of Nutrition and Dietetics Pocket Guide to Neonatal Nutrition. Second Edition Pediatric Nutrition Dietetic Practice Group, 2016.

Andi Markell is a neonatal dietitian who has worked in a level 4 NICU in Portland Oregon for the last 15 years. As the first dietitian in her NICU, much of her time has been committed to developing policies and protocols. She has used an exclusive human milk diet since 2008 and has published their positive outcomes. She is a founding member of the Nutrition Advisory Committee from Prolacta Bioscience. This guideline is intended to provide a guideline for healthcare providers in the use of an Exclusive Human Milk Diet in infants ≤1250 g birth weight. The information within is the collective opinion of the Nutrition Advisory Committee, a committee sponsored by Prolacta Bioscience. As with all feeding guidelines, appropriate medical judgement should be exercised. Be sure to review your clinical experience and outcomes around the management of nutrition in very low-birth-weight infants.

Value of Capnography in Infants

Greg Spratt BS RRT CPFT

Capnography can be a cost-effective way to monitor real-time carbon dioxide (CO_2) levels and trends in intubated and non-intubated infants and neonates. Recent innovations in capnography sampling and measurement are directed at ease of use and accuracy. Capnography provides the continuous measurement of partial pressure of carbon dioxide in the breath during inhalation and exhalation and displays:

- The partial pressure of end-tidal carbon dioxide ($etCO_2$ or $PetCO_2$), the maximal concentration of CO_2 during exhalation
- Fraction of inspired CO_2 (F_iCO_2) which should generally be zero as inhaled air contains minute amounts of CO_2
- Capnogram (aka, capnograph, $etCO_2$ waveform) which is a graphic representation of the CO_2 waveform
- Respiratory rate derived from the waveform
- Trends of these readings

Capnography is the standard of care for continuously monitoring adequacy of ventilation for intubated patients during general anesthesia in the operating room,[1] and is recommended by the American Heart Association and American Association for Respiratory Care to confirm and monitor endotracheal tube (ETT) placement as well as monitoring for effective chest compressions and return of spontaneous circulation during CPR[2,3,4] In addition to its value in confirming proper ETT placement, capnography may also be useful for trending CO_2 levels during ventilator management.

With the advent of newer technology which allows for improved sampling in non-intubated patients including neonates, capnography is rapidly growing in use in many non-intubated applications where adequacy of ventilation may be compromised. These applications include use during procedural sedation, monitoring of patients on opioids or other respiratory depressants, and monitoring for respiratory compromise in patients both within and outside the hospital setting.[5]

Capnography is measured using two primary methods. Mainstream capnography measures CO_2 by placing a sensor chamber directly in the breathing circuit, attached at the ETT and provides a graph of the CO_2 concentration against volume. Sidestream capnography measures CO_2 by drawing a sample of the breath from the breathing circuit to the sensor within the monitor and plots a CO_2-time capnogram. Each offers advantages which are summarized in Table 1. Microstream technology[6] is an innovation of sidestream technology which uses a CO_2 -specific IR wavelength that is unaffected by the presence other gases (ie O_2, N_2O, He or inhaled anesthetics).[7] Other capnography technology requires correction for these gases or may report inaccurate results. Additionally, Microstream permits the use of a very low sample flow rate (50 ml/min), minimizing removal of tidal volume (Vt) which is important in neonates.

Mainstream	Sidestream
Advantages: 1. Some devices provide estimates of dead space (Vd/Vt) 2. No removal of air from Vt to sample for measurement	**Advantages:** 1. Less weight/obtrusion on the end of the ETT which may reduce the potential for kinking and migration/extubations[8] and improve patient comfort 2. No external exposure of expensive sensor to damage/ replacement 3. Easy to use with intubated and non-intubated applications

Capnography in Intubated Infants

In patients with normal ventilation to perfusion (V/Q) matching, the $etCO_2$ is generally 2-5 mmHg less than the arterial CO_2 (P_aCO_2). When V/Q mismatching occurs secondary to changes in dead space or perfusion, this gradient widens; however, McSwain et al found that the correlation of $etCO_2$ to P_aCO_2 remained strong at all ranges of increasing dead space.[9] McSwain states, "In patients with a $Vd/Vt \leq 0.40$ there was an excellent correlation ($p=0.95$) between $PetCO_2$ and $PaCO_2$. Though the strength of the association diminishes slightly as Vd/Vt increases, the correlation remains strong ($p=0.86$) even at Vd/Vt of 0.56-0.70, and moderately strong ($p=0.78$) at $Vd/Vt > 0.7$. Thus, $PetCO_2$ appears to be a useful indicator of $PaCO_2$, even in patients with substantial lung disease, provided that the expected increase in the $PetCO_2$-$PaCO_2$ difference is taken into consideration."

In a review of publications to explore the value of end-tidal carbon dioxide in ventilated neonates, Naidu found that all the studies in this review showed that a correlation exists between $etCO_2$ and $PaCO_2$.[10] However, this correlation was stronger in the groups with no underlying lung disease. Naidu concluded that while $etCO_2$ cannot replace ABGs, it can be used as a valuable trending tool understanding the impact of gradient.

Greg Spratt BS RRT CPFT is the Director of Clinical Marketing in Patient Monitoring Market Development at Medtronic. Correspondence can be sent to gregory.k.spratt@medtronic.com.

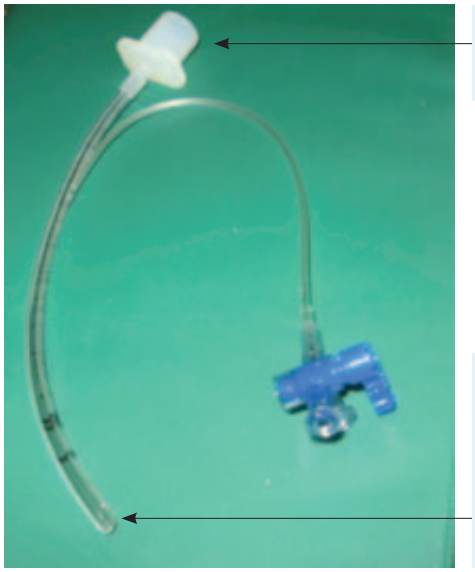


Figure 1. ETT with monitoring lumen[11] permitting sampling at the distal end of the ETT (at carina).

From a cost savings perspective, this can have a significant impact. In a retrospective review comparing the utilization of blood gases before and after the implementation of continuous capnography in a pediatric ICU, Rowan et al found the average number of blood gases per encounter decreased from 20.8 and 21.6 in the two years pre-implementation to 13.8 post intervention. The total charge savings over a 6-month period was $880,496.[8]

$etCO_2$ Sampling at the Carina

Kugelman et al explored an innovative method of sampling $etCO_2$ at the carina through the use of an endotracheal tube (ETT) with a monitoring lumen (Figures 1 and 2),[11] which may be less affected by the ventilator circuit flow and leaks around the uncuffed ETTs, thus improving the correlation with $PaCO_2$.[12,13] Kugelman states "Since 2008 and even before, we have used the double lumen ET tube and Microstream capnography monitoring as a routine in our unit. We continue to use it routinely for other studies and during routine care within the department and in the delivery room. I would say that in 80 to 90% of the infants we use Microstream capnography monitoring via the double lumen tube. We have good agreement between $etCO_2$ and $PaCO_2$ for most infants; $etCO_2$ is typically two to five millimeters of mercury lower than $PaCO_2$ for most babies. For infants where the gradient is higher, such as those with higher ventilation/perfusion mismatch, we get an idea of the agreement and as there may be fluctuations as the baby's condition changes, we still periodically check the blood gas to ensure the gradient is staying relatively consistent"

In their study of 27 infants which included analysis of 222 and 212 measurements of end-tidal CO_2 at the carina and ETT connector respectively, carinal end-tidal CO_2 had a better correlation with $PaCO_2$ and a better agreement with $PaCO_2$ than $etCO_2$ sampled at the ETT connector. In patients with significant lung disease (P_aO_2/P_AO_2 ratio < 0.3), the gradient between carinal $etCO_2$ and $PaCO_2$ increased, but the bias remained < 5 mm Hg. The average agreement with P_aCO_2 was –1.5mmHg.

More recently, Kugelman used this same sampling method in infants using high-frequency ventilation (HFV).[14] Sixteen

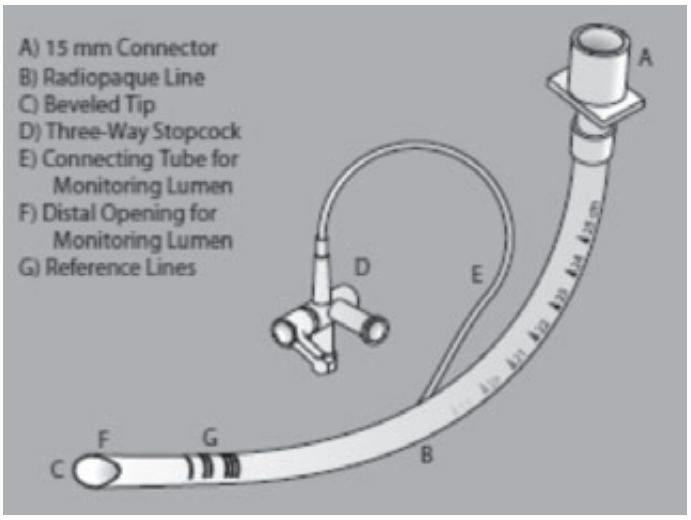


Figure 2. Detail on ETT with monitoring lumen[11]

premature infants with a median gestational age of 26.5 weeks were ventilated with HFV. Analysis included 195 measurements and the correlation of carinal $etCO_2$ with $PaCO_2$ ($r = 0.68$, $P < 0.0001$) and the agreement (bias ± precision: -2.0 ± 10.7 mmHg) were adequate. They concluded that continuous integrated $etCO_2$ measured at the carina is feasible in HFV, has adequate correlation and agreement with $PaCO_2$ and can be helpful for trends and alarm for unsafe levels of $PaCO_2$ in premature infants ventilated with HFV.

Capnography in Non-Intubated Infants

In a study of the performance of capnography in non-intubated infants by Coates et al, the correlation of sidestream CO_2 with ABG was excellent ($r^2 = 0.907$).[15] Results were not significantly altered when weight and respiratory rate were added as independent variables. Bland-Altman analysis revealed a bias of –2.7 with a precision of ±6.5 when comparing sidestream CO_2 to ABG.

In a retrospective study, Moses et al investigated the correlation and level of agreement between end-tidal carbon dioxide and venous CO_2 (P_vCO_2) in non-intubated children with moderate to severe respiratory distress.[16] $EtCO_2$ was correlated highly with P_vCO_2 in non-intubated pediatric patients with moderate to severe respiratory distress across respiratory illnesses. They concluded that although the level of agreement between the two methods precludes the overall replacement of blood gas evaluation, $etCO_2$ monitoring remains a useful, continuous, non-invasive measure in the management of non-intubated children with moderate to severe respiratory distress.

Summary

Capnography can play an important role in the management of both intubated and non-intubated infants in providing a continuous trend of CO_2. Sampling at the carina may play a role in improving the correlation of end-tidal and arterial CO_2. It is important for the clinician to clearly understand the benefits and limitations in the use of the technology, as well as factors that impact the gradient between end-tidal and arterial CO_2.

References

1 American Society of Anesthesiologists Policy Statements on Practice Parameters: Standards for Basic Anesthetic Monitoring http://www.asahq.org/~/media/sites/asahq/files/public/resources/standards-guidelines/standards-for-basic-

MICROSTREAM™ CAPNOGRAPHY MATTERS.

FROM NEONATE TO ADULT, YOUR PATIENTS COUNT ON YOU.

Microstream capnography monitoring helps you detect subtle, but clinically significant variations in your patient's breathing. This means if your patient shows signs of respiratory compromise, you can respond faster and provide earlier intervention.

- Intubated and non-intubated CO_2 continuous monitoring
- 50ml/min sample size for measurement of CO_2 partial pressure
- CO_2-specific algorithm for enhanced accuracy
- Ability to accurately detect up to 150bpm for CO_2 qualified respiration rate
- Smart alarm management technology

Visit our website to learn more about respiratory compromise:

www.covidien.com/rms/clinical-solutions/respiratory-compromise

Medtronic
Further, Together

anesthetic-monitoring.pdf Accessed April 12, 2016
2 Link MS, Berkow LC, Kudenchuk PJ, Halperin HR, Hess EP, Moitra VK, Neumar RW, O'Neil BJ, Paxton JH, Silvers SM, White RD, Yannopoulos D, Donnino MW. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015; 132(suppl 2):S444–S464
3 Walsh BK, Crotwell DN, Restrepo RD. Capnography/ Capnometry During Mechanical Ventilation: Respiratory Care 2011; 56(4):503-509.
4 de Caen AR, Berg MD, Chameides L, Gooden CK, Hickey RW, Scott HF, Sutton RM, Tijssen JA, Topjian A, van der Jagt E, Schexnayder SM, Samson RA. Part 12: Pediatric Advanced Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015; 132(suppl 2):S526–S542.
5 Restrepo RD, Nuccio P, Spratt G, Waugh J. Current applications of capnography in non-intubated patients. Expert Rev. Respir. Med. Early online, 1–11 (2014). http://www.ncbi.nlm.nih.gov/pubmed/25020234 Accessed April 12, 2016
6 Microstream Technology– Medtronic Website http://www.covidien.com/rms/brands/microstream Accessed April 12, 2016
7 Microstream Technology– Medtronic Website http://solutionscontent.covidien.com/uploads/11/11292-14PM0020_SS_MicrostreamTechnologyAdvantageFINAL020314-1392132899.pdf Accessed April 12, 2016
8 Rowan CM, Speicher RH, Hedlund T, Ahmeda SS, Swigonskid NL.Implementation of Continuous Capnography Is Associated With a Decreased Utilization of Blood Gases. J Clin Med Res. 2015;7(2):71-75
9 McSwain SD, Hame DS, Smith PB, et al. End-tidal and arterial carbon dioxide measurements correlate across all levels of physiologic dead space. Respir Care 2010;55(3):288-293
10 Naidu S. Is ETCO2 a predictor of PaCO2 in ventilated neonates on the Neonatal Intensive Care Unit? Working Papers in Health Sciences 1:1 ISSN 2051-6266 / 20120005 http://www.southampton.ac.uk/assets/centresresearch/documents/wphs/Is%20ETCO2%20a%20predictor%20of%20PaCO2%20in%20ventilated%20neonates%20on%20the%20Neonatal%20Intensive%20Care%20Unit.pdf. Accessed May 3, 2016.
11 Mallinckrodt Oral/Nasal Tracheal Tube - Cuffless w/ Monitoring Lumen - http://aemprod.covidien.com/covidien/products/intubation/mallinckrodt-oral-nasal-endotracheal-tube-cuffless-monitoring-lumen
12 Kugelman A. Capnography Use in the NICU. Neonatal Intensive Care 2015; 28 (4):21-23
13 Kugelman A, Zeiger-Aginsky D, Bader D, Shoris I, Riskin A. A Novel Method of Distal End-Tidal CO2 Capnography in Intubated Infants: Comparison With Arterial CO2 and With Proximal Mainstream End-Tidal CO2. Pediatrics 2008; 122:1219-1224
14 Kugelman A, Riskin A, Shoris I, Ronen M, Stein IS, Bader D. Continuous Integrated Distal Capnography in Infants Ventilated With High Frequency Ventilation. Pediatr Pulmonol. 2012; 47(9):876-83.
15 Coates BM, Chaize R, Goodman DM, Rozenfeld RA. Performance of capnometry in non-intubated infants in the pediatric intensive care unit. BMC Pediatrics 2014, 14:163 doi:10.1186/1471-2431-14-163
16 Moses JM1, Alexander JL, Agus MS. The correlation and level of agreement between end-tidal and blood gas pCO2 in children with respiratory distress: a retrospective analysis. BMC Pediatr. 2009 Mar 12;9:20. doi: 10.1186/1471-2431-9-20.

Can Weekly Antepartum Testing Decrease Near Term and Term Stillbirth?

M Terrani, MD, F Gonzales, MD, J Korman, MD, A Dillon, RDMS

Introduction

In industrialized countries, there is an expectation that every pregnancy will end with the birth of a healthy child. Yet, one fetus out of 200 is stillborn. Sudden fetal death syndrome, also known as stillbirth, continues to be an emotionally devastating outcome for both parents and caregivers. The global burden of stillbirth is estimated at 3.2 million fetal deaths every year worldwide. In the USA, the mortality rate from stillbirths is equal to that from prematurity and sudden infant deaths combined.[1] Fretts, et al [2] conducted a study to compare three strategies for the prevention of stillbirth in women aged 35 years and older, who were provided standard care; namely, no antepartum testing or induction before 41 weeks, weekly testing at 37 weeks with induction after a positive test, and no testing with induction at 41 weeks. This study showed that without a strategy of antepartum surveillance between 37 and 41 weeks, women over 35 years old will experience 5.2 unexplained stillbirths per 1000 pregnancies. Weekly antepartum testing initiated at 37 weeks would avert 3.9 stillbirths per 1000 pregnancies.[2,3] Since the majority of patients experiencing stillbirth are younger than 35 years of age, the purpose of this study was to assess if weekly antepartum testing can decrease stillbirth rate in all age groups as well.

Materials and methods

Our antepartum testing model (full biophysical profile weekly from 36 weeks on) started with a cohort of 6900 women over a 10-year period (2006-2016). Patients who experienced stillbirth prior to the onset of testing were excluded. Biweekly testing was used in high-risk patients using standard indications. A positive test served as an indication for delivery (induction of labor or cesarean section). Women with a negative test result remained undelivered until a subsequent positive test or the onset of labor. The control group consisted of 4420 patients for whom antepartum testing was performed using indications proposed by ACOG. The following parameters were analyzed: the stillbirth rate per 1,000 births and the total number of inductions needed to avert a single stillbirth. Stillborns with congenital anomalies and lethal chromosomal and genetic syndromes were excluded. A number of cesarean sections were not included because some were performed on maternal demand. Only deliveries, which took place after 36 full weeks, were included in both groups. All statistical computations were performed using DATA 4.0; Trec Age software, Williamstown, MA). All statistical tests were two-sided and a probability value of $<.05$ was considered statistically significant.

The authors are with the Garden Obstetrics and Gynecology, Garden City, New York.

Results

Without a strategy of weekly antepartum fetal surveillance between 36 and 41 weeks, women of all age groups experienced 1.6 stillbirths per 1000 pregnancies. For women undergoing weekly testing, the stillbirth rate was 0.9 per 1000.

Obstetrical statistics related to weekly antepartum testing is reflected on Tables 1 and 2.

Table 1. Effect of unexplained stillbirth risk on outcomes of weekly antepartum testing initiated at 36th week of gestation

Fetal deaths per 1,000	0.9
Fetal deaths averted	0.7
Tests per pregnancy	6.2 ± 2.8
Tests per fetal death averted	1284
Inductions per fetal death averted	266

Table 2. Individual data on stillbirth in the study group

Mother's Age	Gravity	GA	Pathology (if available)
1. 31	G_4P_1	37 weeks	N/A
2. 36	G_5P_1	36 weeks	N/A
3. 30	G_2P_1	35 plus weeks	Placental abruption
4. 30	G_2P_1	35 plus weeks	Placental abruption
5. 36	G_2P_1	39 weeks	N/A
6. 41	G_2P_1	36 weeks	Hemorrhagic vasculopathy

Table 3. Distribution of stillbirth rates per week of gestation and number of inductions per fetal death averted

	Gestation week at initiation of testing*			
Outcome*	36	37	38	39
Fetal deaths per 1,000	0.4	0.2	0.1	0.2
Inductions per fetal death averted	14	18	31	38

*Fetal deaths averted per 1000 pregnancies compared with no testing.

Discussion

In the USA, the prevalence of stillbirth is about 1 out of 200 pregnancies for Caucasian women and 1 out of 87 for African-American women. In an attempt to address the problem, Fretts et al[2] focused on older women because these women are at higher risk of stillbirth and have fewer reproductive opportunities. They concluded that compared with no testing, a policy of weekly antepartum testing beginning at 37 weeks of gestation in women aged 35 years and older, results in a reduction in unexplained fetal deaths. Labor induction reduces stillbirth, but it may also increase the risk of cesarean delivery, which is already on the rise in this older age group.

Recently, Walker et al[4] conducted a randomized trial of labor induction in women over 35 years old. The primary outcome was a cesarean delivery. The trial was not designed or powered to assess the effects of labor induction on stillbirth. Induction at or before the due date in women 35 years of age or older may be beneficial because the gestational age at delivery that is associated with the lowest cumulative risk of perinatal death is 38 weeks. However, induction itself also carries risks (eg, cord prolapse, uterine hyperstimulation, etc). Results of the trial showed that among women of advanced maternal age, induction of labor at 39 weeks of gestation, as compared with expectant management, had no significant effect on the rate of cesarean section and no adverse short-term effects on maternal or neonatal outcomes.

Our practice of performing weekly antepartum testing starting at 36 weeks until delivery in all pregnant women, was instituted in 2006 because the majority of all stillbirths occur in young, low-risk patients. Women with known risk factors for stillbirth (obesity, diabetes, growth restriction, smoking, etc) are routinely subjected to frequent antepartum testing according to ACOG recommendations.

Similar to the results obtained by Fretts, et al[2] in older women, we also observed decreased stillbirth rates in patients of all age groups when weekly antepartum testing was applied. It fell from 1.6 per 1000 births to 0.9 per 1000 births. Recent policies limiting elective deliveries to 39 weeks and beyond which have been supported by ACOG and enforced by most hospitals have further increased the importance of this enhanced testing regimen. Patients should be aware that, in spite of the additional cost of testing and its effects on induction and operative delivery rates, weekly fetal assessment decreases the term stillbirth rate in all age groups significantly. In conclusion, the practice of weekly antepartum surveillance should be applied to all age groups in order to decrease the overall rate of near-term and term stillbirth.

References

1 Walsh C, Vallerie AM, Baxi LV. Etiology of stillbirth at term: a ten-year cohort study. J Mat Fet and Neonat Med 2008; 21 (7) 493-501.

2 Fretts RC, Elkin E, Myers E, Heffner J. Should older women have antepartum testing to prevent unexplained stillbirth? Obstet Gynecol 2004; 104: 56-64.

3 Strehle EM, Gray WK, Gopisetti S, Richardson J, McGurre J, Malone S. Can home monitoring reduce mortality in infants at increased risk of sudden infant death syndrome? A systematic review. American Academy Pediatrics 2012; 101: 8213.

4 Walker KF, Bugg GJ, Macpherson M, et al. Randomized trial of labor induction in women 35 years of age or older. N Engl J Med. 2016;3:814-22.

Redefining The Meaning of Term Pregnancy – Beware of The Risk of Stillbirth

BM Petrikovsky, MD, PhD, B Dynkin, Esq, L Sichinava, MD, DSc

Case eport

A 41 year-old primigravida with long-term history of infertility arrived to New York as an international patient for elective cesarean section, which is not offered in her country without obstetrical indications. She was placed on weekly fetal surveillance and requested that surgery be performed at 38+ weeks of pregnancy with an amniocentesis if indicated. A well-known New York hospital declined to perform the surgery at the time requested by the patient and her doctor in accordance with its policy to not perform elective cesarean delivery procedures until the fetus reached 40 complete weeks. Fetal demise was detected at 39 weeks; the patient returned to country of origin to deliver a stillbirth vaginally. No further information eg, cause of death, placental pathology, etc was available.

Comments

In a 2010 manuscript, Clark et al,[1] stated that the practice of elective delivery at 39 weeks is common in the United States despite long-standing recommendations by the American College of Obstetricians and Gynecologists (ACOG) against this practice.[2] Such policies are supported by both the desire to decrease neonatal morbidity and the desire to avoid cesarean sections resulting from failed inductions due to an unripe cervix. A detailed analysis of perinatal outcomes by week of gestation was performed by Cheng et al.[3] This study focused on a population of low risk women who delivered at term in the United States. In these women, pregnancy complications differed by gestational age at delivery. The risk of operative delivery and maternal morbidity is lowest between 37 and 39 weeks of gestation and begins to increase at 40 weeks. Some of the neonatal morbidities exhibit a similar pattern of rising with gestational age beyond 39 weeks (eg, macrosomia and meconium aspiration), others continue to decrease beyond 39 weeks of gestation (eg, RDS).

Our data is derived from a collection of vital statistics obtained from delivery summaries in 1,200 consecutive patients that have been compiled in Table 1. Using a ranking analysis methodology, Table 1 illustrates the most common maternal and fetal complications in order of frequency for various gestational ages. Elective deliveries were performed upon the patient's request with consenting physician starting at 38 plus weeks of pregnancy. We were interested in maternal and fetal outcomes including:

The authors are with the Department of Obstetrics and Gynecology and Anesthesiology, Wyckoff Heights Medical Center, Brooklyn, New York.

1. Maternal:
   - Cesarean section rate
   - Perinatal trauma
   - Incidence of hemorrhage defined as blood loss over 500 cc during vaginal delivery and over 1000 cc during cesarean section
2. Fetal/neonatal
   a. Low Apgar score
   b. Meconium aspiration
   c. Birth trauma
   d. NICU admission
   e. Macrosomia
   f. RDS
   g. Stillbirth
   h. Oligohydramnios

Our collaborative data are summarized in Table 1.

Table 1. Maternal and fetal complications as a result of elective deliveries at various gestational ages.

Gestational age at elective delivery	Maternal complications	Fetal complications
37-38 weeks	Cesarean section due to failed inductions	ICU admission Need for mechanical ventilation Low Apgar score
38.1-39 weeks	Perinatal lacerations	Macrosomia Neonatal injury Stillbirth
39.1-41 weeks	Obstetrical hemorrhage	Oligohydramnios Macrosomia Neonatal injury (including shoulder dystosia) Meconium aspiration Stillbirth

Overall, while the frequency of various complications varies, there is no clear diminishment of overall complications between 38 and 40 weeks of gestation. Furthermore, no variation in long-term morbidity or mortality was detected in that range. This seems troubling in the context of the ACOG Committee opinion and the manuscript of Clark et al[1,4] which seem to insist on a clear lack of cognizable benefits associated with elective birth prior to 39 weeks. While Clark et al[1,4] denies an increase in stillbirths associated with a prohibition of elective cesarean sections before the 39th week, he does acknowledge that the net rate of stillbirths would increase if the population studied is adequately large.[1]

The following parameters were used to justify ACOG's policy limiting the patient's right to choose and the obstetrician's right to suggest the time of the patient's delivery:

1. Increased rate of RDS
2. Increased rate of NICU admissions
3. Increased need for mechanical ventilation
4. Low Apgar scores

Our data agrees that RDS rates and the need for mechanical ventilation in newborns decreases with advancing gestation. However, in the vast majority of cases, no long-term ventilation was required. In our experience, no long-term respiratory problems were detected in babies born at 37 and 38 weeks of pregnancy. The criteria for both NICU admissions and Apgar score are subjective parameters. Some hospitals have policies to admit all 37-week neonates for observation and doctors tend to assign lower Apgar scores to newborn delivered before their due dates. Neither higher rates of asphyxia nor increased frequency of cerebral palsy have been reported in 37-week newborns in comparison to 39 and 40-week neonates.

Most would agree that the most serious issue in late-term gestation is the risk of stillbirth. It is obvious that the rate of stillbirth doesn't stop between 37 and 39 full weeks of pregnancy. The risk of stillbirth after 32 weeks of gestation increased with gestational age, and half of these late fetal deaths occur at near term.[6,7]

Because of the increased prevalence of oligohydramnios, umbilical cord accidents, fetal growth restriction, placental insufficiency with advancing pregnancy, the rate of stillbirth increases. Although there are no clearly identifiable risk factors for stillbirth, advanced maternal age puts fetuses at risk[7,8]. Frequent antepartum testing was shown to decrease stillbirth rate from 5.2/1000 to 3.9/1000 in the advanced maternal age group[8]. Stuck with the hospital's inflexibility with mandatory 39 week elective delivery rule, Terrani et al[9] designed a special protocol of universal weekly antepartum testing. Their antepartum testing model (biophysical profile weekly at 36 weeks on) started in a cohort of 6600 women. Women with a negative test remained undelivered until the subsequent positive test or onset of labor. Control group consisted of 4420 patients in whom antepartum testing was performed using indications accepted by ACOG. A strategy of weekly antepartum testing starting at 36 weeks of pregnancy in women of all age groups reduced the number of stillbirths by 58%.[9]

The immediate negative impact of the implementation of "39 week rule" had been also reported by Nicholson, et al.[10,11] Investigators found that there was a significant increase in the proportion of term stillbirths after the adoption of the rule; from 2007 to 2009, the proportion was 1.103 per 1000 deliveries, whereas from 2011 to 2013, it was 1.177 per 1000 (relative risk [RR], 1.07; 95% confidence interval, 1.038 – 1.096).[10,11] Such changes were more pronounced in larger states. In Ohio, for example, a "significant and clinically important increase" was observed, from 1.04 per 1000 deliveries before the rule was adopted, to 1.26 per 1000 deliveries after (RR, 1.21). Continuous distribution is seen across time, with regression line that has a P value of .034. The slope of the change is an increase of 0.0186 per 1000 deliveries per year. "Given an increase of 0.0186 per 1000 per year, given six yearly intervals from 2007 to 2013, and assuming 3.4 million term births per year in the United States, there could be 335 more term stillbirths in 2013 than in 2007."[11] It is likely that this figure would actually be greater if it were not for the confounding factor of deliveries generally shifting from 40 to 39 weeks.[11] Thus, it seems that a substantial portion of the increase in stillbirths during the period analyzed can be attributed to the 39-week rule.

When considering the manuscripts of Clark, et al,[1,4] what might be more troubling than the purely medical contentions are the policy prescriptions that the research is used to support. The authors advocate for a "hard stop" approach insisting on a policy that would prohibit elective inductions and cesarean deliveries at less than 39 weeks of gestation. This policy would be mandatory and would be enforced by hospital staff members who would prohibit doctors from performing any such deliveries. Furthermore, any "questionable "indications" would be handled in the standard manner by accessing chain of command."[1] This, essentially, amounts to a blanket prohibition of the practice.

Not surprisingly, it was found that this lead to a substantial decrease in elective deliveries before the 39-week mark. What is more interesting is that the study also attempted two other methodologies for decreasing the frequency of elective deliveries before the 39-week mark. Some facilities implemented the "soft stop" approach, whereby a policy discouraging elective deliveries before 39 weeks of gestation would be discouraged, but individual attending physicians would be permitted to perform the procedure if the patient and the physician so decided. All such cases, however would be referred to a peer review committee for evaluation. A third group of facilities were merely provided with professional literature related to such procedures and advised against performing them. In both of these groups, some decrease in the rate of elective deliveries before the 39-week mark was detected. However, the decrease in the "soft stop" cases, while statistically significant, was substantially smaller than that detected when the "hard stop" method was implemented. The education only method yielded an even smaller decrease which was not statistically significant.[1]

Clark, et al,[1] interpret the smaller decreases as documentation that education alone is ineffective in "changing that practice of many obstetricians" and that this "demonstrate[s] how far the specialty has to go in embracing the concept of evidence-based (as opposed to anecdotal experience-based) practice." In doing so, Clark, et al,[1] attribute the persistence of the practice of elective pre-39 week deliveries to the rejection of evidence-based practice by those practitioners who persisted in performing such deliveries. It is likely that some of the practitioners, despite clear awareness of the literature and, in the case of the "soft stop" method, substantial additional hurdles, persisted in performing such procedures because of a consciousness and willful rejection of the evidence to which they were exposed, or for other potentially inappropriate reasons.

Implicit in the logic of the argument in Clark, et al,[1,4] is an ethical judgment that the primary considerations at issue are morbidity and NICU admissions. However, one important issue that is ignored is the distinction between short-term and long-term morbidity. While Clark, et al,[1,4] cite multiple studies indicating that pre-39 week deliveries are associated with higher rates of morbidity, none of these studies seem to distinguish between the two types of morbidity.

In addition to failing to consider the distinction between different sorts of morbidity, the logic of the argument depends

on a particular ethical judgment as to how morbidity and mortality ought to be balanced. In fact, Clark, et al[1,4] explicitly acknowledge that prohibiting elective pre-39 week deliveries will certainly increase stillbirths, but contend that such increase will be minimal. Further they contend that anyone who feels that this risk is of adequate importance to counterbalance the interest in minimizing morbidity that is achieved by prohibiting elective pre-39 week deliveries, must support a policy of broadly mandating pre-39 week deliveries.

However, this line of reasoning is only coherent if one approaches the question from the perspective of implementing a mandatory policy. When viewed from the perspective of a policy-maker implementing mandatory policies that will be binding on all practitioners and all patients, the logic makes sense and individual circumstances cannot be appropriately addressed. However, when viewed from the perspective of an individual decision-maker, be it an obstetrician or a patient, the ability to make an individual decision in accordance with one's ethical and aesthetic values and preferences lies at the core of patient autonomy. In situations where a universal judgment as to relative values that stand in competition to one another is elusive, the default course of action is, and ought to be, to allow individual stakeholders to make their own determinations, so long as they are adequately informed as to all the risks associated with the decision.

It is important to also consider the fact that not all harm is physical. The psychological trauma experienced by a mother resulting from a stillbirth can be tremendous and far reaching.[12] While there has been some focus on dealing with these psychological harms, for example a study by Cacciatore et al,[13] found that there was a statistically significant psychologically therapeutic effect of mother's holding their stillborn babies, there has not been enough focus on addressing this substantial problem because medical professionals are still focusing their attention on understanding and preventing stillbirths and miscarriages. The profound psychological trauma that afflicts mothers who suffer from stillbirths must be carefully considered in the scope of developing policy prescriptions for measures that might affect them.

Autonomy is a central value in modern medical ethics and policymaking. While certain procedures, obviously, can and should be strictly proscribed, the decision to do so should not be taken lightly and the threshold to be met ought to be quite high. The decision whether or not to pursue pre-39 week delivery does not come close to meeting this threshold. The risk of stillbirth and other complications which increase as gestation progresses are not so clearly outweighed by the alternative birth complications and the greater net short-term morbidity which are more prevalent in relation to pre-39 week deliveries. Hospital administrators and insurance companies should not be empowered to make decisions that are binding on all patients and healthcare providers. In a matter of such complexity, there is no single balance that is right for everyone and the only appropriate authority to make a final decision is the patient in close and involved consultation with her obstetrician, who is most intimately familiar with her needs and preferences.

References

1 Clark SL, Frye DR, Meyers JA, et al. Reduction in elective delivery <39 weeks of gestation: comparative effectiveness of 3 approaches to change and the impact on neonatal intensive care admission and stillbirth. Am J Obstet Gynecol 2010;203:449.e1-6.

2 ACOG Practice Bulletin no. 107: Induction of labor. Obstet Gynecol 2009;114:386-97.

3 Cheng YW, Nicholson JM, Nakagawa S, et al. Perinatal outcomes in low-risk term pregnancies: do they differ by week of gestation? Am J Obstet Gyecol 2008;199:370.e1-370.e7.

4 Clark SL, Miller DD, Belfort MA, et al. Neonatal and maternal outcomes associated with elective term delivery. Am J Obstet Gynecol 2009;200:156.e1-156.e4.

5 Tita AT, Landon MB, Spong CY, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. N Engl J Med 2009;360:111-20.

6 Reddy UM, Ko CW, Willinger M. Maternal age and the risk of stillbirth throughout pregnancy in the United States. Am J Obstet Gynecol 2006;195:764-70.

7 Rosensteig MG, Cheng YW, Snowden JM, et al. Risk of stillbirth and infant death stratified by gestational age. Obstet Gynecol 2012;120:76-82.

8 Fretts RC, Elkin E, Myers E, Heffner J. Should older women have antepartum testing to prevent unexplained stillbirth? Obstet Gynecol 2004;104:56-64.

9 Terrani M, Gonzales F, Dillon A, et al. Can weekly antepartum testing decrease stillbirth rate? In Press.

10 Nicholson JM. Stillbirth rates rise after 39-week rule. www.medscape.com

11 Nicholson JM., Kellar LC., Ahmad S. et al. US term stillbirth rates and the 39-week rule: a cause for concern? Am J Obstet Gynecol 2016;2:1-10.

12 Tsartsara, Eirini, and Martin P. Johnson. "The impact of miscarriage on women's pregnancy-specific anxiety and feelings of prenatal maternal–fetal attachment during the course of a subsequent pregnancy: An exploratory follow-up study." Journal of Psychosomatic Obstetrics & Gynecology 27.3 (2006): 173-182.

13 Cacciatore, Joanne, Ingela Rådestad, and J. Frederik Frøen. "Effects of contact with stillborn babies on maternal anxiety and depression." Birth 35.4 (2008): 313-320.

A Safe Pressure Relief Gel Device for Patients in the Neonatal Intensive Care Unit

Chrysty Sturdivant, OTR; Sandra Carroll, OTR; Genna Stone, RN, RNC-NIC, MBA; Mustafa Suterwala, MD

Abstract

Extracranial pressure applied to the occiput of a neonatal and especially a preterm patient can lead to cranial molding including deformational plagiocephaly (DP) and pressure ulcers (PUs). Managing this extracranial pressure either through repositioning or pressure reduction devices is part of clinical care in the neonatal intensive care unit. A new device intended to reduce the pressure applied to the occipital region of an infant's cranium was tested in a clinical setting. The device was evaluated for its potential to cause skin irritation and excessive perspiration, as well as for its ability to remain on the patient's head during normal movement. No adverse events, such as skin irritation, were noted, and the pressure relief device remained securely on the infants' heads throughout the study. This pressure relief device may be a useful tool to mitigate risks associated with external pressure applied to the skull of a neonatal infant.

Keywords

deformational plagiocephaly (DP), cranial molding, pressure ulcers, neonatal, back to sleep, pressure reduction, extracranial pressure, neonatal intensive care unit

Introduction and Purpose

Extracranial pressure applied to the head of an infant over time can result in deformational plagiocephaly (DP) or a pressure ulcer (PU) or both. DP is an asymmetrical posterior flattening of the head that is not caused by craniosynostosis or premature sutural fusion.[1] DP in infants is a significant clinical issue. The prevalence of this condition across the broad population has been reported at about 19% to 30%,[2-4] although Mawji et al. have reported a rate greater than 46%.[5] The variation may be due in part to using different criteria to define DP; eliminating the subjects with the mildest degree of DP in the population of the Mawji study yields a prevalence of about 23%, similar to the other findings. In a study of 380 full-term children, it was found that 84 had plagiocephaly at seven weeks. Of these, 75 (19.7%) did not have plagiocephaly at birth implying that environmental conditions were responsible for the cranial deformation.[6] Interpolating from US Census figures indicates that as many as four million infants under one year of age may be affected.[7] Very preterm infants may be particularly at risk for DP, with 23% having moderate to severe DP, while in the subset of very preterm infants (less than 32 weeks gestational age) 38% have of moderate to severe DP.[8]

The authors are from Baylor University Medical Center, Dallas, Texas.

A goal of clinical care in the neonatal intensive care unit (NICU) is to manage the pressure applied to the head of the patient to help allow the rapid growth of the neonatal brain to fill out the cranium evenly.[9] Several approaches are employed by clinical staff to avoid consistent high pressure on the cranium including manually repositioning the patient and trying to keep the head of the patient on a padded device.[10] This is especially important when the patient has very limited head movement such as in the case of neurologic diseases or difficult airways.[9]

DP has implications for quality of life. Numerous studies highlight the nature and extent of the distinct cranial deformities that can occur, ranging from facial asymmetry, astigmatism, malocclusion of the jaw, otitis media, and malposition of ears to statistically significant dimensional differences of the brain as measured by MRI.[11-18] It is speculated that these anatomical changes can have lasting effects including impaired hearing associated with otitis media raising concerns for "language, speech, and cognitive developments"[16] and misaligned primary dentin associated with plagiocephaly increasing the prevalence of orthodontic abnormalities.[13]

Pressure ulcers are also related to sustained pressure to soft tissue, especially over a bony prominence. Prevalence rates for PUs in neonatal intensive care units (NICUs) have been reported as 23%.[19] Similar rates are reported in pediatric intensive care units (PICUs). In a study of three PICUs, 86 of 322 patient studied (27%) developed PUs.[20] Rates of PUs with pediatric patients tend to be higher in intensive care units than on other units[21]. In this population, the head is a common location of these pressure ulcers.[20,22-24]

The purpose of this study was to evaluate the safety of a new cranial pressure relief device (GELShield, Invictus Medical, Inc, San Antonio, Texas) intended to reduce the pressure applied to the head of a recumbent infant. The secondary purpose was to evaluate the pressure relief device's ability to remain on the heads of patients during normal movement. This study considers issues with the integrity and irritation of the skin that contacts the device, and instances of the device becoming displaced; it also notes the ease of application of the device on the patient.

Materials and Methods

The study protocol was reviewed and approved by the Institutional Review Board of Baylor University Medical Center. A prospective, single-site phase I safety trial was conducted on 42 consecutive patients admitted to the NICU at Baylor

Figure 1. Pressure relief device oriented on patient.

University Medical Center (Dallas, Texas) that met the inclusion criteria. The inclusion criteria for this study included informed consent by the parent or guardian of the patient, greater than or equal to 30 weeks gestational age at the time of enrollment, medically stable, spontaneously breathing on room air, no observable distress, visibly intact skin in areas where the pressure relief device would be applied, a head circumference between 28 and 34.3 cm, and the absence of any genetic dermatological or other medical conditions deemed medically incompatible with this study.

The pressure relief device is a head-worn multi-layer device comprising an occipital cup portion approximately 5 mm thick and a head strap portion. The device weighs 37 gm and is sized and shaped to fit on the head of an infant with the crown exposed. The head strap portion consists of two wings affixed as they come together over the forehead of the infant with a hook and loop (Velcro) material. All areas of the pressure relief device are padded and the occipital cup portion also contains an interior hydrogel material. Both the inner and outer surfaces of the device comprise a low-friction material containing an anti-microbial compound. A pattern of silicone material is printed on the inner surface of the device.

Once the subject was enrolled, one of three investigators that had been trained applied the pressure relief device by orienting the occipital cup portion under the infant's head and placing one of the wings of the head strap portion on the forehead, pulling the other wing over the first wing without tugging or stretching the device. This device positioned on an infant is shown in Figure 1.

Safety of the pressure relief device was evaluated by examining the subjects for any skin irritation or excessive perspiration and ensuring that the device did not become dislodged from the infant's head. The status of the skin of the head was quantified with a Skin Appearance Assessment Score tool adapted from Maibach and Patrick[25] on a scale from 0 to 7 (Table 1), and excessive perspiration was scored as either Yes or No. The *a priori* criterion for an adverse event (AE) was a skin irritation score of greater than 2 ("Definite erythema, readily visible; minimal edema or minimal popular response"). Instances of the pressure relief device becoming dislodged at any point from the subject were also noted.

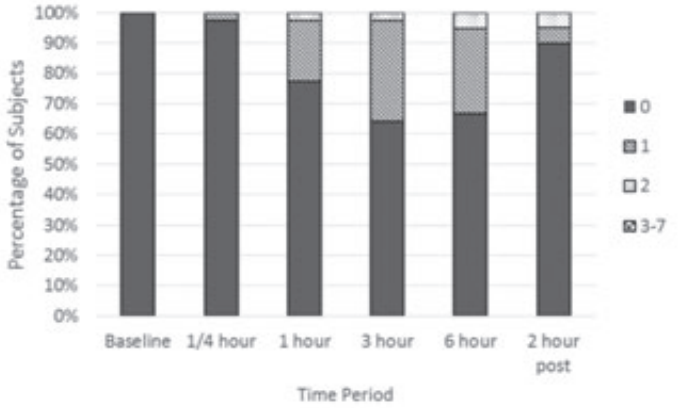


Figure 2. Skin appearance assessment score by time periods.

Before placing the pressure relief device on the head of the subject, the investigator evaluated the infant's head using the Skin Appearance Assessment Score tool. After placing the pressure relief device on the infant's head at baseline, subsequent assessments of skin appearance using the Skin Appearance Assessment Score tool, as well as assessments of excessive perspiration, were made at 15 minutes, one hour, three hours, and six hours after baseline. After six hours, the pressure relief device was removed from the subject's head. Two hours after device removal, a final evaluation was made with the Skin Appearance Assessment Score tool. After the pressure relief device was removed from the subject, it was secured in a storage area and was not reused on another patient per the manufacturer's instructions for use.

Results

Forty-two patients were enrolled in the study, and one subject was withdrawn after the one-hour assessment. The gestational ages of the subjects ranged from 33 weeks, 3 days to 40 weeks, 3 days (mean = 35 weeks, 3 days), while the chronological ages of the subjects ranged from 5 to 94 days (mean = 24.6 days). Of the 42 subjects, 20 were male. Head circumference ranged from 28.0 cm to 34.3 cm (mean = 30.6 cm).

No AEs (Skin Appearance Assessment Score > 2) were reported throughout the study. All baseline Skin Appearance Assessment Scores were 0. Following baseline, a total of 208 assessments were made at the four periods during which the pressure relief device was worn and the one period after the device had been removed. The scores recorded at all time points are shown in Table 2. None of the skin redness noted (score of 1 or 2) was non-blanching erythema. These scores and those of the baseline assessment are summarized in Figure 2.

Excessive scalp perspiration was evaluated at each of the four time points during which the pressure relief device had been worn. Of the 166 observations for excessive perspiration, one observation (<1%) at six hours was deemed to be excessive. At no point in the study did the pressure relief device become dislodged from the head of any subject while the infant was lying in the crib.

Discussion

The executed six-hour study comprising one three-hour period of continuous use of the pressure relief device was designed to match the NICU standard of care practice of handling and examining infants at least every three hours. Neonatal nursing protocols state that periods of needed, undisturbed rest be

provided for the infant, but that these periods usually do not extend beyond three hours so that appropriate assessments and interventions can be completed.[26] The duration of the study period was selected to accurately mimic actual clinical care.

The use of the device did not interfere with our routine clinical care of the infant. No monitoring modality was adversely affected, our routine inspection of the patient's skin was unaffected, and the device was sufficiently stable on the infant's head that the clinicians did not have to reposition the device between skin assessments.

While the AAP's "Back to Sleep" guidelines may have originally been directed to parents' caring for their infants, NICUs have also established protocols to implement these guidelines,[27] including providing firm sleeping surfaces and supine sleep positioning prior to hospital discharge. In part because of the hydrogel layer in the occipital cup portion of the pressure relief device, the peak pressure experienced in the occipital region is likely to be reduced, especially when the infant is in the supine position, the prevalent position recommended in the NICU to facilitate, for instance, mechanical ventilation when airway management is critical or as part of an intraventricular hemorrhage-prevention protocol. All factors taken together, a mechanism to alleviate the pressure on the occipital region would be useful.

Specific guidelines for managing and preventing pressure ulcers prescribe several practices for which use of the pressure relief device may be beneficial. For instance, an international consensus document describes a two-pronged approach of increased contact area and pressure relief.[28] The first prong, increased contact area, is accomplished by two techniques: patient repositioning and use of a support surface of, for instance, a gel or a foam material. The pressure relief device promotes both of these techniques, enveloping the head of the infant, providing an easy means of rolling the infant's head from one side to the other based on clinical judgment, and maintaining the layers of foam and gel found within the pressure relief device between the head of the infant and the mattress. The second prong is to provide pressure relief or attenuation. According to the consensus document, this is accomplished by providing a pressure-redistributing support surface, such as an overlay on an existing mattress. The pressure relief device is in essence an overlay system that travels with the infant's head, providing the same type of pressure relief by increasing the contact area between the infant and the surface with which it is in contact.

While mobility, perfusion, and pressure over time are the most important risk factors for pressure ulcers, skin moisture is another predictor.[29] In the current study, only one instance of perspiration was noted under the pressure relief device, and this occurred after three hours of continuous application, the time at which the device would typically be removed per the instructions for use to allow the healthcare provider to wipe away moisture. The clinicians executing the study did not detect any alteration in neck position while the device was used on the infants.

One limitation of the study was limiting the number of users to the three trained investigators. This was done to help ensure consistent application of the device however, a broader range of users may have found variations in skin response secondary to differing application techniques. Also related to application technique, the circumferential pressure of the device on the infant's head was dictated by the experienced perception of the trained investigator using the manufacturer's recommended application technique rather than being confirmed by a pressure sensor oriented between the device and the infant's skin. Such a pressure sensor could have confirmed consistent circumferential pressure however. Another limitation of this study was the lack of long-term assessment of the effect of the device on cranial molding during an infant's stay in the NICU. However, we believe that the pressure-reduction attributes of the construction of the pressure relief device would help deter cranial molding. In theory, molding occurs at least in part when cranial growth is resisted in a specific area by an external force.[30] To the extent that this force is reduced by distributing it over a larger area, the resistance to growth should be reduced, thereby decreasing the chance of cranial molding.

In the future, a phase II efficacy study would be appropriate. Such a study could evaluate the trajectory of cranial molding in neonatal patients, tracking any improvements in the change in asymmetry while the patient was being treated in the NICU. The study would have to assiduously avoid any Hawthorne effect in which the staff, recognizing that head shape was being carefully monitored, would change their turning and positioning protocol or technique. A historic control may be one approach to minimize the Hawthorne effect. A consistent application methodology would have to be ensured so the device was not too tight or too loose. Finally, it would be essential to perform a repeatability and reliability evaluation on the cranial deformation measurement. This would ensure that the variability of the measurements did not confound the dependent asymmetry variable. Beyond that, a study comparing this device with currently marketed positioning aids and pillows would be beneficial. This study would also consider secondary endpoints such as the amount of nursing or therapist time required for

Table 1. Skin appearance assessment score tool (adapted from Maibach and Patrick[19])

Skin Appearance	Score
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible; minimal edema or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond the application site	7

Table 2. Summary of skin appearance assessment scores at all time points

Score	Baseline	15 min	1 hr	3 hr	6 hr	2 hr post
0	42	41	33	27	28	38
1	0	1	8	13	11	2
2	0	0	1	1	2	2
3	0	0	0	0	0	0
4	0	0	0	0	0	0
5	0	0	0	0	0	0
6	0	0	0	0	0	0
7	0	0	0	0	0	0

reorienting the infant on the various devices or other side effects due to movement restrictions and airway management.

Conclusions

The data indicate that the pressure relief device is safe to use on infants in a NICU setting and is unlikely to have any adverse effects on the tissue with which it comes in contact. The use of device was readily accommodated in the clinical care of the patient during the duration of the study and would likely not interfere with routine clinical care over longer periods. The benefits of the force distribution and accompanying pressure reduction of the hydrogel and other materials in the device to a supine infant would be enhanced by the device remaining securely on the infant's head, as it did throughout the study periods. Further, the security of the device during normal movement should minimize any hazard associated with loose objects in the vicinity of the infant. Thus, this pressure relief device may be a useful tool to mitigate risks associated with pressure applied to the skull of a neonatal infant.

References

1. Hutchison BL, Stewart AW, Mitchell EA. Characteristics, head shape measurements and developmental delay in 287 consecutive infants attending a plagiocephaly clinic. Acta Paediatr Int J Paediatr. 2009;98(9):1494-1499.
2. Hutchison BL, Hutchison LA, Thompson J, Mitchell EA. Plagiocephaly and brachycephaly in the first two years of life: a prospective cohort study. Pediatrics. 2004;114(4):970-980.
3. Cavalier A, Picot MC, Artiaga C, et al. Prevention of deformational plagiocephaly in neonates. Early Hum Dev. 2011;87(8):537-543.
4. Kane AA, Mitchell LE, Craven KP, Marsh JL. Observations on a recent increase in plagiocephaly without synostosis. Pediatrics. 1996;97(6 Pt 1):877-885.
5. Mawji A, Vollman AR, Hatfield J, McNeil DA, Sauve R. The incidence of positional plagiocephaly: A cohort study. Pediatrics. 2013;132(2):298-304.
6. van Vlimmeren LA, van der Graaf Y, Boere-Boonekamp MM, L'Hoir MP, Helders PJM, Engelbert RHH. Risk factors for deformational plagiocephaly at birth and at 7 weeks of age: a prospective cohort study. Pediatrics. 2007;119(2):e408-e418.
7. Howden L, Meyer J. Age and Sex Composition: 2010.; 2011. http://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf.
8. Ifflaender S, Rüdiger M, Konstantelos D, Wahls K, Burkhardt W. Prevalence of head deformities in preterm infants at term equivalent age. Early Hum Dev. 2013;89(12):1041-1047.
9. Sillifant P, Vaiude P, Bruce S, et al. Positional plagiocephaly. J Craniofac Surg. 2014;25(4):1365-1368.
10. Hemingway M, Oliver S. Bilateral Head Flattening in Hospitalized Premature Infants. Online J Knowl Synth Nurs. 2000;7(3):3.
11. Cabrera-Martos I, Valenza MC, Benítez-Feliponi a., Robles-Vizcaíno C, Ruiz-Extremera a., Valenza-Demet G. Clinical profile and evolution of infants with deformational plagiocephaly included in a conservative treatment program. Child's Nerv Syst. 2013;29(10):1893-1898.
12. Collett B, Breiger D, King D, Cunningham M, Speltz M. Neurodevelopmental implications of "deformational" plagiocephaly. J Dev Behav Pediatr. 2005;26(5):379-389.
13. Kluba S, Roßkopf F, Kraut W, et al. Malocclusion in the primary dentition in children with and without deformational plagiocephaly. Clin Oral Investig. January 2016.
14. Kluba S, Schreiber R, Kraut W, Meisner C, Reinert S, Krimmel M. Does helmet therapy influence the ear shift in positional plagiocephaly? J Craniofac Surg. 2012;23(5):1301-1305.
15. St John D, Mulliken JB, Kaban LB, Padwa BL. Anthropometric analysis of mandibular asymmetry in infants with deformational posterior plagiocephaly. J Oral Maxillofac Surg. 2002;60(8):873-877.
16. Purzycki A, Thompson E, Argenta L, David L. Incidence of otitis media in children with deformational plagiocephaly. J Craniofac Surg. 2009;20(5):1407-1411.
17. Siatkowski RM, Fortney AC, Nazir SA, et al. Visual field defects in deformational posterior plagiocephaly. J AAPOS. 2005;9(3):274-278.
18. Gupta PC, Foster J, Crowe S, Papay FA, Luciano M, Traboulsi EI. Ophthalmologic findings in patients with nonsyndromic plagiocephaly. J Craniofac Surg. 2003;14(4):529-532.
19. Baharestani MM, Ratliff CR. Pressure ulcers in neonates and children: an NPUAP white paper. Adv Skin Wound Care. 2007;20(4):208, 210, 212, 214, 216, 218-220.
20. Curley MAQ, Quigley SM, Lin M. Pressure ulcers in pediatric intensive care: Incidence and associated factors*. Pediatr Crit Care Med. 2003;4(3):284-290.
21. McLane KM, Bookout K, McCord S, McCain J, Jefferson LS. The 2003 national pediatric pressure ulcer and skin breakdown prevalence survey: a multisite study. J Wound Ostomy Continence Nurs. 2004;31(4):168-178.
22. McCord S, McElvain V, Sachdeva R, Schwartz P, Jefferson LS. Risk factors associated with pressure ulcers in the pediatric intensive care unit. J Wound Ostomy Continence Nurs. 2004;31(4):179-183.
23. Groeneveld A, Anderson M, Allen S, et al. The prevalence of pressure ulcers in a tertiary care pediatric and adult hospital. J Wound Ostomy Continence Nurs. 2004;31(3):108-120.
24. Baldwin KM. Incidence and prevalence of pressure ulcers in children. Adv Skin Wound Care. 2002;15(3):121-124.
25. Maibach H, Patrick E. Dermatotoxicology. In: Hayes AW, ed. Principles and Methods of Toxicology. Vol 4th ed. Philadelphia: Taylor & Francis; 2001:1039-1084.
26. Kenner C, Amlung SR, Flandermeyer AA. Protocols in Neonatal Nursing. Philadelphia: Saunders; 1998.
27. Gelfer P, Cameron R, Masters K, Kennedy K a. Integrating "Back To Sleep" recommendations into neonatal ICU practice. Pediatrics. 2013;131(4):e1264-e1270.
28. Takahashi M, Black J, Dealey C, Gefen A. Pressure, shear, friction and microclimate in context: A consensus document. In: MacGregor L, ed. Wounds International. Vol London: Wounds International; 2010:1-10.
29. Coleman S, Gorecki C, Nelson EA, et al. Patient risk factors for pressure ulcer development: Systematic review. Int J Nurs Stud. 2013;50(7):974-1003.
30. Rogers GF. Deformational plagiocephaly, brachycephaly, and scaphocephaly. Part I. J Craniofac Surg. 2011;22(1):9-16.

Neonatal Research: Great Advances Over Time, But Keep Research Moving Forward

Deb Discenza

In early March, I was honored to attend the 2nd Annual International Neonatal Consortium meeting at the Food & Drug Administration. As the parent of a premature infant and a professional in the community supporting families and educating professionals, it gave me hope to see so many neonatal professionals in one room working to improve neonatal outcomes. Every day on my "Preemie Support" Forum on Inspire.com, I have parents on every continent continually plagued by the very issues being discussed in that meeting. In attendance was Tonse NK Raju, MD, DCH, Branch Chief of the Pregnancy and Perinatology Branch (PPB) of NIH/NICHD. It was wonderful to catch up afterward to ask him his unique view of neonatal research.

Deb Discenza: As a neonatologist that is heavily focused on research—what areas of the NICU research have come a long way?

Dr Raju: From my perspective, it is the entire "perinatal care" that has made a huge advance: these are subtle, but cumulatively, and I believe they have had huge impact on the overall status of preterm infants at birth. This includes infants born as early as 23-25 weeks of gestation, often called "periviable" infants. And, neonatal and obstetric teams have been working together in enforcing general approaches to fetal/maternal management.

The specific areas of major advances are: the use of pulmonary surfactants to reduce the seriousness of respiratory distress syndrome. The drug was introduced to the market in early 1990s, and within a few years nearly a dozen new and improved products have been approved, and their use today is nearly 100% if preterm infants have respiratory distress.

More generalized use of corticosteroids before childbirth in women who come to the hospital in labor and are under 34 weeks of gestation. In the early 1970s, both animal studies and human trials showed that antenatal corticosteroids enhance fetal lung maturation, leads to reduced mortality and lung disease severity, reduces intracranial bleed, and reduces the frequency of necrotizing enterocolitis—as you may know, a very bad infection of the intestines. But, the frequency of use of this very helpful medication until the mid-1990s was less than 20% for eligible patients. In 1994, NICHD organized an expert panel NIH Consensus Conference, which concluded that this treatment is lifesaving. The statement was released on the day of the meeting and a subsequent publication summarized the recommendations. Within a few years, the use of the medication went up to 80—90% among those who deliver preterm babies before four weeks, and there is an appropriate time lag between when the mom gets to the the hospital and when she will have her baby.

The other major area on pulmonary care is the introduction of inhaled Nitric Oxide (iNO) for such conditions as "persistent pulmonary hypertension," often secondary to meconium aspiration syndrome, congenital diaphragmatic hernia, and often from unknown causes. iNO led to dramatic reduction in infants needing ECMO support, improving their survival, and reducing complications due to this invasive procedure.

The successful campaign for safe sleep—previously called Back To Sleep Campaign—had led to dramatic reduction in Sudden Infant Death Syndrome (SIDS). In fact, it was NICHD with collaboration from AAP that were the leaders in this campaign.

Another one is hypothermia for perinatal asphyxia—dramatic benefits, but still much more needs to be done.

Deb Discenza: What areas of research need better attention?

Dr Raju: We have frequent workshops on many topics, and the findings are published with research agenda. These are publicly available documents in which research agenda is provided for each topic.

1: Raju TN, Mercer BM, Burchfield DJ, Joseph GF Jr. Periviable birth: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists. Obstet Gynecol. 2014 May;123(5):1083-96. doi: 10.1097/AOG.0000000000000243. PubMed PMID: 24785861.

2: Higgins RD, Raju T, Edwards AD, Azzopardi DV, Bose CL, Clark RH, Ferriero DM, Guillet R, Gunn AJ, Hagberg H, Hirtz D, Inder TE, Jacobs SE, Jenkins D, Juul S, Laptook AR, Lucey JF, Maze M, Palmer C, Papile L, Pfister RH, Robertson NJ, Rutherford M, Shankaran S, Silverstein FS, Soll RF, Thoresen M, Walsh WF; Eunice Kennedy Shriver National Institute of Child Health and Human Development Hypothermia Workshop Speakers and Moderators. Hypothermia and other

Deb Discenza is the mother to a 30-weeker premature baby now almost 13 years old. Ms Discenza is the head of PreemieWorld, LLC and the co-author of "The Preemie Parent's Survival Guide to the NICU" available at www.PreemieWorld.com.

Are you concerned about oxygen toxicity in neonates?

There are no published national guidelines for hyperoxia management.[1]

We appreciate the complexity of the challenges you face every day. That's why we're proud to offer **OXYGENISADRUG.com**, a comprehensive resource with information about:

- Supplemental oxygen therapy
- Consequences of hyperoxia
- Practice and protocols
- Historical perspectives

Though supplemental oxygen is necessary and often beneficial at appropriate doses, elevated levels can put patients at risk for hyperoxia with the potential for long-term tissue damage.[2]

It is possible to have too much of a good thing. Learn how to manage the challenge at **OXYGENISADRUG.com/toxicity**

OXYGEN IS A DRUG !

References: 1. Agency for Healthcare Research and Quality. National Guideline Clearinghouse website. http://www.guideline.gov/search/search.aspx?term=hyperoxia. Accessed August 18, 2015. **2.** Kulkarni AC, Kuppusamy P, Parinandi N. Oxygen, the lead actor in the pathophysiologic drama: enactment of the trinity of normoxia, hypoxia, and hyperoxia in disease and therapy. *Antioxid Redox Signal*. 2007;9(10):1717-1730.

treatment options for neonatal encephalopathy: an executive summary of the Eunice Kennedy Shriver NICHD workshop. J Pediatr. 2011 Nov;159(5):851-858.e1. doi: 10.1016/j.jpeds.2011.08.004. Epub 2011 Aug 27. PubMed PMID: 21875719; PubMed Central PMCID: PMC3263823.
3: Raju TN, Suresh G, Higgins RD. Patient safety in the context of neonatal intensive care: research and educational opportunities. Pediatr Res. 2011 Jul;70(1):109-15. doi: 10.1038/pr.2011.334. PubMed PMID: 21386749; PubMed Central PMCID: PMC3454497.
4: Higgins RD, Baker CJ, Raju TN. Executive summary of the workshop on infection in the high-risk infant. J Perinatol. 2010 Jun;30(6):379-83. doi: 10.1038/jp.2009.199. Epub 2010 Jan 14. PubMed PMID: 20072133; PubMed Central PMCID: PMC3038782.
5: Higgins RD, Bancalari E, Willinger M, Raju TN. Executive summary of the workshop on oxygen in neonatal therapies: controversies and opportunities for research. Pediatrics. 2007 Apr;119(4):790-6. Review. PubMed PMID: 17403851.
6: Higgins RD, Raju TN, Perlman J, Azzopardi DV, Blackmon LR, Clark RH, Edwards AD, Ferriero DM, Gluckman PD, Gunn AJ, Jacobs SE, Eicher DJ, Jobe AH, Laptook AR, LeBlanc MH, Palmer C, Shankaran S, Soll RF, Stark AR, Thoresen M, Wyatt J. Hypothermia and perinatal asphyxia: executive summary of the National Institute of Child Health and Human Development workshop. J Pediatr. 2006 Feb;148(2):170-175. PubMed PMID: 16492424.
7: Raju TN, Ariagno RL, Higgins R, Van Marter LJ; National Institute of Child Health and Human Development; American Academy of Pediatrics. Research in neonatology for the 21st century: executive summary of the National Institute of Child Health and Human Development-American Academy of Pediatrics workshop. Part I: academic issues. Pediatrics. 2005 Feb;115(2):468-74. PubMed PMID: 15687457.
8: Blackmon LR, Fanaroff AA, Raju TN; National Institute of Child Health and Human Development. Research on prevention of bilirubin-induced brain injury and kernicterus: National Institute of Child Health and Human Development conference executive summary. 2003. Pediatrics. 2004 Jul;114(1):229-33. Review. PubMed PMID:15231933.

Deb Discenza: What do you do on a day-by-day basis to help further neonatal research?

Dr Raju: I answer emails or phone calls from scientists around the country who want to apply for NIH grants related to maternal/neonatal topics. As branch chief, I will direct them to appropriate experts in my Branch or to other branches. I also handle most of the calls related to neonatal research. Other aspects of my job include review of progress made by the researchers of funded grants—typically called in the NIH lingo, "management of my grants portfolio" I attend several major national and international meetings (by the AAP/ACOG/SMFM and so on) to learn the state-of-the-science, and learn about knowledge gaps. This will help me to inform the NICHD and appropriate NIH leadership about the need for stimulating appropriate future research.

Deb Discenza: Where do you hope today's research will take us say in the next 10 years, 20 years?

Dr Raju: Broad question, but some of the key topics are:
- Eliminating the burden of preterm birth
- Improving brain/eye/heart/lungs/kidney and nutritional outcomes for all newborn infants
- Reducing childhood obesity

Deb Discenza: Thank you Dr Raju.

Global Network For Women's And Children's Health Research: A System For Low-Resource Areas To Determine Probable Causes Of Stillbirth, Neonatal, And Maternal Death

Elizabeth M McClure,[1] Carl L Bose,[2] Ana Garces , [3] Fabian Esamai,[4] Shivaprasad S Goudar,[5] Archana Patel,[6] Elwyn Chomba,[7] Omrana Pasha,[8] Antoinette Tshefu,[9] Bhalchandra S Kodkany,[5] Sarah Saleem,[8] Waldemar A Carlo,[10] Richard J Derman,[11] Patricia L Hibberd,[12] Edward A Liechty,[13] K Michael Hambidge,[14] Nancy F Krebs,[14] Melissa Bauserman,[15] Marion Koso-Thomas,[16] Janet Moore,[1] Dennis D Wallace,[1] Alan H Jobe[17] and Robert L Goldenberg[18]

Abstract

Background: Determining cause of death is needed to develop strategies to reduce maternal death, stillbirth, and newborn death, especially for low-resource settings where 98% of deaths occur. Most existing classification systems are designed for high income settings where extensive testing is available. Verbal autopsy or audits, developed as an alternative, are time-intensive and not generally feasible for population-based evaluation. Furthermore, because most classification is user-dependent, reliability of classification varies over time and across settings. Thus, we sought to develop classification systems for maternal, fetal and newborn mortality based on minimal data to produce reliable cause-of-death estimates for low-resource settings.

Results: In six low-resource countries (India, Pakistan, Guatemala, DRC, Zambia and Kenya), we evaluated data which are collected routinely at antenatal care and delivery and could be obtained with interview, observation, or basic equipment from the mother, lay-health provider or family to inform causes of death. Using these basic data collected in a standard way, we then developed an algorithm to assign cause of death that could be computer-programmed. Causes of death for maternal (trauma, abortion, hemorrhage, infection and hypertensive disease of pregnancy), stillbirth (birth trauma, congenital anomaly, infection, asphyxia, complications of preterm birth) and neonatal death (congenital anomaly, infection, asphyxia, complications of preterm birth) are based on existing cause of death classifications, and compatible with the World Health Organization International Classification of Disease system.

Conclusions: Our system to assign cause of maternal, fetal and neonatal death uses basic data from family or lay-health providers to assign cause of death by an algorithm to eliminate a source of inconsistency and bias. The major strengths are consistency, transparency, and comparability across time or regions with minimal burden on the healthcare system. This system will be an important contribution to determining cause of death in low-resource settings.

[1]RTI International, Durham, NC, USA. [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [3]FANCAP, Guatemala City, Guatemala. [4]Moi University Medical Teaching Hospital, Eldoret, Kenya. [5]KLE University's JN Medical College, Belgaum, India. [6]Latta Medical Research Foundation, Indira Gandhi Medical School, Nagpur, India. [7]University of Zambia, Lusaka, Zambia. [8]Aga Khan University, Karachi, Pakistan. [9]Kinshasa School of Public Health, Kinshasa, Democratic Republic of the Congo. [10]University of Alabama at Birmingham, Birmingham, AL, USA. [11]Christiana Health Care, Newark, DE, USA. [12]Massachusetts General Hospital, Boston, MA, USA. [13]Indiana University, Indianapolis, IN, USA. [14]University of Colorado, Denver, CO, USA. [15]UNC Chapel Hill, Chapel Hill, NC, USA. [16]Perinatology and Pregnancy Branch, NICHD, Bethesda, MD, USA. [17]Cincinnati Children's Hospital, Cincinnati, OH, USA. [18]Columbia University Medical Center, New York, NY, USA.

Background

Maternal, fetal and newborn mortality rates remain high in low-resource settings [1-3]. A medical cause of death is an important first step in strategy development to reduce these deaths and to measure changes in death rates from specific causes [4-7]. To date, more than 35 systems have been developed to classify the cause of stillbirths alone, and other classification schemes attempt to define causes of neonatal and maternal deaths [8-12]. Most of these classification systems are best suited for high income settings because the tests to define cause of death are extensive. Few of the classification systems are targeted at low-resource settings where more than 98% of deaths occur. In many low-income countries, minimal resources are available for determining cause of death for mothers, much less cause of death for fetuses and newborns which occur much more frequently, and diagnostic tools such as autopsy, placental histology, X-ray, ultrasound and bacterial cultures are generally not available [13].

Dependence on detailed diagnostics makes many of the existing classification systems quite complicated. Many also use several different types of constructs to determine cause of death including primary and secondary causes, associated causes, contributing causes, underlying causes, or preventable causes [9-22]. One system for perinatal mortality, for example, attempts to determine a main cause, an underlying cause and contributing factors [17]. While such systems are useful for research or in areas where the resources are available to determine the many contributions to each death, these systems are too complicated for routine use, especially to ascertain cause of death on a population basis in low-resource settings [4]. The resources required to determine cause of death is important since few of the poorest countries routinely collect cause of death information [14].

The actual cause of death for any individual mother, fetus or newborn is rarely known with a great degree of certainty, especially in resource-poor areas. Some classification systems

Table 1 Causes of stillbirth, neonatal death and maternal death and their hierarchical position in the Global Network Classification System

	Comment
Stillbirth	
Maternal or fetal trauma	Significant maternal trauma especially if the maternal abdomen is involved or there is evidence of fetal trauma takes precedence as a cause of stillbirth over all other potential causes
Major Congenital anomaly	Major anomaly takes presedence as a cause of death over all other conditions except trauma
Maternal infection	Maternal malaria or syphilis or signs of amnionitis
Asphyxia	Based on the maternal or fetal condition noted including obstructed labor, abruption or previa characterized by antepartum bleeding, preeclampsia/eclampsia, fetal distress and cord complications
Complications of preterm labor	There are some early gestational age stillbirths, generally prior to 24 weeks, where the fetus apparently dies because it is unable to tolerate labor. These very preterm babies are usually not macerated since they usually have died close to delivery
Unknown	No other cause identified
Neonatal death	
Major Congenital anomaly	Significant congenital anomaly takes precedence as a cause of neonatal death
Sepsis/pneumonia/tetanus	The presence of these conditions take precedence as a cause of death except when an anomaly is present
Asphyxia	Breathing difficulties at birth with maternal condition noted including obstructed labor, bleeding, preeclampsia/eclampsia, fetal distress, cord complications, etc.
Complications of prematurity	Deaths in preterm infants not attributable to other causes. Since it is difficult to differentiate asphyxia from respiratory distress syndrome, we have arbitrarily assigned larger infants with respiratory distress to asphyxia and the smaller or earlier preterm infants to complications of prematurity.
Unknown	No other cause identified
Maternal Death	
Significant maternal trauma	Trauma takes precedence as a cause of maternal death
Abortion/miscarriage/medical termination of pregnancy/ectopic pregnancy	If the subject has a history of abortion or is less than 20 weeks, whether she had hemorrhage, sepsis or other conditions, the cause of death is considered an abortion
Infection	If there is no trauma or an abortion, the presence of significant infection takes precedence as a cause of maternal death
Hemorrhage	The most commonly attributed cause of maternal death in most settings
Hypertensive disease of pregnancy	If mother has a seizure, eclampsia is considered the cause of death. If she has only preeclampsia, other causes may take precedence
Thromboembolism	With no other obvious cause and sudden onset of severe respiratory distress and chest pain, the cause of death will be attributed to thromboembolism
Medical condition coincident to pregnancy	If a medical condition such as cancer, cardiac disease, severe anemia, or diabetes is present and there is no other cause of death, the death will be attributed to a medical condition
Unknown	No other cause identified

have attempted to categorize the degree of uncertainty about whether a specific condition caused a specific death by creating categories such as probable cause, possible cause or whether the condition was merely associated with that particular death [10]. While such systems might also be useful in high resource areas or in specific research projects, they are likely to be too resource-intense for population-based estimates.

A related issue for classification systems is the percent of deaths classified as of unknown cause. The more certainty required for classification, the greater the proportion of deaths classified as of unknown cause is likely to be. As an example, the percent of stillbirths classified as having an unknown cause varies widely between classification systems. Depending on the classification system [15] and the level of investigation [16], the proportion of unexplained stillbirths has ranged from 15% to more than 70%. Even in high-income countries, with advanced testing and autopsy, a significant proportion of stillbirths are classified as of undetermined cause [9,23].

Other factors important to all classification systems are how the cause of death is determined and who determines the cause of death [23-26]. A major concern with any cause of death classification system is the reliability of the cause of death determination, over time, for the same evaluator(s), and especially for evaluators in different locations, even when the same information is available. When different clinicians determine the cause of death for any specific case, even with the same information available, major differences in the cause of death often occur [25-28]. For example, for a preterm baby with difficulty breathing at birth, the cause of death may be variably classified as prematurity, respiratory distress syndrome (RDS), asphyxia or pneumonia by different classifiers. Similarly, an anencephalic baby who dies in the neonatal period likely dies of the anomaly itself, but also may die from an infection or asphyxia or both. Different classifiers could evaluate these cases and choose very different causes of death. Thus, in most classification systems, the determination of the primary cause of death may not depend only on the case data available but also

Table 2 Definitions to classify causes of stillbirth, neonatal and maternal death in the Global Network Classification System

Cause of death	Definition
Stillbirth	
Maternal or fetal trauma	Any trauma occurring to the mother during pregnancy including an accident, physical assault, or suicide and/or evidence of traumatic stress to the fetus at time of delivery including severe bruising, cephalohematoma, sub-conjunctival hemorrhage, large caput, long bone fracture, etc.)
Major congenital anomaly	Major congenital malformation or anomaly including neural tube defect, abdominal wall defect or other visible defects
Maternal infection	Evidence of maternal infection during pregnancy or delivery including being positive for malaria, syphilis or presence of fever, significant vaginal or fetal odor at delivery
Asphyxia – *may be associated with maternal preeclampsia/eclampsia, obstructed labor, antepartum hemorrhage, fetal distress or cord accidents*	**Preeclampsia/eclampsia** Characterized by hypertension (blood pressure 140/90 mg Hg) and proteinuria occurring after the 20th week of pregnancy. May include symptoms: severe headache, blurred vision, nausea and/or vomiting, abdominal pain and a diminished urinary output. Eclampsia is characterized by convulsions and coma and may be preceded by signs of pre-eclampsia or the onset may be rapid and sudden.
	Obstructed/prolonged labor Descent is arrested during labor due to an insurmountable barrier, despite strong uterine contractions and further progress cannot be made without assistance. Prolonged labor includes labor > one day.
	Heavy bleeding before delivery Blood loss of >1000 cc (>4 cups) prior to delivery
	Signs of fetal distress during labor Includes decreased fetal movements, fetal bradycardia (<120 beats per minute), fetal tachycardia (>160 beats per minute), and/or meconium stained liquor
	Cord complication Includes cord prolapse, cord around the neck, cord compression or cord rupture prior to delivery
Complications of preterm labor	Gestational age <32 weeks or birth weight <1500 g with evidence that the fetus died in labor or was not macerated
Neonatal death	
Major congenital anomaly	Includes major anomalies such as neural tube defect or anencephaly, abdominal wall defect, etc.
Infection	Signs include high temperature (fever; very warm to touch or >37.5C) or a very low temperature (cool to the touch or <35.5C); fits/seizures ≥2 days after birth; cloudy discharge, pus or bleeding at the umbilical stump; and for pneumonia, chest x-ray or clinical signs including poor feeding and irritability, as well as tachypnea, retractions, grunting, and hypoxemia.
Asphyxia	In term infants and preterm infants >2000 g: Breathing difficulties at birth, fits or seizures <2 days of birth; Infant received bag and mask or other resuscitation effort at birth; maternal complications associated with neonatal asphyxia including maternal preeclampsia/eclampsia, obstructed labor, breech presentation, twins and antepartum hemorrhage, and fetal distress and cord accidents. (see stillbirth causes for definitions)
Complications of prematurity	All deaths <34 weeks or <2000 gs not due to a congenital anomaly or infection are categorized as due to a complication of prematurity as are deaths in larger or late preterm infants not due to congenital anomaly, infection or asphyxia. Many of the deaths categorized as due to complications of prematurity are due to respiratory distress syndrome. These babies may require resuscitation at birth or develop breathing difficulties within hours of birth
Maternal death	
Trauma	Any trauma occurring to the mother during pregnancy including an accident, physical assault, or suicide
Abortion/miscarriage/ectopic pregnancy	Includes any spontaneous or induced pregnancy loss or death of fetus prior to 20 weeks gestation including ectopic pregnancy, defined as Implantation of an embryo somewhere other than the uterus, such as in one of the fallopian tubes

on idiosyncrasies of the classifiers. For this and other reasons, including lack of specific guidelines about how to classify cause of death, there have been large variations in cause of death by the system and evaluators [28-30]. In LIC different types of health care providers may classify causes of death differently [27]. But because there has been no gold standard for these evaluations, the actual cause of death is often unknown, and which type of provider comes closest to selecting the "true" cause of death is unclear. While physicians have traditionally been viewed as better at determining cause of death than providers with less

Table 2 Definitions to classify causes of stillbirth, neonatal and maternal death in the Global Network Classification System *(Continued)*

Eclampsia	One or more convulsion or state of unresponsiveness usually associate with hypertension and proteinuria
Hemorrhage	Heavy bleeding with a blood loss of >1000 cc or 4 cups before or after delivery and may be associated with any surgical procedure to stop maternal bleeding
Infection	Evidence of maternal infection during pregnancy or delivery including evidence of malaria, syphilis or presence of significant vaginal or fetal odor at delivery. Evidence of infection includes fever, defined as body temperature higher than normal limit or being very warm to the touch and chills defined as uncontrolled shivering
Preeclampsia	Blood pressure $\geq$140/90 mm Hg and proteinuria, headache, and may include stroke, loss of consciousness or paralysis
Thromboembolism	Acute shortness of breath and chest pain which may be associated with prolonged bed rest and lower limb venous thrombosis or clots
Medical conditions	If no other cause is defined, any medical condition such as severe anemia, diabetes, renal disease, etc.

training, whether this is the best use of physicians' or other trained providers' time is a concern in geographic areas with limited health provider availability.

There are two main types of classification systems, multi-causal and single causal [6,30-32]. The multicausal approach lists all potential causes and contributing factors, with rules to distinguish 'primary' vs 'underlying' or 'contributing causes.' This type of system may be more meaningful where resources are available to conduct extensive testing and perform analyses. Another type of system includes a hierarchy to select one primary cause of death, when multiple factors are identified and possibly causal [32]. While a limitation to selecting one primary cause of death is that important secondary or contributing factors or nuances for individual cases may be lost, choosing one primary cause helps to increase the consistency of results and likely makes the data easier to comprehend and use by policy makers [5,33]. Thus in addition to reproducibility of results, a single cause system should allow for more meaningful comparisons in the mortality rates associated with specific causes over time and across geographic areas.

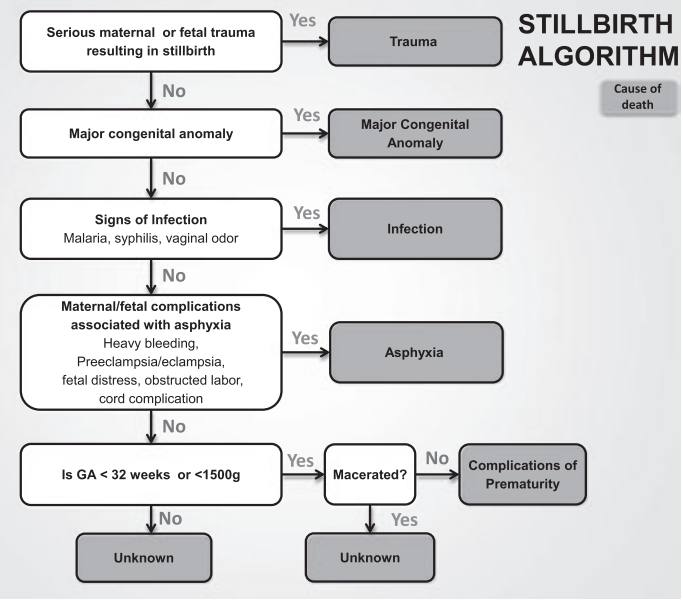


Figure 1 Algorithm to classify causes of stillbirth.

One mechanism to inform cause of death for low-resource settings is based on verbal autopsy (VA) [27,34-37]. VA systems have generally been used for determining cause of maternal deaths. VA requires lengthy family interviews which are a burden on the health system and thus are not practical to conduct on a population-basis. VA for stillbirth or neonatal deaths is more burdensome because they are more frequent than maternal deaths [27]. Furthermore, VA interviews may produce variability in assignment of a cause of death based on the classification system used and the person who assigns a cause of death [27]. Furthermore, in many VA systems, while the clinical information may be gathered in a consistent manner, with few exceptions, a coder determines cause of death, with the limitations of reproducibility noted above [35]. Finally, the diagnostic accuracy of VA has been weak in some field studies, with limited ability to accurately determine some specific causes of death [34,37].

Methods

Our objective was to develop reliable classification systems that would assign cause of maternal, fetal and neonatal death using the minimal amount of descriptive data and would not depend upon individual clinicians for the assignment of cause. Our goal is to increase consistency with a low burden on the health system. We elected to use data that are generally available in low-resource settings from the mother, family or caregivers and that require only basic equipment (eg, a scale for birth weight determination, blood pressure cuff, or thermometer). However, with increasing rates of facility delivery in low-resource settings, we also elected not to ignore hospital-based information, if available (eg, chest X-ray diagnosis of pneumonia). We sought to create a system to classify the primary causes of death, that was practical to use and consistent for deliveries occurring at home and other community settings as well as for hospital births. The system described below, the "Global Network Probable Cause of Death Classification" for stillbirth, maternal and newborn mortality was developed within the Global Network for Women's and Children's Health Research, a multi-country, research network with sites in Sub-Saharan Africa, Asia and Latin America funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development [38,39].

The underlying principle of the Global Network system was to collect basic and simple observational information related to the pregnancy and death. A second principle was that an algorithm would assign cause of death, removing personal choice or

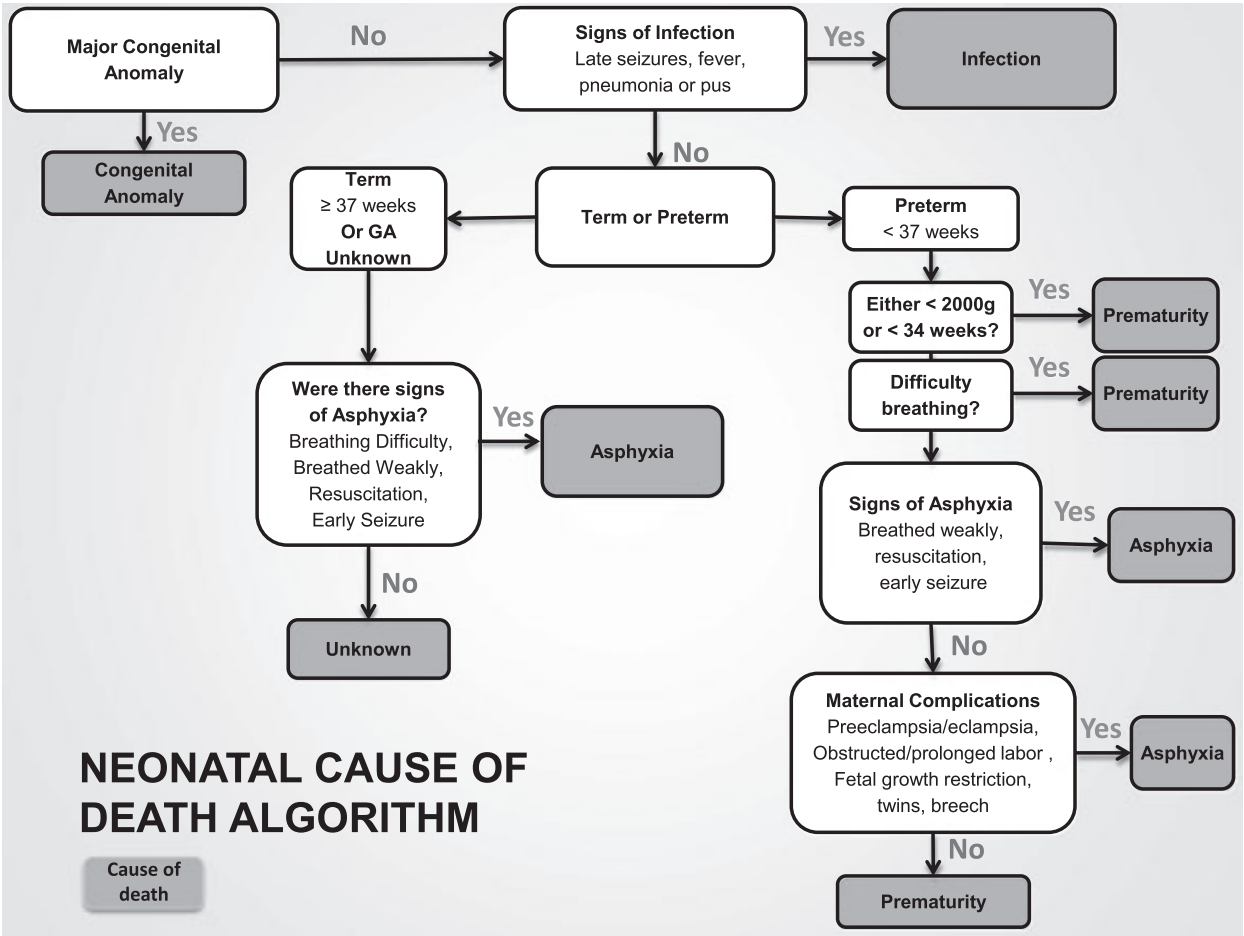


Figure 2 Algorithm to classify causes of neonatal death.

bias from the assignment. The algorithm uses a hierarchical classification system to determine one primary cause of death. The specific causes of stillbirth, neonatal and maternal death defined by this classification system are shown in Table 1 with the rationale for the hierarchy of the system; these causes align with ICD-10 first level classifications [31], as well as with major existing classification systems. Table 2 includes the specific definitions of each cause, as adapted for this system. The advantage of this methodology is that the system can determine which condition is most immediately associated with the death in a consistent manner across all cases. Although this system may at times classify cause of death differently than other systems, we viewed this possibility as acceptable because there is no gold standard for classifying cause of death, and our system has the attributes of transparency and reproducibility.

The classification system was designed as part of the Global Network's Maternal and Newborn Health Registry study, a population-based registry of pregnancy which obtains outcomes from consenting women through 6-weeks postpartum [38]. The institutional review boards and ethics committee at the participating study sites (Aga Khan University, Karachi, Pakistan; Kinshasa School of Public Health, Kinshasa, DRC; Moi University, Eldoret, Kenya; San Carlos University, Guatemala City, Guatemala; University of Zambia, Lusaka, Zambia) and their affiliated US partner institutions (University of Alabama at Birmingham, University of North Carolina at Chapel Hill, Columbia University, University of Indiana, Christiana Healthcare, and Massachusetts General Hospital) and the data coordinating center (RTI International) approved the study.

Results and discussion

The stillbirth classification algorithm

Stillbirths are generally considered to be deaths in utero occurring at 20 weeks gestation or greater, depending on the setting [40]. Among maternal, fetal and neonatal deaths, determining cause of stillbirth has historically been the most challenging type of death to define, as the fetus is not directly observed when death occurs [6]. To date, cause of death in stillbirths has generally been determined from the underlying maternal or obstetric conditions that may be directly or indirectly associated with the fetal death. Additionally, autopsy and placental data may be used to help classify of cause death in stillbirths in high resource settings. At least one high-income country system primarily attributes the cause of stillbirth to placental causes [16], and placental conditions are considered in many other stillbirth classification systems [41]. However, despite their value in determining cause of death in high-income settings, we have deliberately chosen not to include autopsy and placental findings in this classification system since autopsies are almost never done and placentas are rarely examined histologically in low-income settings.

Where antenatal care is limited and a significant proportion of deliveries occur in home or low-level clinics with community birth attendants [42], distinguishing stillbirth from early neonatal death has been problematic [43]. Thus, some authors have proposed a classification system in which 'intrapartum death' encompasses both stillbirths and early neonatal deaths due to intrapartum causes such as asphyxia [44]. To date, no system to determine cause of stillbirth with basic data has been

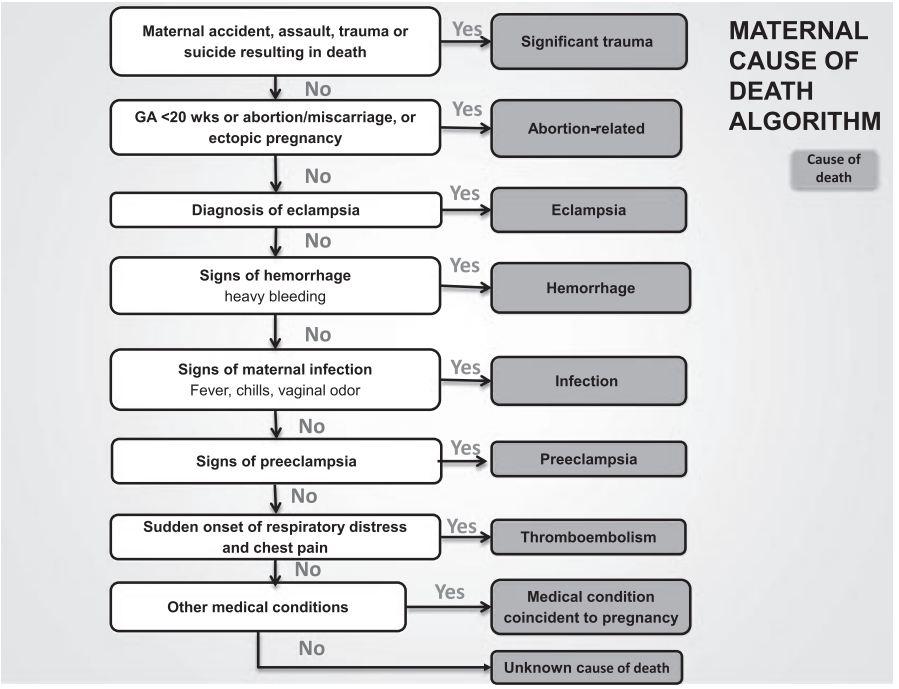


Figure 3 Algorithm to classify causes of maternal mortality.

widely used [6]. To address these issues with an emphasis on low-resource settings, our system first distinguishes stillbirth from miscarriage/abortion through utilizing the lower limit of 20 weeks gestation (or 500 g if GA is unavailable). We next distinguish stillbirth from neonatal death by whether any signs of life such as a heartbeat, crying, breathing or movement are present at delivery. Because distinguishing antepartum deaths from intrapartum deaths may be crucial for designing interventions in the appropriate time period, the system also considers whether signs of maceration are present, suggesting that the stillbirth likely occurred >12 hours prior to the delivery and was likely antepartum [45].

In low resource settings, for most stillbirths, whether antepartum or intrapartum, the final common pathway is most likely asphyxia. However, even with placental and autopsy data, it is difficult to prove that a fetus died of asphyxia. Thus we have chosen to focus on the presence of maternal and fetal conditions (eg abruption, preeclampsia) highly predictive of asphyxia. Therefore, signs and symptoms addressing maternal and fetal conditions that have been associated with stillbirth are also specified. These include obstructed labor, antepartum or intrapartum hemorrhage, preeclampsia/eclampsia, cord complications, fetal distress and intrauterine growth restriction.

The criteria for assigning a cause of stillbirth are shown in Table 2. Our hierarchical method of determining cause of stillbirth relies on a discreet data set. The algorithm first determines whether the stillbirth was associated with maternal or fetal trauma (ie, assault, suicide, accident, fetal trauma); if so, the cause of death is classified by algorithm as trauma. Second, if trauma did not occur and there is a major (visible) congenital anomaly, the death is categorized as due to a congenital anomaly. If neither trauma nor anomalies are identified and signs of maternal or fetal infection are present, the stillbirth is classified as due to infection. If none of the above are present and any of a list of maternal or fetal conditions associated with intrauterine asphyxia are present, the cause of death is classified as asphyxia. (The specific maternal or fetal condition likely leading to the asphyxia is noted.) In many areas, very preterm fetuses in labor even with distress are not delivered by cesarean section because they do not survive in the neonatal period and are allowed to die in labor. We therefore have created a category of stillbirth due to preterm labor to capture these stillbirths. If the stillbirth does not fit into one of these categories, only then is it classified by algorithm as of unknown cause. Thus, using these categories, the stillbirth cause of death is classified by the major conditions associated with the fetal death (Figure 1).

Neonatal death

Neonatal deaths are defined as live births with a death occurring at less than 28 days. The main conditions associated with neonatal death in low-resource areas are asphyxia, sepsis/infection, and complications of preterm birth, with major congenital anomalies less commonly a cause (by percentage) in low compared to high and middle-income countries.

There are many difficulties in assigning cause of death in neonates even in high-income countries with X-ray, culture and autopsy availability. For example differentiating sepsis and asphyxia is difficult even in term births, while in preterm births where respiratory distress syndrome is a common cause of respiratory failure and death, distinguishing among these three causes of neonatal death is even more difficult.

The criteria for assigning a cause of neonatal death are shown in Table 2. In our system, we first determine if a major congenital anomaly is present (Figure 2). If so, the algorithm assigns congenital anomaly as cause of death. If an anomaly is not present and signs of infection are present (eg, tetanus, omphalitis, sepsis, pneumonia (signs such as late onset respiratory difficulty, fever or hypothermia or X-ray if available), infection is assigned as the cause of death. If neither an anomaly nor infection is present, the algorithm then separates the deaths into those occurring in term or preterm infants. In the term infants, if there were signs of breathing difficulty or no cry at birth, the algorithm assigns the cause of death as birth asphyxia. The maternal or fetal condition likely associated with the birth

asphyxia is noted. If no signs of difficulty breathing at birth or respiratory distress were present, the cause of death is assigned as unknown.

For preterm infants, especially those ≥2000 grams or ≥34 weeks at birth, among those with breathing difficulties or no cry at birth, asphyxia is a common cause of death [46]. In those infants, if breathing difficulty or no cry is present at birth, and maternal conditions such as abruption associated with asphyxia are present, the algorithm assigns cause of death as asphyxia. Otherwise, the cause of death is assigned to prematurity. If the infant is <2000 grams or <34 weeks at birth, the algorithm assigns the cause of death as being due to preterm birth regardless of whether respiratory distress is present, since RDS is common and pneumonia has previously been considered and rejected as a cause. In infants born at <37 weeks, with no congenital anomaly or infection, the algorithm does not classify any death as of unknown cause, because prematurity is always considered as the primary contributor to death.

Maternal death

Maternal deaths generally are defined as those that occur at any time during pregnancy up to 6 weeks postpartum, regardless of the cause. Maternal deaths are rare compared to stillbirths and neonatal deaths, and fewer classification systems exist to assign cause of maternal death. Furthermore, compared to neonatal deaths or stillbirths, maternal deaths are less likely to have an 'unknown' cause of death. However, some reports suggest misclassification of maternal deaths (ie, not recognizing a woman was pregnant at time of her death), with under-reporting of maternal mortality. Maternal deaths have generally been classified as directly or indirectly associated with pregnancy (eg medical causes not brought on or exacerbated by the pregnancy or trauma) [47]. Obstetric conditions directly associated with maternal death include hypertensive diseases of pregnancy (preeclampsia/eclampsia), obstetric hemorrhage (ante or postpartum, with or without severe anemia), sepsis/infection and thromboembolism. Obstructed labor may be associated with maternal death, leading to either hemorrhage or severe infection but the primary cause of death in the current World Health Organization (WHO) international classification system (ICD-10) would be infection or hemorrhage, not obstructed labor. Deaths associated with ruptured uterus are presumed to be secondary to hemorrhage. Conversely, abortion related deaths result from infection or hemorrhage, but deaths occurring at less than 20 weeks gestational age, including from ectopic pregnancy, are classified as abortion related. Indirect causes of maternal death include trauma or medical conditions such as cardiac disease, cancer, or diabetes.

In the Global Network classification system, to assign a cause of maternal death, the major clinical signs and symptoms most often associated with maternal death are identified and defined (Table 2). Next, we developed an algorithm to assign cause of death based on the clinical signs (Figure 3). The algorithm first identifies significant maternal trauma and if present, the cause of death is trauma. If there is no trauma and the pregnancy is less than 20 weeks or an abortion was induced at ≥20 weeks, the cause of maternal death is classified as abortion related. If neither of these is present, and the woman experienced a seizure, eclampsia is considered the cause of death. If none of these are present and any signs of hemorrhage are present, hemorrhage is assigned as the cause of death. If none of the above are present and signs of infection are present, infection is assigned as the cause of death. Next, other signs of hypertensive disease and especially preeclampsia are handled in a similar manner. If at this point, acute shortness of breath and chest pain are present, thromboembolism would be considered the cause of death. Finally, if none of the above are present, the algorithm considers medical conditions not directly associated with the pregnancy, such as renal disease, heart disease, cancer or diabetes, and if any of these are present, the medical condition is assigned as the cause of death. If none of the above is present, the cause of death is classified as unknown.

Conclusions

The Global Network classification system uses minimal, basic data from the mother, family or lay-health providers. No laboratory tests, placental examinations or autopsies are necessary. Easily identifiable signs are noted and collected in a standard way and entered into a database. The cause of death is then assigned by an algorithm. No person assigns the actual cause of death which eliminates a source of inconsistency and bias. Thus the major strengths are consistency and transparency, with an ability to provide comparability across time or regions with minimal burden on the healthcare system. Even if one does not completely agree with the algorithm, the method of assignment is transparent. Also, since all data used to inform the cause of death assignment reside in the database, alterations and/or improvements in the algorithm at a later time will permit reclassification of the cause of death.

The system assigns a single cause of death, although, the algorithm could be altered to select several possible causes if that output is desired. For example, using this system in addition to the primary cause, other conditions that also were present as secondary conditions could be characterized without relying on the subjective judgment of researchers or caregivers. Additionally, other clinical or laboratory questions that might better help to assign cause of death could be added, depending on available resources and the setting where the death occurred. For now, however, we believe that the assignment of a single cause of death is sufficient to guide most public health and medical system policy decisions. More nuanced assignment of cause of death, such as identification of the type of infection that caused a death, would require additional data and is beyond the scope of this system. The system uses the major causes of death that have been well-established, and are commonly used for cause of death classifications, especially in low-resource settings. These attributes make this system potentially useful both for research and public health policy purposes.

We recognize that this system necessarily is a simplification compared to more complicated systems, and subtle and rare causes of death in low-income settings may be missed. It also does not attempt to address social or other factors that may contribute in low-resource settings. Preventable causes of death are not specifically addressed as such. However, with these limitations, the major causes of death related to pregnancy are collected and the portion of deaths attributable to the major causes can be quantified.

We have developed a system to classify causes of death for stillbirth, neonatal and maternal death that should be applicable for low-resource settings. In these areas, where most pregnancy-related mortality occurs, reliable and reproducible classification of maternal, fetal and neonatal death is needed both to advance research and to inform public health strategies to reduce

pregnancy-related mortality. While preliminary analyses have been done to address the system, validation of the system is ultimately necessary, and this system should be compared to other classification systems. A reliable system to determine cause of death will ultimately serve to inform public health strategies necessary to reduce the high maternal, fetal and newborn mortality burden in low-resource settings.

References

1. Lozano R, Wang H, Foreman KJ, Rajaratnam JK, Naghavi M, Marcus JR, et al. Progress towards Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. Lancet. 2011;378(9797):1139–65.
2. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, Shackelford KA, Steiner C, Heuton KR, et al. Global, regional, and national levels and causes of maternal mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9947):980–1004.
3. McClure EM, Pasha O, Goudar SS, Chomba E, Garces A, Tshefu A, et al. Epidemiology of stillbirth in low-middle income countries: a Global Network Study. Acta Obstet Gynecol Scand. 2011;90(12):1379–85.
4. Frøen JF, Gordijn SJ, Abdel-Aleem H, Bergsjø P, Betran A, Duke CW, et al. Making stillbirths count, making numbers talk — issues in data collection for stillbirths. BMC Pregnancy Childbirth. 2009;9:58.
5. Lawn JE, Osrin D, Adler A, Cousens S. Four million neonatal deaths: counting and attribution of cause of death. Paediatr Perinat Epidemiol. 2008;22(5):410–6.
6. Flenady V, Froen JF, Pinar H, Torabi R, Saastad E, Guyon G, et al. An evaluation of classification systems for stillbirth. BMC Pregnancy Childbirth. 2009;9:24.
7. Edmond KM, Quigley MA, Zandoh C, Danso S, Hurt C, Owusu Agyei S, et al. Aetiology of stillbirths and neonatal deaths in rural Ghana: implications for health programming in developing countries. Paediatr Perinat Epidemiol. 2008;22(5):430–7.
8. Agampodi S, Wickramage K, Agampodi T, Thennakoon U, Jayathilaka N, Karunarathna D, et al. Maternal mortality revisited: the application of the new ICD-MM classification system in reference to maternal deaths in Sri Lanka. Reprod Health. 2014;11(1):17.
9. Ego A, Zeitlin J, Batailler P, Cornec S, Fondeur A, Baran-Marszak M, et al. Stillbirth classification in population-based data and role of fetal growth restriction: the example of RECODE. BMC Pregnancy Childbirth. 2013;13:182.
10. Dudley DJ, Goldenberg R, Conway D, Stillbirth Research Collaborative Network, Dudley DJ, Goldenberg R, et al. A new system for determining the causes of stillbirth. Obstet Gynecol. 2010;116(2 Pt 1):254–60.
11. Reddy UM, Goldenberg R, Silver R, Smith GC, Pauli RM, Wapner RJ, et al. Stillbirth classification–developing an international consensus for research: executive summary of a National Institute of Child Health and Human Development workshop. Obstet Gynecol. 2009;114(4):901–14.
12. Chan A, King JF, Flenady V, Haslam RH, Tudehope DI. Classification of perinatal deaths: development of the Australian and New Zealand classifications. J Paediatr Child Health. 2004;40(7):340–7.
13. Committee on Genetics. ACOG Committee Opinion No. 383. Evaluation of stillbirths and neonatal deaths. Obstet Gynecol. 2007;110(4):963–6.
14. Mahapatra P, Shibuya K, Lopez AD, Coullare F, Notzon FC, Rao C, et al. Civil registration systems and vital statistics: successes and missed opportunities. Lancet. 2007;370(9599):1653–63.
15. Frøen JF, Pinar H, Flenady V, Bahrin S, Charles A, Chauke L, et al. Causes of death and associated conditions (Codac): a utilitarian approach to the classification of perinatal deaths. BMC Pregnancy Childbirth. 2009;9:22.
16. Korteweg FJ, Gordijn SJ, Timmer A, Holm JP, Ravisé JM, Erwich JJ. A placental cause of intra-uterine fetal death depends on the perinatal mortality classification system used. Placenta. 2008;29(1):71–80.
17. Varli IH, Petersson K, Bottinga R, Bremme K, Hofsjö A, Holm M, et al. The Stockholm classification of stillbirth. Acta Obstet Gynecol Scand. 2008;87(11):1202–12.
18. Measey M, Charles A, d'Espaignet E, Harrison C, Douglass C. Aetiology of stillbirth: unexplored is not unexplained. Aust N Z J Public Health. 2007;31:5.
19. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. BMJ. 2005;331(7525):1113–7.
20. CESDI. Confidential Enquiry into Stillbirths and Deaths in Infancy: 8th Annual Report. London: Maternal and Child Health Research Consortium; 2001.
21. Korteweg FJ, Erwich JJ, Timmer A, van der Meer J, Ravisé JM, Veeger NJ, et al. Evaluation of 1025 fetal deaths: proposed diagnostic workup. Am J Obstet Gynecol. 2012;206(1):53. e1-53.e12.
22. Christiansen LR, Collins KA. Pregnancy-associated deaths: a 15-year retrospective study and overall review of maternal pathophysiology. Am J Forensic Med Pathol. 2006;27(1):11–9.
23. Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY, et al. Stillbirths: the way forward in high-income countries. Lancet. 2011;377 (9778):1703–17.
24. Manandhar SR, Manandhar DS, Shrestha J, Karki C. Analysis of perinatal deaths and ascertaining perinatal mortality trend in a hospital. J Nepal Health Res Counc. 2011;9(2):150–3.
25. Hirst JE, Ha LT, Jeffery HE. Reducing the proportion of stillborn babies classified as unexplained in Vietnam by application of the PSANZ clinical practice guideline. Aust N Z J Obstet Gynaecol. 2012;52(1):62–6.
26. Kent AL, Dahlstrom JE, Ellwood D, Bourne M, ACT Perinatal Mortality Committee. Systematic multidisciplinary approach to reporting perinatal mortality: lessons from a five-year regional review. Aust N Z J Obstet Gynaecol. 2009;49(5):472–7.
27. Engmann C, Jehan I, Ditekemena J, Garces A, Phiri M, Mazariegos M, et al. An alternative strategy for perinatal verbal autopsy coding: single versus multiple coders. Trop Med Int Health. 2011;16(1):18–29.
28. Woods CR, Davis DW, Duncan SD, Myers JA, O'Shea TM. Variation in classification of live birth with newborn period death versus fetal death at the local level may impact reported infant mortality rate. BMC Pediatr. 2014;14:108.
29. Lawn JE, Gravett MG, Nunes TM, Rubens CE, Stanton C, GAPPS Review Group. Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data. BMC Pregnancy Childbirth. 2010;10 Suppl 1:S1.
30. Gordijn SJ, Korteweg FJ, Erwich JJ, Holm JP, van Diem MT, Bergman KA, et al. A multilayered approach for the analysis of perinatal mortality using different classification systems.

Eur J Obstet Gynecol Reprod Biol. 2009;144 (2):99–104.
31. WHO: ICD-10. International statistical classification of diseases and related health problems: tenth revision. In: Instruction manual. Secondth ed. Geneva: World Health Organization; 2004.
32. Alberman E, Blatchley N, Botting B, Schuman J, Dunn A. Medical causes on stillbirth certificates in England and Wales: distribution and results of hierarchical classifications tested by the Office for National Statistics. Br J Obstet Gynaecol. 1997;104(9):1043–9.
33. Baqui AH, Darmstadt GL, Williams EK, Kumar V, Kiran TU, Panwar D, et al. Rates, timing and causes of neonatal deaths in rural India: implications for neonatal health programmes. Bull World Health Organ. 2006;84(9):706–13.
34. Setel PW, Whiting DR, Hemed Y, Chandramohan D, Wolfson LJ, Alberti KG, et al. Validity of verbal autopsy procedures for determining cause of death in Tanzania. Trop Med Int Health. 2006;11(5):681–96.
35. Byass P, Chandramohan D, Clark SJ, D'Ambruoso L, Fottrell E, Graham WJ, et al. Strengthening standardised interpretation of verbal autopsy data: the new InterVA-4 tool. Glob Health Action. 2012;5:1–8.
36. Engmann C, Garces A, Jehan I, Ditekemena J, Phiri M, Mazariegos M, et al. Causes of community stillbirths and early neonatal deaths in low-income countries using verbal autopsy: an International. Multicenter Study J Perinatol. 2012;32(8):585–92.
37. Edmond KM, Quigley MA, Zandoh C, Danso S, Hurt C, Owusu Agyei S, et al. Diagnostic accuracy of verbal autopsies in ascertaining the causes of stillbirths and neonatal deaths in rural Ghana. Paediatr Perinat Epidemiol. 2008;22(5):417–29.
38. Goudar SS, Carlo WA, McClure EM, Pasha O, Patel A, Esamai F, et al. The Maternal and Newborn Health Registry Study of the Global Network for Women's and Children's Health Research. Int J Gynaecol Obstet. 2012;118(3):190–3.
39. Saleem S, McClure EM, Goudar SS, Patel A, Esamai F, Garces A, et al. A prospective study of maternal, fetal and neonatal deaths in low- and middle-income countries. Bull World Health Organ. 2014;92(8):605–12.
40. McClure EM, Saleem S, Pasha O, Goldenberg RL. Stillbirth in developing countries: a review of causes, risk factors and prevention strategies. J Matern Fetal Neonatal Med. 2009;22(3):183–90.
41. Pinar H, Goldenberg RL, Koch MA, Heim-Hall J, Hawkins HK, Shehata B, et al. Placental findings in singleton stillbirths. Obstet Gynecol. 2014;123(2 Pt 1):325–36.
42. Garces A, McClure EM, Chomba E, Patel A, Pasha O, Tshefu A, et al. Home birth attendants in low income countries: who are they and what do they do? BMC Pregnancy Childbirth. 2012;12:34.
43. Goldenberg RL, McClure EM, Jobe AH, Kamath-Rayne BD, Gravette MG, Rubens CE. Stillbirths and neonatal mortality as outcomes. Int J Gynaecol Obstet. 2013;123(3):252–3.
44. Lawn J, Lee A, Kinney M, Sibley L, Carlo W, Paul V, et al. Two million intrapartum-related stillbirths and deaths: where, why, and what can be done? Int J Gynecol Obstet. 2009;107:S5–19.
45. Gold KJ, Abdul-Mumin AR, Boggs ME, Opare-Addo HS, Lieberman RW. Assessment of "fresh" versus "macerated" as accurate markers of time since intrauterine fetal demise in low-income countries. Int J Gynaecol Obstet. 2014;125(3):223–7.
46. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10 Suppl 1:S2.
47. Say L, Chou D, Gemmill A, Tunçalp O, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33.

Antimicrobial therapy in neonatal intensive care unit

Chryssoula Tzialla,[1] Alessandro Borghesi,[1] Gregorio Serra,[2] Mauro Stronati1 and Giovanni Corsello[2]

Abstract
Severe infections represent the main cause of neonatal mortality accounting for more than one million neonatal deaths worldwide every year. Antibiotics are the most commonly prescribed medications in neonatal intensive care units (NICUs) and in industrialized countries about 1% of neonates are exposed to antibiotic therapy. Sepsis has often nonspecific signs and symptoms and empiric antimicrobial therapy is promptly initiated in high risk of sepsis or symptomatic infants. However continued use of empiric broad-spectrum antibiotic treatment in the setting of negative cultures especially in preterm infants may not be harmless.

The benefits of antibiotic therapy when indicated are clearly enormous, but the continued use of antibiotics without any microbiological justification is dangerous and only leads to adverse events. The purpose of this review is to highlight the inappropriate use of antibiotics in the NICUs, to exam the impact of antibiotic treatment in preterm infants with negative cultures and to summarize existing knowledge regarding the appropriate choice of antimicrobial agents and optimal duration of therapy in neonates with suspected or culture-proven sepsis in order to prevent serious consequences.

Introduction

Sepsis represent the main cause of neonatal mortality accounting for more than one million neonatal deaths worldwide every year, and antibiotics are the most commonly prescribed medications in the neonatal intensive care units (NICU) [1,2]. Sepsis has often nonspecific signs and implies in serious consequences; as a result, empirical antimicrobial therapy is promptly initiated in symptomatic infants with suspected sepsis after obtaining biological material for culture [1]. However, neonates who do not have infection often receive antimicrobial agents during hospital stay, and inappropriate empirical antibiotic treatment may have serious side effects [3].

Nearly all extremely low birth weight infants (ELBW) infants admitted to a NICU receive an empirical antibiotic treatment in the first postnatal days, in spite of sterile cultures and low incidence of culture-proven bacterial sepsis in this population [1,3,4]. This observation has been confirmed by a study of the National Institute of Child Health and Human Development National Research Network on 6956 very low birth weight (VLBW) infants, showing that 56% of all infants received at least one course of antibiotic treatment, even if proven sepsis was diagnosed in only 21% of all infants [5].

In this review we describe the use of antibiotics in the NICU, focusing on the potential serious adverse effects of inappropriate use; we identify the opportunities for improving antibiotic prescription in the NICU, and we discuss the future directions of antimicrobial therapy.

Epidemiology of bacterial infections in the NICU

Neonatal sepsis can be classified as early-onset (EOS) and late-onset (LOS) sepsis. EOS is most often caused by group B streptococcus (GBS) (43%), followed by Escherichia coli (15.5-29%). Among VLBW infants, the rate of Escherichia coli infection exceeds that of GBS infection (5.1 vs 2.1 per 1000 live births) [3].

LOS is mainly caused by Gram-positive bacteria (GPB) (49%), most often coagulase-negative Staphylococcus (CoNS) (45%). Gram-negative LOS is less common (23%), but is associated with greater mortality in the NICU (19-36%) [6,7].

As showed by various studies, antibiotics such as ampicillin, gentamicin and cefotaxime commonly used for empirical therapy appear to be appropriate. In a recent study, investigators revealed that more than 94% of the EOS isolates were susceptible to penicillin and gentamicin, to amoxicillin and cefotaxime and to cefotaxime alone. The LOS isolates (excluding CONS) had a more than 96% susceptibility to flucloxacillin or amoxicillin and gentamicin, to amoxicillin and cefotaxime, but only 78% to cefotaxime alone. The investigators concluded that cefotaxime should not be included in the empiric regimen of suspected sepsis, because of lower susceptibility levels [7].

Blackburn et al, in a study of neonatal septicemia found that only 1.4% of Gram-negative bacteria (GNB) were resistant to penicillin plus gentamicin, whereas 10.4% of isolates tested against amoxicillin plus cefotaxime were resistant to this association [8].

Most hospital acquired CoNS are resistant to many commonly prescribed antibiotics. In the NICU, enterococci are less frequently isolated than staphylococcal species. Nevertheless,

[1]Neonatologia, Patologia Neonatale e Terapia Intensiva neonatale, Fondazione IRCCS Policlinico San Matteo, Piazzale Golgi 19, 27100 Pavia, Italy. [2]Terapia Intensiva Neonatale Dipartimento di Scienze per la Promozione della Salute e Materno Infantile "G. D'Alessandro", Università degli Studi di Palermo, Via Alfonso Giordano, 390127 Palermo, Italy.

ampicillin-resistant, and, more recently, vancomycin-resistant enterococci have been described and have become endemic in some NICUs [9].

GNB are often resistant to at least one class of antibiotics usually used, and bacteria that are multi- or extensively-resistant to conventional antibiotics are frequently isolated. Pan-resistant pathogens are rarely isolated in the NICUs, where resistance is most frequently found to piperacillin-tazobactam, ceftazidime, and/or gentamicin [9,10].

Moreover, the emergence of extended-spectrum β-lactamase (ESBL)-producing GNB confers resistance to penicillins and cephalosporins, often coexisting with resistance to other antibiotic categories as fluoroquinolones and aminoglycosides [9,11].

Risks associated with empirical administration of broad-spectrum antibiotics

The use of broad-spectrum antibiotics is associated with different adverse effects: alteration of gut colonization, emergency of resistant strains, and increasing risk of Candida colonization and subsequent invasive candidiasis [4].

All antibiotics can alter gut colonization of the patient, promoting either antibiotic resistance among normal commensal organisms or the emergence of other pathogens [4,12].

A number of in vitro and in vivo studies have shown that, although short courses of carbapanems and third-generation cephalosporins cover a broad spectrum of bacteria, their prolonged and intensive use selects resistant bacteria. Overuse of third-generation cephalosporins favors the emergence of ESBL-producing strains of GNB in NICUs [10,13].

In order to study the effects of empirical antibiotics on the emergence of resistant pathogens, de Man et al. [14] examined 436 infants admitted to 2 NICUs who were assigned initially to either a narrow-spectrum antibiotic regimen (penicillin or flucloxacillin plus tobramycin) or a broad-spectrum regimen (amoxicillin plus cefotaxime) and exchanged regimens after 6 months. The investigators demonstrated that the relative risk for colonization with strains resistant to empirical therapy per 1000 patients at risk was 18-fold higher in the broad-spectrum regimen group than in the narrow-spectrum regimen group.

Exposure to broad spectrum antibiotics has been also associated with the emergence of invasive candidiasis. In a cohort of 3,702 ELBW infants, previous use of third generation cephalosporins or carbapenems were associated with an increased risk of invasive candidiasis (OR 2.2, 95% CI 1.4-3.3). The incidence of candidiasis between centers varied from 2.4% to 20.2% and correlated with the average number of days of broad spectrum antibiotic use per infant with sterile cultures throughout hospitalization [15].

A multicenter cohort study of 128,914 neonates, revealed that the use of ampicillin/cefotaxime during the first 3 days after birth is associated with an increased risk of death before discharge (OR 1.5, 95% CI 1.4-1.7) compared with the use of ampicillin/gentamicin, even if the authors highlighted that this observation may be limited by selection bias. The authors concluded that, for patients receiving ampicillin, the concurrent use of cefotaxime during the first three days after birth is either a surrogate for an unrecognized factor or is itself associated with an increased risk of death, compared with the concurrent use of gentamicin [1].

Adverse effects of prolonged courses of empirical antibiotic treatment

For culture-proven sepsis a full course of antibiotics is indicated. Conversely, concerns remain about the optimal length of antibiotic therapy for clinical, not microbiologically demonstrated sepsis. Recent cohort studies show an association between the duration of empirical antibiotic therapy and mortality, necrotizing enterocolitis (NEC) and LOS.

Cotten et al. [16] conducted a retrospective cohort analysis of 5,693 ELBW infants admitted to 19 tertiary centers. Of 5,693 infants, 4,039 survived >5 days, received initial empirical antibiotic treatment and had sterile initial blood culture at 72 hours of life. In a multivariate analysis adjusted for risk factors, prolonged duration of therapy was associated with increased odds of NEC or death or death alone. Each additional day of antibiotic therapy was associated with a 4% increase in the odds of NEC or death, a 7% increase in the odds of NEC alone and a 16% increase in the odds of death alone.

A retrospective 2:1 control case analysis examined the association between antibiotic exposure and the risk of NEC. When neonates with sepsis were removed from cohort, antibiotic

Table 1 Choice of antibiotics

EOS	Penicillin + gentamicin
	- if *Listeria monocytogenes*: amoxicillin + gentamicin
	- if *S.aureus*: flucloxacillin + gentamicin
LOS	*First line*: flucloxacillin + gentamicin
	Second line:
	- vancomycin + gentamicin (with caution)
	- vancomycin + piperacillin/tazobactam (to extend Gram-negative cover)
	Third line: meropenem, ciprofloxacin
Meningitis	*First line*: cefotaxime with amoxicillin ± gentamicin
	Second line: meropenem
Gram positive multiresistant bacteria	Currently: glycopeptide antibiotics are the mainstay of therapy, especially vancomycin; if necessary linezolid, clindamycin, rifampicin and daptomycin could be alternative regimens
	In the future: novel cephalosporins like ceftaroline and ceftobiprole; novel lipoglycopeptide antibiotics are oritavacin and dalbavancin; telavacin has been approved in the USA in adults
Gram negative multiresistant bacteria	Currently: aminoglycosides and cephalosporins are the antibiotics of choice; carbapenems, colistin, co-trimoxazole, ticarcillin-clavulanic acid could be the an alternative; fluoroquinolone, ciprofloxacin, tigecycline and tetraciclins could only be justified in extreme cases.
	In the future: treatment options are extremely limited

Modified from: Russell AB, Sharland M, Heath PT. Improving antibiotic prescribing in neonatal units: time to act. *Arch Dis Fetal Neonatal* 2012; 97:F141-146 and Gray JW, Patel M. Management of antibiotic-resistant infection in the newborn. *Arch Dis Child Educ Pract* 2011 Aug;96(4):122–7.

duration increased the risk of NEC by approximately 20% per day of exposure (OR = 1.2). Exposure for >10 days resulted in nearly a threefold increase in the risk of developing NEC [17].

Prolonged antibiotic therapy has also been associated with LOS. A retrospective study of 365 infants ≤32 weeks gestational age (GA) and ≤1500 g birth weight (BW), who survived free of sepsis and NEC in the first week of life, found that prolonged antibiotic therapy (≥5 days) initiated on the day of birth was independently associated with LOS alone and the composite outcome of LOS, NEC or death. Each additional day of antibiotics was associated with a significantly increased risk of these outcomes. For infants who received any initial empirical antibiotic exposure, the adjusted attributable risk for LOS, NEC or death was 32% and the number needed to harm was 3 [18].

Recommendations for a judicious use of antibiotics

Choice of the antibiotic agent

Concerning the newborn infants, there are no randomized controlled trials that can definitely prove the best choice of antibiotics. However, many authors agree that an association of a penicillin or semisynthetic penicillin (ampicillin) together with an aminoglycoside is effective against microorganisms causing EOS, and therefore can be considered the best empirical regimen [10,19,20].

For the treatment of suspected LOS, different authors agree that the best regimen is an antistaphylococcal penicillin (oxacillin, flucloxacillin) together with an aminoglycoside; the choice of vancomycin should be restricted to microbiologically demonstrated cases of methicillin-resistant Staphylococcus aureus (MRSA) or CoNS [19,20].

In a recent review, Sivanandan et al. [21] recommended the same antibiotic combinations for empirical therapy of EOS and LOS in neonates. In case of LOS in an instable neonate and in areas where MRSA is prevalent, vancomycin and a third-generation cephalosporin should be considered. For the treatment of suspected early-onset meningitis the authors recommended a combination of ampicillin and aminoglycoside or ampicillin and cefotaxime, and in case of late-onset meningitis a combination of an antistaphilococcal antibiotic (nafcillin or vancomycin) plus a third-generation cephalosporin with or without aminoglycoside.

Russel et al. [12] for the therapy of meningitis suggest as first line treatment the combination of cefotaxime and amoxicillin with or without gentamicin.

Different authors state that empirical therapy should never be started with a broad spectrum antibiotic such as a third-generation cephalosporin or a carbapenem, and their use should be restricted to particular cases [13,19]. Gray et al. [10] suggest the use of piperacillin-tazobactam in the units where aminoglycoside-resistant GBN are prevalent as an alternative to third generation cephalosporins.

Russel et al. in a recent review, based on epidemiological data from UK neonatal infection surveillance studies, suggest for EOS and LOS treatment, antibiotic strategies reported in Table 1 [12].

Duration of the antibiotic course

Culture-proven neonatal sepsis is treated with full course of appropriate antibiotics; the appropriate duration of the antibiotic course is more difficult to be established in case of suspected (clinical) sepsis with negative cultures. Usually, antibiotics are discontinued as soon as blood cultures are confirmed negative (48–72 hours), and if laboratory results and the evolution of the clinical signs allow to exclude an infection [15,21-24].

In case of abnormal laboratory tests [white blood cell count and C-reactive protein (CRP) at age 6–12 h] in well-appearing neonate with negative blood culture Polin and the Committee on Fetus and Newborn [11] (COFN) suggest to continue empiric antibiotic therapy if mother received antibiotics during labor and delivery in case of infants <37 weeks' gestation with risk factors for sepsis and infants ≥ 37 weeks' gestation born from mothers with chorioamnionitis.

The algorithms for duration of empiric therapy when cultures are sterile suggested by COFN generated discussion about the lack of strong supportive evidence to guide decisions to stop antimicrobials at 48 h in certain cases.

Cotten et al. [25] in a recent review highlight that current studies are inadequate to specify appropriate testing a timing of diagnostic tests in all situations in which empirical therapy have been started. The authors offer the following suggestions for the management of term and late preterm neonates on empirical therapy for EOS with negative cultures at 48 postnatal hours: i) continuation of treatment for 7 days if clinical signs of sepsis persist over 24 hours; ii) stop antibiotics at 48 hours in asymptomatic neonates with initial (4 postnatal hours) normal complete blood count (initial laboratory tests drawn by risk factors), and in neonates with transient clinical signs (lasting less than 24 h), and abnormal initial complete blood count, if serial CRP measurements at 24 and 48 hours are low in a well-appearing neonate.

In case of culture-proven sepsis, Sivanandan et al [21] suggest that it is reasonable to treat for 10–14 days with appropriate antimicrobial agents infants with blood culture-proven sepsis without meningitis. However, in selected situations [ie neonates >32 weeks GA and >1500 g BW, who became asymptomatic with 5 days of appropriate therapy], it is reasonable to discontinue antibiotics at 7–10 days if laboratory results are normal and cultures are sterile in a well-appearing child. For neonatal meningitis, the same authors suggest a duration of therapy of 14 to 21 days for GBS, ≥ 21 days for Lysteria monocytogenes, a minimum of 21 days for Gram-negative meningitis and 4 to 6 weeks in cases complicated with intracranial abscesses.

Therapies for resistant pathogens

Even though an increase in vancomycin MIC values, within the susceptible range, has been registered among isolates of MRSA, CoNS or S. aureus strains vancomycin-intermediate or vancomycin-resistant have not been isolated from a NICU population so far. Consequently, glycopeptides remain an appropriate treatment for most staphylococcal infections in this setting [9,26]. However in case of unresponsive Gram-positive infections, linezolid has been the most used in neonatology, even if the use of daptomycin have been described in few reports in case of persistent staphylococcal bacteremia in neonates [26].

Several novel antibiotics active against GPB are currently in diverse phases of development and clinical trials are ongoing. In particular, advanced-generation cephalosporins like ceftaroline and ceftobiprole with activity against multidrug-resistant staphylococci have been reported in adults [26,27], as well as

lipoglycopeptides agents with activity against multidrug-resistant gram-positive pathogens like oritavancin and dalbavancin and telavancin. All three agents are promising alternatives for the treatment of complicated skin and soft-tissue infections in adults but there are no data about their pharmacokinetics in neonates [26,28].

For serious antibiotic-resistant GNB infections, carbapenems have become the mainstay of treatment with meropenem being the most widely used and doripenem as a newer carbapenem with greater activity against Pseudomonas aeruginosa [10]. However rapid emergence of resistance to these antibiotics means that the use of agents such as colistin, fosfomycin and tigecycline must be considered. Colistin is largely experienced in the neonatal population, but it must be kept in mind that is not effective against Proteus and Serratia. There is little experience of using fosfomycin in neonates but is worth considering as a final-resort therapy for extensively drug-resistant GNB [10,26]. Tigecycline, active against hard to treat pathogens like many multidrug-resistant GPB e GNB, is inactive against Pseudomonas Aeruginosa [10,29], but due to the possible effects on the bone growth in children, the use in neonates could only be justified in extreme cases (Table 1) [10,26].

Future strategies

Appropriate antibiotic policies

Antimicrobial stewardship programs (ASP) were introduced in the 1980s, with the aim to reduce unnecessary therapies. Nevertheless, only in 2007, the Infectious Diseases Society of America, together with other professional organizations, published guidelines in order to implement multidisciplinary ASP [30]. However, in spite of positive experiences on adults, data about the consequences of ASPs in neonatal settings are lacking.

Recently, several authors suggested different strategies that might be helpful in a NICU that include implementation of systems for surveillance of bloodstream infections, education of practitioners concerning the development of resistance, use of narrow spectrum empirical antibiotic policy and stop of empirical treatment or documented justification for continuation when blood cultures are negative, use of narrowest spectrum antibiotics for a proven infection, formulary restriction and pre-authorization requirements for selected antimicrobial agents like cephalosporins, meropenem, vancomycin and teicoplanin [11,12].

Patel et al [31] suggest that although specific guidelines for neonates are often lacking, antibiotic stewardship principles like those proposed by the Get Smart for Health Care Campaign of the Centers for Disease Control and Prevention can be applied to the NICU along with the development of an interdisciplinary antimicrobial stewardship team and metrics to measure successful implementation of ASP.

Development of innovative treatments

Spellberg et al [32] suggest future strategies to combat antibiotic-resistance like therapies with diminished potential to drive resistance (pe infusion of monoclonal antibodies and white cells that kill microbes or biologic agents that alter bacterial ability to trigger inflammation) and treatments that alter host-microbe interactions like moderation of host inflammation and limitation of microbial growth (pe sequestration of host nutrients, probiotics administration that compete with microbial growth).

Discovery of new antibiotics

The discovery of new antibiotics must face a number of challenges that make the development of new antibiotic drugs more difficult compared to other non-antibiotic drugs. These have been well summarized in a recent review by Lewis et al [33].

First, the poor penetration of antibiotics in prokaryotic cells requires the delivery of higher amounts of a compound which, in turn, increases the risk of toxicity and narrows the therapeutic range.

In addition, specifically targeting GNB is even more challenging, as not only the inner membrane restricts the penetration of hydrophilic substances, but also the outer membrane further reduces the number of compounds that may be effective, and the multidrug-resistant pumps extrude any compounds that leak in through the outer membrane.

Even when these pharmacodynamics-related issues are resolved, the development of a new drug needs to face the pharmacokinetics-related issues; indeed, the search for molecules with physicochemical properties to improve the likelihood of bioavailability (eg by applying the Lipinski's rules) may not match with the need of a compound with physicochemical properties that improve penetration into prokaryotes.

Once discovered, the compound must be tested in clinical trials; however, the identification and recruitment of patients infected with multi-resistant bacteria may be difficult, as most infections are caused by pathogens susceptible to the available compounds.

Finally, there is modest return on investment on antibiotic development compared to other drugs. Indeed, antibiotic therapy is typically short-term, lasting only some days, while therapies with cholesterol-lowering drugs or with anti-hypertensive drugs last for years, or lifelong; and, in any case, resistance to the new antibiotics will eventually develop, limiting their use and the profits that it produces.

Despite all these considerations, most of the potential bacterial targets for antibiotics are still unexploited. It is assumed that there are approximately 200 conserved essential proteins in bacteria, but the current antibiotics only hit few targets or pathways [33]. Future efforts should focus on the discovery of compounds directed against these new targets.

Conclusions

Sepsis represents the main cause of neonatal mortality and antibiotics are the most commonly prescribed medications in the NICUs. Wise choice of antimicrobial agents and optimal duration of therapy in neonates with suspected or culture-proven sepsis is crucial in order to limit the use of unnecessary broad spectrum antibiotic therapy, and to provide local solutions to the world-wide race against antimicrobial resistance. While there is an increasing choice of drugs for treating multiresistant GPB, alternatives for GNB will be seriously restricted for the foreseeable future. This makes important the need to promote attitudes that fortify measures for infection-control and to develop new treatments that complement traditional approaches.

References

1. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. Pediatrics. 2006;117(1):67–74.
2. Depani SJ, Ladhani S, Heath PT, Lamagni TL, Johnson AP, Pebody RG, et al. The contribution of infections to neonatal deaths in England and Wales. Pediatr Infect Dis J. 2011;30(4):345–7.
3. Stoll BJ, Hansen NI, Sánchez PG, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics. 2011;127(5):817–26.
4. Tripathi N, Cotton CM, Smith PB. Antibiotic use and misuse in the neonatal intensive care unit. Clin Perinatol. 2012;39(1):61–8.
5. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110(2):285–91.
6. Vergnano S, Menson E, Kennea N, Embleton N, Russell AB, Watts T, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed. 2011;96:F9–14.
7. Muller-Pebody B, Johnson AP, Heath PT, Gilbert R, Henderson KL, Sharland M. iCAP Group (Improving Antibiotic Prescribing in Primary Care.) Empirical treatment of neonatal sepsis: are the current guidelines adequate? Arch Dis Child Fetal Neonatal Ed. 2011;96:F4–8.
8. Blackburn RM, Verlander NQ, Heath PT, Muller-Pebody B. The changing antibiotic susceptibility of bloodstream infections in the first month of life: informing antibiotic policies for early- and late-onset neonatal sepsis. Epidemiol Infect. 2014;142(4):803–11.
9. Patel SJ, Saiman L. Antibiotic Resistance in Neonatal Intensive Care Unit Pathogens: Mechanism, Clinical Impact, and Prevention including Antibiotic Stewardship. Clin Perinatol. 2010;37(3):547–63.
10. Gray JW, Ubhi H, Milner P. Antimicrobial treatments of serious Gram-negative infections in newborns. Curr Infect Dis Rep. 2014;16(2):400–8.
11. Polin RA, Denson S, Brady MT. Committee on Fetus and Newborn, Committee on Infectious Diseases. Strategies for prevention of health care-associated infections in the NICU. Pediatrics. 2012;129(4):e1085–93.
12. Russell AB, Sharland M, Heath PT. Improving antibiotic prescribing in neonatal units: time to act. Arch Dis Fetal Neonatal. 2012;97:F141–6.
13. Isaacs D. Unnatural selection: reducing antibiotic resistance in neonatal units. Arch Dis Child Fetal Neonatal Ed. 2006;91(1):F72–4.
14. de Man P, Verhoeven BA, Verbrugh H, Vos MC, van den Anker JN. An antibiotic policy to prevent emergence of resistant bacilli. Lancet. 2000;355(9208):973–8.
15. Cotten CM, McDonald S, Stoll B, Goldberg RN, Poole K, Benjamin Jr DK. National Institute for Child Health and Human Development Neonatal Research Network. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. Pediatrics. 2006;118(2):717–22.
16. Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sánchez PJ, et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely-low birth weight infants. Pediatrics. 2009;123:58–66.
17. Alexander VN, Northrup V, Bizzarro MJ. Antibiotic exposure in the newborn intensive care unit and risk of necrotizing enterocolitis. J Pediatr. 2011;159:392–7.
18. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. J Pediatr. 2011;159:720–5.
19. Fanos V, Cuzzolin L, Atzei A, Testa M. Antibiotics and antifungals in neonatal intensive care units: a review. J Chemother. 2007;19(1):5–20.
20. Kaufman D, Fairchild KD. Clinical microbiology of bacterial and fungal sepsis in very-low-birth-weight infants. Clin Microbiol Rev. 2004;17(3):638–80.
21. Sivanandan S, Soraisham AS, Swarnam K. Choice and duration of antimicrobial therapy for neonatal sepsis and meningitis. Int J Pediatr. 2011;2011(712150):1–9.
22. Borghesi A, Stronati M. Strategies for the prevention of hospital-acquired infections in the neonatal intensive care unit. J Hospital Infect. 2008;68(4):293–300.
23. Polin RA. Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012;129(5):1006–15.
24. Kaiser JR, Cassat JE, Lewno MJ. Should antibiotics be discontinued after 48 hours for negative late-onset sepsis evaluation in neonatal intensive care unit? J Perinatol. 2002;22:445–7.
25. Cotten CM, Smith PB. Duration of empirical antibiotic therapy for infants suspected of early-onset sepsis. Curr Opin Pediatr. 2013;25(2):167–71.
26. Gray JW, Patel M. Management of antibiotic-resistant infection in the newborn. Arch Dis Child Educ Pract. 2011;96(4):122–7.
27. Bazan JA, Martin SI, Kaye KM. Newer beta-lactam antibiotics: Doripenem, Ceftobiprole, Ceftaroline, and Cefepime. Med Clin N Am. 2011;95:743–60.
28. Stryjewski ME, Barriere SL, O'Riordan W, Dunbar LM, Hopkins A, Genter FC, et al. Efficacy of telavancin in patients with specific types of complicated skin and skin structure infections. J Antimicrob Chemother. 2012;67(6):1496–502.
29. Stein GE, Babinchak T. Tigecycline: an update. Diagn Microbiol Infect Dis. 2013;75(4):331–6.
30. Dellit TH, Owens RC, McGowan Jr JE, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44(2):159–77.
31. Patel S, Saiman L. Principles and strategies of antimicrobial stewardship in the neonatal intensive care unit. Semin Perinatol. 2012;36:431–6.
32. Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotics and resistance. N EngL J Med. 2013;368(4):299–302.
33. Lewis K. Platforms for antibiotic discovery. Nat Rev Drug Discov. 2013;12(5):371–87.

Neonatal Effect Of Remifentanil In General Anaesthesia For Caesaean Section: A Randomized Trial

Pavlina Noskova,[1] Jan Blaha,[1] Hana Bakhouche,[2] Jana Kubatova,[1] Jitka Ulrichova,[1] Patricia Marusicova,[1] Jan Smisek,[3] Antonin Parizek,[4] Ondrej Slanar[2] and Pavel Michalek[1]

Abstract

Background: Remifentanil has been suggested for its short duration of action to replace standard opioids for induction of general anaesthesia in caesarean section. While the stabilizing effect of remifentanil on maternal circulation has been confirmed, its effect on postnatal adaptation remains unclear, as currently published studies are not powered sufficiently to detect any clinical effect of remifentanil on the newborn.

Methods: Using a double-blinded randomized design, a total of 151 parturients undergoing caesarean delivery under general anaesthesia were randomized into two groups – 76 patients received a bolus of remifentanil prior to induction, while 75 patients were assigned to the control group. Remifentanil 1 µg/kg was administered 30 seconds before the standard induction of general anaesthesia. The primary outcome measure was an assessment of neonatal adaptation using the Apgar score, while secondary outcomes included the need for respiratory support after delivery and differences in umbilical blood gas analysis (Astrup).

Results: The incidence of lower Apgar scores between 0 and 7 was significantly higher in the remifentanil group at one minute (25% vs 9.3% of newborns, p = 0.017); whilst at five minutes and later no Apgar score differences were observed. There was no difference in the need for moderate (nasal CPAP) or intensive (intubation) respiratory support, but significantly more neonates in the remifentanil group required tactile stimulation for breathing support (21% vs 7% of newborns, p = 0.017). There was no difference in the parameters from umbilical cord blood gas analysis between the groups.

Conclusion: At a dose of 1 µg/kg, remifentanil prior to induction of general anaesthesia increases the risk of neonatal respiratory depression during first minutes after caesarean delivery but duration of clinical symptoms is short.

Background

Opioids are routinely avoided during induction to general anaesthesia for caesarean section because of the potential for respiratory depression in the neonate [1,2]. On the other hand, insufficient depth of analgesia in parturients until foetal delivery remains a concern for obstetric anaesthetists [3,4]. Therefore, the ultra short-acting µ1-receptor agonist remifentanil has been suggested as a replacement for longer acting opioids in parturients undergoing caesarean delivery [5-11]. Remifentanil rapidly crosses the placenta but simultaneously is quickly eliminated from the neonatal circulation by degradation with nonspecific esterases in plasma and/or redistribution [12-14]. With a half-life of 3–10 minutes, remifentanil should be almost entirely eliminated from foetal circulation by the time of delivery [15]. However, in obstetrics, despite promising pharmacokinetics and pharmacodynamics, remifentanil is currently more frequently used as a systemic alternative to epidural labour analgesia rather than for general anaesthesia for caesarean delivery [16].

While the stabilizing effect of remifentanil on maternal circulation has been clearly and consistently described in several studies, including the systematic review and meta-analysis published by Heesen and colleagues [17], the effect on postnatal adaptation remains unclear, as these studies have not been sufficiently powered. We therefore aimed our study primarily as a comparison of postnatal adaptation of neonates after caesarean delivery in parturients receiving remifentanil bolus of 1 µg/kg prior to induction of general anaesthesia with those having standard opioid-free induction.

Methods

Study design

This prospective, randomized, controlled, and double-blinded study was conducted at a tertiary care university hospital with an average of 4,600 births per year, in the period between March 2011 and April 2014.The study was approved by the Ethics Committee of the General University Hospital in Prague (MZ10-UK1LF-Slanar) and registered at the Clinical Trials Database (ClinicalTrials.gov NCT01550640). Study was conducted in accordance with Helsinki Declaration principles. Signed informed consent was obtained from each participant.

[1]Department of Anaesthesiology, Resuscitation and Intensive Medicine, 1st Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, U Nemocnice 2, 128 08 Praha 2, Czech Republic. [2]Institute of Pharmacology, 1st Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Albertov 4, 128 00 Praha 2, Czech Republic. [3]Neonatology, Department of Gynaecology and Obstetrics, 1st Faculty of Medicine, Charles University and General University Hospital in Prague, Apolinarska 18, 128 51 Praha 2, Czech Republic. [4]Department of Gynaecology and Obstetrics, 1st Faculty of Medicine, Charles University and General University Hospital in Prague, Apolinarska 18, 128 51 Praha 2, Czech Republic.

Primary objective of the study was to compare newborn postnatal adaptation in parturients undergoing caesarean delivery under general anaesthesia with a remifentanil bolus 1 µg/kg administered prior to the induction of general anaesthesia with those undergoing standard induction. Secondary outcomes were requirements for postoperative respiratory support of neonates and differences in umbilical cord blood gas analysis.

Study population

Eligible patients were parturients undergoing caesarean delivery under general anaesthesia. Patients were screened and enrolled in the study by an anaesthetist during the pre-anaesthesia visit before caesarean delivery. Inclusion criteria were: age of 18 – 45 years. Exclusion criteria included known allergy to remifentanil, multiple pregnancy, gestational age below the 35th week, estimated weight of foetus below 2500 grams, severe foetal hypoxia, severe maternal hypotension, and other serious foetal or maternal conditions. Discontinuation criterion was difficult foetal delivery defined as uterine incision-to-delivery interval >3 min.

Study interventions

Parturients were randomly assigned to two study groups — remifentanil (RMF) or standard (STD). Treatment allocation was performed using online randomization generator (www.randomization.com). Each patient was allocated before entering the operating room. The randomization was kept blinded for the patient, surgeon, and neonatologist. Patients in the RMF group received a bolus of remifentanil 1 µg/kg 30 seconds prior to induction with thiopentone; while all other preoperative, anaesthetic, obstetric and postoperative procedures, were identical for both groups.

General anaesthesia

Standard departmental protocol for caesarean delivery under general anaesthesia was used with metoclopramide and ranitidine administered orally for aspiration prevention. After preoxygenation, general anaesthesia was induced using i.v. thiopentone 5 mg/kg followed by succinylcholine 1.25 mg/kg, and, until delivery, maintained with sevoflurane at an expired concentration of 0.5-0.7% in a 50% gas mixture of nitrous oxide/oxygen. After ligation of the umbilical cord, sufentanil 0.5 µg/kg and atracurium 0.35 mg/kg were administered for analgesia and muscle relaxation and sevoflurane was increased to 1%.

Obstetric management

Pfannenstiel supra-cervical laparotomy and Geppert uterotomy were used in all cases. Oxytocin 5 IU as a bolus was administered intravenously, diluted in 20 ml of saline after removal of the placenta.

Monitoring and evaluation

Intraoperative monitoring was performed using Datex Ohmeda S/5 TM Compact Anaesthesia Monitor (Datex-Ohmeda Inc., USA) according to general standards for patient monitoring during general anaesthesia. Time 0 was determined as the time of remifentanil administration in the RMF group or time 30 sec prior to thiopentone administration in the STD group. The following parameters were monitored; systolic and diastolic non-invasive blood pressure (NIBPsyst; NIBPdiast), mean blood pressure (MAP), heart rate (HR), electrocardiography (ECG) with ST segment analysis (lead II), pulse oximetry (SpO_2), capnography ($EtCO_2$), % of oxygen and volatile anaesthetic, and ventilation parameters (minute ventilation, tidal volume, respiratory rate and maximal inspiratory pressure). To evaluate the depth of anaesthesia, continuous bispectral index analysis (BIS) was used.

Evaluation of newborn adaptation was performed using Apgar scores at 1, 5 and 10 minutes, simultaneously with arterial and venous umbilical cord blood gas analysis and clinical examination. Clinical assessment was undertaken by an experienced neonatologist and acid/base balance status was evaluated directly in the delivery room with ABL 90 Flex (Radiometer Medical, Denmark) blood gas analyser.

Statistical analysis

The sample size of 150 parturients was calculated to detect an overall twofold difference between the groups in the primary outcome (Apgar scores 0–7) with a two-sided 5% significance level and a power of 80%. For sample size calculation, we used data from long term departmental baseline statistics, where Apgar score of 0–7 was observed in 9.5% of caesarean sections under general anaesthesia. A 36-month inclusion period was anticipated to recruit this number of patients.

Statistical analysis was performed with the STATISTICA 10 software (StatSoft, Czech Republic). All data was tested for normality using Kolmogorov-Smirnov test prior to final analysis. Numerical data from both groups was compared using Student's t-test or Mann–Whitney Rank Sum Test, as appropriate. For categorical variables the Fisher's exact test and chi-square test were used. All statistical tests were performed two-tailed and values of $P < 0.05$ were considered statistically significant.

Results

A total of 151 parturients were included in the study, 76 patients were allocated to the remifentanil group while another 75 were assigned to the standard group. All participants were in physical status class I-II according to the American Society of Anesthesiologists. Demographic characteristics of parturients are expressed in Table 1. Figure 1 represents study flow diagram.

Table 1 Characteristics of parturients and newborns

	Remifentanil group (n = 76)	Standard group (n = 75)	*P*
Age (years)	33.1 ± 5.1	32.3 ± 5.3	*0.362*
Weight prior to pregnancy (kg)	68.1 ± 13.1	69.8 ± 13.4	*0.473*
Actual weight (kg)	82.0 ± 13.4	81.4 ± 14.3	*0.813*
Height (cm)	168.9 ± 6.8	167.6 ± 5.8	*0.233*
BMI ($kg.m^{-2}$)	24.0 ± 4.4	24.9 ± 5.0	*0.254*
Medical concomitant diseases			
Hypertension	6 (8%)	6 (8%)	*0.981*
Asthma	4 (5%)	3 (4%)	*0.712*
Thyreopathy	3 (4%)	3 (4%)	*0.987*
Diabetes	3 (4%)	2 (3%)	*0.660*
Placenta praevia centralis	3 (4%)	3 (4%)	*0.987*
Other	11 (14%)	13 (17%)	*0.796*
Newborns			
Weight of newborns (g)	3162.9 ± 467	3122.5 ± 618	*0.334*
Gestational age (weeks)	38.6 ± 1.1	38.9 ± 1.4	*0.541*

Data are presented as mean ± standard deviation or n (%).
BMI = Body Mass Index.

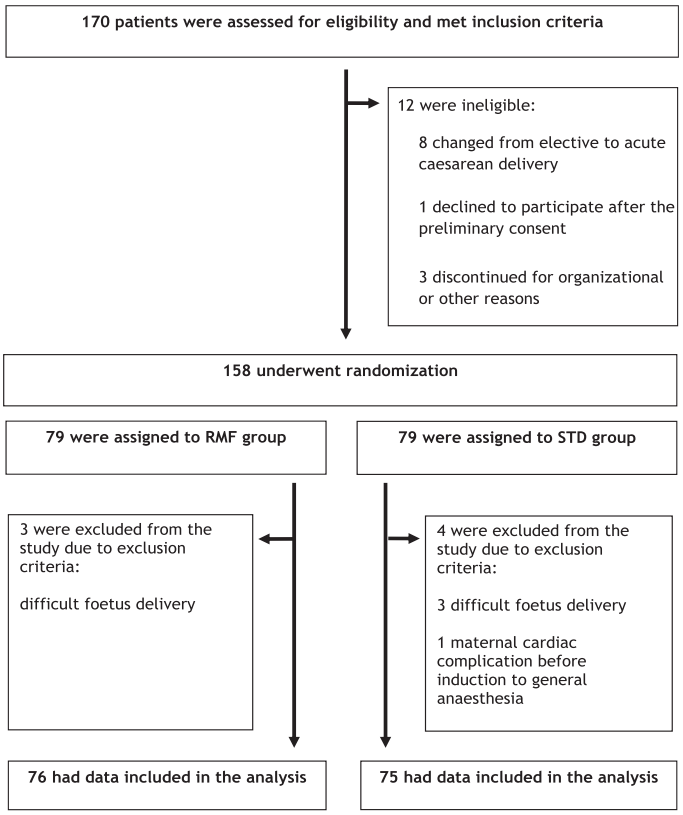


Figure 1 Assessment, randomization, and follow-up of the study patients.

The most frequent reason for employment of general anaesthesia in this study was refusal of regional anaesthesia by the parturient (67 vs 68 patients). In only 9 (RMF group) and 7 (STD group) cases, respectively, the choice of general anaesthesia was based on medical considerations — placenta praevia centralis (6 pts.), thrombocytopenia (3 pts.), psychosis (3 pts.), tokophobia (2 pts.), history of spinal trauma (1 pt.) and hypersensitive tetany (1 pt.).

Table 2 Data related to general anaesthesia

	Remifentanil group (n = 76)	Standard group (n = 75)	*P*
Anaesthesia prior foetal delivery			
Thiopentone bolus (mg)	398 ± 64	401 ± 68	*0.745*
Sevoflurane (%)	0.57 ± 0.2	0.58 ± 0.3	*0.586*
$SatO_2$ (%)	98.4 ± 1.7	97.9 ± 2.3	*0.219*
$ETCO_2$ (kPa)	4.5 ± 0.5	4.4 ± 0.4	*0.529*
Induction-to-delivery interval (min)	4.0 ± 1.4	3.9 ± 1.2	*0.884*
Duration of surgery (min)	43 ± 9.2	41 ± 9.4	*0.724*
Estimated blood loss (ml)	594 ± 196	576 ± 148	*0.648*
BIS (%)			
Baseline	95.4 ± 4.3	96.2 ± 4.2	*0.360*
Tracheal intubation	52.4 ± 16	52.2 ± 12.9	*0.930*
Delivery	57.7 ± 13.7	55.7 ± 12.2	*0.401*
At 10 min after induction	58.3 ± 10.5	55.8 ± 12.3	*0.231*

Data are presented as mean ± standard deviation. Sevoflurane = mean end expiratory concentration of sevoflurane from induction to delivery; $SatO_2$ = mean oxygen saturation from induction to delivery; $ETCO_2$ = mean end tidal capnography from induction to delivery; BIS = bispectral index analysis. Baseline means time before induction to general anaesthesia.

Table 3 Neonatal outcome

	Remifentanil group (n = 76)	Standard group (n = 75)	P value
Apgar score			
1-minute	8.1 ± 2.0	8.9 ± 1.4	*0.005*
5-minute	9.2 ± 1.1	9.6 ± 0.8	*0.022*
10-minute	9.8 ± 0.5	9.8 ± 0.4	*0.198*
Apgar score 0 -7			
1-minute	19 (25.0%)	7 (9.3%)	*0.017*
5-minute	5 (6.6%)	2 (2.7%)	*0.442*
10-minute	0 (0%)	0 (0%)	-
Need for respiratory support			
Tactile stimulation	16 (21.1%)	5 (6.7%)	*0.017*
CPAP	5 (6.6%)	5 (6.7%)	*0.983*
Mechanical ventilation	0 (0%)	0 (0%)	-
Administration of naloxone	0 (0%)	0 (0%)	-

Data are presented as mean ± standard deviation or n (%).
CPAP = continuous positive airway pressure ventilation.

Anaesthesia and surgical baseline management characteristics including delivery time (induction to delivery interval) are shown in Table 2. No intra- or postoperative major complications were recorded during the study.

Neonatal outcome

Table 3 and Figure 2 show the characteristics of neonatal postnatal adaptation – Apgar scores and the need for respiratory support. We noted a higher incidence of low Apgar scores between 0 and 7 in the remifentanil group at the first minute (19 vs 7 newborns, p = 0.017), but after the fifth minute no difference between the groups was observed. No difference between the study groups was found in requirement for moderate or intensive respiratory support following delivery (p = 0.983). Temporary CPAP (continuous positive airway pressure) ventilation was employed in 10 newborns (5 in each group), but none required

Table 4 Umbilical cord blood gas analysis

	Remifentanil group (n = 76)	Standard group (n = 75)	P value
Arterial			
pH	7.3 ± 0.0	7.3 ± 0.0	*0.210*
pCO_2 (kPa)	6.7 ± 0.7	6.6 ± 0.7	*0.450*
HCO_3-act (mmol/l)	25.0 ± 1.9	24.9 ± 1.9	*0.786*
HCO_3-std (mmol/l)	22.2 ± 1.9	22.0 ± 1.3	*0.567*
BE (mmol/l)	−1.4 ± 1.7	−1.2 ± 1.7	*0.645*
pO_2 (kPa)	2.8 ± 0.6	2.6 ± 0.6	*0.189*
$satO_2$ (%)	41.9 ± 14.6	38.0 ± 13.6	*0.137*
Venous			
pH	7.4 ± 0.0	7.3 ± 0.0	*0.203*
pCO_2 (kPa)	5.8 ± 0.5	5.8 ± 0.6	*0.721*
HCO_3-act (mmol/l)	23.5 ± 1.6	23.4 ± 1.9	*0.848*
HCO_3-std (mmol/l)	22.4 ± 1.1	22.2 ± 1.4	*0.421*
BE (mmol/l)	−1.7 ± 1.7	−1.8 ± 1.7	*0.801*
pO_2 (kPa)	4.6 ± 0.8	4.3 ± 1.1	*0.157*
$satO_2$ (%)	72.6 ± 10.4	68.3 ± 14.4	*0.069*

Data are presented as mean ± standard deviation.

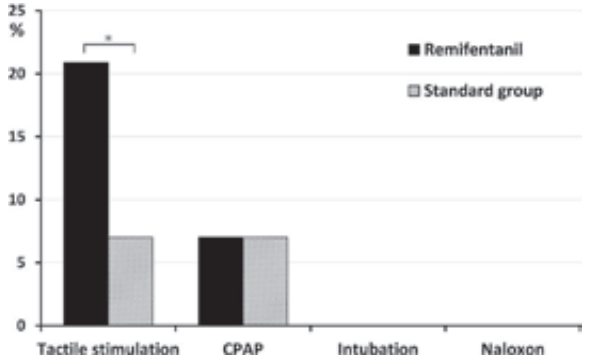


Figure 2 Bar graph showing the need for management of newborn respiratory depression. The bar graph plots the percentage of newborns requiring each level of respiratory stimulation or support (n = 76 in the remifentanil group and n = 75 in standard group). The black column represents the remifentanil group; the cross-hatched column the control group. *P = 0.017. CPAP = continuous positive airway pressure ventilation.

intubation or admission to a neonatal intensive care unit. There was however, a significant difference in the need for mild breathing support using tactile stimulation during the first 5 minutes (16 vs 5 newborns, p = 0.017) (Table 3). No newborn required administration of an μ1-opioid receptor antagonist.

Table 4 shows umbilical cord arterial and venous blood gas analysis. No difference was observed for any parameter including number of pH values <7.2; such a value was recorded only once (7.18, in the remifentanil group).

Maternal haemodynamics

The study groups were equal in basal haemodynamic parameters (blood pressure and heart rate at time 0), but they varied significantly at the time of intubation (both blood pressure and heart rate) and delivery (heart rate). The basal haemodynamic profiles are shown in Table 5.

Depth of anaesthesia

No difference was found between the groups after induction of general anaesthesia in depth of anaesthesia (BIS), ST-analysis, or respiratory-ventilation parameters ($SatO_2$, $EtCO_2$). The profiles of BIS values are shown in Table 2.

Discussion

Our study is not the first one to evaluate the effect of remifentanil in parturients undergoing caesarean delivery under general anaesthesia. However, to our knowledge, it is the only one adequately powered to assess the effect on the incidence of respiratory depression during postnatal adaptation of newborns. Moreover, the other important aspect of our study is its sample size. With 151 patients participating in the study and 76 in the remifentanil group, this is the largest remifentanil assessment in obstetric patients undergoing caesarean delivery. The size of our homogenous study group should be highlighted especially in comparison to the meta-analysis conducted and published in 2013 by a German-Belgian team with the inclusion of 186 patients from 5 randomized clinical trials [17].

Table 5 Maternal haemodynamic profiles

	Remifentanil group (n = 76)	Standard group (n = 75)	*P*
Systolic blood pressure (mmHg)			
Baseline	140.8 ± 16.2	140.6 ± 18.0	*0.948*
At intubation	145.4 ± 23.5	164.1 ± 26.4	<0.0001
At delivery	146.6 ± 22.5	149.9 ± 25.4	*0.444*
At 10 min after induction	125.7 ± 17.3	122.5 ± 17.0	*0.283*
Heart rate (bpm)			
Baseline	89.4 ± 12.8	93.1 ± 16.9	*0.187*
At intubation	91.8 ± 16.6	109.7 ± 17.2	<0.0001
At delivery	88.9 ± 13.7	101.3 ± 20.1	<0.001
At 10 min after induction	73.0 ± 16.3	76.6 ± 14.7	*0.204*

Data are presented as mean ± standard deviation. Baseline means time before induction to general anaesthesia.

While published studies agree on the positive effect of remifentanil on reducing adverse haemodynamic response to intubation and surgery during caesarean delivery, they vary in terms of its effect on neonatal adaptation. Yoo [18] and Ngan Kee [15] used an identical bolus of remifentanil — 1 μg/kg. They highlighted, similarly to our study, a risk of transient, neonatal respiratory depression. In contrast, Bouattour and colleagues did not demonstrate any attenuation of neonatal adaptation after administration of 0.5 μg/kg of remifentanil [19]. More worryingly, 14.3% of newborns in another study had to be intubated for respiratory support, following a pre-induction dose of remifentanil 0.5 μg/kg [20]. The determination of a remifentanil "safe dose", not causing adverse effect on neonate, was not even unravelled by the aforementioned meta-analysis performed by Heesen et al. [17].

In our study, we observed a significantly higher incidence of moderate to severe aggravation of neonatal adaptation (Apgar scores 0–7) after remifentanil administration (p =0.017). However, in all cases, neonatal respiratory depression lasted only for several minutes because lower Apgar scores were observed at the 1st minute only. The Apgar scores were similar at 5 minutes, which is a more crucial time for subsequent neonatal care and/or eventual transfer to neonatal intensive care unit. In total, 28% of neonates in the remifentanil group required some form of respiratory support after delivery, however they mostly responded only to tactile stimulation.

The observed incidence of short-time lasting, deteriorated postpartum neonatal adaptation was quite high in the remifentanil group, although its clinical significance and severity are not clear. A hypothetical explanation of diffe`rent results in published studies could be the existence of genetic polymorphism of the placenta transporting system glycoprotein P (multidrug resistance gene 1, MDR1) and polymorphism of μ-receptors and then divergent transfer of remifentanil into the foetal circulation [21,22]. Another reason for relatively higher incidence of respiratory depression in our study may also be shorter time of foetal delivery (4.0 min induction-to-delivery time) compared to some other centres [20,23,24]. We may hypothesize that remifentanil with its half-life of 3–10 minutes was not completely eliminated at the time of delivery. This could explain why Yoo et al. [24] found no significantly higher depression rate, even with a dose of 1.25 μg/kg. It should be noted that they reported interval to delivery approximately 10 minutes, which is potentially longer than expected effect of remifentanil.

It should be also highlighted that postnatal adaptation of the newborn is affected by previous intrauterine foetal condition, concurrent administration of thiopentone and volatile anaesthetics, as well as by induction-to-delivery interval

and technique of caesarean section. Therefore we excluded parturients with expected alteration of neonatal respiratory function (immaturity of foetus or in utero pathologies). In order to decrease bias of the study, we also excluded females with multiple pregnancy (risk of low birth weight and prematurity) and newborns following difficult delivery with uterine incision-to-delivery interval more than 3 min [25-27]. Nevertheless, we observed 14% incidence of moderate respiratory depression even in the standard group, with 5 newborns requiring the use of CPAP. Specific reasons for this depression remain unclear even after detailed analysis of individual cases (with no noted significant differences in delivery interval, gestational age or weight, blood gas analysis results or maternal demographic, respiratory or haemodynamic parameters).

In contrast to other studies, we did not find any difference in the umbilical cord blood gas analysis parameters, including Base Excess reported in Heesen's meta-analysis [17]. Acid/base balance parameters in umbilical cord blood correspond with the status of foetal oxygenation at the time of delivery. We detected only one newborn in the remifentanil group presenting with pH <7.2, which may be associated with increased neonatal morbidity [28]. Therefore, our assessment of remifentanil effect on neonatal adaptation should not have been affected by concurrent foetal intrauterine hypoxia.

We are aware of limitations of our study. Although the adaptation of each newborn was evaluated by experienced neonatologist, requirements to stimulate their breathing by tactile stimulation might still be biased by inter-individual differences. Another limitation may be exclusion of deliveries indicated for acute foetal hypoxia. General anaesthesia is most commonly administered in such cases, where suppression of stress response to tracheal intubation and surgical stimuli would be theoretically desirable.

Forming a consensus with other published trials, we also recorded the positive effect of remifentanil on the suppression of cardiovascular stress response to tracheal intubation and surgery. A dose of remifentanil 1 µg/kg given 30 seconds prior to induction of general anaesthesia effectively reduced a rise in both blood pressure and heart rate until delivery of foetus. Whereas the haemodynamic monitoring wasn't the main aim of this study, it was not blinded for anaesthesiologist. Therefore its assessment might be burdened by a potential bias, albeit most likely only an insignificant. The haemodynamic profile herein is given primarily within an overall description of intraoperative course of our study.

Unlike its stabilizing effect on the cardiovascular system, the dose of remifentanil 1 µg/kg did not affect the depth of anaesthesia. BIS values were below 60 in both groups throughout the study. This value has been accepted as a threshold which should decrease the incidence of awareness [29,30]. Similar results have been reported in other studies [18]. It is assumed that the majority of hypnotic effect during induction is achieved by the initial dose of thiopentone potentiated by anaesthetic gases, while remifentanil in this dose has only small effect on depth of anaesthesia [31].

Conclusion

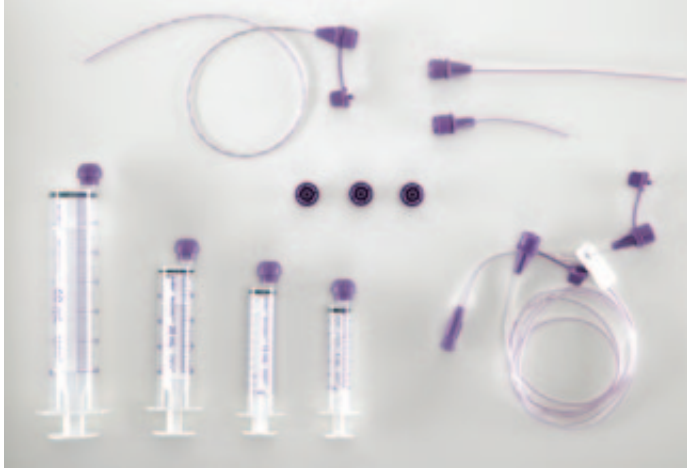
We demonstrated that a pre-induction dose of remifentanil 1 µg/kg is associated with a relatively high risk of neonatal respiratory depression. However, this attenuation was present only in the first five minutes after delivery and its clinical significance seems to be rather mild. Remifentanil is a suitable choice of co-induction agent in parturients who could be prone to excessive hypertension and tachycardia during induction to anaesthesia. In these cases, careful postnatal care must be applied if respiratory depression is observed.

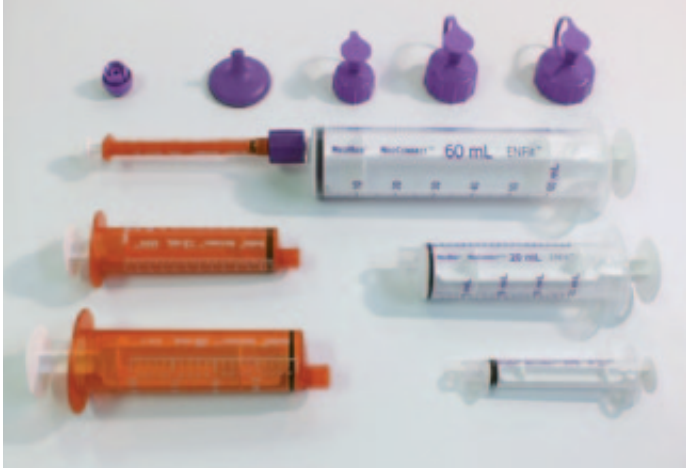
References

1. Morishima HO, Pedersen H, Finster M. The influence of maternal psychological stress on the fetus. Am J Obstet Gynecol. 1978;131(3):286–90.
2. Vogl SE, Worda C, Egarter C, Bieglmayer C, Szekeres T, Huber J, et al. Mode of delivery is associated with maternal and fetal endocrine stress response. BJOG. 2006;113(4):441–5.
3. Tsen L. Anesthesia for cesarean delivery. In: Chestnut D, Polley L, Tsen L, Wong C, editors. Obstetric anesthesia. 4th ed. Philadelphia, PA: Mosby-Elsevier; 2009. p. 521–74.
4. Lyons G, Akerman N. Problems with general anaesthesia for caesarean section. Minerva Anestesiol. 2005;71(1–2):27–38.
5. Bedard JM, Richardson MG, Wissler RN. General anesthesia with remifentanil for cesarean section in a parturient with an acoustic neuroma. Can J Anaesth. 1999;46(6):576–80.
6. Johannsen EK, Munro AJ. Remifentanil in emergency caesarean section in pre-eclampsia complicated by thrombocytopenia and abnormal liver function. Anaesth Intensive Care. 1999;27(5):527–9.
7. Johnston AJ, Hall JM, Levy DM. Anaesthesia with remifentanil and rocuronium for caesarean section in a patient with long-QT syndrome and an automatic implantable cardioverter-defibrillator. Int J Obstet Anesth. 2000;9(2):133–6.
8. Manullang TR, Chun K, Egan TD. The use of remifentanil for cesarean section in a parturient with recurrent aortic coarctation. Can J Anaesth. 2000;47(5):454–9.
9. McCarroll CP, Paxton LD, Elliott P, Wilson DB. Use of remifentanil in a patient with peripartum cardiomyopathy requiring caesarean section. Br J Anaesth. 2001;86(1):135–8.
10. Orme RM, Grange CS, Ainsworth QP, Grebenik CR. General anaesthesia using remifentanil for caesarean section in parturients with critical aortic stenosis: a series of four cases. Int J Obstet Anesth. 2004;13(3):183–7.
11. Scott H, Bateman C, Price M. The use of remifentanil in general anaesthesia for caesarean section in a patient with mitral valve disease. Anaesthesia. 1998;53(7):695–7.
12. Ltd. GG. ULTIVA 1 MG. SPC – Summary of product characteristics. http://www. sukl.eu/modules/medication/detail.php?kod=0017711&tab=texts&lang=2: SUKL. State Institute for Drug Control; 2011.
13. Egan TD. Pharmacokinetics and pharmacodynamics of remifentanil: an update in the year 2000. Curr Opin Anaesthesiol. 2000;13(4):449–55.
14. Kan RE, Hughes SC, Rosen MA, Kessin C, Preston PG, Lobo EP. Intravenous remifentanil: placental transfer, maternal and neonatal effects. Anesthesiology. 1998;88(6):1467–74.
15. Ngan Kee WD, Khaw KS, Ma KC, Wong AS, Lee BB, Ng FF. Maternal and neonatal effects of remifentanil at induction of general anesthesia for cesarean delivery: a randomized, double-blind, controlled trial. Anesthesiology. 2006;104(1):14–20.
16. Stourac P, Suchomelova H, Stodulkova M, Huser M, Krikava I, Janku P, et al. Comparison of parturient – controlled remifentanil with epidural bupivacain and sufentanil for labour analgesia: randomised controlled trial. Biomed

Pap Med Fac Univ Palacky Olomouc Czech Repub. 2014;158(2):227–32.
17. Heesen M, Klohr S, Hofmann T, Rossaint R, Devroe S, Straube S, et al. Maternal and foetal effects of remifentanil for general anaesthesia in parturients undergoing caesarean section: a systematic review and meta-analysis. Acta Anaesthesiol Scand. 2013;57(1):29–36.
18. Yoo KY, Jeong CW, Park BY, Kim SJ, Jeong ST, Shin MH, et al. Effects of remifentanil on cardiovascular and bispectral index responses to endotracheal intubation in severe pre-eclamptic patients undergoing caesarean delivery under general anaesthesia. Br J Anaesth. 2009;102(6):812–9.
19. Bouattour L, Ben Amar H, Bouali Y, Kolsi K, Gargouri A, Khemakhem K, et al. Maternal and neonatal effects of remifentanil for general anaesthesia for caesarean delivery. Ann Fr Anesth Reanim. 2007;26(4):299–304.
20. Draisci G, Valente A, Suppa E, Frassanito L, Pinto R, Meo F, et al. Remifentanil for cesarean section under general anesthesia: effects on maternal stress hormone secretion and neonatal well-being: a randomized trial. Int J Obstet Anesth. 2008;17(2):130–6.
21. Pechandova K, Buzkova H, Slanar O, Perlik F. Polymorphisms of the MDR1 gene in the Czech population. Folia Biol. 2006;52(6):184–9.
22. Smith HS. Variations in opioid responsiveness. Pain Physician. 2008;11(2):237–48.
23. Rossouw JN, Hall D, Harvey J. Time between skin incision and delivery during cesarean. Int J Gynaecol Obstet. 2013;121(1):82–5.
24. Yoo KY, Kang DH, Jeong H, Jeong CW, Choi YY, Lee J. A dose–response study of remifentanil for attenuation of the hypertensive response to laryngoscopy and tracheal intubation in severely preeclamptic women undergoing caesarean delivery under general anaesthesia. Int J Obstet Anesth. 2013;22(1):10–8.
25. Bader AM, Datta S, Arthur GR, Benvenuti E, Courtney M, Hauch M. Maternal and fetal catecholamines and uterine incision-to-delivery interval during elective cesarean. Obstet Gynecol. 1990;75(4):600–3.
26. Luthra G, Gawade P, Starikov R, Markenson G. Uterine incision-to-delivery interval and perinatal outcomes in transverse versus vertical incisions in preterm cesarean deliveries. J Matern Fetal Neonatal Med. 2013;26(18):1788–91.
27. Doherty DA, Magann EF, Chauhan SP, O'Boyle AL, Busch JM, Morrison JC. Factors affecting caesarean operative time and the effect of operative time on pregnancy outcomes. Aust N Z J Obstet Gynaecol. 2008;48(3):286–91.
28. Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis. BMJ. 2010;340:c1471.
29. Chin KJ, Yeo SW. A BIS-guided study of sevoflurane requirements for adequate depth of anaesthesia in Caesarean section. Anaesthesia. 2004;59(11):1064–8.
30. Yeo SN, Lo WK. Bispectral index in assessment of adequacy of general anaesthesia for lower segment caesarean section. Anaesth Intensive Care. 2002;30(1):36–40.
31. Dyer RA. Update on general anaesthesia for caesarean section. South Afr J Anaesth Analg. 2011;17(1):110–2.

Partnership for a Smooth ENFit™ Transition





NeoConnect Products for the NICU

- Complies with ASPEN recommendations for effective cleaning options of the ENFit feeding tube hub to protect against bacteria colonization
- Keeps features from the legacy line, such as self-righting tip caps and off-centered tip syringes
- Available in orange and purple
- Cleaning Tool, Low Dose syringes, and the DoseMate Oral Administration Tip

NeoConnect Products for the Pharmacy

- Complies with ISMP Recommendations and GEDSA Position Statements
- Eliminates the need for transition sets or temporary adapters, which can create unrecognized priming volume and dead space
- Low dose syringes, bottle caps, click-to-close tip caps, straws and the DoseMate to meet the needs of all patient populations in all clinical settings

NeoMed is committed to the highest level of service to our customers during the transition to ENFit. The NeoMed Loyalty Program helps align your product needs and supply chain integrity with Go Live dates, while supporting hospital staff training and process protocol review.

NEOMED®
www.neomedinc.com

NEOCONNECT™
with ENFit™ Connectors

(770) 516-2225
100 Londonderry Ct, Suite 112
Woodstock, GA 30188
www.neomedinc.com

The Gold Standard Protecting & Preparing Breast Milk

Custom Nightstand

- ***Built-in Refrigerator***
- *Doubles as a* ***Preparation Cart***
- **Color Choices** to match décor with solid surface options
- ***Built-in Electrical Outlets*** *for patient convenience*
- ***Family Locker***
  Storage of personal belongings

Penguin® Nutritional Warmer

The BEST Nutritional Warmer just got BETTER!

- ***New Enteral Warming Feature***
- ***Superior Infectious Control***
- ***30% Reduced Footprint***
- ***Large Color HD Display***

Penguin® Refrigerator

- ***Drawer Design***
  Quick cooling recovery
- ***Whisper™ Quiet Technology***
  Ambient noise level of less than ***"39 decibels"***
- ***Micro-Size / Space Saving***
  Mounts under a standard/ADA counter

Penguin® Enteral Warmer

- ***Works with ALL BRANDS of Enteral Pumps & Sets***
- ***FDA 510 (K) Certified***

Creche INNOVATIONS
17745 Metcalf, One Penguin Plaza, Stilwell, KS 66085
(913) 948.6290 info@crecheinnovations.com www.CrecheInnovations.com