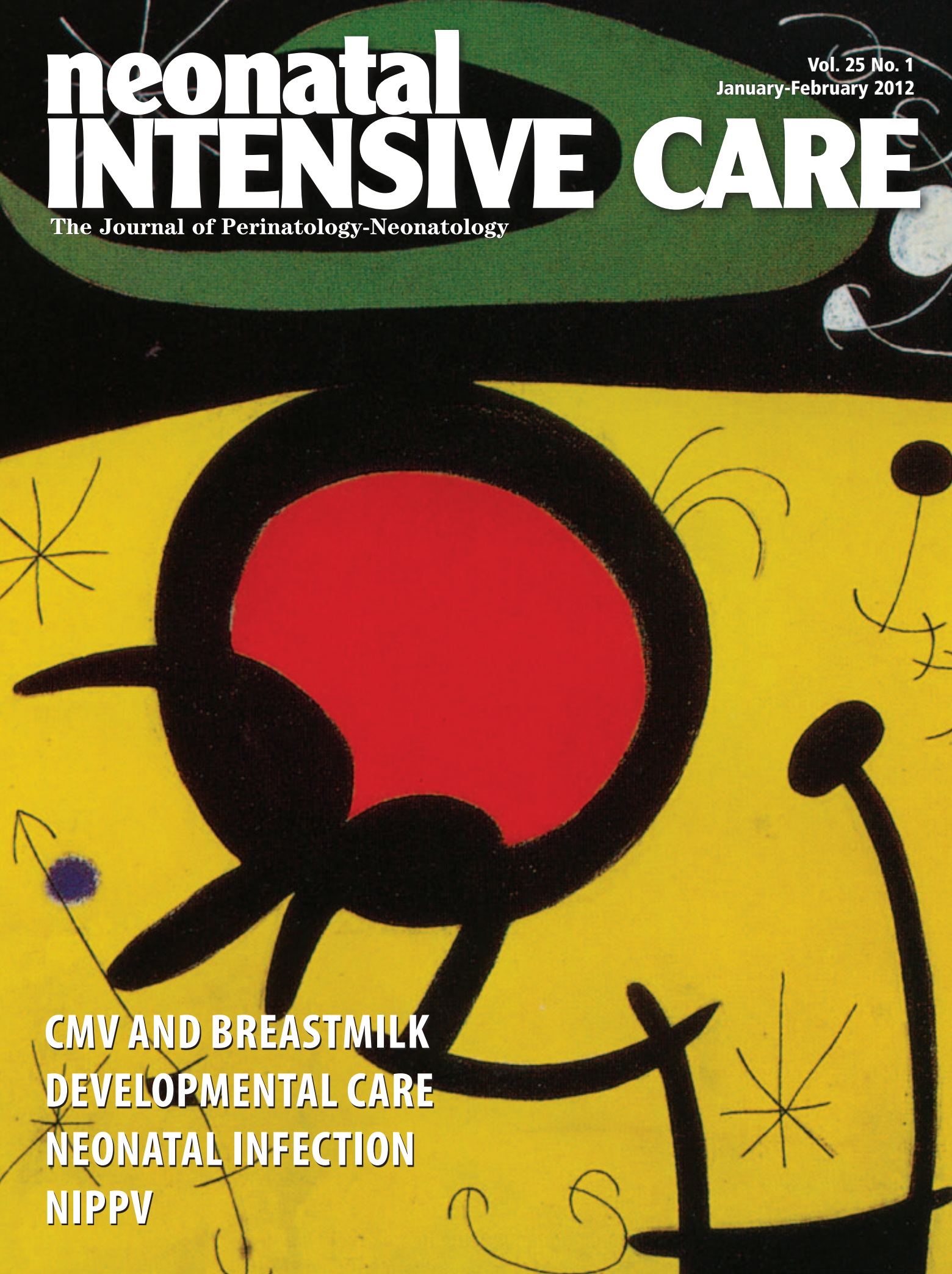
Vol. 25 No. 1
January-February 2012

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology



CMV AND BREASTMILK
DEVELOPMENTAL CARE
NEONATAL INFECTION
NIPPV

Choose the most nutrition options for the infants who need them most

Only Abbott Nutrition provides 27 different nutrition options for the NICU

12 calorie options for human milk fortification

15 calorie options with the Similac® Special Care® Liqui-Mix® System

+ Similac Expert Care® NeoSure® for the NICU to year 1

80349.001/December 2011 LITHO IN USA

Abbott
A Promise for Life

When you can detect subtle variations,
you get **a better sense**
of where your patient is headed.

THE SENSING SYSTEMS OF COVIDIEN

INVOS™ Cerebral/Somatic Oximetry | **Nellcor**™ pulse oximetry with OxiMax™ Technology | **BIS**™ Brain Monitoring | **LiDCO**™ Hemodynamic Monitoring

All monitors connect to patients. But the Sensing Systems of Covidien also connect patients to you. With revealing, real-time data that speaks to both your mind and your intuition. It's the timely intelligence you need to respond decisively to every unique situation. And the Sensing Systems of Covidien also keep you continuously aware of each patient's ongoing status, alerting you only when it's imperative.

TO GET A BETTER SENSE OF OUR CAPABILITIES, VISIT WWW.RESPIRATORYSOLUTIONS.COVIDIEN.COM.

COVIDIEN
positive results for life™

neonatal
INTENSIVE CARE

Vol. 25 No. 1
January-February 2012

Table of Contents

DEPARTMENTS

ARTICLES

Editorial

Attention

The New Yorker recently ran a lengthy piece on neonatology. The article, "A Child in Time," by Jerome Groopman, was subtitled "New frontiers in treating premature babies." It followed numerous cases and interviewed scores of neonatologists, parents of NICU patients, and researchers. To show just how far neonatology has progressed, the author used the case of John Kennedy's second son, born in 1963, five and a half weeks early, weighing four pounds and ten and a half ounces. The baby was diagnosed with hyaline membrane disease and rushed to a hyperbaric chamber, which at the time was a new device. The boy died thirty-nine hours later. A researcher noted, "We hardly worry anymore about a baby like the Kennedy infant. Survival at 32 weeks gestational age is nearly a hundred percent."

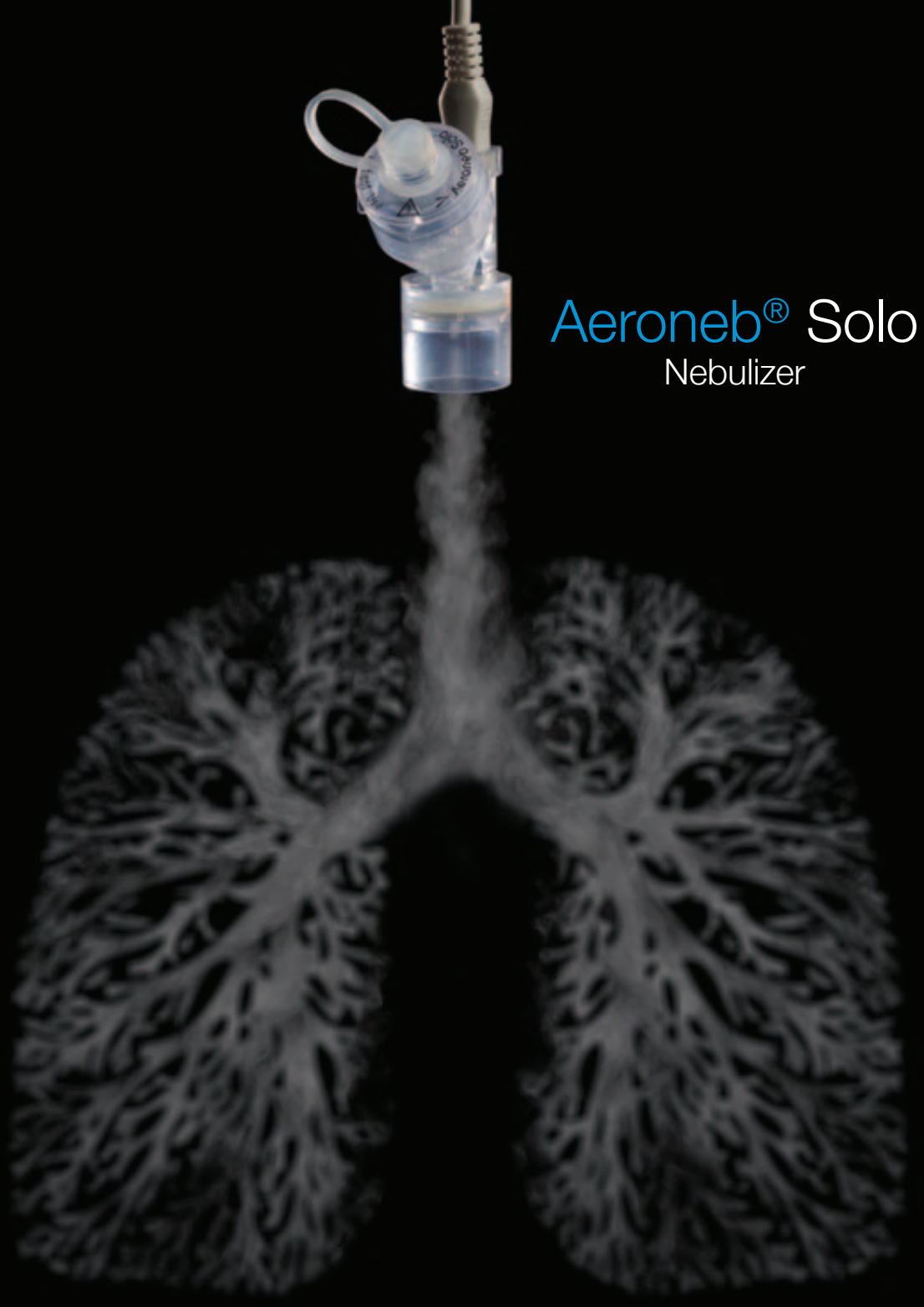
Despite all the advances, the article notes, "Babies die despite months of intensive care. And each treatment brings its own set of risks." The article discusses the Web-based algorithmic calculations currently used to ascertain a premature infant's chances of death and disability, and its pros and cons. As one physician noted, "There are limitations of averages of data… We prefer not to use the calculator when consulting with families. I value more the time necessary to discuss with the families the various possibilities as best we know them." The article noted, "Although the algorithm was designed to provide estimates, often it actually reinforces the uncertainty of outcomes." The article also went on to say that algorithms could give false reassurance when a baby tested well, and caused concern about making decisions based on short-term complications in the NICU.

Advances in the NICU, the article explained, "can also cause rifts between parents and caregivers," and highlighted a case where a baby was delivered at 23 weeks, intubated, and received a transfusion and surfactant, and on her fourth day had a major brain hemorrhage. The child was discharged after six months, and the parents have had to care for her at home since she has cerebral palsy, can't talk or walk, and is blind and incontinent. The parents sued the hospital, saying "they hadn't wanted any extraordinary, heroic measures to be taken," and that the baby was treated without their consent. A jury awarded the family a huge sum of money but the state Supreme Court reversed the decision and said that the hospital care was appropriate under the circumstances. Still, the New Yorker article went on, a case can be made for following a neonatologist's recommendations instead of forcing the parents to make the decision whether to provide care: "A study of French and American NICUs supports the idea that the doctor's recommendation whether to continue intensive care can relieve parents of guilt…. French parents did not express the same level of grief and distress shown by their American counterparts. The explanation appeared to be that French parents whose children died had not personally made the choice not to pursue treatment."

The piece also discussed how neonatologists may disagree with when to treat, walked through several examples, and talked about cost. (The Institute of Medicine pegged healthcare costs for preemies at $18 billion per year.) This exhaustive, lengthy article in a major consumer publication is a must-read for all neonatal caregivers, perhaps specifically *because* it is written for a lay audience. In other words, you can see how others see you. The article appeared in the October 24, 2011 issue of The New Yorker.

Les Plesko,
Editor

PS: For more commentary on the above, please see "Endnote" on page 58.



Aeroneb® Solo
Nebulizer

We Love Lungs!

The Aeroneb® Solo is your trusted nebulizer for making your patients better.

We deliver more drug to the lungs than traditional MDI, Ultrasonic and Jet nebulizers. No added flow, no added pressure, no fuss. Find out why MDI, USN and Jet neb users are switching to the Aeroneb® Solo on www.aerogen.com

Aerogen

www.aerogen.com

neonatal INTENSIVE CARE

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

Publisher
Steve Goldstein

Editor
Les Plesko

Senior Editor
Laszlo Sandor

Associate Editor
Jordana Hammeke

Design, Typography, Prepress and Production Management
http://accugraphics.net

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.

Editorial Advisory Board

News

☐ January-February 2012

TAKING THEIR PULSE

Pulse oximetry can be used as a screening tool to detect critical congenital heart disease in infants, and is more readily available than echocardiography, according to research presented at the AAP Conference in Boston. Recently, the Department of Health and Human Services added pulse oximetry to the list of core screening standards; however, no research has been conducted that looks at the availability of these devices, or their frequency of use. Researchers surveyed nurse managers and administrators at 88 Wisconsin hospitals, all of which had pulse oximetry available in the nursery, of which 28.4%, one-third of all newborns in Wisconsin, routinely used this device to screen for CCHD. Same-day echocardiography was available at only 37.5% of the hospitals. More than 26% of births occurred in a facility where same-day neonatal echocardiography was not available, with the average distance to a higher-level care facility of choice being 53.1 miles. According to the lead researcher, "Although the use of pulse oximetry is a relatively new tool in screening for critical congenital heart disease, its use is expanding rapidly. The implementation of pulse oximetry is likely to expand further as more and more states pass legislation requiring this type of screening in all newborns."

AT RISK

Babies who are born early and small are five times as likely as normal infants to develop autism, according to a two-decade-long study at the University of Pennsylvania. Researchers tracked 862 preemies (from 500 to 2,000 g) from birth to young adulthood. Five percent of the low-birth weight babies were diagnosed with autism, compared to the one percent prevalence in the general population. Reported by Agence France-Presse.

TOP NURSES

AWJPMM announced its 2012 Board of Directors: Rebecca Cypher, MSN, PNNP, with Madigan Army Medical Center, Tacoma, WA; Yvonne Dobbenga-Rhodes, MS, RNC-OB, CNS, CNS-BC, Clinical Nurse Specialist, Washington Hospital Healthcare System, Fremont, CA; Kathleen Matta, RNC, CNS, IBCLC, MSN, self-employed, recently retired as Director of the Department of Nursing Education, Santa Fe Community College, NM; Mimi Pomerleau, DNP, MSN, RNC-OB, Course Coordinator/ Assistant Clinical Professor, Lawrence Memorial Regis College and OB staff Nurse, Massachusetts General Hospital; Linda Snell, DNS, RN, WHNP-BC, Associate Dean of the School of Health and Human Performance and Associate Professor of Nursing, College of Brockport, NY; and Raquel "Kelly" Walker, MSN, RNC-MMN, Clinical Nurse Specialist for Women's Services, Roper Saint Francis Healthcare, Charleston, SC.

THE END

Joseph Maraachli, the terminally ill 20-month old baby at the center of a legal and ethical battle, recently died at his Windsor, Ontario, home. The baby had Leigh's disease. The parents wanted him to have a tracheotomy so he could die at home. After Canadian doctors refused to perform a tracheotomy, calling the procedure invasive and futile, Maraachli's parents fought to have him transferred to the US, arguing that while Joseph's disease was terminal, a tracheotomy would extend his life and allow him to die at home. After several months, Maraachli was transferred to a Catholic hospital in St Louis, where the procedure was performed. The Canadian hospital had said the baby was in a persistent vegetative state, but the parents said he responded to tickling. The parents said he breathed mostly on his own but medical personnel claimed he remained on a ventilator. In any event, the child died five months after the tracheotomy.

CRUEL AND UNUSUAL

AWHONN issued a new position statement that outlines its opposition to the practice of the shackling pregnant women who are incarcerated. "Approximately 6 to 10 percent of incarcerated women are pregnant, and the vast majority of these women are non-violent offenders," said AWHONN's Chief Executive Officer Karen Peddicord, PhD, RNC. "Shackles can interfere with a nurse's ability to adequately assess or treat pregnant women who are incarcerated. In emergency situations, such as a maternal hemorrhage or abnormal fetal heart rate patterns, shackles may cause unnecessary delays in implementing potentially lifesaving measures." Pregnancies among incarcerated women are often high risk and unplanned. Prior to entering the criminal justice system, these women are less likely to receive prenatal care and are more likely to experience poor nutrition and chronic diseases. Further, research suggests that shackles can make the labor and birth process more difficult than it needs to be and can inhibit a woman's mobility during delivery, leading to negative birth outcomes. In addition to AWHONN, a number of organizations oppose the use of shackles during labor, birth, and in the period immediately postpartum, including the American Medical Association. The American College of Obstetricians and Gynecologists (ACOG) and Amnesty International oppose the use of restraints for all pregnant women who are incarcerated.

GUIDELINES

Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) recently reminded nurses and other healthcare providers about the importance of its Assessment and Care of Late Preterm Infant Evidence-Based Clinical Practice Guideline and its accompanying Quick Care Guide. In 2005, AWHONN launched its Late Preterm Infant (LPI) Initiative to help raise

awareness of the special needs of this population of vulnerable newborns. Since that time, AWHONN has progressed from raising awareness to the development of educational resources and is now in the third phase of this project: evaluating change in nursing practice related to caring for these babies. Based on evaluation of the best available scientific evidence, the AWHONN Guideline provides nurses with detailed information about the risks associated with late preterm birth and guidelines for providing nursing care for these infants. The Guideline also includes evidence-based recommendations for parent education and support to help clinicians prepare parents for the care their newborn will need after discharge. Contact awhonn.org.

GIRL PROBLEMS

Exposure to BPA in the womb is linked to behavioral and emotional difficulties in girls, according to researchers at the Harvard School of Public Health. Exposure to BPA is a daily hazard for all people living in industrialized countries. Animal studies show it disrupts normal development and human studies have linked it to cardiovascular disease and diabetes. The study examined data from 244 mothers and their young children, using urine samples taken from the moms during pregnancy and at birth, and from their kids at ages 1, 2 and 3. Eighty-five percent of the mothers and 96% of the children had detectable levels of BPA in their urine. The BPA levels in the children's urine samples decreased from age 1 to age 3, but they were higher and varied more than their mothers' levels. BPA levels in pregnancy were linked to more hyperactive, aggressive, anxious, and depressed behavior and poorer emotional control and inhibition in the girls, but not the boys. The study also demonstrated that BPA exposure in the womb is more important than exposure after birth. Information is from Medical News Today, copyright Medical News Today, original article written by Catharine Paddock, PhD.

GET MORE SLEEP

Poor sleep quality in both early and late pregnancy has been linked to an increased risk of delivering preterm. A study published in a recent issue of SLEEP shows a significant risk for preterm birth in women reporting sleep disruptions during their first and third trimesters. The connection remained even after medical risk factors and income levels were taken into account. Sleep quality in the second trimester did not correlate with increased risk, perhaps because sleep often improves modestly during this part of pregnancy. The authors of the study suggested a biological cause for the increase in preterm births with disrupted sleep: Poor sleep quality has been shown to initiate inflammation, possibly activating the processes associated with premature childbirth. Sleep disruption also might do this in combination with stress, a known activator of inflammation.

MITIGATING PAIN

Poorly managed infant pain in the NICU has serious consequences and causes behavioral instability in preterm infants and long-term changes in their pain sensitivity, stress arousal systems, and developing brains, according to researchers at BC Children's Hospital and the University of British Columbia. They conducted a study to learn if preterm infants would show lower pain scores when breastfed during blood collection. They also looked at whether breastfeeding during the painful procedure would have a negative impact on the development of breastfeeding skills, and whether infants who had more mature breastfeeding behaviors would have lower pain scores and heart rates during blood collection than less experienced feeders. Fifty-seven infants born at 30 to 36 weeks gestational age were divided into two groups, one breastfed during blood collection and the other given a pacifier. During the procedure, their faces and hands were videotaped, their responses scored, and their heart rates measured. Breastfeeding didn't reduce behavioral or physiological pain during blood collection, and no immediate adverse effects were found on breastfeeding skill development. In the breastfed group, infants who were more advanced in their ability to feed had significantly lower behavioral pain scores. Despite concerns that blood sampling during breastfeeding may be more difficult, the authors said that the time taken for the procedure in the breastfed group was significantly shorter, making blood collection more efficient.

FEARFUL

Some women are so afraid of giving birth that they avoid becoming pregnant or seek an abortion, even though they want to have children. The Norwegian Institute for Public Health has studied the phenomenon and its effect. The fear can lead to prolonged labor, a greater need for pain relief, and an increased risk of an emergency C-section. In some cases, the fear of childbirth is so serious that it can be classified as a specific phobia. In Oslo, 5-10 percent of all pregnant women are treated for fear of childbirth, and it's the underlying reason for about 20% of all planned C-sections. The study enrolled about 4,000 women.

EXPOSED

Preemies exposed to glucocorticoids are at an increased risk for having impaired growth of the cerebellum, according to researchers at the University of San Francisco. It has been posited that low dosages of the steroids can help preemie lung maturation. But the researchers found that hydrocortisone or dexamethasone given to preemies resulted in a 10% smaller cerebellar volume by the time the babies were full term. Studies have shown that smaller cerebellar volumes in children born prematurely are associated with significant motor and cognitive impairments by teenage years. The researchers studied 172 preemies. Eighty-five percent were given betamethasone before, and 20% got hydrocortisone or dexamethasone. The investigators then measured brain volume.

A GOOD NIGHT'S SLEEP

Breastfed babies wake up more at night for feedings, but their sleep time stabilizes later, and becomes comparable to non breastfed babies, according to researchers. They collected surveys from 89 moms who breastfed their infants and 54 who formula-fed them. Breastfed infants woke up more at first, took fewer naps, and more didn't sleep in their own beds. But by six months to nine months, the amount of sleep and sleep patters become stabilized.

DIRTY CHINA

Pesticides and pollutants are being blamed for a 450% increase in the risk of spina bifida and anencephaly in rural China, according to scientists at The University of Texas at Austin and Peking University. Two of the pesticides found in high concentrations in the placentas of affected newborns and stillborn fetuses were endosulfan and lindane. Endosulfan is only now being phased out in the US for treatment of cotton, potatoes, tomatoes and apples. Lindane was only recently banned in the US for treatment of barley, corn, oats, rye, sorghum and wheat seeds. Strong associations were also found between spina bifida and anencephaly and high concentrations of polycyclic aromatic

hydrocarbons (PAHs), which are byproducts of burning fossil fuels such as oil and coal. Researchers collected placentas from 80 newborn or stillborn fetuses who suffered from spina bifida or anencephaly. The placenta of a healthy newborn with no congenital malformations born in the same hospital was selected as a control. The researchers screened the placentas for persistent organic pollutants, including agricultural pesticides, industrial solvents, and fuel burning byproducts.

LISTEN UP

Preemies exposed to their parents voices in the NICU tend to have better vocalizations at 32 and 36 weeks gestational age, according to researchers in the Department of Pediatrics, Women and Infants Hospital, Providence, RI. The scientists wanted to find out if infants exposed to more adult language would make more vocalizations, and also studied the sound environment in the NICU. Their study included 36 infants weighing 1,250 grams or less. The researchers made numerous sound recordings, gathering data on how many words were spoken by adults, and total infant vocalizations. Infant vocalizations were detected at as early as 32 weeks, with a significant increase between 32 and 36 weeks. The number of conversational turns in the vocalizations were higher when a parent was present. Preemies started making vocalizations eight weeks earlier than the usual start date for newborns, and these increased considerably. Reported in Medical News Today, by Christian Nordqvist, copyright Medical News Today.

HYPERTENSION

A study by the Kaiser Foundation for research suggests that hypertension during early pregnancy increases the risk of giving birth to babies with birth defects, and that the risk is from the hypertension, not the drugs used to treat it. Drugs for hypertension contain ACE inhibitors which are known to have a toxic effect on fetuses during the second or third trimesters of pregnancy, but little is known about their effects on a fetus during the first trimester of pregnancy. Researchers evaluated data on 465,754 mothers and their infants. The findings revealed that women using ACE inhibitors during their first pregnancy trimester had a potentially higher risk of having a baby with some form of birth defect compared with women without hypertension or those who were not taking any form of antihypertensive medication. They also discovered a comparable higher risk among women using other hypertensive drugs and those who suffered from hypertension but who did not take any antihypertensive drugs. As such, the findings leaned toward the conclusion that the underlying hypertension in the first trimester is what caused the increases in birth defects. Information is from Medical News Today, from an article written by Petra Rattue, copyright Medical News Today.

MIND THE GFAP

Johns Hopkins researchers have discovered that increased blood levels of glial fibrillary acidic protein are vital to the brain's structure and can help physicians identify newborns with brain injuries due to lack of oxygen. Measurement of GFAP can also track how well whole-body-cooling therapy designed to prevent permanent brain damage is working. The study looked at levels of GFAP in 23 newborns born between 36 and 41 weeks' gestation who were diagnosed with HIE and compared them with those in babies born at the same point in the pregnancy. Researchers obtained the GFAP protein from cord blood at the time of birth, from neonatal blood drawn upon admission to the NICU and from daily blood specimens over a seven day period. GFAP levels were significantly higher in babies with brain injury due to a lack of oxygen during the first week of life. Infants who had abnormal brain MRI scans and were treated with whole-body cooling had the highest levels of GFAP. Half of the babies with brain injury in this study had increased levels of GFAP after completion of the 72 hour cooling period.

SICKLE CELL

Research at Howard Hughes Medical Institute and Harvard Medical School revealed that silencing the protein BCL11A can reactivate fetal hemoglobin production in adult mice and effectively reverses sickle cell disease. The new finding showed that BCL11A is one of the primary factors involved in turning off fetal hemoglobin production. BCL11A is likely one of a suite of factors that influence fetal hemoglobin levels, and the study provides evidence that it is one of the key players in regulating the production of fetal hemoglobin. Elevating fetal hemoglobin in sickle cell patients can help alleviate the disease's episodes of fatigue and abdominal and bone pain that are hallmarks of the condition. Production of fetal hemoglobin begins about two months into gestation and helps deliver oxygen from the mother's bloodstream to the developing fetus. By about 3-6 months after birth, fetal hemoglobin is almost completely replaced by adult hemoglobin. The timing explains why sickle cell patients don't experience symptoms of the disease until several months after birth. Drug therapy with hydroxyurea helps ramp up fetal hemoglobin in some patients and reduces the number of painful episodes, but the drug isn't uniformly effective and has bad side effects. The new study was done through genetic manipulation of a mouse model of sickle cell disease, demonstrating that in the future, gene therapy may be feasible. The research also holds promise for devising new treatments for thalassemias.

GROWING BRAINS

The growth rate of the cerebral cortex in preemies may predict how well they are able to think, speak, plan and pay attention later in childhood. A study at the Imperial College in London looked at brain growth rates of 82 infants who were born before 30 weeks gestational age using MRI scans between 24-44 weeks. The scans were collected repeatedly from birth until the babies' full-term due date. Their cognitive abilities were tested at two years old and again at six years old. The study found that the faster the rate of cerebral cortex growth in infancy, the higher the kids scored on the developmental and intelligence tests as children. A five to 10% reduction in the surface area of the cerebral cortex at full-term age predicted approximately one standard deviation lower score on the intelligence tests in later childhood.

NICU BRAIN STRESS

Exposure to stressors in the NICU is associated with alterations in the brain structure and function of very preterm infants, according to a study at St Louis Children's Hospital. Researchers recruited 44 preterm infants within 24 hours of birth. Study participants were less than 30 weeks gestation, and stress was measured by using the Neonatal Infant Stressor Scale. MRI and neurobehavioral examinations were used to evaluate cerebral structure and function. The average daily exposure to stressors was greatest in the first 14 days following birth. The greater number of stressors that an infant was exposed to was associated with decreased frontal and parietal brain width. Researchers also reported altered brain microstructure and functional connectivity within the temporal lobes in infants with early stress exposure. Abnormal movement pattern and reflex scores were lower among preterm infants exposed to higher stress in the first two weeks of life.

INFECTION

Babies born by elective cesarean section are more likely to get bronchiolitis in the first year of life, according to a study at the Telethon Institute for Child Health Research in Australia. The study is based on birth data and hospitalization records of 212,068 babies over a 10- year period. Researchers noted that it was plausible that delivery without labor could impair a newborn's immune system and explain the link between c-sections and asthma. Reported by Jason Gale, Bloomberg News.

PRODUCTS

CONTROLLED PRESSURE

The F&P Neopuff Infant T-Piece Resuscitator is designed to provide controlled pressures each time a breath is delivered. T-Piece resuscitation is the standard of care that is recommended by all major resuscitation guidelines, including the International Liaison Committee on Resuscitation (ILCOR) and American Heart Association's (AHA) Neonatal Resuscitation Program (NRP). Since its introduction to the United States in 1991, the F&P Neopuff has established a proven track record in T-Piece Resuscitation. Today, the Neopuff is used in over 120 countries around the world and continues to be supported by clinical data. The F&P Neopuff gives clinicians confidence in accurate pressure control. Controlled pressures are delivered to help protect the lungs from injury while a fast-acting and easy-to-read medical-grade manometer displays accurate pressure settings up to 80cmH_2O (+/-1.6cm H_2O). Ease is vital to responsiveness and positive outcomes. The Neopuff answers this need with a number of design innovations such as an easy-grip knob to set PIP pressure, a larger handle for ease in portability and a range of mounting options for ideal placement in L&D, NICU, on transports and in other departments within the hospitals where neonatal resuscitations occur. In addition, the Neopuff comes with a complete range of accessories including gas supply line, three circuit options and a full range of infant resuscitation masks. Fisher & Paykel Healthcare has also released the new Ergonomic T-Piece Circuit. This unique circuit comes with a duckbill port to allow for suctioning and surfactant delivery. The Neopuff is the only T-Piece device to provide a Humidified T-Piece Circuit option. This allows for Optimal Humidity during resuscitation. The Neopuff Infant T-Piece Resuscitator facilitates the delivery of warm humidified gas to help protect the pulmonary epithelium and reduce heat and moisture loss especially during prolonged resuscitation. The Neopuff remains very affordable for hospitals regardless of the continuous enhancements to the Neopuff. F&P recognizes the necessity of T-Piece Resuscitation and continues to bring this value to clinicians around the world. Contact fphcare.com or (800) 446-3908.

CLEARED

Siemens Healthcare Diagnostics has received FDA clearance for its Neonatal Total Bilirubin (nBili) assay on the RAPIDPoint 405 Blood Gas Analyzer, with Version 3.7.1 Software. The nBili test offers results in about 60 seconds, benefiting neonatal intensive care unit (NICU) patients. With one small blood sample—only 100 µL—a full range of analytes can be measured at the point of care, including neonatal bilirubin, blood gases, electrolytes, glucose, total hemoglobin and other critical care parameters required to assess critically ill infants. The Siemens nBili assay on the RAPIDPoint 405 Blood Gas Analyzer is intended to measure the concentration of bilirubin in an infant's blood as an aid for assessing the risk for kernicterus in a point-of-care setting. Contact medical.siemens.com.

ARE YOU HELPING TO PROTECT YOUR HIGH-RISK INFANTS FROM RSV ALL SEASON LONG?

MONTHLY DOSING IS KEY TO HELPING PROTECT HIGH-RISK INFANTS

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Clinical studies established the safety and efficacy of Synagis® in the following infants[1]:

- Premature infants ≤35 weeks GA[1]
- Infants with CLDP/BPD*
- Infants with hemodynamically significant congenital heart disease (CHD)[1]

Adherence to a regular monthly Synagis dosing schedule can help lower RSV-related hospitalization rates in those who are compliant vs. those who are not compliant

- Infants who were compliant with all Synagis doses given <35 days of previous dose had a significantly lower rate of RSV-related hospitalization vs. those infants who were noncompliant (odds ratio, 0.702; 95% CI; 0.543 to 0.913)[2]

*CLDP/BPD = chronic lung disease of prematurity/bronchopulmonary dysplasia

Important Safety Information

Synagis® (palivizumab) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease and is administered by intramuscular injection. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD). Synagis has been used in more than one million children in the U.S. since its introduction in 1998. The first dose of Synagis should be administered prior to commencement of the RSV season. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the season.

Synagis should not be used in pediatric patients with a history of severe prior reaction to Synagis or its components. Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a severe hypersensitivity reaction occurs, therapy with Synagis should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on re-administration of Synagis. In post-marketing reports, cases of severe thrombocytopenia (platelet count <50,000/microliter) have been reported.

In clinical trials, the most common adverse events occurring at least 1% more frequently in Synagis-treated patients than controls were upper respiratory infection, otitis media, fever, and rhinitis. Cyanosis and arrhythmia were seen in children with CHD. There have also been post-marketing reports of injection site reactions.

Please see accompanying full Prescribing Information, including patient information.

References: 1. Synagis [package insert]. Gaithersburg, MD: MedImmune. **2.** Frogel M, Nerwen C, Cohen A, VanVeldhuisen P, Harrington M, Boron M; for the Palivizumab Outcomes Registry Group. Prevention of hospitalization due to respiratory syncytial virus: results from the Palivizumab Outcomes Registry. *J Perinatol*. 2008;28:511–517.

MedImmune
Gaithersburg, MD 20878
Customer Support Network: 1-877-633-4411
10232 ZN Printed in USA November 2011

Change is needed.
Visit **www.letschangethat.com** or scan this code to begin.* To download a free scanner, visit **www.getscanlife.com** on your mobile device.
*Data rates may apply.

SYNAGIS®
PALIVIZUMAB

SYNAGIS® (PALIVIZUMAB)

for Intramuscular Administration **Rx only**

DESCRIPTION: Synagis (palivizumab) is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Synagis is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor (1) and Cess (2). The human light chain sequence was derived from the constant domain of C_K and the variable framework regions of the V_L gene K104 with J_K -4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Synagis is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis is supplied as a sterile, preservative-free liquid solution at 100 mg/mL to be administered by intramuscular injection (IM). Thimerosal or other mercury containing salts are not used in the production of Synagis. The solution has a pH of 6.0 and should appear clear or slightly opalescent.

Each 100 mg single-dose vial of Synagis liquid solution contains 100 mg of Synagis, 3.9 mg of histidine, 0.1 mg of glycine, and 0.5 mg of chloride in a volume of 1 mL.

Each 50 mg single-dose vial of Synagis liquid solution contains 50 mg of Synagis, 1.9 mg of histidine, 0.06 mg of glycine, and 0.2 mg of chloride in a volume of 0.5 mL.

CLINICAL PHARMACOLOGY: *Mechanism of Action:* Synagis exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis (5). Synagis serum concentrations of ≥ 40 mcg/mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The *in vivo* neutralizing activity of the active ingredient in Synagis was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, Synagis significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

Pharmacokinetics: In pediatric patients < 24 months of age without congenital heart disease (CHD), the mean half-life of Synagis was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean ± SD 30 day trough serum drug concentrations of 37 ± 21 mcg/mL after the first injection, 57 ± 41 mcg/mL after the second injection, 68 ± 51 mcg/mL after the third injection and 72 ± 50 mcg/mL after the fourth injection (7). Trough concentrations following the first and fourth Synagis dose were similar in children with CHD and in non-cardiac patients. In pediatric patients given Synagis for a second season, the mean ± SD serum concentrations following the first and fourth injections were 61 ± 17 mcg/mL and 86 ± 31 mcg/mL, respectively.

In 139 pediatric patients ≤ 24 months of age with hemodynamically significant CHD who received Synagis and underwent cardio-pulmonary bypass for open-heart surgery, the mean ± SD serum Synagis concentration was 98 ± 52 mcg/mL before bypass and declined to 41 ± 33 mcg/mL after bypass, a reduction of 58% (see *DOSAGE AND ADMINISTRATION*). The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on Synagis systemic exposure. However, no effects of gender, age, body weight or race on Synagis serum trough concentrations were observed in a clinical study with 639 pediatric patients with CHD (≤ 24 months of age) receiving five monthly intramuscular injections of 15 mg/kg of Synagis.

The pharmacokinetics and safety of Synagis liquid solution and Synagis lyophilized formulation administered IM at 15 mg/kg were studied in a cross-over trial of 153 pediatric patients ≤ 6 months of age with a history of prematurity. The results of this trial indicated that the trough serum concentrations of palivizumab were comparable between the liquid solution and the lyophilized formulation, which was the formulation used in the clinical studies described below.

CLINICAL STUDIES: The safety and efficacy of Synagis were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in pediatric patients at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1,502 patients ≤ 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (≤ 35 weeks gestation) who were ≤ 6 months of age at study entry (7). Trial 2 was conducted over four consecutive seasons among a total of 1287 patients ≤ 24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg/kg Synagis or an equivalent volume of placebo IM monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1.

Table 1: Incidence of RSV Hospitalization by Treatment Group

Trial		Placebo	Synagis	Difference Between Groups	Relative Reduction	p-Value
Trial 1 Impact-RSV	N	500	1002			
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55%	< 0.001
Trial 2 CHD	N	648	639			
	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%	0.003

In Trial 1, the reduction of RSV hospitalization was observed both in patients with BPD (34/266 [12.8%] placebo vs. 39/496 [7.9%] Synagis), and in premature infants without BPD (19/234 [8.1%] placebo vs. 9/506 [1.8%] Synagis). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] Synagis) and cyanotic children (27/343 [7.9%] placebo versus 19/339 [5.6%] Synagis).

The clinical studies do not suggest that RSV infection was less severe among RSV hospitalized patients who received Synagis compared to those who received placebo.

INDICATIONS AND USAGE: Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD) (see *CLINICAL STUDIES*).

CONTRAINDICATIONS: Synagis should not be used in pediatric patients with a history of a severe prior reaction to Synagis or other components of this product.

WARNINGS: Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to Synagis. Symptoms may include dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, hypotension, and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a severe hypersensitivity reaction occurs, therapy with Synagis should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of Synagis. **If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.**

PRECAUTIONS: *General:* Synagis is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution to patients with thrombocytopenia or any coagulation disorder.

The safety and efficacy of Synagis have not been demonstrated for treatment of established RSV disease.

The single-dose vial of Synagis does not contain a preservative. Administration of Synagis should occur immediately after dose withdrawal from the vial. The vial should not be re-entered. Discard any unused portion.

Drug Interactions: No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of patients in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis, mutagenesis and reproductive toxicity studies have not been performed.

Pregnancy: Pregnancy Category C. Synagis is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether Synagis can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

ADVERSE REACTIONS: The most serious adverse reactions occurring with Synagis treatment are anaphylaxis and other acute hypersensitivity reactions (see *WARNINGS*). The adverse reactions most commonly observed in Synagis-treated patients were upper respiratory tract infection, otitis media, fever, rhinitis, rash, diarrhea, cough, vomiting, gastroenteritis, and wheezing. Upper respiratory tract infection, otitis media, fever, and rhinitis occurred at a rate of 1% or greater in the Synagis group compared to placebo (Table 2).

Because clinical trials are conducted under widely varying conditions, adverse event 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 does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

The data described reflect Synagis exposure for 1641 pediatric patients of age 3 days to 24.1 months in Trials 1 and 2. Among these patients, 496 had bronchopulmonary dysplasia, 506 were premature birth infants less than 6 months of age, and 639 had congenital heart disease. Adverse events observed in the 153 patient crossover study comparing the liquid and lyophilized formulations were similar between the two formulations, and similar to the adverse events observed with Synagis in Trials 1 and 2.

Table 2: Adverse Events Occurring at a Rate of 1% or Greater More Frequently in Patients* Receiving Synagis

Event	Synagis (n=1641) n (%)	Placebo (n=1148) n (%)
Upper respiratory infection	830 (50.6)	544 (47.4)
Otitis media	597 (36.4)	397 (34.6)
Fever	446 (27.1)	289 (25.2)
Rhinitis	439 (26.8)	282 (24.6)
Hernia	68 (4.1)	30 (2.6)
SGOT Increase	49 (3.0)	20 (1.7)

*Cyanosis (Synagis [9.1%]/placebo [6.9%]) and arrhythmia (Synagis [3.1%]/placebo [1.7%]) were reported during Trial 2 in CHD patients.

Immunogenicity

In Trial 1, the incidence of anti-Synagis antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In pediatric patients receiving Synagis for a second season, one of the fifty-six patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Synagis in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Synagis with the incidence of antibodies to other products may be misleading.

With any monoclonal antibody, the possibility exists that a liquid solution may be more immunogenic than a lyophilized formulation. The relative immunogenicity rates between the lyophilized formulation, used in Trials 1 and 2 above, and the liquid solution have not yet been established.

Post-Marketing Experience

The following adverse reactions have been identified and reported during post-approval use of Synagis. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: severe thrombocytopenia (platelet count < 50,000/microliter)

General Disorders and Administration Site Conditions: injection site reactions.

Immune System Disorders: severe acute hypersensitivity reactions and anaphylaxis have been reported (see *WARNINGS*).

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis are similar in character and frequency to those after the initial five doses.

OVERDOSAGE: No data from clinical studies are available on overdosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis at a dose of 50 mg/kg.

DOSAGE AND ADMINISTRATION: The recommended dose of Synagis is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardio-pulmonary bypass (see *CLINICAL PHARMACOLOGY*). Patients undergoing cardio-pulmonary bypass should receive a dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly.

Synagis should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = patient weight (kg) x 15 mg/kg ÷ 100 mg/mL of Synagis. Injection volumes over 1 mL should be given as a divided dose.

Administration of Synagis

- **DO NOT DILUTE THE PRODUCT**
- **DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL**
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the Synagis vial, and wipe the rubber stopper with a disinfectant (e.g., 70% isopropyl alcohol). Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution. Administer immediately after drawing the dose into the syringe.
- Synagis is supplied as a single-dose vial and does not contain preservatives. Do not re-enter the vial after withdrawal of drug; discard unused portion. Only administer one dose per vial.
- To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. DO NOT reuse syringes and needles.

HOW SUPPLIED: Synagis is supplied in single-dose vials as a preservative-free, sterile liquid solution at 100 mg/mL for IM injection.

50 mg vial NDC 60574-4114-1
The 50 mg vial contains 50 mg Synagis in 0.5 mL.

100 mg vial NDC 60574-4113-1
The 100 mg vial contains 100 mg Synagis in 1 mL.

There is no latex in the rubber stopper used for sealing vials of Synagis. Upon receipt and until use, Synagis should be stored between 2°C and 8°C (35.6°F and 46.4°F) in its original container. DO NOT freeze. DO NOT use beyond the expiration date.

REFERENCES:

1. Press E, and Hogg N. The Amino Acid Sequences of the Fd Fragments of Two Human Gamma-1 Heavy Chains. Biochem. J. 1970; 117:641-660.
2. Takahashi N, Norma T, and Honjo T. Rearranged Immunoglobulin Heavy Chain Variable Region (V_H) Pseudogene that Deletes the Second Complementarity-Determining Region. Proc. Nat. Acad. Sci. USA 1984; 81:5194-5198.
3. Bentley D, and Rabbitts T. Human Immunoglobulin Variable Region Genes - DNA Sequences of Two V_K Genes and a Pseudogene. Nature 1980; 288:730-733.
4. Beeler JA, and Van Wyke Coelingh K. Neutralization Epitopes of the F Protein of Respiratory Syncytial Virus: Effect of Mutation Upon Fusion Function. J. Virology 1989; 63:2941-2950.
5. Johnson S, Oliver C, Prince GA, et al. Development of a Humanized Monoclonal Antibody (MEDI-493) with Potent In Vitro and In Vivo Activity Against Respiratory Syncytial Virus. J. Infect. Dis. 1997; 176:1215-1224.
6. Malley R, DeVincenzo J, Ramilo O, et al. Reduction of Respiratory Syncytial Virus (RSV) in Tracheal Aspirates in Intubated Infants by Use of Humanized Monoclonal Antibody to RSV F Protein. J. Infect. Dis. 1998; 178:1555-1561.
7. The IMpact RSV Study Group. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-Risk Infants. Pediatrics 1998; 102:531-537.

MedImmune

Manufactured by:
MedImmune, LLC
Gaithersburg, MD 20878
U.S. Gov't. License No. 1799
(1-877-633-4411)

Revision Date: April 2011

RAL-SYNV14
Component No.: 8308

Information for Patients and Their Caregivers

SYNAGIS® (SĬ-nă-jĭs)

(palivizumab)

Read this Patient Information before your child starts receiving SYNAGIS and before each injection. The information may have changed. This leaflet does not take the place of talking with your child's healthcare provider about your child's condition or treatment.

What is SYNAGIS?

SYNAGIS is a prescription medication that is used to help prevent a serious lung disease caused by Respiratory Syncytial Virus (RSV). Your child is prescribed SYNAGIS because he or she is at high risk for severe lung disease from RSV.

SYNAGIS contains man-made, disease-fighting proteins called antibodies. These antibodies help prevent RSV disease. Children at high risk for severe RSV disease often do not have enough of their own antibodies. SYNAGIS is used in certain groups of children to help prevent severe RSV disease by increasing protective RSV antibodies.

SYNAGIS is not used to treat the symptoms of RSV disease, once a child already has it. It is only used to prevent RSV disease.

SYNAGIS is not for adults.

Who should not receive SYNAGIS?

Your child should not receive SYNAGIS if they have ever had a severe allergic reaction to it or any of its ingredients. Signs and symptoms of a severe allergic reaction could include:

- a drop in blood pressure
- severe rash, hives or itching skin
- difficult, rapid or irregular breathing
- closing of the throat, difficulty swallowing
- swelling of the lips, tongue, or face
- bluish color of skin, lips or under fingernails
- muscle weakness or floppiness
- unresponsiveness

See the end of this leaflet for a list of ingredients in SYNAGIS.

What should I tell my child's healthcare provider before my child receives SYNAGIS?

Tell your child's healthcare provider about:

- **Any reactions** you believe your child has ever had to SYNAGIS.
- All your child's medical problems, including **any bleeding or bruising problems.** SYNAGIS is given by injection. If your child has a problem with bleeding or bruises easily, an injection could cause a problem.
- **All the medicines your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements.** Especially tell your child's healthcare provider if your child takes a blood thinner medicine.

How is SYNAGIS given?

- SYNAGIS is given as a monthly injection, usually in the thigh (leg) muscle, by your child's healthcare provider. Your child's healthcare provider will prescribe the amount of SYNAGIS that is right for your child (based on their weight).
- Your child's healthcare provider will give you detailed instructions on when SYNAGIS will be given.
    - "RSV season" is a term used to describe the time of year when RSV infections most commonly occur (usually fall through spring). During this time, when RSV is most active, your child will need to receive SYNAGIS shots. Your child's healthcare provider can tell you when the RSV season starts in your area.
    - Your child should receive their **first SYNAGIS shot before the RSV season starts** to help protect them before RSV becomes active. If the season has already started, your child should receive their first SYNAGIS shot as soon as possible to help protect them when exposure to the virus is more likely.
    - **SYNAGIS is needed every 28-30 days during the RSV season.** Each dose of SYNAGIS helps protect your child from severe RSV disease for about a month. **Keep all appointments with your child's healthcare provider.**
- **If your child misses an injection, talk to your healthcare provider and schedule another injection as soon as possible.**
- Your child may still get severe RSV disease after receiving SYNAGIS. Talk to your child's healthcare provider about what symptoms to look for.
- If your child already has an RSV infection and is sick, they still need to get their scheduled SYNAGIS injections to help prevent severe disease from new RSV infections.
- If your child has certain types of heart disease and has corrective surgery, your healthcare provider may need to give your child an additional SYNAGIS injection soon after surgery.

What are the possible side effects of SYNAGIS?

Over one million babies have been given SYNAGIS. Like all medicines, SYNAGIS has been associated with side effects in some patients. Most of the time, the side effects are not serious. If side effects do occur, your child may need medical attention.

Possible, serious side effects include:

- Severe allergic reactions (may occur after any dose of SYNAGIS). Such reactions may be life-threatening or cause death.
    - See "Who should not take SYNAGIS?" for a list of signs and symptoms.
- Unusual bruising and/or groups of tiny red spots on the skin.

Call your child's healthcare provider or get medical help right away if your child has any of the serious side effects listed above after any dose of SYNAGIS.

Common side effects of SYNAGIS include:

- fever
- cold-like symptoms (upper respiratory infection), including runny nose and ear infection
- rash

Other possible side effects include skin reactions around the area where the shot was given (like redness, swelling, warmth, or discomfort).

In children born with certain types of heart disease, other possible side effects include bluish color of the skin, lips or under fingernails and abnormal heart rhythms.

These are not all the possible side effects of SYNAGIS. Tell your child's healthcare provider about any side effect that bothers your child or that does not go away.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or call MedImmune at 1-877-633-4411.

General Information about SYNAGIS

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets.

This leaflet summarizes important information about SYNAGIS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SYNAGIS that is written for health professionals.

For more information, go to www.synagis.com or call 1-877-633-4411.

What are the ingredients in SYNAGIS?

Active Ingredient: palivizumab

Inactive Ingredients: histidine, glycine, and chloride

What is RSV?

Respiratory Syncytial Virus (RSV) is a common virus that is easily spread from person to person. RSV infects nearly all children by their second birthday. In most children, RSV infection is usually no worse than a bad cold. For some children, RSV infection can cause serious lung disease (like pneumonia and bronchiolitis) or breathing problems, and affected children may need to be admitted to the hospital or need emergency care.

Children who are more likely to get severe RSV disease (high risk children) include babies born prematurely (35 weeks or less), or babies born with certain heart or lung problems.

MedImmune
Manufactured by: MedImmune, LLC
Gaithersburg, MD 20878

Issued April 2011 RAL-SYNV14

Component No.: 8308

PARTNERING

Hamilton Medical and Rega are joining together, with Hamilton's recently-launched HAMILTON T1 mobile ventilator to be used on Rega's fleet of air ambulances. Rega is the first air rescue service in the world to equip their fleet of air ambulances with this advanced mobile intensive care ventilator HAMILTON-T1 as launching partner. The HAMILTON-T1 ventilator features a compact, powerful design that increases the availability of appropriate modes of therapy for ventilated intensive care patients outside the hospital. It covers the full range of clinical requirements: invasive ventilation, automated ventilation with Adaptive Support Ventilation (ASV) – invented by Hamilton Medical, and non-invasive ventilation (NIV). This portable transportation platform is appropriate for all patients, from pediatric to adult. Hamilton manufactures al its products at its green manufacturing facility in Switzerland. Contact www.hamilton-medical.com.

NEWS FROM MASIMO

Masimo presented 25 new clinical studies evaluating Masimo noninvasive patient monitoring technologies at the American Society of Anesthesiologists (ASA) Annual Meeting in Chicago. Researchers at Johns Hopkins Hospital in Maryland found that the combination of continuous SpHb and PVI monitoring "may improve the efficacy and safety of the intraoperative autologous normovolemic hemodilution (IAHD) blood conservation technique that helps avoid allogeneic blood transfusions." Two studies, conducted by the Long Beach Veterans Healthcare System in California, found that noninvasive SpHb measurements provided valuable clinical assessment information in remote, rural, and community settings. The first, using the Radical-7 in rural India, concluded that SpHb measurements provided "reliable information compared to the invasive method" with a bias and precision of 0.2+/- 1.2 g/dL and was "very convenient to use in a rural camp setting" while also eliminating "biohazard risks of venipuncture and blood handling." The second study concluded that the Pronto-7 spot-check device, with a bias and standard deviation of -0.06 +1.07 g/dL, provides "similar values and offers acceptable accuracy" when compared to values obtained from laboratory analysis of invasive blood samples. Two separate studies showed that the new In Vivo Adjustment feature for noninvasive SpHb measurements, included as part of the new 2011 Radical-7, along with the newest generation rainbow ReSposable Sensors (Rev. E) helped clinicians to improve the agreement in subsequent comparisons between invasive (tHb) and noninvasive (SpHb) hemoglobin measurements. Researchers at Dartmouth Hitchcock Medical Center in New Hampshire found that the "accuracy and descriptive statistics improved when each time-matched SpHb value was adjusted by the magnitude of difference between the first tHb and corresponding SpHb." They concluded that "if this type of adjustment were performed in real-time in vivo (intra-operatively), overall accuracy of SpHb values may be further improved," which may also "add value to care" during high risk surgical procedures in patients with co-morbidities and "in many other clinical locations and scenarios (ICU, PACU, pediatrics, emergency medicine, surgical ward)." Another study at the Sapporo Medical University School of Medicine, Japan, found that "SpHb values corrected using the novel program were more accurate than those obtained conventionally." Study results showed that In Vivo Adjustment improved bias and standard deviation from 1.1 + 1.0 to 0.0 + 0.61 g/dL) and concluded that In Vivo Adjustment should "contribute to the accurate measurement of SpHb in the clinical setting." Researchers at Nationwide Children's Hospital showed that SpHb measurements obtained in pediatric patients undergoing acute blood loss correlated to hemoglobin values obtained from a point-of-care device. They evaluated the use of SpHb in a pediatric population undergoing phlebotomy and concluded that SpHb provided "accurate and continual real-time data which can inform medical care." In a separate study at the same hospital, researchers found that monitoring changes in PVI could be used as a guide for volume replacement during isovolemic hemodilution in pediatric patients undergoing congenital cardiac surgery. Patients were evaluated in two groups—group 1 had starting PVI values less than 14 and group 2 had starting PVI values greater than 14. Results showed that the average crystalloid replacement in group 1 was 5ml/kg, while volume replacement in group 2 was 11ml/kg in order to maintain the same hemodynamics during hemodilution. Researchers noted that the "data demonstrates the possible advantage of using the PVI value as a tool for identifying patients who would be good candidates for isovolemic hemodilution." For more studies, visit masimo.com.

AT THE ZENITH

Covidien received the prestigious American Association for Respiratory Care (AARC) Zenith Award for 2011. The Zenith Award, established in 1989, recognizes manufacturers and service organizations in the respiratory care industry for outstanding service. The award is presented to five companies annually on behalf of AARC's 52,000 members. This year, more than 400 companies were evaluated using the following criteria: quality of equipment and/or supplies, accessibility and helpfulness of sales personnel, responsiveness, service record, truth in advertising, and support of the respiratory care profession. This marks the 22nd consecutive year that Covidien has received this award. Contact covidien.com.

CRITICAL ROLE

The Passy-Muir Valve plays a very critical role in the rehabilitation of tracheostomy and ventilator patients of all ages across the continuum of care. Beginning in the intensive care unit, the valve is an essential component for achieving the multiple and complex rehabilitation goals of tracheostomy and ventilator patients. Clinicians who understand the importance of the multidisciplinary team shared their strategies for successful rehabilitation in Passy-Muir's fall newsletter, Talk Muir. Subjects include Developmental Therapy in the NICU, Pulmonary Rehab, Sensory Stimlation and TBI, and new products. For more about developmental therapy in the NICU, and the use of the Passy-Muir Valve, see our November/December issue. Passy-Muir also announced a new product, Passy-Muir Cleaning Tablets, made from a detergent used for other medical supplies because it leaves no residue as do some commercially available soaps. The tablets are biodegradable, and come with easy-to-read instructions for patients. Contact passy-muir.com.

PUMP IT UP

Smiths Medical has received 510(k) clearance from the FDA for its new Medfusion 4000 wireless syringe infusion pump with the PharmGuard infusion management software suite. The new customizable system, which helps prevent medication errors, will allow health care providers to send and receive medication delivery information more efficiently. The Medfusion 4000 system with wireless connectivity capability allows hospitals to capture many types of infusion data. The PharmGuard infusion management software suite allows for simple, easy reporting of this data for evidence- based practice improvements. Having

a wireless system to update drug libraries on pumps improves both patient safety as well as clinical care by allowing quick and easy wireless update of pumps. The Medfusion 4000 Syringe Infusion Pump with PharmGuard Medical Software is a Smart infusion pump that now has wireless (802.11b/g) and wired Ethernet connectivity for efficient drug library, syringe and firmware management, eliminating the need to physically search for pumps and manually update them. The PharmGuard Toolbox Medication Safety Software is PC software that allows pharmacists to develop drug libraries according to hospital-defined medication dosing best practices and then deploy them to the pumps. Its Server Software is a scalable and upgradeable web-based application that enables the wireless collection, management, and Continuous Quality Improvement (CQI) reporting of patient infusion data to track trends in compliance with medication dosing and clinical best practices. SureLink Remote Support Software is an agent that runs in the background on a hospital's Windows-based workstation or server and allows Smiths Medical Customer Support specialists to monitor devices and software, diagnose problems, provide software installation and upgrades, and supply remote support of Smiths Medical products. Contact smiths-medical.com.

PETITIONED

FDA petitioned to retract pediatric extension for Ikaria's INOmax nitric oxide product: The US Department of Health and Human Services has been sent a Citizen Petition requesting that the Food and Drug Administration rescind the Pediatric Exclusivity extension approved for Ikaria in 2010 that extends their patent protection for their nitric oxide gas for six months beyond the US patent expiration date. The Pediatric Exclusivity Statute was designed to give extended protection to pharmaceutical companies that perform new pediatric studies at the request of the FDA. FDA documents disclosed that Ikaria first approached the FDA in April of 2008 requesting that the FDA write them a letter requesting additional studies for INOmax nitric oxide gas to study the effects on premature infants to prevent BPD.[1] Ikaria submitted three studies, two of which were statistically negative trials, to fulfill the requirements of the Statute. The third study demonstrated a statistical benefit, however the FDA found that because of issues raised by their analysis (data quality, different post hoc statistical analyses, and lack of p value adjustments for interim analyses), the statistical determination was difficult to discern.[2] However, the Pediatric Exclusivity Guidance Document specifically states that, "FDA does not believe it would be consistent with the intent of the statute to accept data collected prior to the Written Request if such data are already known to provide no useful information."[3] The petitioner cited the irregularity of the Ikaria request in that all three studies were completed by March of 2008, two of which were completed in 2005. Therefore, at the time of the Ikaria letter to the FDA and the subsequent FDA letter to Ikaria, the data from the negative trials had been collected (two of the trials were published in 2006)[4,5] and therefore as negative trials, should never have been submitted or accepted by the FDA in applying for coverage by this statute. The petitioner argued that this extension granted to Ikaria prevents generic suppliers of pharmaceutical nitric oxide gas from entering the market. The petitioner expects that the FDA will review their granting of the Pediatric Exclusivity and hopefully open the market to generic competition six months earlier, potentially saving the US healthcare system

tens of millions of dollars in that period. [Footnotes: 1. Curtis J. Rosebraugh, Department of Health and Human Services, Food and Drug Administration, Written Request, IND 106088, NDA 020845, Application Type: GI-1, Ino Therapeutics Inc., 04/30/2010. 2. Medical Officer Review, Division of Pulmonary, Allergy and Rheumatology Drug Products (HFD-570), Application #: 20-845, Proprietary Name: INOmax, Review Date: November 19, 2010. 3. Guidance for Industry, Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Revised, September 1999. 4. Kinsella JP, et al. Early Inhaled Nitric Oxide Therapy in Premature Newborns with Respiratory Failure. N Engl J Med 2006;355:354-64. 5. Ballard RA, et al. Inhaled Nitric Oxide in Preterm Infants Undergoing Mechanical Ventilation. N Engl J Med 2006;355:343-53.]

ACQUISITION

Siemens Healthcare announced that the company has entered into a definitive agreement to acquire all issued and outstanding equity of MobileMD, Inc, of Yardley, PA, a provider of health information exchange (HIE) solutions. MobileMD's cloud-deployed HIE service liberates patient information across a community of providers, regardless of geographic, organizational, or health IT system boundaries. The HIE solution is in use by more than 110 hospitals and more than 2,000 physician practices. When hospitals and physician practices connect through MobileMD they can engage in a clinical dialog that can better coordinate care by including results delivery, online ordering, referrals, scheduling, and more. The solution reduces providers' reliance on paper, phone and faxed information, and can lead to fewer duplicative or unavailable patient records, improved utilization, and a better patient experience. MobileMD has been active in the health information exchange space since 2005. The company markets the cloud-based 4D HIE, which addresses information sharing in four dimensions: care, service, economics and technology – providing physicians with near real-time, secure, clinical and administrative information regardless of location, affiliation, EMR technology or vendor.

DRINK UP

Bottle Buddy is an electronic formula dispenser that counts a pre-set amount of powdered formula into a baby's bottle with accuracy and precision. It features a clear, LCD display for easy, one-touch operation. It eliminates human error when making formula bottles; it's 50% quicker than manually scooping the formula and 100% hygienic. The Bottle Buddy, designed for parents, is made of BPA-free plastic and is compatible with all leading formula brands. Contact jbcumberland.com, (646) 230-6942.

RELIABLE

Dräger announced the availability of its new ventilator for pediatric and adult patients. The Savina 300 ventilator provides reliable ventilation therapy and is suitable for use nearly anywhere in the hospital. The Savina 300 provides invasive and non-invasive ventilation (NIV) capability which helps to reduce intubation and infection rates. The open breathing concept lets patients breathe freely at any time during the cycle and at any pressure level, increasing overall patient comfort levels and potentially helping to reduce weaning times. The large, color touch screen and intuitive operating system make configuration and operation very simple, requiring minimal training. Developed in consultation with clinicians from the United States, and building on the success of the original Savina ventilator over the past ten years, the Savina 300 will meet the growing demands of emergency rooms, recovery rooms, and other acute care settings. The Savina 300 was showcased at this year's AARC. For more information contact draeger.com.

COMPLETING THE CIRCUIT

The new Neonatal Circuit with Column Kit product line from Hudson RCI (Teleflex) is designed to elevate patient protection and offer convenience and peace of mind for the clinician. Today, our current offering can be confusing to the clinician as we offer multiple column choices depending on the therapy and recommended use for our Neptune Heated Humidifier. The new Circuit with Column Kit packaging will eliminate this confusion by kitting the desired column and heated wire circuit for each intended therapy. By simplifying the current product offering and packaging, the clinician will feel confident in providing optimum patient care. The graph below identifies each neonatal circuit with the clinically appropriate concha column. The Circuit with Column Kit was inspired by the clinician. We listened, and made it possible - for the clinician. Contact Teleflex Medical, (866) 246-6990.

NEONATAL	DESCRIPTION	COLUMN	CASE QTY
780-01KIT	Single Heated Limb with Remote Temperature Port (SIPAP, ARABELLA ETC)	Standard Compliance	20
780-07KIT	Dual Heated Limb with 18" Remote Temperature Port	Low Compliance	20
780-08KIT	Dual Heated-Limb - 48 inches	Low Compliance	20
780-09KIT	Dual Heated Limb - 60 inches	Low Compliance	20
780-15KIT	Dual Heated Limb with 18" Remote Temperature Port. Water Traps in Both Limbs	Low Compliance	20
780-17KIT	Dual Heated-Limb with 12" Remote Temperature Port (INFANT NASAL CPAP)	Standard Column	20
780-18KIT	Dual Heated Limb with 18" Remote Temperature Port - 60 inches	Low Compliance	20

COMPANY PROFILE

NeoMed, Inc.

Describe your neonatal/perinatal product(s) and their features.

NeoMed designs and manufactures neonatal and pediatric enteral delivery systems utilizing oral/enteral syringes, feeding tubes and extension sets, a SafeBaby Breast Milk Tracking System and our NeoBottle. Some unique features of our enteral safety system include "enteral only" connections that eliminate misconnection errors, an orange color coding that serves as a visual cue to identify enteral paths and both silicone and polyurethane feeding tubes that feature an open distal tip to prevent pooling of breast milk or formula to minimize the

potential for bacterial growth. Our upcoming PVC feeding tube is offered for short-term use and provides hospitals with another cost-saving option. In addition, NeoMed offers umbilical catheters, insertion trays, urinary drainage catheters and trays.

How does your product directly affect patient care?
Our products are designed to deliver enteral nutrition safely and effectively to the patient, mitigating misconnection and feeding errors. Our devices and technology are designed to maximize the nutritional value of both breast milk and formula delivered to the patient.

Tell us about the latest advances in the area your product serves.
As NeoMed targets to identify, fortify and effectively track breast milk and formula, we have created the SafeBaby Breast Milk Tracking System. With SafeBaby, the clinician receives 100% validation that the baby is receiving the correct breast milk or formula. Another milestone for NeoMed is the release of our 100 mL oral/enteral syringe with two breakthrough features: barrel volume that exceeds the standard 60 mL enteral syringe and a vented zone position that allows for the syringe volume to flow during a gravity feed without the need to completely remove the plunger. NeoMed's NeoBottle is the first truly closed system breast milk container for collecting, storing, fortifying and delivering human breast milk and formula. First on the market, the NeoBottle allows for unit dose dispensing of nutrition and oral medications without breaching the closed system barrier.

What sets your product apart from others in the field?
We focus on patient safety and enhanced clinical outcome when developing new products or adding new features to existing products. The NeoMed Enteral Safety System is the only enteral safety system approach that maintains color coordination from the enteral syringe to the feeding tube during gravity or pump feeds per the Joint Commission, ASPEN and ISMP recommendations.

Discuss your R&D process, including clinician and nurse input.
NeoMed's product development effort is driven by input from clinicians and medical professionals and supported by an internal engineering department with vast experience in medical device design and manufacturing. At the core of every NeoMed product is our goal to support the care of neonatal and pediatric patients with products that significantly improve patient safety and medical outcomes. We integrate our field experiences and assessment of neonatal needs to insure that our products meet the specific needs of the population we serve.

What are your goals for R&D in the near future?
We approach the design of our products with the goal of extending shelf life, reducing environmental contamination and maintaining a feeding path that doesn't offer the ability to be breached or misconnected. Introduction of ancillary products that support neonatal nutrition are a major focus of both long-term and short-term development. Directing resources into enhanced electronic tracking, shortening engineering development cycles, evaluating performance characteristics of leading edge polymers and responding to the needs of the neonatal community remain the focus of our R&D efforts.

Discuss the educational services you offer for neonatal caregivers.
NeoMed's dealer network is comprised of seasoned neonatal product specialists having the clinical expertise to provide in-service product training. We support targeted clinical research and hold periodic training conferences each year for all sales representatives. In addition, NeoMed also sends out quarterly newsletters and maintains a website consisting of informative clinical literature.

PRODUCT FEATURES

MOTION TOLERANT

Late last year, the HHS made critical congenital heart defect screening using motion-tolerant pulse oximetry a nationwide newborn screening standard. In addition, the largest UK study of pulse oximetry screening for CHD detection, published online in the Lancet (November) demonstrates that when Masimo SET Measure-Through Motion and Low Perfusion pulse oximetry was used to screen newborns before hospital discharge, it enabled clinicians to increase CHD detection and provided a cost-effective method for universal screening with high sensitivity. Among the approximately 4.2 million babies born in the U.S. annually, CHD is the most prevalent form of birth defect and is the number one cause of infant death. HHS estimates that approximately 7-9 babies per 1,000 live births have some form of CHD. Yet, up to 30% of infant deaths from CHD occur before diagnosis, leading many to question the effectiveness of current newborn screening methods. Current methods of CHD detection rely largely on newborn physical examination but fail to identify

approximately 50% of CHD cases, leaving many vulnerable newborns undiagnosed at hospital discharge. HHS Secretary Kathleen Sebelius outlined the decision to adopt expert panel recommendations for universal CCHD screening by pulse oximetry for all newborns into federal Recommended Uniform Screening Panel (RUSP) Guidelines—the national newborn screening system standards and policies. Citing the "emerging evidence base for the utility of early diagnosis and detection of CCHD via measurement of blood oxygen saturation" and the "momentum and commitment" at the state and federal levels, Sebelius directed federal agencies to "proceed expeditiously with implementation." The federal Agency Plan of Action outlined by HHS calls for the National Institutes of Health (NIH) to fund technology, process, care, and outcomes research activities; the Centers for Disease Control and Prevention (CDC) to fund surveillance activities to monitor infant morbidity and mortality outcomes; and the Health Resources and Services Administration (HRSA) to guide development of screening standards and implementation infrastructure, including training materials. In August 2011, a panel of pediatric and cardiac experts from the American Academy of Pediatrics (AAP), the American College of Cardiology (ACC), and the American Heart Association (AHA), in conjunction with the HHS Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC), acted on the HHS recommendations and outlined a strategy for routine screening of newborns to improve detection of CHD. The 28-page report recommends that newborn screening be done with "motion-tolerant pulse oximeters that report functional oxygen saturation, have been validated in low perfusion conditions, have been cleared by the FDA for use in newborns, and have a 2% root-mean-square accuracy." The report also outlined a 5-point implementation strategy and follow-up procedures, which includes screening, diagnostic confirmation, electronic results reporting, primary care follow-up, surveillance and tracking.

In the current Lancet-published study, researchers screened 20,055 asymptomatic newborn babies (gestation >34 weeks) at six UK maternity units using Masimo SET pulse oximetry before discharge. Newborns with oxygen saturation (SpO_2) of less than 95% in either limb or a difference of more than 2% between limbs were considered positive for CHD and underwent echocardiography. Results showed that 53 babies had major CHDs (24 critical)—a prevalence of 2.6 per 1,000 live births. Masimo SET pulse oximetry achieved sensitivity of 75% for critical CHDs (causing death or requiring invasive intervention before 28 days) and 49% for all major CHDs (causing death or requiring invasive intervention within 12 months of age.)

Findings also showed that Masimo SET pulse oximetry helped clinicians increase CHD detection by 34% versus antenatal ultrasonography alone (from 35 cases to 53 cases). In addition, out of the 0.8% false-positive results (169), 27% had other problems that required medical intervention (6 were significant but not major congenital heart defects and 40 were other illnesses like respiratory disorders and infections)—showing that the sensitivity of Masimo SET enabled identification of other life-threatening newborn conditions that likely would have otherwise gone undiagnosed. Researchers concluded that: "Pulse oximetry is a safe, feasible test that adds value to existing screening. It identifies cases of critical congenital heart defects that go undetected with antenatal ultrasonography. The early detection of other diseases is an additional advantage." Reported by Masimo on its website.

NON PROFIT PARTNER

GE announced it will partner with the East Meets West Foundation, a non-profit organization dedicated to improving health outcomes for children in Asia, to distribute GE's Maternal Infant Care solutions in developing and rural regions. Specifically, East Meets West will distribute GE Healthcare's Lullaby warmers, incubators and phototherapy equipment through its Breath of Life program, which provides clinical solutions to significantly reduce neonatal mortality and morbidity in developing countries. In India alone there are an estimated 27 million births each year, with over 2 million premature births and over 1 million infant deaths. The United Nation's Millennium Development Goals (MDG4) aim to reduce child mortality by two-thirds by the year 2015. While projects focused on improving nutrition and providing clean water and lifesaving vaccines have done wonders in reducing deaths of children five and under, more must be done to achieve the MDG4 goal. In many countries, infant death is now the leading cause of under-5 child mortality. East Meets West's Breath of Life goes beyond providing specialized equipment to hospitals. The program also provides comprehensive support to providers, including intensive clinical training for medical personnel, frequent monitoring, three-year warranties, advanced medical conferences and on-site clinical evaluations. "Increasing access to low-cost neonatal care solutions in developing regions supports our healthymagination commitment to deliver high-quality, affordable healthcare to more people worldwide," said Carrie Eglinton Manner, General Manager of GE Healthcare's Maternal Infant Care business. "We are excited to work with East Meets West to not only distribute our Lullaby solutions, such as warmers and phototherapy products, but to collaborate in the development of additional technologies to help save the lives of newborns in underserved, rural areas." Through the partnership with GE Healthcare, East Meets West will be able to serve a larger number of communities, with initial plans to expand distribution in India, the Philippines and Indonesia over the next several years. The organization will also share important insights from its work with healthcare providers in the field to support the development of new technologies customized to the needs of patient populations in the rural and developing regions East Meets West serves and that GE Healthcare can help bring to life through their expertise in engineering, manufacturing and distribution.

Cytomegalovirus Transmission to Preterm Infants via Breastmilk: Issues in Research and Practice

Jean Rhodes, PhD, CNM, IBCLC

Breastmilk, with all of its bioactive, immunological, anti-inflammatory and nutritive components, is generally believed to be the most beneficial form of nourishment for human infants. However, breastmilk is also a common mode of cytomegalovirus (CMV) transmission to infants. While term infants infected with CMV via breastmilk rarely exhibit any outward signs of illness, preterm infants can present with a variety of signs and symptoms, some quite serious, related to CMV infection. How to approach this clinical issue is both complex and controversial.

Women who have had CMV at some point in their lives are seropositive for CMV antibodies. During pregnancy and lactation, CMV reactivates in a woman's breasts and reproductive tract, causing asymptomatic infection with viral shedding in the mother's breastmilk, cervical secretions and urine. Term infants can acquire CMV infection from breastmilk through what is thought to be a natural immunization process.[1] Infants receive CMV antibodies from their mothers during the third trimester of pregnancy such that at the time of birth, they have a form of passive immunity to the virus. CMV-infected term infants will shed the virus in urine and saliva, but are generally asymptomatic for the infection.

Researchers hypothesize that preterm infants miss the transmission of maternal antibodies to CMV.[2] Thus, when preterm infants — who are by nature physically immature and vulnerable — acquire CMV postnatally via breastmilk, they are at greater risk than term infants of exhibiting symptoms of the disease.[3]

Distinctions among asymptomatic infection, symptomatic infection and a severe CMV sepsis-like syndrome in preterm infants have evolved through clinical studies and case reports. Asymptomatic infection is the most common scenario in term and preterm infants: the infant sheds CMV in urine and saliva but otherwise shows no signs or symptoms of illness. In studies reporting symptomatic infections in preterm infants, infants present with a variety of laboratory and/or clinical conditions.

In a 2010 systematic review, Kurath et al[4] examined the short and long-term outcomes of preterm infants who become infected with CMV via maternal breastmilk. As with most meta-analyses or systematic reviews, studies evaluated varied in methodology, testing procedures, populations and outcomes. Kurath and colleagues' analysis of 26 prospective studies suggests the majority of women of childbearing age are CMV-positive with more than three-quarters of CMV-seropositive women shedding the virus in their breastmilk. CMV infection occurs at a rate of approximately 20% in preterm infants receiving breastmilk from CMV-positive mothers. Additionally, a small percent (median rate of 3.7% or mean of 9.3%) of preterm infants of breastfeeding seropositive mothers develop symptomatic CMV infection. Symptoms vary widely in terms of severity and can include one or more of the following: hepatitis, pneumonia or pneumonitis, neutropenia, thrombocytopenia, elevated liver enzymes, hepatosplenomegaly, gray pallor, fever and hyberbilirubinemia.[5-8] The most commonly reported single symptom is neutropenia alone without other indications of illness.[9,10] In studies reporting symptomatic infections in preterm infants, the infants generally recover spontaneously without evidence of long-term consequences.[4,9,11,12]

Of greatest concern to researchers, health care providers and parents is a severe CMV sepsis-like syndrome evidenced by a very small percent of preterm infants. This analysis by Kurath and colleagues suggests a median of less than 1% of preterm infants of CMV-positive mothers will demonstrate symptoms of severe infection. Of note, Kurath et al do not report any deaths in infants with breastmilk-acquired CMV. In a separate review of multiple clinical and case studies, Hamprecht et al [5] reported very similar results and infant outcomes. Their total sample size was over 1000 infants. Unlike Kurath et al, they identified two infant deaths in one study by Cheong,[13] both deaths occurred in infants with NEC and CMV.

In 1998, Vochem et al[14] identified in five preterm infants with breastmilk-acquired CVM a pattern of more acute illness now known as sepsis-like symptoms or syndrome. These infants exhibited apnea, bradycardia, distended abdomens and gray pallor. Later studies reported similar and additional clinical findings in infected infants, many of whom were extremely low birth weight.[5,6,9,13] However, despite the severity of sepsis-like infections, almost all infants recovered and were discharged home.[5,9]

Shortly after CMV was first reported in breastmilk in 1967,[15] researchers began publishing reports of the effects of breastmilk freezing and pasteurization on CMV. In 1982 Friis and Andersen reported freezing breastmilk significantly reduced the virus in breastmilk.[16] The same year Dworsky et al[17] investigated the effects of pasteurization and freezing on CMV in breastmilk. In the Dworsky study, CMV was destroyed completely by Holder

This article was provided by Medela.

pasteurization (heat treatment at 62°C for 30 minutes) but only reduced by freezing. The authors expressed concerns, just as important today as it was then, about the effects of temperature treatment on the immunological properties of human milk.

Breastmilk pasteurization and freezing studies increased in the literature in response to reports of preterm infants with breastmilk-acquired CMV infection. In an attempt to preserve the beneficial properties in human milk, Hamprecht et al[18] compared the effects of Holder pasteurization, short-term pasteurization (5 seconds at 72°C) and freezing at -20°C on CMV-positive breastmilk. Both methods of pasteurization destroyed the CMV, but breastmilk enzymes were also significantly reduced. The authors recommended more study to find the pasteurization temperature at which CMV could be inactivated and breastmilk preserved. Study continues on pasteurization[19] but as Hayashi[20] points out, it is not always practical in a clinical setting.

However, freezing breastmilk is common practice in neonatal intensive care units. Breastmilk is often stored in the freezer for later use or per protocol to reduce CMV transmission. In 2011, Hayashi et al[20] reported a 4.3% CMV transmission rate in preterm infants receiving previously frozen milk from seropositive mothers. Other researchers also report lower rates of breastmilk-acquired CMV transmission in infants fed primarily frozen breastmilk. In Taiwan, where 95% of mothers are seropositive for CMV and all breastmilk is frozen before use, Jim et al[21] found a 15% CMV transmission rate by seropositive mothers to their preterm infants. In Japan, another country where breastmilk is routinely frozen, Yasuda[22] reported 10% CMV transmission via breastmilk with no infant exhibiting clinical symptoms.

While freezing breastmilk seems to reduce CMV transmission, its effects are not entirely benign. The notion that "freezing breastmilk preserves the biochemical and immunologic quality of the milk…" (p. 529)[18] is often taken out of context and repeated. However, this assertion is not consistent with current evidence regarding important breastmilk components and properties. For example, freezing breastmilk kills or significantly reduces cellular components, including macrophages and lymphocytes.[23] Freezing also reduces antioxidants[24] and immunoglobulins IgG, IgM and IgA.[23] This information along with recent breastmilk discoveries such as stem cells[25,26] and the specific immunologic actions of breastmilk lymphoid T and B cells[27,28] should be included in discussions about freezing, pasteurizing or withholding breastmilk for preterm infants.

Studies of CMV transmission via fresh – not previously frozen or pasteurized – breastmilk suggest outcomes similar to those previously discussed. Miron et al[11] in 2005, studied 70 preterm infants fed fresh breastmilk from CMV sero-positive mothers. These researchers reported a 5.7% CMV infection rate with all infants recovering. In 2009 Capretti et al[2] studied 80 infants ≤32 weeks and ≤1500 grams fed fresh breastmilk. CMV transmission occurred in 35% of infants exposed to CMV-positive milk. In this study, 11.5% of infected infants had mild sepsis-like symptoms but all infected infants had positive outcomes with no neurosensory deficits at two years.

The study by Capretti and associates included an additional variable that could have influenced results: immunoglobulin therapy. The neonatal unit's treatment policy for infants less than 28 weeks included IVIGMA therapy at birth. IVIGMA contained variable titers of anti-CMV antibodies. Nineteen study infants less than 28 weeks received IVIGMA; only one developed CMV. In comparison, three of five infants less than 28 weeks who did not receive IVIGMA became infected with CMV. Capretti et al hypothesized the administration of IVIGMA may have helped the very preterm infants compensate for the lack of maternal antibodies they would have received in utero if they had delivered at term.

This is not the first mention in the literature of immunoglobulin therapy to prevent breastmilk CMV transmission: a thin thread of this idea runs through the literature from beginning to end. As early as 1983, Yeager et al[8] recommended the administration of CMV immunoglobulin to preterm infants if the connection between the lack of maternal antibodies and CMV infection could be confirmed. In a later report, Mosca and associates[29] used intravenous immunoglobulins in preterm infants less than 34 weeks receiving CMV-positive breastmilk. In their study, five of 20 exposed infants were CMV infected, but none had any clinical signs or consequences of infection. Lastly, in 2010 Kurath and Resch concluded, "passive immunization with either HCMV monoclonal antibodies or immune globulins might be a case of debate for high-risk low birth weight infants"[30] (p. 680).

Capretti et al[2] concluded the benefits of giving fresh breastmilk outweigh the risks of CMV infection in most preterm infants. For the past 40 years, when interventions for breastmilk-acquired CMV were proposed, they have centered on treating or withholding breastmilk. The discussion of immunoglobulin therapy could shift the focus from treating breastmilk to treating the infant. The more we understand about breastmilk-acquired CMV and breastmilk itself, the closer we come to a comprehensive appreciation of all the relevant issues and options.

Concluding Remarks

The survival of very premature infants presents challenges in neonatal care that did not exist forty years ago. The majority of reports of acute and serious CMV illness are clinical cases of extremely low birth weight infants born before 28 weeks gestation. Kurath and colleagues point out it is often difficult to distinguish between complications related to prematurity and complications from CMV infection.[4] However, research evidence suggests the actual risk of severe, symptomatic CMV infection is very low, even in very immature infants.

At the time postnatal CMV came of interest, techniques for milk pasteurization were well established; thus, they were logical interventions for study and practice. Since that time, human milk science has expanded exponentially. This new information obligates more comprehensive analyses of temperature treatments on human milk or withholding fresh milk from preterm infants. Prophylactic immunoglobulin therapy might also warrant further consideration. Undoubtedly, additional research is needed before clinicians and researchers come closer to a consensus on the issue of CMV transmission via breastmilk.

References

1 Stagno S, Reynolds DW, Pass RF, Alford CA. Breast milk and the risk of cytomegalovirus infection. N Engl J Med. May 8 1980;302(19):1073-1076.

2 Capretti MG, Lanari M, Lazzarotto T, et al. Very low birth weight infants born to cytomegalovirus-seropositive mothers fed with their mother's milk: a prospective study. J Pediatr. Jun 2009;154(6):842-848.

3 Forsgren M. Cytomegalovirus in breast milk: reassessment of pasteurization and freeze-thawing. Pediatric research. Oct 2004;56(4):526-528.
4 Kurath S, Halwachs-Baumann G, Muller W, Resch B. Transmission of cytomegalovirus via breast milk to the prematurely born infant: a systematic review. Clin Microbiol Infect. Aug 2010;16(8):1172-1178.
5 Hamprecht K, Maschmann J, Jahn G, Poets CF, Goelz R. Cytomegalovirus transmission to preterm infants during lactation. J Clin Virol. Mar 2008;41(3):198-205.
6 Kerrey BT, Morrow A, Geraghty S, Huey N, Sapsford A, Schleiss MR. Breast milk as a source for acquisition of cytomegalovirus (HCMV) in a premature infant with sepsis syndrome: detection by real-time PCR. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. Mar 2006;35(3):313-316.
7 Schleiss MR. Acquisition of human cytomegalovirus infection in infants via breast milk: natural immunization or cause for concern? Reviews in medical virology. Mar-Apr 2006;16(2):73-82.
8 Yeager AS, Palumbo PE, Malachowski N, Ariagno RL, Stevenson DK. Sequelae of maternally derived cytomegalovirus infections in premature infants. The Journal of pediatrics. Jun 1983;102(6):918-922.
9 Hamprecht K, Maschmann J, Vochem M, Dietz K, Speer CP, Jahn G. Epidemiology of transmission of cytomegalovirus from mother to preterm infant by breastfeeding. Lancet. Feb 17 2001;357(9255):513-518.
10 Maschmann J, Hamprecht K, Dietz K, Jahn G, Speer CP. Cytomegalovirus infection of extremely low-birth weight infants via breast milk. Clin Infect Dis. Dec 15 2001;33(12):1998-2003.
11 Miron D, Brosilow S, Felszer K, et al. Incidence and clinical manifestations of breast milk-acquired Cytomegalovirus infection in low birth weight infants. J Perinatol. May 2005;25(5):299-303.
12 Neuberger P, Hamprecht K, Vochem M, et al. Case-control study of symptoms and neonatal outcome of human milk-transmitted cytomegalovirus infection in premature infants. J Pediatr. Mar 2006;148(3):326-331.
13 Cheong JL, Cowan FM, Modi N. Gastrointestinal manifestations of postnatal cytomegalovirus infection in infants admitted to a neonatal intensive care unit over a five year period. Archives of disease in childhood. Fetal and neonatal edition. Jul 2004;89(4):F367-369.
14 Vochem M, Hamprecht K, Jahn G, Speer CP. Transmission of cytomegalovirus to preterm infants through breast milk. The Pediatric infectious disease journal. Jan 1998;17(1):53-58.
15 Diosi P, Babusceac L, Nevinglovschi O, Kun-Stoicu G. Cytomegalovirus infection associated with pregnancy. Lancet. Nov 18 1967;2(7525):1063-1066.
16 Friis H, Andersen HK. Rate of inactivation of cytomegalovirus in raw banked milk during storage at -20 degrees C and pasteurisation. Br Med J (Clin Res Ed). Dec 4 1982;285(6355):1604-1605.
17 Dworsky M, Stagno S, Pass RF, Cassady G, Alford C. Persistence of cytomegalovirus in human milk after storage. The Journal of pediatrics. Sep 1982;101(3):440-443.
18 Hamprecht K, Maschmann J, Muller D, et al. Cytomegalovirus (CMV) inactivation in breast milk: reassessment of pasteurization and freeze-thawing. Pediatric research. Oct 2004;56(4):529-535.
19 Czank C, Prime DK, Hartmann B, Simmer K, Hartmann PE. Retention of the immunological proteins of pasteurized human milk in relation to pasteurizer design and practice. Pediatric research. Oct 2009;66(4):374-379.
20 Hayashi S, Kimura H, Oshiro M, et al. Transmission of cytomegalovirus via breast milk in extremely premature infants. Journal of perinatology : official journal of the California Perinatal Association. Jun 2011;31(6):440-445.
21 Jim WT, Shu CH, Chiu NC, et al. Transmission of cytomegalovirus from mothers to preterm infants by breast milk. The Pediatric infectious disease journal. Sep 2004;23(9):848-851.
22 Yasuda A, Kimura H, Hayakawa M, et al. Evaluation of cytomegalovirus infections transmitted via breast milk in preterm infants with a real-time polymerase chain reaction assay. Pediatrics. Jun 2003;111(6 Pt 1):1333-1336.
23 Young FS, Heicher DA, Uemura HS, Sia CC. The effects of freezing and pasteurization on human milk. Hawaii Med J. Nov 1979;38(11):330-332.
24 Hanna N, Ahmed K, Anwar M, Petrova A, Hiatt M, Hegyi T. Effect of storage on breast milk antioxidant activity. Arch Dis Child Fetal Neonatal Ed. Nov 2004;89(6):F518-520.
25 Fan Y, Chong YS, Choolani MA, Cregan MD, Chan JK. Unravelling the mystery of stem/progenitor cells in human breast milk. PLoS One. 2010;5(12):e14421.
26 Cregan MD, Fan Y, Appelbee A, et al. Identification of nestin-positive putative mammary stem cells in human breastmilk. Cell and tissue research. Jul 2007;329(1):129-136.
27 Tuaillon E, Valea D, Becquart P, et al. Human milk-derived B cells: a highly activated switched memory cell population primed to secrete antibodies. Journal of immunology. Jun 1 2009;182(11):7155-7162.
28 Sabbaj S, Ghosh MK, Edwards BH, et al. Breast milk-derived antigen-specific CD8+ T cells: an extralymphoid effector memory cell population in humans. Journal of immunology. Mar 1 2005;174(5):2951-2956.
29 Mosca F, Pugni L, Barbi M, Binda S. Transmission of cytomegalovirus. Lancet. Jun 2 2001;357(9270):1800.
30 Kurath S, Resch B. Cytomegalovirus and transmission via breast milk: how to support breast milk to premature infants and prevent severe infection? Pediatr Infect Dis J. Jul 2010;29(7):680-681.

Developmental Care Matters

Yamile Jackson, PhD, PE, PMP

In 2001 I became the mother of a micro-preemie, and I realized that I was the only source of comfort and sense of protection for Zachary for the 155 days he spent in the NICU. Soon after his birth, I moved from being an impotent and hopeless "visitor" to becoming an important member of the team that provided the best possible developmental care for my now healthy son. My maternal instinct made it easy to nurture him and I was ready to provide love, undivided attention, positive stimulation, and energy. My PhD in ergonomics and human factors engineering made me effective in assessing and enhancing his environment to help him grow, develop, and heal. I was the best habitat for my baby in Kangaroo Care for 6 to 7 hours a day, and invented The Zaky, a device that held my scent and simulated the touch, weight and feel of my hands and forearms when I had to be away.

Zachary changed not only my personal and professional life, but he has touched lives around the globe. Applying ergonomics' best practices and maternal instinct to help nurses provide sound developmental care to newborns has been my passion for over a decade. Zachary and the thousands of babies around the world that I have helped make it very clear that the care that we provide (or fail to provide) to the preemies in the NICU have lifelong repercussions. The development of preemies no longer should be left to the personal preference of the caregiver nor to devices that are available or used for decades, but it should be supported by evidence, now available thanks to many research projects.

To me as a neonatal ergonomist, proper developmental care must be baby-centered with two main goals: Neurological development, by providing any care that promotes homeostasis and that is supported by positive physical, physiological, social and emotional development; and the effective integration of the baby into his/her family and that does not completely separate the baby from the mother.

Babies who are born prematurely are welcomed to a world of life, death and separation, and their parents' shock to the dream they had in their hearts of providing a healthy start for their baby. NICU nurses are challenged to keep up with the advancing developmental growth of the infants and individualize the care depending on the gestational age, medical condition, family situation, etc, and learn/practice evidence-based developmental care that starts with knowing the vast variety of positioning requirements due to the baby's lack of muscle tone and skeletal development.

Tone starts developing from the toes and goes up, so it is backwards from the development of any other system. An infant born at 24 weeks basically only has ankle dorsiflexion which, if not protected, plantar flexion might eventually result in the child walking on the toes and require many therapy sessions to resolve. At 27-28 weeks an infant has flexion to the knee but no tone in upper extremities so she or he requires full support to maintain good alignment and musculoskeletal development. Infants begin to show some flexor tone in the upper extremities and increasingly in the lower extremities around 31-36 weeks. Arms and legs are flexed around 36-37 weeks so the infant can finally attempt to pull the body into midline.

Organized behavior also develops on a continuum, like tone. Nurses, therapists and parents have to pay attention to hips, shoulders, necks, airways and molding of the soft heads, not to mention the loud monitors, bright lights, scent of alcohol, and the large number of interventions and devices in a variety of challenging settings including different modes of ventilation, sensors, leads, vascular access devices, catheters, wounds, stomas and drains.

If you were a baby, would you be able to self-regulate and sleep soundly under these conditions or while you are scared or feeling excruciating pain? Not likely; however we are expecting babies to sleep so they can develop their brain—and the mother, the principal source of comfort for the baby, is often denied the opportunity to be the primary developmental caregiver of her own child.

Many things that happen in the NICU are "common" but they are far from "normal," for example, the baby's association of touch with pain (which may prevent the baby from enjoying human touch for the rest of his life), of movement with stress (which may prevent proper development of joints and muscles), the detachment or inability to bond with the mother or other family members (we all know the implications of this), some musculoskeletal deformities,

---

For information about the author, please see the sidebar; This is the first in a series of articles.

or even apnea/bradycardia of prematurity. I work to significantly decrease, and in some cases even eliminate them by providing an ergonomic environment/habitat to the baby, and without the need of expensive equipment, stimulants, medications, or invasive procedures.

The best developmental care is not possible without maternal intervention. There is significant evidence that Kangaroo Care helps the baby survive and thrive; however, the mother is not always available or the baby is not always stable for skin-to-skin sessions. A recent randomized clinical trial entitled "Effect of a Maternal Simulated Intervention on Physiologic and Developmental Behaviors of 28-34 Week Gestation Infants in a Level III NICU" (Russell, Weaver, Vogel, 2011) suggests that the maternal simulation intervention device used in the study called The Zaky was effective in decreasing apnea and bradycardia and improving self-regulation and organization for babies in the study. Why is this significant? Maybe apnea and bradycardia of prematurity are not caused by the immaturity of the brain, heart, and respiratory system and we don't have to use stimulants that don't help the baby to sleep. It is unlikely a coincidence that the eleven babies in this study that used The Zakys Maternally Scented had zero episodes of apnea and bradycardia.

As I thank you for the job that you do, I challenge you to not only save the lives of babies like Zachary, but to improve the environment/habitat of the baby, which without a doubt will in turn improve the quality of their life for a lifetime. I invite you to encourage parents to hold their babies in Kangaroo Care at least as much as I did 10 years ago (6-7 hours a day) and simulate their presence when they are not there. Enhance your standard of care by providing only evidence-based practices that are now available for developmental care. I request that you always question the need of each intervention before touching or waking up a baby that is in quiet sleep developing the brain. Your decision might help that baby decrease future neurological deficiencies such as learning disabilities and ADHD.

Yamile C. Jackson (PhD in ergonomics and human factors engineering, a licensed Professional Engineer, and a certified Kangaroo Care Professional) gave birth prematurely to Zachary, who weighed less than 2 pounds and was hospitalized for 155 nights in 2001. Three weeks after his birth he survived the deluge of Tropical Storm Allison that flooded his hospital in Houston and shut down all power to his life-support machines. Yamile held Zachary on kangaroo care and her husband Larry and the NICU staff "bagged" him for 9 hours until he was evacuated. Yamile promised Zachary that his pain and struggle to survive were not going to be in vain, so she founded Nurtured by Design, Inc, a leader in neonatal ergonomics, developmental care, and Kangaroo Care.

More than products, Zachary inspired Yamile to design ergonomic devices that effectively facilitate evidence-based developmental care around the clock while engaging the parents' natural instincts to nurture and heal: The Zaky and the Kangaroo Zak. She is also one of the facilitators of the Kangaroo Care Certification Course offered by the United States Institute for Kangaroo Care (USIKC) since 2010.

For her work and inventions, Yamile has won over 16 awards including "Groundbreaking Latina Entrepreneur of the Year" by Catalina Magazine, "Outstanding Woman-Owned Small Business of the Year" by the SCORE Foundation, "Ultimate Latina Award - Health Category" by the US Hispanic Chamber of Commerce, and was a finalist for the Institute of Industrial Engineers' "Creativeness in Ergonomics Practitioner of the Year Award." Zachary's story of survival and/or the products have been featured in national and international media and even served as inspiration for the made-for-TV movie called "14:Hours" aired on TNT in 2005.

Join the conversation at http://bit.ly/vkdUBp or visit www.nurturedbydesign.com for more information. Yamile's email is yamile@nurturedbydesign.com.

Trends in Use of Neonatal CPAP

Christine L. Roberts, Tim Badgery-Parker, Charles S. Algert, Jennifer R. Bowen, Natasha Nassar

Abstract

Background: Continuous positive airway pressure (CPAP) is used widely to provide respiratory support for neonates, and is often the first treatment choice in tertiary centers. Recent trials have demonstrated that CPAP reduces need for intubation and ventilation for infants born at 25-28 weeks gestation, and at >32weeks, in non-tertiary hospitals, CPAP reduces need for transfer to NICU. The aim of this study was to examine recent population trends in the use of neonatal continuous positive airway pressure.

Methods: We undertook a population-based cohort study of all 696,816 liveborn neonates ≥24 weeks gestation in New South Wales (NSW) Australia, 2001-2008. Data were obtained from linked birth and hospitalizations records, including neonatal transfers. The primary outcome was CPAP without mechanical ventilation (via endotracheal intubation) between birth and discharge from the hospital system. Analyses were stratified by age ≤32 and >32 weeks gestation.

Results: Neonates receiving any ventilatory support increased from 1,480 (17.9/1000) in 2001 to 2,486 (26.9/1000) in 2008, including 461 (5.6/1000) to 1,465 (15.8/1000) neonates who received CPAP alone. There was a concurrent decrease in mechanical ventilation use from 12.3 to 11.0/1000. The increase in CPAP use was greater among neonates >32 weeks (from 3.2 to 11.8/1000) compared with neonates ≤32 weeks (from 18.1 to 32.7/1000). The proportion of CPAP >32 weeks initiated in non-tertiary hospitals increased from 6% to 30%. Conclusions: The use of neonatal CPAP is increasing, especially >32 weeks gestation and among non-tertiary hospitals. Recommendations are required regarding which infants should be considered for CPAP, resources necessary for a unit to offer CPAP and monitoring of longer term outcomes.

Background

Continuous positive airway pressure (CPAP) is used widely to provide respiratory support for neonates, and is often the first treatment choice in tertiary centers. There are multiple ways of providing CPAP (eg via underwater bubble CPAP, flow driver or ventilator), different patient interfaces (eg binasal prongs, a single nasopharyngeal prong, face mask, high flow nasal cannula) and various levels of water pressure may be used (usually 4-8 cm water). For extremely preterm neonates, CPAP is an alternative to intubation and mechanical ventilation and at later gestational ages, CPAP may be an alternative to headbox oxygen therapy. CPAP is an attractive option for supporting neonates with respiratory distress, because it preserves spontaneous breathing, does not require endotracheal intubation, and may result in less lung injury than mechanical ventilation. Older and larger neonates appear to be managed effectively using CPAP as the initial and primary method for support without the need for surfactant. However, a significant proportion of neonates born very preterm, particularly prior to 28 weeks, may require combinations of respiratory support modes, which could include surfactant treatment, endotracheal intubation and mechanical ventilation and/or CPAP.

Until recently, there was a lack of data from randomized controlled trials (RCTs) on the effectiveness of CPAP. Between 2002 and 2006, Buckmaster and colleagues conducted an RCT comparing CPAP with headbox oxygen for neonates >31 weeks born in non-tertiary hospitals and found CPAP reduced the need for transfer to a neonatal intensive care unit (NICU). Trials in very preterm babies published since 2008 suggest that starting CPAP at birth may have important benefits, with 50% of babies 25-28 weeks gestation never requiring intubation and ventilation, and that neonates of this gestational age who commence CPAP from birth have no increased risk of death or bronchopulmonary dysplasia, and in fact are less likely to be on oxygen at 28 days of age.

Other potential advantages of CPAP compared with intubation and subsequent conventional mechanical ventilation include lower costs, easier operation, potentially fewer risks, and less training. Nevertheless, CPAP is still considered resource-intensive, requiring skilled and experienced staff to ensure the success of the treatment and may result in an increased risk of pneumothorax and nasal trauma. The aim of this study was to use population data to examine statewide trends in CPAP use. An additional aim was to assess whether CPAP use changed in hospitals that participated in the Buckmaster CPAP trial.

Methods

The study population included all live births in New South

The authors are with Clinical and Population Perinatal Health Research, Kolling Institute of Medical Research, University of Sydney, the Department of Obstetrics & Gynaecology, Royal North Shore Hospital; the NSW Department of Health, North Sydney, and the Department of Neonatology, Royal North Shore Hospital. Reprinted from BioMed Central, BMC Pediatrics,

Table 1. Characteristics of neonates receiving CPAP or mechanical ventilation, NSW 2001-2008

Infant and hospital characteristics	CPAP alone N = 6188		Mechanical ventilation* N = 8229		No ventilation or CPAP N = 682,399	
	n	(%)	n	(%)	n	(%)
Male	3625	(58.6)	4908	(59.6)	350346	(51.3)
Female	2563	(41.4)	3321	(40.4)	332053	(48.7)
Singleton	4870	(78.7)	6846	(83.2)	663798	(97.3)
Multiple	1318	(21.3)	1383	(16.8)	18601	(2.7)
Gestational age						
24–26	80	(1.3)	1008	(12.3)	207	(0.03)
27–29	559	(9.0)	1506	(18.3)	276	(0.04)
30–32	1734	(28.0)	1355	(16.5)	2337	(0.3)
33–34	1115	(18.0)	803	(9.8)	7598	(1.1)
35–36	800	(12.9)	682	(8.3)	26332	(3.9)
37–38	681	(11.0)	995	(12.1)	151713	(22.2)
39–40	803	(13.0)	1282	(15.6)	371034	(54.4)
41–42	413	(6.7)	597	(7.3)	122056	(17.9)
>42	3	(0.05)	1	(0.01)	846	(0.12)
Size at birth						
<10th centile	636	(10.3)	1127	(13.7)	64996	(9.5)
10th–90th centile	4865	(78.6)	6241	(75.8)	545275	(79.9)
>90th centile	687	(11.1)	861	(10.5)	72128	(10.6)
Apgar at 1 minute						
<4	626	(10.2)	2450	(30.1)	10011	(1.5)
≥4	5538	(89.8)	5701	(69.9)	670734	(98.5)
Apgar at 5 minutes						
<7	529	(8.6)	2375	(29.1)	6355	(0.9)
≥7	5634	(91.4)	5783	(70.9)	674538	(99.1)

* with or without CPAP

Wales (NSW), Australia, from January 2001 to December 2008 with a gestational age of at least 24 weeks and for whom the birth record linked to at least one hospital record. Neonates transferred interstate within 7 days of birth (N = 585, <0.1%) were excluded because no further information was available for these neonates. New South Wales is the most populous state in Australia with a population of 7.2 million and over one-third of all Australian births.

The data for this study were obtained from the NSW Midwives Data Collection (MDC) and the NSW Admitted Patient Data Collection (APDC). The MDC (referred to as 'birth' records) is a population-based surveillance system covering all livebirths and stillbirths in NSW. The information is recorded by either the midwife or medical practitioner attending the birth, and includes demographic, medical and obstetric information on the mother and information on the labor, delivery and condition of the neonate. The APDC (referred to as 'hospital' records) is a census of all inpatient admissions (public and private) in NSW. It includes a range of demographic data and clinical information. The diagnoses and procedures related to the admission are coded according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, Australian Modification (ICD-10-AM) and the affiliated Australian Classification of Health Interventions, respectively.

The birth record and the infant hospital record associated with the birth were linked for each neonate. Hospital records were also linked longitudinally to identify hospital-to-hospital transfers and readmissions. Probabilistic record linkage was conducted independent of the research by the NSW Centre for Health Record Linkage. No health information is used for linkage, and at no time is identifying information made available to researchers. The study was approved by the NSW Population and Health Services Research Ethics Committee.

Outcome and explanatory factors: The primary outcome was whether a neonate received CPAP or mechanical ventilation (via endotracheal intubation) between birth and initial discharge from the hospital system, identified from any of 20 procedure

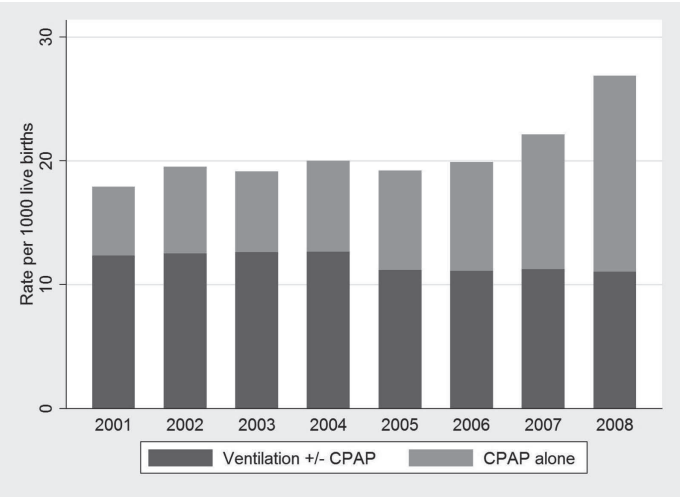


Figure 1. Trend in ventilation and CPAP rates among neonates, NSW 2001-2008

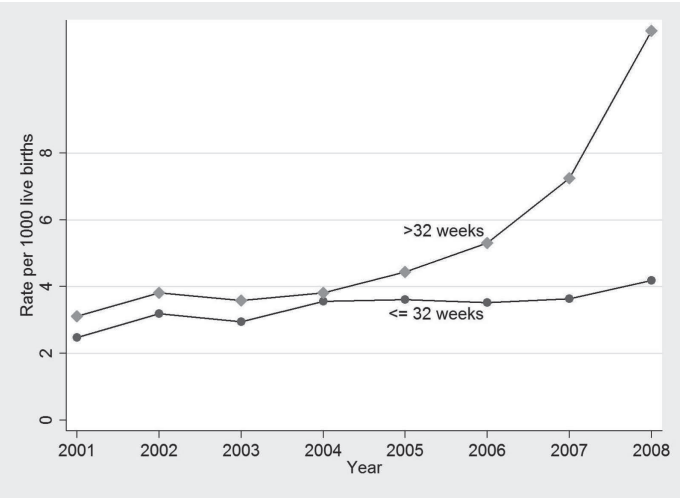


Figure 2. Trend in the CPAP rate per 1000 live births, by gestational age, NSW 2001-2008

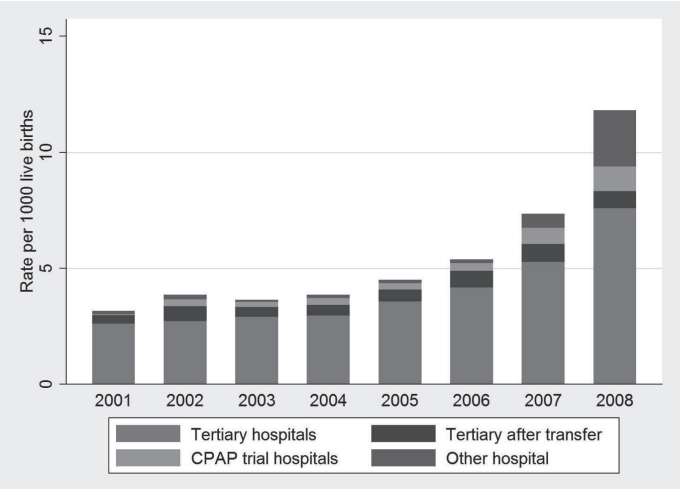


Figure 3. CPAP initiation for neonates >32 weeks by type of hospital

fields in any of the neonate's hospital records. A NSW validation study found that any mechanical ventilation and CPAP are reliably reported in population health data. For analysis, neonates were classified as "ventilation" if they received mechanical ventilation, whether or not they received CPAP, and as 'CPAP' if they received CPAP alone and did not receive

mechanical ventilation in the period from birth to discharge from the hospital system. Neonatal transfer to a NICU was a secondary outcome.

Hospitals were categorized as "tertiary," "CPAP trial" and "other non-tertiary." Tertiary hospitals (n=7) have a Level III neonatal intensive care unit (NICU) which provides mechanical ventilation and care for neonates with severe and/or complex illness. The CPAP trial hospitals were the five NSW hospitals that participated in the Buckmaster CPAP trial. Participation in this trial required a pediatric registrar onsite 24-hours and nursing staff trained in use of CPAP for neonates. The 'other non-tertiary' hospitals (n=78) included all other public and private hospitals at which babies were born in NSW, and have service levels ranging from general practitioner or midwife care with low level neonatal care to special care nurseries. The neonatal factors available for analysis included gender, plurality (singleton vs multiple), gestational age, small for gestational age (SGA, <10th percentile) and large for gestational age (LGA, >90th percentile), Apgar score less than 4 at 1 minute and Apgar score less than 7 at 5 minutes. Gestational age is reported in completed weeks of gestation as determined by the best clinical estimate, including early ultrasound (>97%) and date of the last menstrual period. Only factors that are accurately reported were included in the analyses.

Analysis: We determined rates of CPAP over time and by neonate characteristics, gestational age and hospital of CPAP initiation. Gestational age was categorized as ≤32 weeks and >32 weeks, based on national policy recommending neonates ≤32 weeks be delivered in tertiary centers.

Results

The study included 696,816 live births of at least 24 weeks gestation born in NSW between 2001 and 2008, increasing from 82,542 in 2001 to 92,461 in 2008. Of all infants, 191,511 (27.5%) were born at tertiary hospitals, 94,390 (13.5%) at CPAP-trial hospitals and 410,915 (59.0%) at other non-tertiary hospitals. Overall 6,188 (8.9/1000 livebirths) neonates received CPAP alone and 8,229 (11.8/1000) received mechanical ventilation with or without CPAP, including 3,700 (5.3/1000) who received both mechanical ventilation and CPAP. Compared to neonates who did not receive any ventilatory support, those receiving CPAP alone were more likely to be male (59% versus 51%), of multi-fetal pregnancies (21% versus 3%), born at <37 weeks (69% versus 5%) and have low Apgar scores at 1 (10% versus 2%) and/or 5 minutes (9% versus 1%) (Table 1). Twins and triplets were 8.6 times more likely than singletons to receive CPAP alone, but after adjusting for gestational age this risk decreased substantially (adjusted RR: 1.13; 95% CI: 1.07–1.20). For the gestational ages 31 through 36 weeks, more neonates received CPAP alone than were ventilated. Ventilation numbers only exceeded CPAP alone at ≤30 weeks gestation (Table 1). The gestation-specific rates of CPAP alone were 261.9/1000 among neonates ≤32 weeks, 51.3/1000 at 33-36 weeks and 2.9/1000 at ≥37 weeks. Among infants who required respiratory support, those with transient tachypnea were more than twice as likely to be managed with CPAP alone (RR=2.5; 95% CI 2.3-2.7) compared to those with other diagnoses; 65% of infants with transient tachypnea as one of their admitting diagnoses and requiring respiratory support received CPAP alone.

The number and rate of neonates receiving any ventilatory support increased from 1,480 (17.9/1000) in 2001 to 2,486 (26.9/1000) in 2008 (P<0.001), including an increase from 461 (5.6/1000) to 1,465 (15.8/1000) neonates who received CPAP alone (P<0.001) (Figure 1). There was a concurrent decrease in any use of mechanical ventilation from 12.3 to 11.0/1000 livebirths. However, there was no significant change in the use of combined mechanical ventilation and CPAP (P=0.52). The relative increase in the use of CPAP alone was greater among neonates >32 weeks (increasing 3.7-fold from 3.2/1000 in 2001 to 11.8/1000 livebirths in 2008) compared with neonates aged ≤32 weeks (increasing 1.8-fold from 18.1 to 32.7/1000 livebirths) (Figure 2).

When examined by hospital of initiation, 89% of CPAP was initiated in tertiary centers, including 8% that was initiated following neonatal transfer. Although in absolute numbers CPAP initiated in tertiary centers among neonates >32 weeks increased, the proportion provided by tertiary hospitals declined from 94% (3.0/1000) in 2001 to 70% (8.3/1000) in 2008 (P<0.001, Figure 3). Compared with 2003-2006 (the period of Buckmaster trial), the number of neonates >32 weeks receiving CPAP alone at the CPAP trial hospitals doubled in 2007. From 2001 to 2006, between 3 (2.5%) and 11 (9.6%) other non-tertiary hospitals provided CPAP to neonates (Figure 3). In 2007, this number had doubled, with 22 (23.4%) hospitals providing CPAP to 56 neonates, and by 2008 further increased to 27 hospitals (28.1%) treating 222 infants. From 2001 to 2008, the proportion of neonates born outside a tertiary center and transferred to a NICU declined slightly from 755 (1.2%) to 745 (1.1% P<0.001). Neonates who received CPAP at the CPAP trial hospitals were significantly less likely to be transferred to a NICU than neonates who received CPAP at other non-tertiary hospitals (13.6% versus 20.1%, P=0.03).

Discussion

Use of CPAP without mechanical ventilation for neonates increased from 2001 to 2008, with a particularly notable rise among infants of > 32 weeks gestation and at non-tertiary hospitals in 2008. Although the rates of CPAP use were highest among infants ≤30 weeks, in terms of absolute numbers of neonates exposed, the burden was higher among more mature neonates. The relatively slower increase in CPAP use among neonates ≤32 weeks may relate to greater difficulty in supporting very premature neonates on CPAP alone without a period of mechanical ventilation or may reflect the lack of evidence regarding use of CPAP in very preterm neonates available during the study period. Trials in very preterm neonates published from 2008 support the consideration of CPAP as an alternative to intubation and surfactant, and as these findings are translated into practice we may see a further increase in CPAP rates.

CPAP use among neonates >32 weeks increased slowly from 2001 through 2004, followed by greater increases, particularly in 2008. During this period, there was no increase in the temporal trend of births ≤32 or >32 weeks gestation. The overall increase in neonates receiving CPAP was offset by a small decrease in rate of mechanical ventilation, resulting in a significant increase in total number of infants receiving ventilatory support (CPAP or mechanical ventilation). This suggests that the increase was primarily due to an increase in CPAP in neonates who would previously have received only supplemental oxygen in either a tertiary or non-tertiary unit. The 2007 increase coincided with publication of the Buckmaster CPAP trial results, which showed CPAP for selected neonates at appropriately resourced nontertiary hospitals could reduce transfers to a NICU. At the

hospitals involved in the CPAP trial the number of neonates receiving CPAP doubled after the trial, implying that neonates who would previously have been randomized to oxygen were instead being given CPAP.

The use of large, linked, validated population-based databases that provide information on all neonates is a strength of this study. However, these data do not have detailed clinical information such as the severity of disease, use of surfactant or the duration of CPAP. Furthermore, the temporal sequence of events (eg CPAP, mechanical ventilation, pneumothorax) cannot be determined, only that the events occurred during an admission. This limits the ability to assess complications or reasons for changes in the respiratory support methods.

Nasal CPAP has been adopted by many NICUs as a way of reducing rates of bronchopulmonary dysplasia in premature neonates, but assessment of its benefits is complicated by questions about the simultaneous effects of concomitant surfactant treatments and other NICU interventions. Most research into the potential benefit of CPAP has used a study population of very preterm or extremely preterm neonates who were delivered in tertiary referral hospitals. Little is known about the benefits of CPAP use in more mature neonates in tertiary NICUs. The Buckmaster trial compared CPAP use with supplemental oxygen in neonates >30 weeks gestation in non-tertiary centers to prevent transfer of neonates for intensive care. The study showed a reduction in both treatment 'failure' (RR=0.54; 95% CI 0.32, 0.91) and the rate of up-transfer (RR=0.51; 95% CI 0.31, 0.89), but did not show any statistically significant reduction in outcomes such as length of admission. The results also show an increased risk of pneumothorax in the CPAP arm but the confidence interval is wide (RR=2.76; 95% CI 1.02, 7.48). The possibility of increased rates of pneumothorax has been a concern with use of CPAP, and the COIN trial reported a rate of pneumothorax three times higher in the CPAP group compared with the mechanical ventilation group. However, the recently published results of the SUPPORT trial found no difference in the rates of pneumothorax for extremely preterm neonates randomized to initial treatment with either CPAP or endotracheal administration of surfactant. Further, the long term consequences of CPAP remain undetermined and need to be monitored.

Although our findings highlight that most neonates treated with CPAP are cared for in tertiary centers, there was an increase in the proportion treated outside these hospitals. Our study found that most non-tertiary non-CPAP-trial hospitals that provided CPAP support treated relatively few neonates in 2007-2008; and this may be inadequate to ensure safety and cost effectiveness of the intervention. CPAP is resource-intensive and caution has been advised with the use of CPAP in units that are not well staffed or experienced in its use. Furthermore, it is important that the availability of CPAP facilities does not lead to complacency regarding policies of antenatal transfer of high risk pregnancies, particularly as in utero transfer has been demonstrated to be more beneficial and improve neonate outcomes.

Buckmaster estimated that on average, across an neonatal population, a cost saving of ~AU$1,700 would accrue for every neonate treated with CPAP. However, increased use of CPAP is likely to increase costs at an individual hospital if additional resources, such as experienced staff and ongoing monitoring of CPAP neonates, are required. Additional costs associated with CPAP use in non-tertiary hospitals may be offset by a reduction in neonatal transfers, decreased length of stay or better outcomes for neonates and should be investigated. Although the Buckmaster CPAP trial did show a benefit in reduced transfers, it is not known if this remains true in the wider group of hospitals now providing CPAP and among the potentially broader group of neonates exposed, especially given the small numbers treated at each hospital. Recommendations should be developed regarding which neonates should be considered for CPAP, and the appropriate resources necessary for a unit to offer CPAP. In addition, longer term outcomes for neonates who receive CPAP need to be monitored.

Conclusions

CPAP use has increased since 2001, most notably among neonates >32 weeks and this represents an extension of ventilatory support rather than replacement of mechanical ventilation. Furthermore, CPAP use appears to have increased in non-tertiary hospitals following publication of a randomized trial showing CPAP decreased the need for neonatal transfer. Our study highlights the need for recommendations about which neonates should be considered for CPAP and the appropriate resources necessary to offer CPAP.

Altered Cardiac Rhythm in Infants with Bronchiolitis and Respiratory Syncytial Virus Infection

Susanna Esposito, Patrizia Salice, Samantha Bosis, Silvia Ghiglia, Elena Tremolati, Claudia Tagliabue, Laura Gualtieri, Paolo Barbier, Carlotta Galeone, Paola Marchisio, Nicola Principi

Abstract

Background: Although the most frequent extra-pulmonary manifestations of respiratory syncytial virus (RSV) infection involve the cardiovascular system, no data regarding heart function in infants with bronchiolitis associated with RSV infection have yet been systematically collected. The aim of this study was to verify the real frequency of heart involvement in patients with bronchiolitis associated with RSV infection, and whether infants with mild or moderate disease also risk heart malfunction.

Methods: A total of 69 otherwise healthy infants aged 1-12 months with bronchiolitis hospitalised in standard wards were enrolled. Pernasal flocked swabs were performed to collect specimens for the detection of RSV by real-time polymerase chain reaction, and a blood sample was drawn to assess troponin I concentrations. On the day of admission, all of the infants underwent 24-hour Holter ECG monitoring and a complete heart evaluation with echocardiography. Patients were re-evaluated by investigators blinded to the etiological and cardiac findings four weeks after enrolment.

Results: Regardless of their clinical presentation, sinoatrial blocks were identified in 26/34 RSV-positive patients (76.5%) and 1/35 RSV-negative patients (2.9%) ($p < 0.0001$). The blocks recurred more than three times over 24 hours in 25/26 RSV-positive patients (96.2%) and none of the RSV-negative infants. Mean and maximum heart rates were significantly higher in the RSV-positive infants ($p < 0.05$), as was low-frequency power and the low and high-frequency power ratio ($p < 0.05$). The blocks were significantly more frequent in the children with an RSV load of ≥100,000 copies/mL than in those with a lower viral load ($p < 0.0001$). Holter ECG after 28 ± 3 days showed the complete regression of the heart abnormalities.

Conclusions: RSV seems associated with sinoatrial blocks and transient rhythm alterations even when the related respiratory problems are mild or moderate. Further studies are needed to clarify the mechanisms of these rhythm problems and whether they remain asymptomatic and transient even in presence of severe respiratory involvement or chronic underlying disease.

Authors Esposito, Bosis, Tremolati, Tagliabue, Gualtieri, Marchisio and Principi are with the Department of Maternal and Pediatric Sciences; Salice and Ghiglia are with the Cardiology Unit, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; Barbier is with the Echocardiography Laboratory, IRCCS Centro Cardiologico Monzino; Galeone is with the Department of Epidemiology, Istituto di Ricerche Farmacologiche Mario Negri and the Luigi Devoto Department of Occupational Health, Giulio A. Maccacaro Section of Medical Statistics, University of Milan, Milan, Italy. Reprinted from BioMed Central, BMC Infectious Diseases,

Background

The most frequent extra-pulmonary manifestations of respiratory syncytial virus (RSV) infection involve the cardiovascular system,[1] and include cardiovascolar failure with hypotension and inotrope requirement, associated with myocardial damage, cardiac arrhythmias and pericardial tamponade, particularly in patients admitted to pediatric intensive care units (PICUs).[2-9] However, the reasons leading to heart involvement during RSV infection are not fully known. As severe bronchiolitis can be associated with pulmonary hypertension,[10] it has been thought that the disease itself may lead to right ventricular decompensation with myocardial damage, high cardiac troponin levels and systolic hypotension.[11] Furthermore, it has been demonstrated in other lung diseases, such as bacterial pneumonia, that severe lung involvement can be accompanied by a significant increase in troponin I and T concentrations[12,13] and it is well known that right ventricular strain may precipitate arrhythmias.[14] However, the detection of RSV in myocardial tissue[15,16] and the occurrence of significant pericardial effusion in children with severe RSV bronchiolitis[17-19] suggest that the virus itself may play a direct role in causing heart disease.

As clinically relevant heart problems are usually found in infants whose bronchiolitis is severe enough to require mechanical ventilation,[3,6] it is recommended that heart rate and blood pressure should be systematically and carefully monitored in those admitted to PICUs,[19] but not in those admitted to semi-intensive or normal pediatric wards. However, no data regarding heart function in infants with bronchiolitis associated with RSV infection have yet been systematically collected although they could throw new light on the pathogenesis of heart involvement during RSV infection and further define the best approach to bronchiolitis.

The aim of this study was to verify the real frequency of heart involvement in patients with bronchiolitis associated with RSV infection, and whether infants with mild or moderate disease also risk heart malfunction.

Table 1 Demographic characteristics of the study population

Characteristic	RSV- positive n = 34	RSV-negative n = 35	*P* value
Males, No. (%)	18 (52.9)	18 (51.4)	0.90
Mean age at enrolment, days ± SD	142.41 ± 104.8	114.69 ± 108.4	0.22
Type of delivery			
Eutocic, No. (%)	20 (58.8)	20 (57.1)	0.89
Caesarean, No. (%)	14 (41.2)	15 (42.9)	
Gestational age at birth, mean weeks ± SD	37.06 ± 3.63	36.66 ± 3.80	0.66
Birth weight, mean ± SD	2.95 ± 0.86	2.77 ± 0.75	0.34
Respiratory problems at birth, No. (%)	7 (20.6)	8 (22.9)	0.82
Ventilatory support at birth, No. (%)	5 (14.7)	8 (22.9)	0.39
Patients with respiratory infections in previous 3 months, No. (%)	12 (35.3)	8 (22.9)	0.25
Patients treated with antibiotic courses in previous 3 months, No. (%)	6 (17.7)	5 (14.3)	0.70

SD: standard deviation. P-value for comparison between groups, using chi-square or Fisher's exact test, as appropriate, for categorigal data and Student's test or Wilcoxon rank-sum test, as appropriate, for continuous variables.

Methods

Study design: This prospective study was carried out at the Department of Maternal and Pediatric Sciences of the University of Milan, Italy, during the winter seasons 2007-2008 and 2008-2009. The protocol was approved by the local Ethics Committee, and written informed consent to study participation was obtained from the patients' parents or legal guardians.

Study population: The study involved otherwise healthy infants aged 1-12 months who were admitted to hospital because of bronchiolitis during the study period. The exclusion criteria were the presence of a chronic disease increasing the risk of complications of respiratory infection, including chronic disorders of the pulmonary or cardiovascular system, chronic metabolic disease, neoplasms, kidney or liver dysfunction, hemoglobinopathies, immunosuppression, and genetic or neurological disorders. There was no refusal to participate.

Upon admission, the infants' demographic characteristics and medical history were systematically recorded using standardized

Table 2 Clinical presentation at enrolment

Characteristic	RSV- positive n = 34	RSV-negative n = 35	*P* value
Severe bronchiolitis, No. (%)	3 (8.8)	3 (8.6)	1.00
Acute onset, No. (%)	6 (17.7)	11 (31.4)	0.18
Rectal temperature ≥38°C, No. (%)	7 (20.6)	6 (17.1)	0.29
Mean temperature ± SD, °C	37.44 ± 0.74	37.02 ± 0.74	0.19
Mean breath frequency ± SD	54.79 ± 14.06	53.73 ± 12.34	0.78
Dyspnea, No. (%)	21 (61.8)	16 (45.7)	0.18
Wheezing, No. (%)	17 (50.0)	16 (45.7)	0.72
Rales, No. (%)	28 (82.3)	29 (82.9)	0.96
Difficulties in feeding, No. (%)	18 (52.9)	12 (34.3)	0.12
Normal clinical heart assessment, No. (%)	34 (100.0)	35 (100.0)	1.00
Normal echocardiographic parameters, No. (%)	34 (100.0)	35 (100.0)	1.00
Mean cTnI ± SD, IU/L	0.009 ± 0.02	0.013 ± 0.02	0.51
Mean CPK ± SD, IU/L	99.27 ± 69.45	79.88 ± 47.32	0.24
Mean LDH ± SD, IU/L	701.96 ± 190.74	597.95 ± 154.17	0.06
Mean SGOT ± SD, IU/L	38.83 ± 10.91	39.57 ± 19.93	0.86
Mean SGPT ± SD, IU/L	23.93 ± 10.98	28.00 ± 14.30	0.22
Pneumonia at X-ray, No. (%)	22 (64.7)	17 (48.6)	0.18
Need for intravenous infusion, No. (%)	15 (44.1)	13 (37.1)	0.56
Need for oxygen therapy, No. (%)	18 (52.9)	21 (60.0)	0.55
Treated with antibiotics, No. (%)	24 (70.6)	21 (60.0)	0.36
Treated with inhalatory bronchodilator, No. (%)	34 (100.0)	35 (100.0)	1.00
Treated with steroids			
Oral steroids, No. (%)	6 (17.6)	5 (14.3)	0.75
Intravenous steroids, No. (%)	2 (5.9)	2 (5.7)	1.00
Treated with drugs interacting with cardiovascular system, No. (%)	0 (0.0)	0 (0.0)	-
Chest physiotherapy, No. (%)	1 (2.9)	2 (5.7)	0.98

SD: standard deviation; cTnI: cardiac troponin I; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; SGOT: serum glutamyl oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase. P-value for comparison between groups, using chi-square or Fisher's exact test, as appropriate, for categorigal data and Student's test or Wilcoxon rank-sum test, as appropriate, for continuous variables.

Table 3 Heart rate variability in infants with bronchiolitis, by etiology

Variable	Admission		28 ± 3 days after admission	
	RSV-positive (n = 34)	RSV-negative (n = 35)	RSV-positive (n = 34)	RSV-negative (n = 35)
Sinoatrial block, No. (%)	26 (76.5)°^	1 (2.9)	0 (0.0)	0 (0.0)
Sinoatrial block 1-2 sec., No. (%)	21 (61.8)°^	1 (2.9)	0 (0.0)	0 (0.0)
Sinoatrial block > 2 sec., No. (%)	5 (14.7)*"	0 (0.0)	0 (0.0)	0 (0.0)
More than 3 sinoatrial blocks, No. (%)	25 (96.2)°^	0 (0.0)	0 (0.0)	0 (0.0)
Mean heart rate, bpm ± SD	139.23 ± 15.7*"	116.65 ± 15.9	119.37 ± 19.6	112.06 ± 10.1
Maximum heart rate, mean bpm ± SD	204.29 ± 20.6*"	173.30 ± 28.8	179.49 ± 21.8	170.10 ± 21.3
Minimum heart rate, mean bpm ± SD	49.62 ± 17.1	45.61 ± 26.10	49.31 ± 19.45	48.44 ± 20.14
SDNN (ms), mean ± SD	58.34 ± 26.37	54.61 ± 24.11	56.46 ± 22.21	55.39 ± 22.68
SDANN (ms), mean ± SD	49.61 ± 28.75	45.57 ± 25.70	47.66 ± 25.55	46.91 ± 26.96
ASDNN (ms), mean ± SD	37.11 ± 17.20	33.33 ± 13.70	35.64 ± 18.52	34.39 ± 16.31
rMSSD (ms), mean ± SD	20.31 ± 19.55	19.30 ± 16.99	19.25 ± 19.43	19.77 ± 19.03
PNN50, mean % ± SD	4.21 ± 7.2	2.93 ± 4.5	3.33 ± 5.3	3.22 ± 4.9
LF (ms^2), mean ± SD	636.13 ± 306.7*"	369.48 ± 276.7	373.49 ± 269.73	369.55 ± 288.76
LF (nu), mean ± SD	33.93 ± 6.8*"	24.91 ± 5.6	25.01 ± 5.9	24.99 ± 6.1
HF (ms^2), mean ± SD	271.06 ± 573.5	106.09 ± 152.5	143.9 ± 155.5	176.73 ± 169.6
HF (nu), mean ± SD	7.10 ± 7.6	6.76 ± 2.8	6.76 ± 4.5	6.85 ± 4.9
LF/HF ratio, mean ± SD	4.78 ± 1.60*"	3.68 ± 1.48	3.69 ± 1.40	3.64 ± 1.55

SD: standard deviation; bpm: beats per minute; SDNN: standard deviation of all NN intervals; SDANN: standard deviation of the average of NN intervals in all 5-minute segments of the 24-h recording; ASDNN: mean of the standard deviation in all 5-minute segments of the 24-h recording; rMSSD: square root of the mean of the squares of the differences between adjacent NN intervals; pNN50: percentage of differences between adjacent NN intervals of > 50 msec; LF: low-frequency power; HF: high-frequency power; nu: normalised units.

°p < 0.0001 and *p < 0.05 for the comparison between groups (i.e., RSV-positive *vs* RSV-negative upon admission); ^p < 0.0001 and "p < 0.05 for the comparison within group (i.e., admission *vs* 28 ± 3 days after admission in the RSV-positive group); no other significant difference between or within-group.

written questionnaires and, after a complete physical examination, the subjects with a diagnosis of bronchiolitis based on well-established criteria[20] were enrolled. The severity of the disease was defined on the basis of a global evaluation of the signs and symptoms. In particular, on the basis of previously published criteria,[20] respiratory illness was considered severe in the presence of all of ≤ 92% pulse oximetry, a respiratory rate of ≥60 breaths/min, marked accessory muscle use, nasal flare or grunting, a heart rate of > 180 beats/min, an inability to feed and a toxic appearance. All of the patients underwent chest radiography, and pneumonia was defined on the basis of the presence of a reticular-nodular infiltrate, segmental or lobar consolidation, or bilateral consolidation.[21]

Upon enrolment, Virocult (Medical Wire and Equipment, Corsham, UK) nasopharyngeal swabs were used to collect specimens for the detection of RSV, and a blood sample was drawn to assess troponin I concentrations. On the basis of our previous experience in children with bronchiolitis in which we showed that RSV was the main cause of acute episodes in hospitalized children,[22] in this study only RSV was searched on nasopharyngeal secretions. Finally, on the day of admission, all of the infants underwent 24-hour Holter ECG monitoring and a complete heart evaluation with echocardiography. It was decided to estimate pulmonary pressure as well as signs of pulmonary hypertension only in presence of pathologic findings at echocardiography.

During their hospital stay, the infants' clinical signs and symptoms were monitored daily. They were treated with oxygen when saturation was ≤ 95%, and received inhalatory bronchodilators, steroids, antibiotics, intravenous fluids and chest physiotherapy on the basis of the judgement of the attending pediatrician. They were discharged when they were able to maintain > 95% oxymetry without oxygen, but their parents were asked to bring them immediately to the study centre if there were any recurrent or worsening signs and symptoms.

The medical history, general physical condition and clinical symptoms of each patient were re-evaluated by investigators blinded to the etiological and cardiac findings four weeks after enrolment. During this follow-up visit, the patients' history of respiratory tract infections was carefully assessed and 24-hour Holter ECG monitoring 24 hours was repeated.

Identification of RSV virus: The Virocult nasopharyngeal swabs were tested by means of previously described real-time polymerase chain reaction (PCR) for RSV types A and B,[21-24] with total nucleic acids being routinely isolated at the MagnaPureLC Isolation Station (Roche Applied Science, Penzberg, Germany). A universal internal control virus (phocine distemper virus, PDV) was used to monitor the whole process from nucleic acid isolation to real-time detection. The in-house real-time PCRs for RSV and PDV were designed using primer express software (Applied Biosystem, Nieuwerkerk a/d Ijssel, The Netherlands).

RNA was amplified in a single tube, two-step reaction using Taqman reverse transcriptase and PCR core reagent kits (Applied Biosystems, Foster City, CA, USA) and an ABI 7700 or ABI 7500 sequence detection system (Applied Biosystems). A cultured positive control virus was used for each assay. On the basis of proficiency testing data, the sensitivity of each assay was estimated to be less than 500 copies/mL.

Evaluation of myocardial damage: To evaluate myocardial damage, serum troponin I levels were measured using the Abbott AxSYM system (Abbott Laboratories, Mississauga, Ontario, Canada) at the time of hospital admission, and were considered

Table 4 Associations between sinoatrial block and different variables in infants with bronchiolitis and RSV infection

Variable	Patients with sinoatrial block (n = 26)	Patients without sinoatrial block (n = 8)	P
RSV viral load			
< 100.000 cp/mL	4 (15.4)	8 (100.0)	< 0.0001
≥100.000 cp/mL	22 (84.6)	0 (0.0)	
Gestational age			
≥37 weeks	10 (38.5)	4 (50.0)	0.69
< 37 weeks	16 (61.5)	4 (50.0)	
Birth weight			
≥2,500 g	5 (19.2)	2 (25.0)	1.00
< 2,500 g	21 (80.8)	6 (75.0)	
Respiratory problems at birth			
No	21 (80.8)	6 (75.0)	1.00
Yes	5 (19.2)	2 (25.0)	
Ventilatory assistance at birth			
No	23 (88.5)	6 (75.0)	0.57
Yes	3 (11.5)	2 (25.0)	
Severe bronchiolitis			
No	23 (88.5)	8 (100.0)	1.00
Yes	3 (11.5)	0 (0.0)	
Rectal temperature ≥38°C			
No	21 (80.7)	6 (75.0)	0.98
Yes	5 (19.2)	2 (25.0)	
Dyspnea			
No	9 (34.6)	4 (50.0)	0.68
Yes	17 (65.4)	4 (50.0)	
Wheezes			
No	12 (46.1)	5 (62.5)	0.69
Yes	14 (53.9)	3 (37.5)	
Rales			
No	4 (15.4)	2 (25.0)	1.00
Yes	22 (84.6)	6 (75.0)	
Difficulties in feeding			
No	13 (50.0)	3 (37.5)	0.69
Yes	13 (50.0)	5 (62.5)	
Pneumonia at X-ray			
No	8 (30.8)	4 (50.0)	0.41
Yes	18 (69.2)	4 (50.0)	

Percentages in parenthesis. P-value for comparison between groups, using chi-square or Fisher's exact test, as appropriate.

indicative of myocardial damage when they were > 1.2 µg/L. The measurements had a coefficient of variation of 10%, and the lower detection limit was 0.3 µg/L.

Holter ECG monitoring: Three-channel Holter monitors (ElaMedical Spider View 3 channel recorders, Le Plessis-Robinson, France) were positioned immediately after hospital admission, and 24-hour recordings were obtained. After the skin had been prepared, the electrodes were placed to record leads II, V1 and V5; a 1 mV calibration signal was also recorded. The built-in clock started after the electrodes had been attached.

A commercial Holter analysis software (SyneScope, Elamedical, Sorin Group, Le Plessis-Robinson, France) was used to analyse rhythm and heart rate variability (HRV, time-, frequency- and geometric-domain indices) from the Holter tapes. QRS was detected using a level detector, but was manually over-read by a physician. All of the tapes were edited in order to assure the accuracy of the QRS classification. Ectopic beats, noisy data, and artifacts were manually identified and excluded from the HRV analysis. Non-stationarities were avoided by means of trigger adjustment. Average hourly heart rates were determined from the computerized Holter scanner, and maximum, minimum, and mean 24-hour heart rates (with standard deviations, SDs) were calculated for each subject.

The time-domain parameters measured from the Holter tapes were: 1) the average of all normal-to-normal beats (mean NN interval) (mean heart rate); 2) the SD of all NN intervals (SDNN); 3) the SD of the average of NN intervals in all 5-minute segments of the 24-hour recording (SDANN); 4) the mean of the standard deviation in all 5-minute segments of the 24-hour recording (ASDNN); 5) the square root of the mean of the squares of the differences between adjacent NN intervals (rMSSD); and 6) the percentage of > 50 msec differences between adjacent NN intervals. Frequency-domain heart rate variability was also determined, including low-frequency power (LF, total NN interval spectral power between 0.04 and 0.15 Hz), high-frequency power

(HF, total interval spectral power between 0.15 and 0.4 Hz), and the LF/HF ratio.[25]

Echocardiographic studies: The echocardiographic studies were made using a real-time ultrasound imaging system system (Acuson Sequoia 512) equipped with 3-, 5-, 7 and 10A, MHz transducers. The echocardiographic measurements were made using standard techniques.[26]

M-mode measurements were made in accordance with the recommendations of the Cornmittee of M-Mode Standardization of the American Society of Echocardiography,[27] and were used to determine right ventricular internal dimension in diastole (RVID) and left ventricular internal dimensions in diastole (LVID) and systole (LVIS). Left ventricular function was assessed by calculating the percentage fractional shortening of the internal dimension and ejection fraction using standard formulas. Left ventricular mass was also calculated.

The flow velocities across the mitral, tricuspid, aortic and pulmonary valves were recorded from standard pericordial and subcostal positions using pulsed-wave and continuous-wave Doppler transducers.

Statistical analysis: Continuous variables are given as mean values ± SD, and categorical variables as numbers and percentages. For the comparison between groups (ie, RSV-positive vs RSV-negative), the continuous data were analyzed using a two-sided Student's test if they were normally distributed (on the basis of the Shapiro-Wilk statistic) or a two-sided Wilcoxon rank-sum test if they were not. For the comparison within group (ie, admission vs 28 ± 3 days after admission in the RSV-positive and RSV-negative groups, separately), the continuous data were analyzed using a paired two-sided Student's test or signed-rank test, as appropriate. Categorical data were analyzed using contingency table analysis and the chi-square or Fisher's exact test, as appropriate.

Results

Sixty-nine children with bronchiolitis were enrolled: 34 (49.3%) RSV-positive and 35 (50.7%) RSV-negative. Table 1 shows that there were no differences in gender, age at enrolment, type of delivery, gestational age at birth, birth weight, respiratory problems at birth, respiratory infections or antibiotic courses in the previous three months between the two groups.

Table 2 shows the data regarding clinical presentation. Bronchiolitis was mild or moderate in most cases: only three RSV-positive (8.8%) and three RSV-negative patients (8.6%) had severe disease. Disease signs and symptoms, laboratory parameters, radiographic findings, the need for rehydration and oxygen, and the use of antibiotics, steroids, inhalatory bronchodilators, drugs interacting with cardiovascular system and chest physiotherapy were similar in the two groups. None of the patients required PICU admission. None was treated with oral or intravenous bronchodilators. Clinical and echocardiography evaluations showed that the cardiovascular system was always normal, as were cardiac troponin I concentrations.

Table 3 summarizes the Holter ECG monitoring data. Sinoatrial blocks occurred in 26 RSV-positive patients (76.5%) and only one RSV-negative patient (2.9%) ($p < 0.0001$). Twenty-five of the 26 RSV-positive patients (96.2%), but not the RSV-negative patient, experienced more than three sinoatrial blocks during the 24 hours, with a maximum of 18 times in one patient. The blocks lasted longer than one second in all cases, and more than two seconds in five (14.7%) ($p < 0.05$ vs RSV-negative patients). Mean and maximum heart rate were significantly higher in the RSV-positive infants ($p < 0.05$). Among the HRV time-domain parameters, the prevalence of LF periods was significantly higher in the RSV-positive infants ($p < 0.05$) as was the LF/HF ratio ($p < 0.05$). Twenty-four hour Holter ECG monitoring 28 ± 3 days later demonstrated the complete regression of the heart abnormalities in all of the RSV-positive infants: no block was recorded and their HRV parameters were similar to those recorded in the RSV-negative patients during the acute phase of the disease and during the convalescent period.

Table 4 shows the associations between sinoatrial block and the other variables in the infants with RSV infection. The only variable that was independently associated with the occurrence of sinoatrial block was RSV viral load: blocks were significantly more frequent in the infants with a viral load of ≥100,000 copies/mL than in those with a lower viral load ($p < 0.0001$). The association remains significant even after excluding patients with severe disease. There was no association between sinoatrial block and gestational age, birth weight, neonatal problems, or the presentation or severity of bronchiolitis.

Discussion

The results of this study indicate that bronchiolitis during the course of RSV infection is frequently associated with sinoatrial blocks, an increase in absolute heart rate, and an increase in the LF component of HRV. All of these findings seem to be specific of RSV infection because they have not been demonstrated in children with bronchiolitis caused by a different infectious agent. Our data confirm and extend what has been previously reported by other authors who have found that RSV infection can be associated with cardiac rhythm alterations.[8,9,28]

Sinoatrial blocks are rare in pediatrics but, when symptomatic, have been described in otherwise healthy children and patients with heart malformations or myocarditis.[29] To the best of our knowledge, this is the first report that associates sinoatrial blocks and RSV bronchiolitis. In our study population, the sinoatrial blocks were always asymptomatic and disappeared with recovery from the respiratory disease, thus suggesting that they are reversible. Furthermore, the significantly increased mean heart rates and the high incidence of the LF components of HRV (usually considered a possible marker of cardiac damage),[25,26] were only observed during the acute phase of RSV infection. Moreover, none of the children showed any clinical sign or symptom resembling those described in subjects with symptomatic sinoatrial block, any echocardiographic alteration or any increase in troponin I concentrations. All of these findings support the hypothesis that RSV can specifically alter the electrical conduction system, but that these alterations are benign and transient. Considering that current arrhythmia guidelines do not recommend any kind of intervention in transient sinoatrial block,[30] on the basis of our findings we do not recommend routine cardiac monitoring of infants with bronchiolitis in general wards. However, our findings highlight the need of further studies on the impact of sinoatrial blocks in patients with chronic underlying disease at risk of complications during RSV infection.

One limitation of this study is that the population is too small

to allow any definite conclusions to be drawn and so further studies of larger series are needed. It seems to be particularly important to study more severe cases in order to verify whether more significant lung involvement can precipitate arrhythmias and cause more serious clinical problems. It is interesting that in our population all the three cases of severe bronchiolitis showed a sinoatrial block. The very low number of subjects with severe infection could have limited the statistical power to detect between group differences according to disease severity. Another limitation is the fact that only RSV has been searched in respiratory secretions. Despite it represents the absolute main cause of bronchiolitis in infants and in various studies it has been detected as single pathogen in more than 60% of the cases,[1,22] it could be interesting to understand whether other viruses may cause a similar cardiac involvement as well as sinoatrial blocks could be more severe and persistent when RSV acts as a co-pathogen with another virus. On the basis of our data, it can be hypothesised that RSV infection is one of the possible causes of these alterations and may even be the direct cause in some cases.

Our data support the hypothesis that the heart involvement diagnosed in some cases of bronchiolitis associated with RSV infection[2-8] could be due to direct viral damage of heart tissue or to immunologic mechanisms rather than the lung alterations that follow respiratory infection. In addition to the changes in the heart electrical conduction system, which was exclusively recorded in our RSV-positive patients, this hypothesis is supported by the fact that most of our children had mild or moderate disease, and were therefore presumably free of pulmonary hypertension and the significant lung damage conditioning right heart failure. Furthermore, although the small number of patients prevented the use of multivariate analysis, the close correlation between sinoatrial block and RSV load suggests that RSV could play a direct role in inducing arrhythmia. This association between high viral load in respiratory secretions and prevalence of sinoatrial blocks is intriguing because since the role of viral load in respiratory secretions is controversial several recent studies have highlighted its importance in conditioning respiratory symptoms and disease's severity.[31-35]

Conclusions

RSV seems associated with sinoatrial blocks and rhythm alterations even when the resulting respiratory difficulties are mild or moderate. Further studies are needed to clarify the mechanisms of these rhythm problems and whether they remain asymptomatic and transient even in presence of severe respiratory involvement or chronic underlying disease. Finally, as RSV can cause respiratory illnesses other than bronchiolitis, further researches specifically aimed at defining the relationships between RSV and the heart are urgently needed regardless of the clinical picture.

References

1 American Academy of Pediatrics. Subcommittee on Diagnosis and Management of Bronchiolitis: Diagnosis and management of bronchiolitis. *Pediatrics* 2006, 118:1774-1793.

2 Puchkov GF, Minkovich BM: Respiratory syncytial infection in a child complicated by interstitial myocarditis with fatal outcome. *Arkh Patol* 1972, 34:70-73.

3 Armstrong DS, Menahem S: Cardiac arrhythmias as a manifestation of acquired heart disease in association with paediatric respiratory syncytial virus infection. *J Paediatr Child Health* 1993, 29:309-311.

4 Donnerstein RL, Berg RA, Shehab Z, Ovadia M: Complex atrial tachycardias and respiratory syncytial virus infections in infants. *J Pediatr* 1994, 125:23-28.

5 Hutchison JS, Joubert GIE, Whitehouse SR, Kissoon N: Pericardial effusion and cardiac tamponade after respiratory syncytial viral infection. *Pediatr Emerg Care* 1994, 10:219-221.

6 Thomas JA, Raroque S, Scott WA, Toro-Figueroa LO, Levin DL: Successful treatment of severe dysrhythmias in infants with respiratory syncytial virus infections: two cases and a literature systematic review. *Crit Care Med* 1997, 25:880-886.

7 Huang M, Bigos D, Levine M: Ventricular arrhythmia associated with respiratory syncytial viral infection. *Pediatr Cardiol* 1998, 19:498-500.

8 Playfor SD, Khader A: Arrhythmias associated with respiratory syncytial virus infection. *Pediatr Anesthesia* 2005, 15:1016-1018.

9 Menahem S: Respiratory syncytial virus and complete heart block in a child. *Cardiol Young* 2010, 20:103-104.

10 Sreeram N, Watson JG, Hunter S: Cardiovascular effect of acute bronchiolitis. *Acta Paediatr Scand* 1991, 80:133-136.

11 Konstantinides S, Geibel A, Olschewski M, Kasper W, Hruska N, Jaeckle S, Binder L: The importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. *Circulation* 2002, 106:1263-1268.

12 Weinberg I, Cukierman T, Chajek-Shaul T: Troponin T elevation in lobar lung disease. *Postgrad Med J* 2002, 78:244-245.

13 Labugger R, Organ L, Collier C, Atar D, Van Eyk JE: Extensive troponin I and T modification detected in serum from patients with acute myocardial infarction. *Circulation* 2000, 102:1221-1226.

14 Chen RL, Penny DJ, Greve G, Lab MJ: Stretch-induced regional mechanoelectric dispersion and arrhythmia in the right ventricle of anesthetized lambs. *Am J Physiol Heart Circ Physiol* 2004, 286:H1008-H1014.

15 Fishaut M, Tubergen D, McIntosh K: Cellular response to respiratory viruses with particular reference to children with disorders of cell-mediated immunity. *J Pediatr* 1980, 96:179-186.

16 Bowles NE, Ni J, Kearney DL, Pauschinger M, Schultheiss HP, McCarthy R, Hare J, Bricker JT, Bowles KR, Towbin JA: Detection of viruses in myocardial tissues by polymerase chain reaction. Evidence of adenovirus as a common cause of myocarditis in children and adults. *J Am Coll Cardiol* 2003, 42:466-472.

17 Hutchison JS, Joubert GIE, Whitehouse SR, Kissoon N: Pericardial effusion and cardiac tamponade after respiratory syncytial viral infection. *Pediatr Emerg Care* 1994, 10:219-221.

18 Armstrong DS, Menahem S: Cardiac arrhythmias as a manifestation of acquired heart disease in association with paediatric respiratory syncytial virus infection. *J Paediatr Child Health* 1993, 29:309-311.

19 Eisenhut M: Extrapulmonary manifestations of severe respiratory syncytial virus infection - a systematic review. *Crit Care* 2006, 10:R107.

20 Scarfone RJ: Controversies in the treatment of bronchiolitis. *Curr Opin Pediatr* 2005, 17:62-66.

21 Zambon MC, Stockton JD, Clewley JP, Fleming DM: Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet* 2001, 358:1410-1416.

22 Bosis S, Esposito S, Niesters H, Zuccotti GV, Pelucchi C, Osterhaus A, Principi N: Role of respiratory pathogens in

infants hospitalized for their first episode of wheezing and their impact on subsequent recurrences. *Clin Microbiol Infect* 2008, 14:677-684.
23 Bosis S, Esposito S, Niesters HGM, Crovari P, Osterhaus ADME, Principi N: Impact of human metapneumovirus in childhood: comparison with respiratory syncytial virus and influenza viruses. *J Med Virol* 2005, 75:101-104.
24 Bosis S, Esposito S, Osterhaus AD, Tremolati E, Begliatti E, Tagliabue C, Corti F, Principi N, Niesters HG: Association between high nasopharyngeal viral load and disease severity in children with human metapneumovirus infection. *J Clin Virol* 2008, 42:286-290.
25 Adan V, Crown LA: Diagnosis and treatment of sick sinus syndrome. *Am Fam Physician* 2003, 67:1725-1732.
26 Feigenbaum H: *Echocardiography.* 2nd edition. Philadelphia: Lea & Febiger; 1976.
27 Sahn DJ, DcMaria A, Kisslo J, Weyman A, the Committee on M-mode Standardization of the American Society of Echocardiography: Recommendations regarding quantificatiom in M mode echocardiography: results of survey of echocardiographic measurements. *Circulation* 1978, 58:1072-1083.
28 Donnerstein RL, Berg RA, Shehab Z, Ovadia M: Complex atrial tachycardias and respiratory syncytial virus infections in infants. *J Pediatr* 1994, 125:23-28.
29 Ector H, van der Hauwaert LG: Sick sinus syndrome in childhood. *Br Heart J* 1980, 44:684-689.
30 Epstein AE, Dimarco JP, Ellenbogen KA, Estes NA, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, American College of Cardiology/American Heart Association Task Force on Practice, American Association for Thoracic Surgery, Society of Thoracic Surgeons: ACC/AHA/HRS 2008 guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: executive summary. *Heart Rhythm* 2008, 5:934-955.
31 Campanini G, Percivalle E, Baldanti F, Rovida F, Bertaina A, Marchi A, Stronati M, Gerna G: Human respiratory syncytial virus (hRSV) RNA quantification in nasopharyngeal secretions identifies the hRSV etiologic role in acute respiratory tract infections of hospitalized infants. *J Clin Virol* 2007, 39:119-124.
32 Gerna G, Campanini G, Rognoni V, Marchi A, Rovida F, Piralla A, Percivalle E: Correlation of viral load as determined by real-time RT-PCR and clinical characteristics of respiratory syncytial virus lower respiratory tract infections in early infancy. *J Clin Virol* 2008, 41:45-48.
33 Houben ML, Coenjaerts FE, Rossen JW, Belderbos ME, Hofland RW, Kimpen JL, Bont L: Disease severity and viral load are correlated in infants with primary respiratory syncytial virus infection in the community. *J Med Virol* 2010, 82:1266-1271.
34 Devincenzo JP, Wilkinson T, Vaishnaw A, Cehelsky J, Meyers R, Nochur S, Harrison L, Meeking P, Mann A, Moane E, Oxford J, Pareek R, Moore R, Walsh E, Studholme R, Dorsett P, Alvarez R, Lambkin-Williams R: Viral load drives disease in humans experimentally infected with respiratory syncytial virus. *Am J Respir Crit Care Med* 2010. Epub Jul 9
35 Franz A, Adams O, Willems R, Bonzel L, Neuhausen N, Schweizer-Krantz S, Ruggeberg JU, Willers R, Henrich B, Schroten H, Tenenbaum T: Correlation of viral load of respiratory pathogens and co-infections with disease severity in children hospitalized for lower respiratory tract infection. *J Clin Virol* 2010, 48:239-245.

Severe Bronchopulmonary Dysplasia Improved by Noninvasive Positive Pressure Ventilation

Christian Mann, Walter Bär

This is the first report to describe the feasibility and effectiveness of noninvasive positive pressure ventilation in the secondary treatment of bronchopulmonary dysplasia.

A former male preterm of Caucasian ethnicity delivered at 29 weeks gestation developed severe bronchopulmonary dysplasia. At the age of six months he was in permanent tachypnea and dyspnea and in need of 100% oxygen with a flow of 2.0 L/minute via a nasal cannula. Intermittent nocturnal noninvasive positive pressure ventilation was then administered for seven hours daily. The ventilator was set at a positive end-expiratory pressure of 6cmH_2O with pressure support of 4cmH_2O, trigger at 1.4 mL/second, and a maximum inspiratory time of 0.7 second. Over the course of seven weeks, his maximum daytime fraction of inspired oxygen via nasal cannula decreased from 1.0 to 0.75, his respiratory rate from 64 breaths/minute to 50 breaths/minute and carbon dioxide from 58mmHg to 44mmHg.

Conclusion: Noninvasive positive pressure ventilation may be a novel therapeutic option for established severe bronchopulmonary dysplasia. In the case presented, noninvasive positive pressure ventilation achieved sustained improvement in ventilation and thus prepared our patient for safe home oxygen therapy.

Introduction

Although there is some evidence that nasal noninvasive ventilation has the potential to reduce bronchopulmonary dysplasia (BPD) in preterm newborns,[1-5] there have been no studies of nasal noninvasive positive pressure ventilation (NIPPV) in former preterm infants with an established diagnosis of BPD requiring high oxygen concentrations.

The main pathophysiological finding in BPD is a low functional residual capacity accompanied by inefficient gas mixing. Respiratory rate is increased.[6] Small airway function may worsen during the first year.[7] Significant gas trapping is found in some BPD infants.[8,9] We report the response to intermittent nocturnal therapy with nasal NIPPV in an infant with severe BPD.

Case presentation

Our patient was a male preterm of Caucasian ethnicity, born at 29 weeks and one day gestation by Caesarean section from a spontaneous dichorionic diamniotic twin pregnancy complicated by preterm premature rupture of the membranes with near- total loss of fluid nine days before delivery. His birth weight was 940g. A chest X-ray showed pulmonary hypoplasia and grade 3 hyaline membrane disease. Surfactant (beractant 100mg/kg) was given one hour after birth and repeated 24 hours later.

Our patient was started on high frequency oscillatory ventilation, with highest mean airway pressure 22cmH2O on day one, and then switched to pressure-controlled synchronized intermittent mandatory ventilation on day 20 (highest peak inspiratory pressure 24cmH_2O). Inhaled nitric oxide was delivered for five days in decreasing amounts (starting on day one with 26ppm).

A left pneumothorax was drained on day four. The clinical course was complicated by ventilator-associated pneumonia on day 15. Tracheal aspirates grew coagulase- negative Staphylococci and Enterobacter cloacae. Treatment consisted of piperacillin and tazobactam with fusidic acid for two weeks. Extubation was successful on day 26 after a two-day course of dexamethasone. Ventilatory support was continued with nasal continuous positive airway pressure (nCPAP; 8cm H_2O). BPD was diagnosed at postmenstrual age 36 weeks. Shortly thereafter, nasal swab cultures from copious upper airway secretions proved colonization with Stenotrophomonas maltophilia, Escherichia coli as well as Staphylococcus aureus which was treated with a two-week course of oral sulfamethoxazole and rifampin.

After 10 weeks nCPAP was switched to nasal cannula flow of 2L/minute with a fraction of inspired oxygen (FiO_2) of 0.5. Pulse oximetry target was set at arterial blood oxygen saturation (SaO_2) ≥90%. During subsequent weeks the oxygen concentration had to be increased to a FiO_2 of 1.0 due to progressive deterioration of gas exchange. At the age of six months our patient was in constant dyspnea and tachypnea. Spontaneous inspiratory time was markedly shortened. Streaky densities and cystic areas on a chest X-ray confirmed the diagnosis of severe BPD. Echocardiography revealed concomitant pulmonary hypertension with a tricuspid regurgitation pressure gradient up to 30mmHg. The FiO_2 1.0 requirement created a

The authors are with the Neonatal and Pediatric Intensive Care Unit, Graubuenden Cantonal Hospital, Chur, and the College for Intensive Care, Emergency and Anesthesia Nursing, Children's Hospital, University Clinic, Zurich, Switzerland. The authors thank Axel Zolkos for his technical skills in administering noninvasive ventilation to this infant and for his support in extracting patient data from the chart.

Table 1. Ventilator settings for NIPPV

Pressure support	4 cm H_2O
Positive end-expiratory pressure	6 cm H_2O
Trigger	1.4 mL/second
Ramp	25 ms
Expiratory trigger sensitivity	10%
Backup respiratory rate	8/minute
Maximum inspiratory time	0.7 second

high risk of urgent reintubation in the event of sudden desaturation. The boy's increasing drive to move around ruled out reintroducing nCPAP.

A ventilator set to NIPPV was installed providing nocturnal ventilatory support for an average of seven hours every night. Ventilator settings are presented in Table 1. For the first 18 days, sedation was provided with chloral hydrate in decreasing amounts from 52mg/kg to 7mg/kg per evening dose.

The features of the NIPPV device included a limited dead space, highly sensitive automated circuit leak compensation, and high trigger sensitivity. NIPPV was administered via a nasal mask in a semirecumbent position to enhance air entry into West zones 1 and 2 and to diminish expansion of the radiologically over-distended lung bases.

In the course of seven weeks of intermittent nocturnal NIPPV, the spontaneous respiratory rate decreased from 64 breaths/minute to 50 breaths/minute, morning (post-NIPPV) carbon dioxide dropped from 58mmHg to 44mmHg, and—most importantly—nasal cannula maximum FiO_2 decreased from 1.0 to 0.75 and the minimum FiO_2 from 0.8 to 0.6 (Figure 1). At this point, NIPPV was stopped and the baby was discharged on home oxygen (flow rate 0.25L/minute) at the postnatal age of eight months. His weight increased by 200g per week during NIPPV therapy and reached 7490g at discharge.

Two intercurrent lower respiratory tract infections were managed on an outpatient basis. Our patient was completely weaned off oxygen nine months after discharge at the age of 17 months.

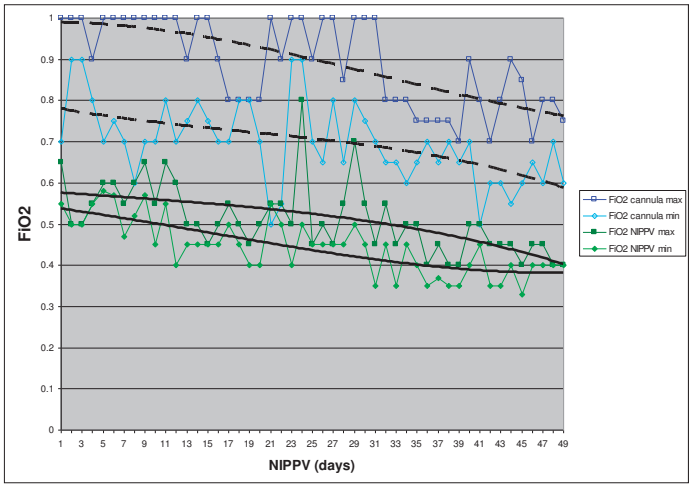


Figure 1. Decrease in FiO_2 requirement over seven weeks of nocturnal NIPPV. Open rectangles and blue lines: oxygen concentrations (maximum and minimum for each day) delivered via nasal cannula during daytime; full rectangles and green lines: oxygen concentrations for nocturnal NIPPV. Oxygen saturation target was set at ≥90%.

Neurological examination at the age of one year showed less delay in the mental scale than in the psychomotor scale (Bayley II) with scores of 76 and 56, respectively. Free walking was achieved at 22 months of age.

Conclusion

The clinical course of this ex-preterm boy suggests that secondary NIPPV therapy has the potential to improve severe BPD. A course of nocturnal intermittent NIPPV in a timely manner (seven weeks) improved ventilation and reduced oxygen need to a degree which provided sufficient safety for subsequent home oxygen therapy. Its positive effect was essential for our patient's discharge after eight months of hospital stay. In terms of practicability, NIPPV was superior to nCPAP in that it reliably avoided hypoventilation when the child initially needed sedation to tolerate a nasal mask.

According to the literature, a bundle of different mechanisms may have contributed to the improvement observed. Synchronized NIPPV is known to increase functional residual capacity, enhance ventilation uniformity, improve respiratory drive, lead to greater lung recruitment and decrease inspiratory effort and respiratory work in comparison to continuous flow nCPAP. The duration of ventilatory support is shorter with primary use of NIPPV than with nCPAP .[4-5,10-15]

We think this observation provides useful information on NIPPV in established BPD before larger randomized studies are performed on this topic. Further studies incorporating lung function tests should identify the level of respiratory support at which the repetitive stimulus of nocturnal NIPPV exerts most of its positive influence. It would be interesting to find out how NIPPV propagates lung remodelling or if it even has the potential to accelerate lung maturation in severe BPD.

References

1 De Paoli AG, Davis PG, Lemyre B: Nasal continuous positive airway pressure versus nasal intermittent positive pressure ventilation for preterm neonates: a systematic review and meta-analysis. Acta Paediatr 2003, 92:70–75.

2 Kulkarni A, Ehrenkranz RA, Bhandari V: Effect of introduction of synchronized nasal intermittent positive-pressure ventilation in a neonatal intensive care unit on bronchopulmonary dysplasia and growth in preterm infants. Am J Perinatol 2006, 23:233–240.

3 Kugelman A, Feferkorn I, Riskin A, Chistyakov I, Kaufman B, Bader D:. Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure for respiratory distress syndrome: a randomized, controlled, prospective study. J Pediatr 2007, 150:521–526.

4 Owen LS, Morley CJ, Davis PG: Neonatal nasal intermittent positive pressure ventilation: what do we know in 2007? Arch Dis Child Fetal Neonatal Ed 2007, 92:F414–F418.

5 Deakins KM: Bronchopulmonary dysplasia. Respir Care 2009, 54:1252–1262.

6 Hjalmarson O, Sandberg KL: Lung function at term reflects severity of bronchopulmonary dysplasia. J Pediatr 2005, 146:86–90.

7 Hofhuis W, Huysman MW, van der Wiel EC, Holland WP, Hop WC, Brinkhorst G, de Jongste JC, Merkus PJ: Worsening of V'maxFRC in infants with chronic lung disease in the first year of life: a more favorable outcome after high-frequency oscillation ventilation. Am J Respir Crit Care Med 2002, 166:1539–1543.

8 Wauer RR, Maurer T, Nowotny T, Schmalisch G: Assessment of functional residual capacity using nitrogen washout and plethysmographic techniques in infants with and without bronchopulmonary dysplasia. Intensive Care Med 1998, 24:469–475.
9 Hülskamp G, Pillow JJ, Dinger J, Stocks J: Lung function tests in neonates and infants with chronic lung disease of infancy: functional residual capacity. Pediatr Pulmonol 2006, 41:1–22.
10 Moretti C, Gizzi C, Papoff P, Lampariello S, Capoferri M, Calcagnini G, Bucci G: Comparing the effects of nasal synchronized intermittent positive pressure ventilation (nSIPPV) and nasal continuous positive airway pressure (nCPAP) after extubation in very low birth weight infants. Early Hum Dev 1999, 56:167– 177.
11 Lin CH, Wang ST, Lin YJ, Yeh TF: Efficacy of nasal intermittent positive pressure ventilation in treating apnea of prematurity. Pediatr Pulmonol 1998, 26:349– 353.
12 Courtney SE, Pyon KH, Saslow JG, Arnold GK, Pandit PB, Habib RH: Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. Pediatrics 2001, 107(2):304-308.
13 Ali N, Claure N, Alegria X, D'Ugard C, Organero R, Bancalari E: Effects of non- invasive pressure support ventilation (NI-PSV) on ventilation and respiratory effort in very low birth weight infants. Pediatr Pulmonol 2007, 42:704–710.
14 Courtney SE, Aghai ZH, Saslow JG, Pyon KH, Habib RH: Changes in lung volume and work of breathing: A comparison of two variable-flow nasal continuous positive airway pressure devices in very low birth weight infants. Pediatr Pulmonol 2003, 36(3):248-252.
15 Lista G, Castoldi F, Fontana P, Daniele I, Cavigioli F, Rossi S,Mancuso D, Reali R: Nasal continuous positive airway pressure (CPAP) versus bi-level nasal CPAP in preterm babies with respiratory distress syndrome: a randomised control trial. Arch Dis Child Fetal Neonatal Ed 2010, 95(2):F85-89.

SUBMISSION GUIDELINES FOR NEONATAL INTENSIVE CARE

Neonatal Intensive Care offers a variety of editorial coverage in every issue. You are invited to send manuscript in the following categories:

- Clinical papers about relevant therapies
- Studies commissioned by companies
- Papers published in support of products and therapies
- Research studies and reports prepared by in-house personnel
- Works in progress in any of the above categories
- Product reviews and product case studies

Submissions are welcomed from anyone involved with the healthcare fields covered by our journals.

How to submit manuscripts: Editorial material should be e-mailed to s.gold4@verizon.net. (No hard copy is necessary.) Figures may be submitted as jpegs or pdfs or embedded in the e-mailed manuscript. E-mailed papers should be attachments as word documents, and unformatted. Please do not "design" your submission. We do not use ® or ™ marks in the journal, nor do we print company names in all caps unless they're acronyms. Please be sure your article submission does not read merely like a product advertisement. Please review your submission carefully; we do not send out proofs prior to publication. For questions please contact us at: s.gold4@verizon.net, phone: 310-443-4109.

Important note: While we will consider all submissions for publication, we prefer clinically-oriented pieces. Goldstein & Associates retains the right to edit and/or reject all submitted material. All papers should include an author byline. In all cases and without exception, we will clearly identify the source of the article and the affiliation of the author. All material submitted is published at the sole discretion of the publisher and editors.

Copeptin Concentration in Cord Blood in Infants with Early-onset Sepsis, Chorioamnionitis and Perinatal Asphyxia

Luregn J. Schlapbach, Stefanie Frey, Susanna Bigler, Chiem Manh-Nhi, Christoph Aebi, Mathias Nelle, Jean-Marc Nuoffer

Abstract

Background: Vasopressin is one of the most important physiological stress and shock hormones. Copeptin, a stable vasopressin precursor, is a promising sepsis marker in adults. In contrast, its involvement in neonatal diseases remains unknown. The aim of this study was to establish copeptin concentrations in neonates of different stress states such as sepsis, chorioamnionitis and asphyxia.

Methods: Copeptin cord blood concentration was determined using the BRAHMS kryptor assay. Neonates with early-onset sepsis (EOS, n = 30), chorioamnionitis (n = 33) and asphyxia (n = 25) were compared to a control group of preterm and term (n = 155) neonates.

Results: Median copeptin concentration in cord blood was 36 pmol/l ranging from undetectable to 5498 pmol/l (IQR 7 - 419). Copeptin cord blood concentrations were non-normally distributed and increased with gestational age ($p < 0.0001$). Neonates born after vaginal compared to cesarean delivery had elevated copeptin levels ($p < 0.0001$). Copeptin correlated strongly with umbilical artery pH (Spearman's Rho -0.50, $p < 0.0001$), umbilical artery base excess (Rho -0.67, $p < 0.0001$) and with lactate at NICU admission (Rho 0.54, $p < 0.0001$). No difference wasfound when comparing copeptin cord blood concentrations between neonates with EOS and controls (multivariate $p = 0.30$). The highest copeptin concentrations were found in neonates with asphyxia (median 993 pmol/l). Receiver-operating-characteristic curve analysis showed that copeptin cord blood concentrations were strongly associated with asphyxia: the area under the curve resulted at 0.91 (95%-CI 0.87-0.96, $p < 0.0001$). A cut-off of 400 pmol/l had a sensitivity of 92% and a specifity of 82% for asphyxia as defined in this study.

Conclusions: Copeptin concentrations were strongly related to factors associated with perinatal stress such as birth acidosis, asphyxia and vaginal delivery. In contrast, copeptin appears to be unsuitable for the diagnosis of EOS.

Authors Schlapbach, Frey, Aebil, Nelle and Nuoffer are with the Neonatal and Pediatric Intensive Care Unit, Department of Pediatrics; Bigler and Aebil are with the Institute for Infectious Diseases, University of Bern; Man-Nhi and Nuoffer are with the University Institute for Clinical Chemistry, University of Bern, Switzerland. The authors wish to thank Claudia Schad, Division of Neonatology, University of Bern. Reprinted from BioMed Central, BMC Pediatrics, Schlapbach et al: Copeptin concentration in cord blood in infants with early-onset sepsis, chorioamnionitis and perinatal asphyxia. BMC Pediatrics 2011 11:38. For references, please visit BioMed Central and type the full title.

Background

Arginine vasopressin (or antidiuretic hormone, ADH), is a nonapeptide acting as a main regulator in the homeostatis of the cardiovascular and renal system. It is produced by the hypothalamus and secreted in the posterior lobe of the pituitary gland upon hemodynamic or osmotic stimuli. Vasopressin plays a crucial role in the endocrine stress response to a variety of diseases such as different shock states. Exogenous vasopressin is a promising therapeutic agent in cardiac arrest and septic shock in adults. A recent multicenter randomized controlled trial evaluated low-dose vasopressin in pediatric vasodilatory shock. Although few authors have reported successful use of vasopressin in neonates with arterial hypotension, data on the role of vasopressin during the neonatal period are scarce.

Since vasopressin is highly instable with a short halflife of 4-20 minutes, reliable determination of Vasopressin is derived from a larger precursor peptide which contains also C-terminal pro-vasopressin, called copeptin. Upon release of vasopressin, equal amounts of copeptin are secreted. Copeptin is relatively stable in serum and thereby reliably mirrors vasopressin level. Copeptin concentrations were strongly elevated in samples from adult patients with sepsis and high copeptin levels were predictive of mortality. Recent studies in adults have shown that copeptin is a valuable biomarker of infection in patients with community-acquired and ventilator associated pneumonia.

Wellmann et al have recently provided normal values for healthy term and near-term infants, but, to the best of our knowledge, copeptin has never been investigated in neonates with major diseases. We hypothesized that copeptin cord blood concentrations in neonates may be associated with different stress situations such as sepsis and perinatal asphyxia.

Neonatal infections account for over one million neonatal deaths worldwide every year. Early-onset sepsis (EOS, presenting within 72 hours of age) occurs in approximately 0.6% of term and up to 1.5% of preterm infants and contributes significantly to neonatal mortality. Therefore, early treatment of neonates with suspected infection is crucial to prevent life threatening complications. New infection markers may potentially improve guidance of therapeutic decisions.

Table 1 Baseline characteristics according to study group

Study group	Early-onset sepsis (N = 30)	Chorioamnionitis (N = 33)	Asphyxia (N = 25)	Control (N = 155)
Gender (male)	12 (40%)	12 (36%)	10 (40%)	87 (56%)
Gestational age [weeks]	31.5 (29-34)	30 (28-34)	36.5 (33-39)	38 (32-40)
Birth weight [gram]	1665 (1161-2490)	1430 (998-1975)	2400 (1573-3213)	2800 (1590-3420)
Prenatal steroids	23 (77%)	27 (82%)	8 (32%)	64 (41%)
Cesarean section	18 (60%)	18 (55%)	17 (68%)	73 (47%)
PROM >24 h	7 (23%)	10 (30%)	2 (8%)	16 (10%)
SGA	3 (10%)	4 (12%)	7 (28%)	11 (7%)
APGAR 1 min	5 (3-7)	6 (4-8)	3 (2-6)	8 (6-8)
APGAR 5 min	8 (6-9)	8 (7-9)	7 (5-8)	9 (8-9)
APGAR 10 min	9 (7-9)	9 (8-9)	8 (7-9)	9 (9-9)
Cord blood arterial pH	7.30 (7.24-7.33)	7.29 (7.24-7.33)	7.03 (7.00-7.07)	7.29 (7.25-7.32)
PDA	6 (20%)	5 (15%)	0 (0%)	11 (7%)
Arterial hypotension	12 (40%)	11 (33%)	11 (44%)	32 (21%)
Mechanical ventilation	16 (53%)	13 (39%)	8 (32%)	13 (8%)

Median (interquartile range) or number (percentage) are shown.

PDA, persistent ductus arteriosus; PROM, prolonged rupture of membranes; SGA, small for gestational age (< 10th percentile)

Perinatal asphxia is, after prematurity and sepsis, the third main cause of neonatal death worldwide. While therapeutic hypothermia has proven to improve survival and to reduce the rate of disability, mortality due to severe perinatal hypoxic-ischemic encephalopathy remains high even in developed countries.

This study therefore aimed to establish copeptin cord blood concentrations in neonates of different gestational ages and to assess the influence of sepsis, chorioamnionitis and asphyxia on copeptin concentrations.

Methods

Infants born between November 2004 and November 2007 at the Department of Obstetrics, University of Bern, Switzerland, were eligible for this study if cord blood serum had been drawn and stored immediately after birth. Neonates with major congenital malformations were excluded. Patients and controls were searched using the institutional neonatal database. Perinatal characteristics and postnatal parameters were extracted from the institutional neonatal database. Arterial umbilical cord pH was obtained routinely. Blood gas analyses and hemoglobin concentrations were obtained routinely in neonates admitted to the neonatal intensive care unit (NICU) and were included in this study if they had been obtained within six hours after birth. Small for gestational age (SGA) was defined as infants with a birth weight below the 10th percentile. Arterial hypotension was defined as mean arterial blood pressure which was below the gestational age limit at two consecutive measurements and that was treated with either a volume bolus administration, intravenous corticosteroids or catecholamines.

The following groups were defined: early-onset sepsis group, chorioamnionitis group, asphyxia group, and control group:

Early onset sepsis group (EOS): EOS cases were defined as neonates who presented with sepsis within the first 72 hours of life as defined by the following criteria: i) at least two clinical signs of sepsis (temperature instability, irritability or apathy, feeding difficulties, poor capillary refill >2 seconds, apnea, tachycardia and/or tachypnea); ii) elevated Creactive protein >20 mg/l, iii) decision of the attending physician to treat for at least 7 days with intravenous antibiotics and iv) recovery of bacterial pathogens in blood-culture. In infants with negative blood cultures but clinical diagnosis of EOS, all first three criteria mentioned above were required to be present.

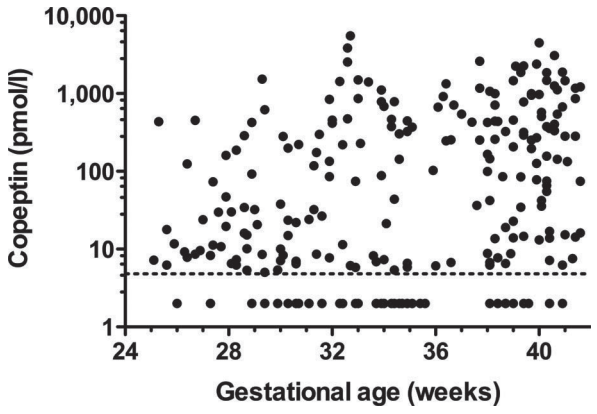


Figure 1 Copeptin and gestational age. Copeptin cord blood concentrations are shown according to gestational age. The dotted line indicates the detection limit (4.8 pmol/l).

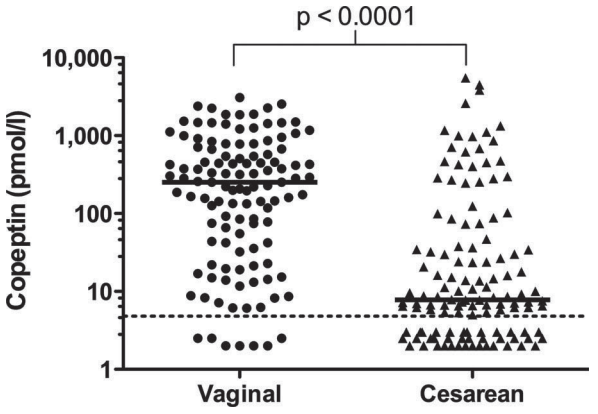


Figure 2 Copeptin concentration is increased after vaginal delivery. Copeptin cord blood concentrations according to the delivery mode are shown. The medians and the p-value of Mann-Whitney U test are shown. The dotted line indicates the detection limit (4.8 pmol/l).

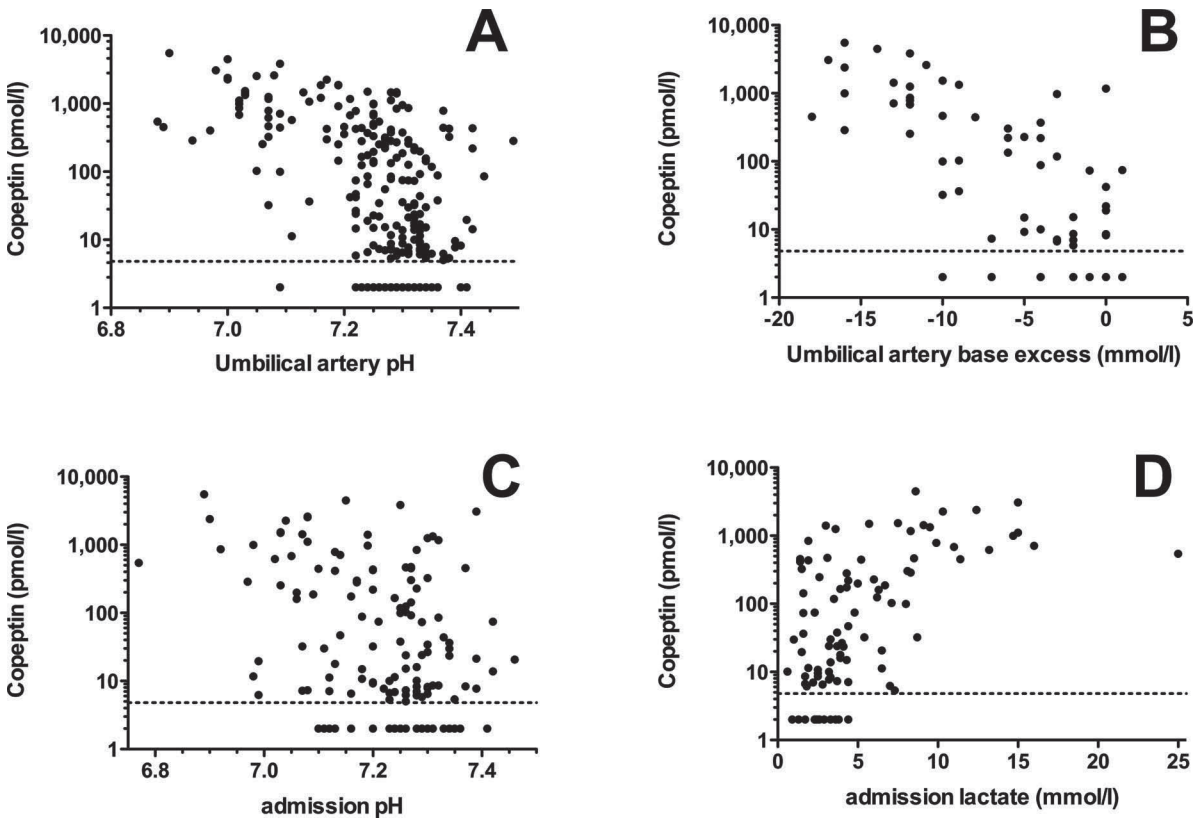


Figure 3 Copeptin concentration correlates with perinatal acidosis. Copeptin cord blood concentrations are plotted against umbilical artery pH (**A**, n = 236), umbilical artery base excess (**B**, n = 60), pH at admission to the NICU (**C**, n = 138) and lactate concentration at admission to the NICU (**D**, n = 100). The dotted line indicates the detection limit (4.8 pmol/l).

Chorioamnionitis group: Chorioamnionitis was defined as either clinically diagnosed chorioamnionitis (requiring presence of maternal fever, elevated maternal CRP, fetal tachycardia and prolonged rupture of membranes >24 h) or histologically diagnosed chorioamnionitis. Only infants exposed to chorioamnionitis without evidence of neonatal infection as defined above were considered in order to avoid overlap with the EOS group.

Asphyxia group: Asphyxia was defined according to our institutional guidelines as arterial cord blood pH below 7.1 plus 10-minute Apgar score below 6 and/or base excess >-12 mmol/l. This definition allowed to include both severe asphyxia, and milder forms of asphyxia. In addition, the asphyxia group required absence of clinically or histologically diagnosed chorioamnionitis and of confirmed EOS as defined above in order to avoid overlap with the EOS and the chorioamnionitis group. Hypoxicischemic encephalopathy (HIE) was graded according to Sarnat stage 0 (no HIE) to stage 3 (severe HIE).

Control group: Based on sample size calculations, a control group of at least 135 controls was required to detect a mean difference of 75 pmol/l between patients and controls with a power of 80% at a 95%-confidence interval. The assumptions were based on preliminary internal data and on published data from adults with sepsis. The control group (n = 155) consisted

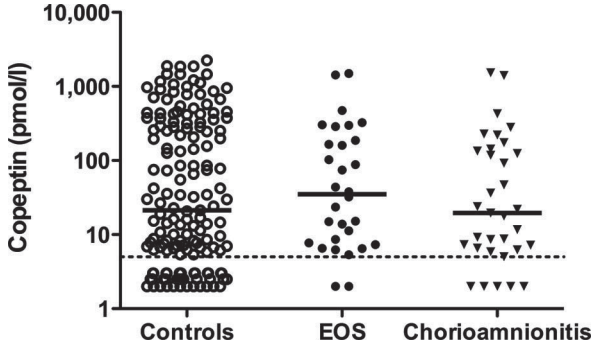


Figure 4 Copeptin concentration and early-onset sepsis. Copeptin cord blood concentrations in neonates with early-onset sepsis (EOS) and chorioamnnionitis compared with controls. The medians are shown. The dotted line indicates the detection limit (4.8 pmol/l).

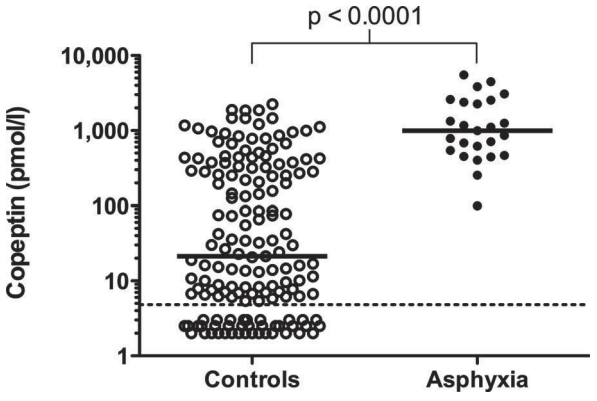


Figure 5 Copeptin concentration in infants with asphyxia. Copeptin cord blood concentrations in neonates with asphyxia compared with controls. The medians and the p-value of Man-Whitney U test are shown. The dotted line indicates the detection limit (4.8 pmol/l).

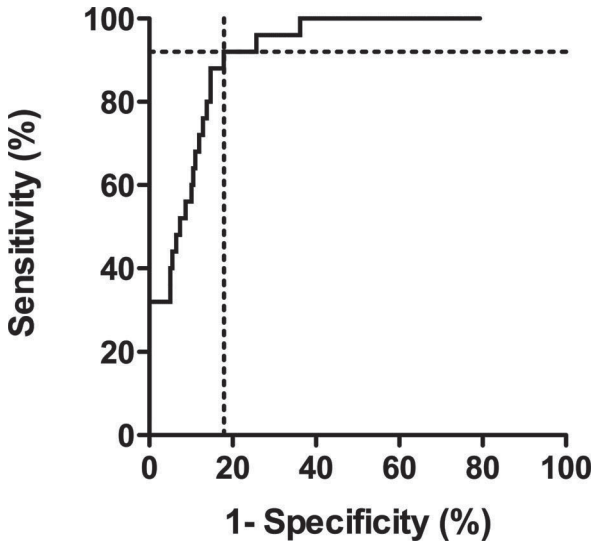


Figure 6 Receiver-operating-characteristic curve of copeptin concentrations in relation to asphyxia. Receiver-operating-characteristic curve is shown for copeptin cord blood concentrations in relation to asphyxia. The dotted lines indicate the optimal discriminative cut-off of 400 pmol/l, resulting in a sensitivity of 92% and a specifity of 82%.

of 75 premature neonates (24 0/7 to 36 6/7 weeks gestational age) without neonatal infection, chorioamnionitis or asphyxia (as defined above) and of 80 healthy term neonates (37 0/7 to 42 0/7 weeks gestational age) with no signs of any neonatal disease. Neonates with major congenital malformations were excluded. The control group infants were all born between January 2007 and November 2007.

Copeptin measurements: Cord blood is routinely collected immediately after delivery of the child from the umbilical vein at the placental side of the cord, and is routinely stored at our institution to determine Toxoplasma gondii serology in neonates of mothers with unknown or negative serostatus. After centrifugation, cord blood serum was frozen in sterile tubes at -80°C. Copeptin cord blood concentrations were determined using the commercial BRAHMS copeptin kryptor assay according to the manufacturer's instructions (BRAHMS, Hennigsdort, Germany). The detection limit of the assay was 4.8 pmol/l.

Statistical analysis: Copeptin concentrations were compared between patients and controls using Mann-Whitney U test and multivariate linear regression analysis. Multivariate analyses included gestational age, birth weight, SGA, mode of delivery and umbilical artery pH as covariates. Spearman's rank test and multivariate linear regression were used to analyze association between copeptin cord blood concentration with linear variables. Copeptin cord blood concentrations were logarithmized for regression analyses. Mann-Whitney U-test was used where appropriate. Receiver-operating-characteristic (ROC) curve analysis was used to assess specifity and sensitivity of copeptin for the diagnosis of EOS, chorioamnionitis and asphyxia. Two-sided tests were used throughout, and Pvalues below 0.05 were considered significant. SPSS 18.0 software was used.

Results

i) Patient characteristics: During the study period, 3896 neonates were born, 42 of whom fulfilled the EOS criteria. Cord blood serum was available in 30 (72%) neonates with EOS, these were thus included in the study. Their median gestational age was 31 weeks. In eight (27%) patients, blood cultures resulted positive. Maximum C-reactive protein during sepsis was at median 44 mg/l (range 22 - 261). Five infants (17%) required treatment with catecholamines due to septic shock and two (7%) infants died during sepsis. The chorioamnionitis group comprised 33 neonates without evidence of neonatal infection with a median gestational age of 30 weeks.

During the study period, 36 neonates were born with asphyxia. Of these, cord blood serum was available in 25 (69%). Their median gestational age was 37 weeks. Two (8%) had HIE Sarnat stage 3 and died, three (12%) Sarnat stage 2, and seven (28%) Sarnat stage 1, while 13 (52%) had no signs of HIE. Their median lactate concentration at NICU admission was 10.7 mmol/l (range 4 - 25).

ii) Copeptin cord blood concentrations in the whole cohort: When analyzing copeptin cord blood concentrations in the whole study population (n = 243), median concentration was 36 pmol/l ranging from undetectable to 5498 pmol/l (IQR 7 - 419). Copeptin concentration correlated significantly with gestational age (Spearman's Rho 0.30, $p < 0.0001$, Figure 1), and birth weight (Rho 0.29, $p < 0.0001$), but did not differ between boys and girls (Mann-Whitney Z -10.98, $p = 0.33$). Infants after vaginal delivery compared to cesarean delivery had significantly higher copeptin levels (Mann-Whitney Z -7.32, $p < 0.0001$), even when adjusting for gestational age ($p < 0.001$). Copeptin cord blood concentration showed a strong negative correlation with umbilical artery pH (Rho -0.50, $p < 0.0001$) and umbilical artery base excess (Rho -0.67, $p < 0.0001$). Similarly, copeptin concentration correlated strongly with pH (Rho -0.34, $p < 0.0001$) and with lactate at NICU admission (Rho 0.54, $p < 0.0001$), see Figure 3. The correlations between copeptin and pH, base excess and lactate remained significant in subgroup analyses on very preterm, late preterm and term neonates (< 32, 32-36 6/7, ≥ 37 weeks gestational age, $p < 0.05$, details not shown). No association was found between copeptin cord blood concentrations and arterial hypotension requiring treatment with volume and/or vasopressors, or with hemoglobin concentration and hematocrit at NICU admission ($p > 0.05$).

iii) Copeptin cord blood concentrations in neonates with EOS and with chorioamnionitis Median copeptin concentrations were 35 pmol/l (IQR 8 - 212) in the EOS versus 20 pmol/l (IQR 6 - 139) in the chorioamnionitis group versus 21 pmol/l (IQR 5 - 324) in controls. Although median copeptin concentrations were higher in EOS infants compared to controls, this was not statistically significantly (Mann- Whitney Z -0.58, $p = 0.56$). This was confirmed by multivariate linear regression analysis adjusted for gestational age, birth weight, SGA, delivery mode and umbilical artery pH (beta coefficient 0.16, 95%-CI -0.14 - 0.45, $p = 0.30$), Copeptin concentrations did not significantly differ between EOS infants with septic shock or with positive blood cultures compared to the rest of EOS infants ($p > 0.05$). ROC curve analysis confirmed that the performance of copeptin to distinguish EOS from controls was poor (area under the curve, 0.53, 95%-CI 0.44 - 0.63, $p = 0.57$). No difference was found when comparing copeptin levels between the chorioamnionitis group and controls or between the chorioamnionitis and the EOS group ($p > 0.1$). Copoeptin was not associated with CRP, leukocyte count or left shift (immature by total neutrophil mratio, $p > 0.05$, details not shown).

iv) Copeptin cord blood concentrations in neonates with asphyxia Copeptin cord blood concentrations were significantly higher in the 25 neonates with asphyxia (median 993 pmol/l, IQR 505 - 2466, range 100 - 5498) compared to controls (Mann-Whitney Z -6.49, $p < 0.0001$). This was confirmed by multivariate analysis (beta coefficient 1.09, 95%-CI 0.41 - 1.76, $p = 0.002$). Notably, the eight highest copeptin values measured, all above 2000 pmol/l, occurred in neonates with asphyxia. None of these eight neonates with very high copeptin levels had more than Sarnat stage one HIE, and all survived. Copeptin concentration was not significantly correlated with Sarnat score (Rho -0.31, $p = 0.133$).

ROC curve analysis showed that copeptin concentrations discriminated with high accuracy between asphyxia, as defined in this study, and controls: the area under the curve resulted at 0.91 (95%-CI 0.87 - 0.96, $p < 0.0001$). A cut-off of 400 pmol/l had a sensitivity of 92% and a specifity of 82%.

Discussion

Our findings indicate that copeptin cord blood concentration reflect perinatal stress with the highest values found in neonates with asphyxia. To the best of our knowledge, this is the first study to investigate copeptin in newborns with EOS and asphyxia.

Copeptin cord blood concentration was strongly and inversely correlated with umbilical artery pH, umbilical artery base excess, and with pH and lactate at admission to the NICU. Perinatal acidosis results from diminished fetal blood and oxygen supply due to maternal, placental or cord complications leading to lactic acidosis. Vasopressin is released by the hypothalamus-hypopituitary upon sensing of increased plasma osmolality, decreased arterial pressure, and reductions in cardiac volume. Our data indicate that the vasopressin system in the neonate is strongly activated upon perinatal stress. Importantly, the strength of these correlations was comparable between very preterm, late preterm and term infants, suggesting that the vasopressin response is already present at an early gestational age.

The highest copeptin cord blood concentrations were found in neonates with perinatal asphyxia. This finding was confirmed by multivariate analysis adjusted for gestational age, birth weight, mode of delivery and umbilical artery pH. Most values in this group, a third of them exceeding 2000 pmol/l, were much higher that concentrations that have been reported in adult studies on patients with septic shock, multiple trauma or myocardial infarction. Copeptin cord blood concentrations above 400 pmol/l had a high sensitivity and specifity for asphyxia. Perinatal asphyxia can be considered as an extreme of a stress situation. In a study on the stress response to hypoxia in neonatal piglets, maintenance of cardiovascular function and a higher serum cortisol concentration were associated with a better neurological outcome. Further studies are needed to determine whether copeptin is related to asphyxia severity and whether copeptin may improve outcome prognostication after asphyxia.

Neonates born by vaginal delivery had significantly elevated copeptin cord blood concentrations compared to those born by cesarean section, even after adjustment for gestational age. Wellmann et al have recently determined copeptin in 177 neonates and found higher levels after vaginal delivery as well. These findings are in line with earlier reports of elevations in the stress hormone cortisol after vaginal delivery. Spontaneous labour physiologically induces important changes in the fetal homeostatic system which serve to prime the fetus for postnatal adaptation.

Copeptin has been shown to be a valuable infection marker in adults with sepsis and community-acquired pneumonia. In contrast, in our study, copeptin concentrations in cord blood were not significantly elevated in EOS infants compared to controls. The specifity and sensitivity of copeptin in the diagnosis of EOS was poor. Similarly, no difference was found between neonates born to mothers with chorioamnionitis and controls. Given the strong influence of perinatal stress on copeptin cord blood concentrations, and considering the very large interindividual variations observed in this study, our data indicate that determining copeptin concentrations is not suitable to diagnose EOS. Potentially, the diagnostic accuracy of copeptin may be improved in late-onset infections, since the effect of perinatal stress on copeptin disappears over the first days of life.

Several limitations of this study need to be mentioned. Firstly, only neonates where cord blood was available were included. A selection bias is, however, unlikely, since cord blood was routinely collected during the study period in neonates of mothers with unknown or negative Toxoplasma gondii serostatus, a condition which is unlikely to affect copeptin cord blood concentrations. Secondly, the relatively small sample sizes limits statistical power. Therefore, confirmation by future prospective cohorts is needed.

We believe that the present study has several strengths. In contrast to the study by Wellmann et al which included only healthy term and near term infants, we included neonates with a wide range of gestational ages. The inclusion of clearly defined and not overlapping groups of infants with EOS, chorioamnionitis and asphyxia allowed to study the influence of these diseases on copeptin concentration. Multivariate analyses were adjusted for the main confounders gestational age, birth weight, delivery mode and umbilical artery pH.

Conclusions

We report that copeptin concentrations in cord blood are strongly correlated to perinatal stress with the highest values found in neonates with perinatal asphyxia. Future studies should prospectively determine copeptin concentrations in combination with novel markers of neonatal brain damage, such as neuron-specific enolase or S-100B, in order to investigate whether copeptin concentrations are of prognostic value during asphyxia.

Association Between Maternal Comorbidity and Preterm Birth by Severity and Clinical Subtype

Nathalie Auger, Thi Uyen Nhi Le, Alison L. Park, Zhong-Cheng Luo

Abstract

Background: Preterm birth (PTB) is a major cause of infant morbidity and mortality, but the relationship between comorbidity and PTB by clinical subtype and severity of gestational age remains poorly understood. We evaluated associations between maternal comorbidities and PTB by clinical subtype and gestational age.

Methods: We conducted a retrospective cohort study of 1,329,737 singleton births delivered in hospitals in the province of Québec, Canada, 1989-2006. PTB was classified by clinical subtype (medically indicated, preterm premature rupture of membranes (PPROM), spontaneous preterm labour) and gestational age (<28, 28-31, 32-36 completed weeks). Odds ratios (OR) of PTB by clinical subtype for systemic and localized maternal comorbidities were estimated using polytomous logistic regression, adjusting for maternal age, grand multiparity, and period. Attributable fractions were calculated.

Results: PTB rates were higher among mothers with comorbidity (10.9%) compared to those without comorbidity (4.7%). Several comorbidities were associated with greater odds of medically indicated PTB compared with no comorbidity, but only comorbidities localized to the reproductive system were associated with spontaneous PTB. Drug dependence and mental disorders were strongly associated with PPROM and spontaneous PTBs across all gestational ages (OR >2.0). At the population level, several major comorbidities (placental abruption, chorioamnionitis, oligohydramnios, structural abnormality, cervical incompetence) were key contributors to all clinical subtypes of PTB, especially at <32 weeks. Major systemic comorbidities (preeclampsia, anemia) were key contributors to PPROM and medically indicated PTBs.

Conclusions: The relationship between comorbidity and clinical subtypes of PTB depends on gestational age. Prevention of PPROM and spontaneous PTB may benefit from greater attention to preeclampsia, anemia and comorbidities localized to the reproductive system.

The authors are with Institut national de santé publique du Québec, the Research Centre of the University of Montreal Hospital Centre, the Department of Social and Preventive Medicine, University of Montreal; and the Department of Obstetrics and Gynecology, CHU Sainte Justine, Canada.

Background

Preterm birth (PTB) is a major cause of mortality and morbidity throughout life and rates are increasing in many countries. The determinants of PTB remain poorly understood. Evidence suggests that maternal comorbidities are associated with PTB, especially preeclampsia, infection, uterine anomalies, and placental complications. Many studies have not considered PTB by clinical subtype. Associations with comorbidities are particularly unclear for preterm premature rupture of membranes (PPROM) and spontaneous preterm labour with intact membranes, the two subtypes of spontaneous PTB that are most challenging to prevent. While medically indicated PTB has clearly been linked with ischemic placental disease, relationships remain to be established for spontaneous PTB which appears to be more closely linked with infectious processes. However, studies are conflicting and often limited by misclassification of gestational age or PTB clinical subtype.

Fewer studies have examined the relationships between comorbidity and PTB clinical subtype at different gestational ages, despite evidence suggesting that factors triggering PTB may differ depending on gestational age. Research suggests that preeclampsia, uterine bleeding, cervical incompetence and chorioamnionitis may be more strongly associated with PTB at <32 weeks of gestation compared with later PTB, though clinical subtype was not differentiated. Research of PTB before 28 or 34 weeks has found associations with preeclampsia, placental abruption, chorioamnionitis, oligohydramnios, cervical insufficiency, and fetal factors, but again without evaluating clinical subtype. Information on how maternal comorbidities influence PTB rates at early gestational ages is needed, especially since PTBs below 32 weeks are responsible for nearly 50% of long term neurologic morbidity and 60% of perinatal mortality, despite accounting for only 1-2% of live births.

This gap in the literature needs to be addressed to better understand which maternal comorbidities to target for prevention of PTB at different gestational ages, especially PPROM and spontaneous preterm labour which are difficult to prevent. This study sought to evaluate the associations between major maternal comorbidities and PTB by clinical subtype and gestational age.

Table 1. Preterm birth (PTB) rates by maternal characteristic, Québec, 1989-2006

	All PTB %	Medically indicated %	PPROM* %	Spontaneous† %	Total births
Maternal age					
<20 years	8.4	1.9	2.1	4.3	56,647
20-24 years	6.7	1.7	2.0	3.0	260,848
25-29 years	5.8	1.6	1.8	2.4	487,831
30-34 years	5.7	1.8	1.8	2.2	373,906
35-39 years	6.9	2.4	2.2	2.3	130,525
≥40 years	8.6	3.5	2.6	2.5	19,979
Grand multiparity	6.1	1.7	1.7	2.7	6,010
Period					
1989-1993	5.9	1.6	1.7	2.7	454,300
1994-1997	6.3	1.8	1.9	2.6	321,884
1998-2001	6.4	1.9	2.1	2.5	276,252
2002-2006	6.5	2.1	2.1	2.3	277,301
Comorbidity					
Systemic	8.7	4.1	2.2	2.4	323,433
Localized	10.9	4.9	2.9	3.0	241,580
No	4.7	0.5	1.7	2.4	839,539
Total	6.2	1.8	1.9	2.5	1,329,737

* Preterm premature rupture of membranes
† Spontaneous preterm labour before 37 gestational weeks with intact membranes

Methods

Data and variables: This study was based on a retrospective cohort of all births in Québec hospitals from 1989 to 2006 (N=1,351,211). Nearly 100% of infants in Québec are delivered in hospitals. Maternal birth records were extracted from hospital discharge abstracts using the ninth revision of International Classification of Disease (ICD) codes for delivery (650, and 640-676 with 1 or 2 in the fifth position) recorded as the principal diagnosis or one of fifteen secondary diagnoses. Hospital transfers (N=21) and foreign visitors with no provincial health insurance number (N=15,399) were excluded. We also excluded multiple births and stillbirths (646.0, 651, 652.6, 656.4, 678.1, V271- V277) and pregnancy terminations (779.6) for which mechanisms driving PTB may differ (N=21,471).

Births at <37 completed weeks of gestation were defined as PTBs. Gestational age estimates in Québec are ultrasound-based which may be more accurate than estimates based on recall of date of last menstruation. Recall-based measures are a common limitation of population-based research. Clinical subtypes of PTB included medically indicated, PPROM, and spontaneous preterm labor. Spontaneous PPROM was identified using ICD-9 codes 658.2-658.4 among births <37 weeks. Medically indicated PTB cases that were not secondary to PPROM were identified using procedure codes for labor induction (855, 850.1, 851.9) and cesarean delivery (860-862, 868, 869). The remaining PTBs were designated spontaneous preterm labour with intact membranes, hereafter denoted spontaneous PTB. PTB subtypes were further categorized as extreme (<28 weeks), very (28-31 weeks), and moderate (32-36 weeks). Four births with missing data on gestational age were excluded, leaving 1,329,737 cases in the final analysis cohort. Births at extremely early gestational ages (under 20 weeks, n=565; 0.04%) were not excluded, as they may represent true cases of PTB [7] (and sensitivity analyses excluding these cases yielded similar findings).

Maternal comorbidities based on the ICD-9 [20] were classified in two broad categories to facilitate data classification (systemic comorbidities vs. comorbidities localized to the reproductive tract). Common comorbidities recorded as the principal or secondary diagnosis were grouped into sub-categories within these two broad categories. Systemic comorbidities representing a more generalized maternal disease process included hypertension (preeclampsia/eclampsia, pre-existing, gestational, unspecified), cardiovascular disease, diabetes (pre-existing, gestational), edema/renal disease, genitourinary infection, general infection, thyroid disease, anemia, drug dependence, mental disorders, and other comorbidity. Localized comorbidities included hemorrhage (placental abruption, placenta previa, other), chorioamnionitis, amniotic sac disorders (polyhydramnios, oligohydramnios, unspecified), cervical incompetence, structural abnormality, previous cesarean delivery, and fetal factors (anomaly, other). Comorbidity variables were expressed categorically for hypertension, diabetes, hemorrhage, amniotic sac disorders, and fetal factors, and dichotomously for the remaining conditions. Covariates included maternal age (<20, 20-24, 25-29, 30-34, 35-39, ≥40 years), grand multiparity (ICD-9 659.4; ≥5 versus <5 previous live births), and period (1989-1993, 1994-1997, 1998-2001, 2002-2006).

Statistical analysis: Descriptive statistics (n, %) were computed. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for comorbidity indicators and overall preterm birth (without considering clinical subtype) in models that were unadjusted and adjusted for maternal age, grand multiparity and period. Polytomous logistic (or multinomial) regression was used to evaluate adjusted associations between each comorbidity and PTB subtype (medically indicated, PPROM, spontaneous) for each gestational age category in models using term births (≥37 weeks) as the referent. Polytomous models containing one indicator of comorbidity at a time were run using the glogit option of the LOGISTIC procedure in SAS. To evaluate the extent to which PTB rates were attributable to each comorbidity, population attributable fractions were computed with the formula ((RR-1)/RR)(exposed cases/overall cases). Analyses were performed with SAS version 9.2 (Statistical Analysis System, Cary, North Carolina) and SPSS version 17.0 statistical software. This study conformed to the 2010 Tri-Council Policy Statement for ethical conduct of research involving humans in Canada. Approval was waived by the research ethics committee of the University of Montreal Hospital Centre.

Results

Overall, 6.2% of births were preterm, of which 28.7% were medically indicated, 30.7% PPROM, and 40.6% spontaneous. Over 5% of PTBs occurred at <28 weeks, 7.3% at 28-31 weeks, and 87.2% at 32-36 weeks. The majority of PTBs at <28 weeks were spontaneous (44.2%), followed by PPROM (29.3%) and medically indicated (26.5%). A similar pattern was observed for PTBs at 32-36 weeks, among which 41.5% were spontaneous, 30.7% PPROM, and 27.8% medically indicated. In contrast, PTBs at 28-31 weeks were more frequently medically indicated (40.6%) than PPROM (31.8%) or spontaneous (27.6%). The proportion of PTB was greater for mothers with localized (10.9%) and systemic comorbidities (8.7%), compared to those without comorbidity (4.7%, Table 1). Systemic and localized comorbidities were present in 34.1% and 31.8% of births, respectively (data not in table). Among mothers with systemic comorbidities, medically indicated PTBs (4.1%) were more frequent than PPROM (2.2%) or spontaneous PTBs (2.4%); a similar pattern was observed for mothers with localized comorbidities. Among mothers with no comorbidity, however, spontaneous PTBs (2.4%) were more common (though just as frequent as in mothers with systemic comorbidities). Spontaneous PTBs accounted for the largest

Table 2. Preterm birth (PTB) rates according to maternal systemic/localized comorbidity and gestational age (weeks) at delivery, and the proportions of comorbidity among PTBs

	All PTB %	Medically indicated %			PPROM* %			Spontaneous† %				Comorbidity‡ %	Total births
	<37	<28	28-31	32-36	<37	<28	28-31	32-36	<37	<28	28-31	32-36	<37	<37	
Systemic comorbidity															
Hypertension															
Preeclampsia/eclampsia	24.1	1.0	3.3	16.3	20.6	0	0.1	1.2	1.3	0	0.1	2.1	2.2	8.7	29,915
Pre-existing	11.0	0.2	0.7	5.8	6.7	0.1	0.1	1.9	2.1	0.1	0.1	1.9	2.1	0.8	7,439
Gestational	6.1	0.1	0.2	3.2	3.5	0	0.1	1.1	1.2	0	0	1.3	1.4	1.0	11,380
Cardiovascular disease	10.3	0.2	0.6	4.4	5.3	0.2	0.3	2.1	2.6	0.2	0	2.2	2.5	0.6	4,434
Diabetes															
Pre-existing	13.1	0.1	0.6	5.5	6.1	0.1	0.5	3.1	3.7	0.1	0.3	2.9	3.2	2.7	16,938
Gestational	8.4	0.1	0.2	2.6	2.8	0.1	0.2	2.4	2.7	0	0.1	2.8	2.9	5.1	50,313
Edema/renal disease	17.0	0.6	1.9	9.9	12.4	0.1	0.2	1.6	2.0	0.3	0.1	2.3	2.6	0.8	3,977
Genitourinary infection	8.4	0.2	0.5	2.7	3.3	0.2	0.4	2.0	2.6	0.2	0.1	2.1	2.5	3.2	31,477
General infection	10.0	0.2	0.4	3.2	3.8	0.3	0.4	2.2	2.9	0.3	0.2	2.7	3.2	1.9	16,024
Thyroid disease	8.9	0.2	0.4	3.0	3.7	0.2	0.3	2.3	2.8	0.2	0.2	2.2	2.5	1.4	12,687
Anemia	6.9	0.2	0.4	2.3	2.9	0.2	0.2	1.5	2.0	0.2	0.1	1.7	2.0	11.7	140,410
Drug dependence	21.4	0.2	0.8	4.5	5.5	0.6	0.7	5.0	6.2	0.6	0.7	8.5	9.8	3.9	3,229
Mental disorders	13.2	0.4	0.5	3.7	4.5	0.3	0.6	3.2	4.1	0.4	0.3	3.9	4.6	9.3	7,688
Localized comorbidity															
Hemorrhage															
Placental abruption	31.9	1.3	2.4	9.9	13.6	1.3	1.6	3.6	6.6	2.3	1.8	7.6	11.7	8.6	22,278
Placenta previa	35.2	0.8	2.9	26.3	30.0	0.9	0.5	2.4	3.8	0.3	0.2	1.1	1.5	2.3	5,265
Chorioamnionitis	11.0	0.3	0.3	1.4	1.9	1.2	1.2	3.1	5.5	1.0	0.5	2.1	3.6	7.3	55,133
Amniotic sac															
Polyhydramnios	12.5	0.3	0.8	4.9	6.0	0.2	0.3	2.0	2.5	0.3	0.5	3.4	4.1	1.3	8,861
Oligohydramnios	20.6	0.8	1.8	10.4	13.0	1.1	1.4	3.2	5.7	0.3	0.2	1.5	1.9	3.8	15,293
Cervical incompetence	47.4	3.4	1.5	6.4	11.2	6.3	2.7	5.7	14.7	11.3	2.1	8.1	21.5	1.5	2,570
Structural abnormality	13.0	0.6	1.1	5.1	6.7	0.4	0.6	3.2	4.2	0.4	0.2	1.5	2.1	3.1	19,515
Previous cesarean delivery	5.8	0.1	0.2	2.9	3.3	0.1	0.1	1.3	1.5	0.1	0.1	0.9	1.0	8.4	118,608
Fetal anomaly	43.2	8.2	1.9	11.7	21.9	0.2	0.6	2.4	3.2	12	0.6	5.5	18.1	0.5	935
Total	6.2	0.1	0.2	1.5	1.8	0.1	0.1	1.7	1.9	0.1	0.1	2.2	2.5		1,329,737

* Preterm premature rupture of membranes

† Spontaneous preterm labour before 37 weeks of gestation with intact membranes

proportion (>41%) of births that were severely (<28 weeks) and moderately (32-36 weeks) preterm, but medically indicated PTBs (40.6%) accounted for the largest proportion of very PTBs (28-31 weeks).

PTB was more frequent among mothers with preeclampsia/eclampsia (24.1%), drug dependence (21.4%), and edema/renal disease (17.0%) (Table 2, systemic comorbidity). Among mothers with drug dependence, spontaneous PTB was more frequent (9.8%) than PPROM (6.2%) or medically indicated PTB (5.5%), especially at 32-36 weeks (8.5%). For all other causes of systemic comorbidity, medically indicated PTB was more frequent than PPROM and spontaneous PTB. Gestational diabetes and mental disorders were exceptions as the frequency of PTB was similar across clinical subtypes.

PTB was very common among mothers with major localized co-morbidities, especially cervical incompetence (47.4%), fetal anomalies (43.2%), placenta previa (35.2%) and placental abruption (31.9%) (Table 2, localized comorbidity). For cervical incompetence, spontaneous PTB was more frequent (21.5%) than PPROM (14.7%) or medically indicated PTB (11.2%). For other causes of localized comorbidity, medically indicated PTB was more frequent than PPROM or spontaneous PTB. An exception was chorioamnionitis, for which PPROM was more frequent (5.5%) than medically indicated (1.9%) or spontaneous PTB (3.6%).

Localized comorbidities as a whole were more strongly associated with overall PTB (OR 2.27, 95% CI 2.24-2.31) than systemic comorbidities (OR 1.66, 95% CI 1.63-1.68) (Table 3). Both systemic and localized comorbidities were associated with statistically significant four-fold greater odds of medically indicated PTB. Associations were modest for PPROM but nonetheless statistically significant. In contrast, spontaneous PTB was only associated with localized (but not systemic) comorbidities. Associations were robust to adjustments for covariates.

Almost all categories of systemic and localized comorbidity were associated with greater odds of overall PTB (data not shown). For systemic comorbidities, associations with overall PTB were highest for preeclampsia/eclampsia (OR 5.1, 95% CI 5.0-5.3), drug dependence (OR 3.9, 95% CI 3.5-4.2), and edema/renal disease (OR 3.1, 95% CI 2.8-3.3). For localized comorbidities, odds of overall PTB were highest for cervical incompetence (OR 13.9, 95% CI 12.8-15.0), fetal anomalies (OR 11.8, 95% CI 10.3-13.4), placenta previa (OR 9.4, 95% CI 8.9-10.0), and placental abruption (OR 7.9, 95% CI 7.7-8.2).

Associations between comorbidities and clinical subtype of PTB depended on gestational age (Table 4). For systemic comorbidities, associations with medically indicated PTB were strongest for preeclampsia/eclampsia, chronic hypertension and edema/renal disease, and ORs were largest at 28-31 weeks of

Table 3. Association between maternal systemic/localized comorbidity and preterm birth (PTB) by clinical subtype

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Population attributable fraction
All PTB			
Systemic comorbidity	1.67 (1.64-1.69)	1.66 (1.63-1.68)	12.8
Localized comorbidity	2.23 (2.20-2.27)	2.27 (2.24-2.31)	16.9
Medically indicated PTB			
Systemic comorbidity	4.11 (4.00-4.22)	4.01 (3.90-4.11)	21.8
Localized comorbidity	4.88 (4.76-5.01)	4.83 (4.71-4.96)	23.3
PPROM†			
Systemic comorbidity	1.23 (1.19-1.26)	1.18 (1.15-1.22)	8.0
Localized comorbidity	1.85 (1.80-1.90)	1.83 (1.78-1.88)	21.1
Spontaneous PTB‡			
Systemic comorbidity	0.99 (0.97-1.02)	1.00 (0.97-1.02)	0
Localized comorbidity	1.31 (1.28-1.35)	1.38 (1.34-1.42)	5.8

* Odds ratio (OR), 95% confidence interval (CI) adjusted for maternal age, grand multiparity, and period
† Preterm premature rupture of membranes
‡ Spontaneous preterm labour before 37 weeks of gestation with intact membranes

gestation. Associations with PPROM also tended to be stronger at 28-31 weeks, especially for mental disorders, genitourinary infection and cardiovascular disease.

Hypertension was not associated with greater odds of PPROM at any gestational age (some ORs suggested a protective association). Diabetes was associated with PPROM after 28 weeks (adjusted ORs: 1.3 to 3.5), but the associations were stronger for pre-existing than for gestational diabetes. Drug dependence (adjusted ORs: 3.3 to 5.9), general infection (adjusted ORs: 1.4 to 3.0), and thyroid disease (adjusted ORs: 1.3 to 1.9) were more strongly associated with PPROM at <32 weeks than 32-36 weeks, while anemia was associated with PPROM at <32 weeks only (adjusted ORs: 1.7 to 2.1). Associations with spontaneous PTB were strongest for drug dependence and mental disorders at all gestational ages, and pre-existing diabetes at 28-31 weeks. Genitourinary infection was weakly associated with spontaneous PTB at <28 weeks only (adjusted OR=1.3), while preeclampsia/eclampsia (but not other categories of hypertension) was weakly associated with spontaneous PTB at 32-36 weeks (adjusted OR=1.1). Thyroid disease was associated with spontaneous PTB only at 28-31 weeks, while anemia was associated with spontaneous PTB only at <28 weeks.

Localized comorbidities were generally associated with medically indicated PTB and PPROM at most gestational ages, while the associations with spontaneous PTB tended to be stronger at <32 weeks of gestation. Previous cesarean delivery was associated with greater odds of medically indicated PTB after 28 weeks, but lower odds of PPROM at 32-36 weeks and spontaneous PTB at all gestational ages.

Attributable fractions suggested that preeclampsia/eclampsia, anemia, placental abruption, structural abnormalities, and chorioamnionitis were important contributors to medically indicated PTB at the population level, though the contribution varied by gestational age (Table 5). Anemia and genitourinary infections, as well as placental abruption, chorioamnionitis, and structural abnormalities, were the largest contributors to PPROM. No particular cause of systemic comorbidity accounted for a substantial fraction of spontaneous PTB, but major localized morbidities including placental abruption, chorioamnionitis, cervical incompetence and structural abnormalities were important contributors, especially at <32 weeks of gestation.

Discussion

To our knowledge, this study is the first to evaluate relations between systemic and localized maternal comorbidities with PTB by clinical subtype and gestational age. In a large population based cohort, we demonstrated that comorbidities overall were associated with higher likelihoods of medically indicated PTB, while only comorbidities localized to the reproductive tract were associated with spontaneous PTB. At the population level, several major localized comorbidities (placental abruption, chorioamnionitis, oligohydramnios, structural abnormality, cervical incompetence) were key contributors to all three clinical subtypes of PTB, especially at <32 weeks of gestation. In contrast, major systemic comorbidities (preeclampsia, anemia) were the key contributors to medically indicated PTBs, but not spontaneous PTBs. This study is the first to identify anemia as the most important maternal systemic comorbidity contributing to PPROM at the population level.

Hypertension is a major pregnancy complication. We found that preeclampsia/eclampsia was strongly associated with medically indicated PTB, confirming the findings from other studies. Data are conflicting as to whether hypertension may be a stronger determinant of early than of late PTB, but previous studies are limited as they often do not differentiate clinical subtypes of PTB. We observed that preeclampsia/eclampsia and preexisting hypertension were strongly associated with medically indicated PTB at all gestational ages. This was not the case for gestational and unspecified hypertension that were only associated with medically indicated PTB at ≥28 weeks, albeit much more weakly. Few studies have evaluated the link between hypertension and spontaneous PTB. Two studies found that pre-existing and gestational hypertension in the US were associated with more than 60% greater odds of spontaneous PTB, but PPROM was not evaluated. In contrast, we found that hypertension was not associated with elevated odds of either PPROM or spontaneous PTB. In fact, ORs were protective for some hypertensive disorders. Close monitoring of hypertensive pregnancies may partly explain the protective associations with PPROM and spontaneous PTB, via shifting of potential PTBs to the medically indicated subtype (through early detection and labor induction).

The influence of diabetes, another common pregnancy complication, also depended on clinical subtype of PTB and gestational age. We confirmed that compared to gestational diabetes, pre-existing diabetes was more strongly associated with medically indicated PTB. Diabetes was associated with greater odds of PPROM after 28 weeks, but the magnitude was also greater for pre-existing than for gestational diabetes. A strong association with spontaneous PTB at 28-31 weeks was only observed for pre-existing diabetes. Other research also suggests strong associations between pre-existing diabetes and spontaneous PTB. One study evaluating the odds of very PTB (<32 weeks) found strong associations with pre-existing type 1 diabetes, but the clinical subtype of PTB was not differentiated.

Drug dependence and mental disorders are increasingly recognized as drivers of PTB. We observed that drug dependence and mental disorders were associated with all clinical subtypes of PTB at most gestational ages. This finding is novel and important because most studies have focused on infections as a cause of PPROM and spontaneous PTB, while other comorbidities have been less studied. Psychological or social stress, psychiatric disorders, and substance abuse have been associated with overall PTB, while other research

Table 4. Association between maternal systemic/localized comorbidity and preterm birth according to clinical subtype and gestational age*

	Medically indicated			PPROM†			Spontaneous‡		
	<28 wk	28-31 wk	32-36 wk	<28 wk	28-31 wk	32-36 wk	<28 wk	28-31 wk	32-36 wk
Systemic comorbidity									
Hypertension									
Preeclampsia/eclampsia	17.6 (15.4-20.1)	38.7 (35.6-42.1)	18.5 (17.8-19.1)	0.2 (0.1-0.5)	0.6 (0.4-0.9)	0.9 (0.8-1.0)	0.3 (0.2-0.5)	0.7 (0.5-1.1)	1.1 (1.0-1.2)
Pre-existing	3.4 (2.1-5.4)	6.7 (5.1-8.8)	5.1 (4.6-5.6)	1.3 (0.7-2.3)	1.2 (0.7-2.0)	1.1 (0.9-1.3)	1.0 (0.5-1.7)	0.9 (0.5-1.9)	0.9 (0.8-1.1)
Gestational	1.1 (0.5-2.0)	2.1 (1.4-3.1)	2.8 (2.5-3.1)	0.1 (0.0-0.6)	0.5 (0.2-0.9)	0.6 (0.5-0.7)	0.2 (0.1-0.6)	0.1 (0.0-0.5)	0.6 (0.5-0.7)
Cardiovascular disease	2.2 (1.2-4.3)	3.4 (2.3-4.9)	3.0 (2.6-3.4)	1.6 (0.8-3.4)	2.4 (1.5-4.0)	1.3 (1.0-1.6)	1.6 (0.8-2.9)	2.0 (1.1-3.7)	1.1 (0.9-1.3)
Diabetes									
Pre-existing	1.2 (0.8-1.9)	3.2 (2.6-3.9)	3.9 (3.6-4.2)	1.2 (0.8-1.8)	3.5 (2.8-4.4)	2.0 (1.9-2.2)	0.9 (0.6-1.4)	2.2 (1.7-3.1)	1.4 (1.3-1.6)
Gestational	0.6 (0.4-0.8)	1.2 (1.0-1.4)	1.7 (1.6-1.8)	0.5 (0.3-0.7)	1.3 (1.0-1.6)	1.5 (1.4-1.6)	0.3 (0.2-0.4)	0.8 (0.6-1.1)	1.3 (1.3-1.4)
Edema/renal disease	6.8 (4.4-10.3)	11.9 (9.4-14.9)	7.3 (6.6-8.1)	1.4 (0.6-3.3)	1.7 (0.9-3.3)	1.1 (0.8-1.4)	1.8 (1.0-3.4)	0.9 (0.3-2.4)	1.1 (0.9-1.4)
Genitourinary infection	1.7 (1.3-2.3)	2.6 (2.2-3.1)	1.8 (1.7-1.9)	2.1 (1.6-2.7)	2.6 (2.1-3.1)	1.2 (1.1-1.3)	1.3 (1.0-1.7)	1.0 (0.7-1.4)	1.0 (0.9-1.1)
General infection	2.5 (1.8-3.5)	2.2 (1.7-2.8)	2.2 (2.0-2.4)	3.0 (2.3-4.0)	2.8 (2.2-3.6)	1.4 (1.2-1.5)	1.7 (1.3-2.4)	2.1 (1.5-2.9)	1.3 (1.2-1.4)
Thyroid disease	2.3 (1.6-3.4)	2.1 (1.6-2.8)	1.9 (1.7-2.1)	1.9 (1.3-2.9)	1.9 (1.3-2.6)	1.3 (1.2-1.5)	1.1 (0.7-1.7)	1.6 (1.0-2.5)	1.1 (1.0-1.2)
Anemia	2.2 (1.9-2.6)	2.7 (2.4-2.9)	1.6 (1.5-1.7)	2.1 (1.8-2.4)	1.7 (1.5-1.9)	0.9 (0.9-0.9)	1.3 (1.2-1.5)	1.0 (0.8-1.2)	0.7 (0.7-0.8)
Drug dependence	1.8 (0.8-4.4)	5.1 (3.5-7.5)	3.3 (2.8-3.9)	5.9 (3.7-9.3)	4.9 (3.2-7.4)	3.3 (2.8-3.9)	3.9 (2.4-6.2)	6.1 (4.0-9.2)	4.1 (3.6-4.6)
Mental disorders	3.6 (2.5-5.3)	2.6 (1.9-3.6)	2.4 (2.1-2.7)	3.3 (2.2-4.8)	4.1 (3.0-5.5)	1.9 (1.7-2.2)	2.7 (1.9-3.8)	2.6 (1.7-3.9)	1.8 (1.6-2.0)
Localized comorbidity									
Hemorrhage									
Placental abruption	27.7 (24.2-31.8)	25.2 (22.9-27.9)	10.7 (10.2-11.3)	24.7 (21.6-28.2)	19.7 (17.5-22.2)	3.0 (2.8-3.2)	30.4 (27.4-33.7)	28.4 (25.3-31.8)	5.1 (4.9-5.4)
Placenta previa	17.7 (12.9-24.2)	30.4 (25.6-36.1)	29.8 (27.9-31.8)	16.8 (12.5-22.7)	6.6 (4.5-9.6)	2.1 (1.8-2.5)	3.4 (2.0-5.9)	3.0 (1.5-5.7)	0.8 (0.6-1.0)
Chorioamnionitis	3.8 (3.3-4.5)	1.5 (1.3-1.8)	0.9 (0.9-1.0)	24.0 (21.5-26.8)	12.4 (11.2-13.6)	2.0 (1.9-2.1)	9.6 (8.7-10.6)	4.5 (3.9-5.2)	1.0 (1.0-1.1)
Amniotic sac									
Polyhydramnios	3.1 (2.0-4.7)	5.1 (4.0-6.5)	3.6 (3.3-4.0)	1.7 (1.0-3.0)	2.4 (1.6-3.5)	1.3 (1.1-1.5)	2.1 (1.4-3.1)	4.1 (3.0-5.6)	1.6 (1.5-1.8)
Oligohydramnios	10.2 (8.4-12.4)	13.0 (11.5-14.8)	8.6 (8.1-9.1)	15.1 (12.8-17.8)	12.6 (10.9-14.6)	2.2 (2.0-2.4)	2.6 (2.0-3.5)	1.7 (1.1-2.5)	0.8 (0.7-0.9)
Cervical incompetence	68.6 (54.6-86.1)	13.6 (9.8-18.9)	7.1 (6.1-8.4)	123 (103-146)	33.4 (26.1-42.7)	6.1 (5.1-7.2)	159 (139-183)	32.4 (24.5-42.9)	6.9 (5.9-7.9)
Structural abnormality	6.8 (5.5-8.3)	6.3 (5.4-7.3)	3.5 (3.2-3.7)	4.2 (3.3-5.2)	4.2 (3.4-5.1)	2.0 (1.9-2.2)	2.5 (2.0-3.2)	2.2 (1.6-2.9)	0.8 (0.7-0.9)
Previous cesarean delivery	1.2 (1.0-1.4)	1.3 (1.1-1.4)	2.0 (2.0-2.1)	1.1 (0.9-1.3)	0.9 (0.7-1.0)	0.8 (0.7-0.8)	0.4 (0.3-0.5)	0.5 (0.4-0.6)	0.4 (0.4-0.4)
Fetal anomaly	159 (123-204)	16.3 (10.2-26.2)	12.4 (10.1-15.3)	3.2 (0.8-12.8)	7.0 (3.1-15.6)	2.3 (1.5-3.5)	142 (115-176)	8.7 (3.9-19.6)	4.1 (3.1-5.5)

* Odds ratio (95% confidence interval) adjusted for maternal age, grand multiparity, and period (rounded to the first decimal to conserve space)
† Preterm premature rupture of membranes
‡ Spontaneous preterm labour before 37 weeks of gestation with intact membranes

has demonstrated associations between depression and medically indicated PTB at <35 weeks, and between anxiety/alcohol use and spontaneous PTB. Our findings confirm an association between infections and all PTB clinical subtypes at all gestational ages. Prevention of PTB would likely benefit from greater attention to drug dependence and mental disorders given the probable underreporting of these causes in pregnancy (with consequently underestimated attributable fractions), since the benefits of treatment for infection are uncertain.

Remaining causes of systemic comorbidity including cardiovascular disease, edema/renal disease, thyroid disease, and anemia were mainly associated with medically indicated PTB at all gestational ages, as observed elsewhere. Thyroid disease and anemia, however, were mainly associated with PPROM at earlier gestational ages (<32 weeks). For spontaneous PTB, associations were strong with cardiovascular disease at 28-31 weeks, and weak with thyroid disease at 28-31 weeks and anemia at <28 weeks. Anemia has been associated with greater odds of spontaneous PTB but not PPROM and medically indicated PTB. Other researchers have observed that thyroid disorders were only associated with PPROM, whereas we found that thyroid disorders were also associated with medically indicated and spontaneous PTBs at 28-31 weeks. More research is needed to better understand the relation between these maternal comorbidities and PTB, especially anemia which was associated with large attributable fractions for PPROM and medically indicated PTB.

Localized comorbidities in general were associated with PTB, especially medically indicated PTB and PPROM at most gestational ages. Several studies have found that overall PTB was associated with cervical incompetence, fetal anomalies, placenta previa, placental abruption, and oligohydramnios, and fewer have, like ours, demonstrated stronger associations at lower gestational ages for placental abruption, chorioamnionitis, oligohydramnios, cervical incompetence, and fetal factors. Spontaneous PTB has been linked with placenta previa and abruption, while polyhydramnios/oligohydramnios were associated with both PPROM and spontaneous PTB. Interestingly, we found that previous cesarean delivery was associated with lower odds of PPROM and spontaneous PTB.

This study was subject to limitations. Some comorbidities could not be examined in finer categories due to limited ICD code availability or sample size (eg, cardiovascular and thyroid disease), and underreporting of certain comorbidities (eg, drug dependence and mental disorders) is probable. Though hospital data are routinely used for surveillance in Québec, validation of diagnostic (or procedure) codes has not been undertaken, and results should be interpreted in light of probable non-differential misclassification which may have attenuated associations. Though spontaneous PTBs that resulted in cesarean deliveries could not be identified and were classified as medically indicated, our results are consistent with other studies indicating greater frequencies of spontaneous PTB compared with other clinical subtypes, which suggests that misclassifications are

Table 5. Population attributable fractions for maternal systemic/localized comorbidity and preterm birth according to clinical subtype and gestational age*

	Medically indicated			PPROM*			Spontaneous†		
	<28 wk	28-31 wk	32-36 wk	<28 wk	28-31 wk	32-36 wk	<28 wk	28-31 wk	32-36 wk
Systemic comorbidity									
Hypertension									
Preeclampsia/eclampsia	21.6	38.0	21.9	-1.2	-0.7	-0.2	-1.2	-0.6	0.2
Pre-existing	0.8	1.1	1.6	0	0.1	0.1	0	0	-0.1
Gestational	0.2	1.8	1.8	-4.5	-0.8	-0.4	-2.4	-4.3	-0.3
Cardiovascular disease	0.4	0.8	0.6	0.1	0.5	0.1	0.2	0.3	0.02
Diabetes									
Pre-existing	0.3	2.7	3.4	0.1	3.0	1.2	-0.1	1.4	0.5
Gestational	-1.9	0.6	2.6	-1.5	1.0	1.8	-3.0	-0.8	1.1
Edema/renal disease	1.6	2.9	1.7	0.1	0.2	0.02	0.2	-0.03	0.03
Genitourinary infection	1.7	3.7	1.9	1.7	3.6	0.5	0.7	-0.02	-0.05
General infection	1.8	1.4	1.4	1.6	2.1	0.4	0.9	1.2	0.3
Thyroid disease	1.4	1.0	0.9	0.6	0.8	0.3	0.1	0.5	0.1
Anemia	11.9	14.8	5.9	6.7	6.6	-1.1	3.3	-0.1	-2.9
Drug dependence	0.03	0.9	0.5	0.8	0.9	0.5	0.7	1.1	0.7
Mental disorders	1.7	0.9	0.8	0.9	1.8	0.5	1.0	0.8	0.4
Localized comorbidity									
Hemorrhage									
Placental abruption	23.5	21.0	9.8	14.1	17.9	2.4	25.2	22.9	4.5
Placenta previa	3.3	5.9	6.6	2.2	1.2	0.3	0.5	0.4	-0.1
Chorioamnionitis	10.5	2.0	-0.3	31.4	30.7	3.8	25.1	11.7	0.04
Amniotic sac									
Polyhydramnios	1.3	2.3	1.5	0.3	0.8	0.2	0.7	1.8	0.4
Oligohydramnios	8.7	10.3	7.0	8.2	10.2	1.2	1.6	0.6	-0.2
Cervical incompetence	7.2	1.4	0.7	8.1	3.5	0.5	14.6	3.1	0.6
Structural abnormality	41.9	36.0	17.3	14.9	22.9	7.0	11.8	6.2	-1.2
Previous cesarean delivery	1.4	2.3	8.7	0.4	-1.3	-2.3	-5.7	-4.7	-5.4
Fetal anomaly	6.5	0.7	0.5	0.1	0.3	0.1	5.7	0.3	0.1

* Preterm premature rupture of membranes
† Spontaneous preterm labour before 37 gestational weeks with intact membranes

relatively infrequent. We did not have detailed data on parity or other individual maternal characteristics such as income, race, smoking, genetics, or infertility treatment that are known to be associated with PTB. These characteristics have complex relationships with PTB, and may be upstream risk factors influencing PTB at least partly through maternal comorbidities. Generalizability of findings to settings without public health insurance is unclear.

Conclusions

This study demonstrated that the associations between maternal comorbidities and PTB may differ by clinical subtype and gestational age. Preventive strategies to reduce PTB should target major systemic and localized co-morbidities that account for large proportions of PTBs, especially maternal hypertension, anemia, placental abruption, and structural abnormalities. Better clinical management of these maternal comorbidities may be helpful, but such measures should take into account variation in associations by clinical subtype and gestational age.

Opitz Trigonocephaly Syndrome Presenting with Sudden Unexplained Death in the Operating Room

Laura Travan, Vanna Pecile, Mariacristina Fertz, Antonella Fabretto, Pierpaolo Brovedani, Sergio Demarini, John M. Opitz

Abstract

Introduction: Opitz trigonocephaly C syndrome (OTCS) is a rare malformation syndrome with the following features: synostosis of metopic suture, craniofacial abnormalities, severe mental retardation and a multitude of pathological findings affecting almost every organ system. OTCS is associated with a high mortality rate. Case presentation: We describe the case of a Caucasian male baby who died at five months of age during surgical correction of the craniofacial anomaly.

Conclusion: As previously reported, OTCS may have an increased mortality rate during craniofacial surgery. Careful evaluation of surgery risk-benefit ratio is warranted in such patients.

Introduction

Opitz trigonocephaly C syndrome (OTCS) is a rare and heterogeneous genetic disorder characterized by synostosis of metopic suture, dysmorphic facial features, variable mental retardation and other congenital somatic and cerebral anomalies. Morbidity and mortality are very high. Fewer than 60 cases have been reported in the literature, mostly as single case reports or small series. We describe a white male baby who died at five months of age during surgery performed to correct the craniofacial anomaly.

Case Presentation

Our patient was a Caucasian baby, born to nonconsanguineous parents at 39 weeks of gestational age. This was the first pregnancy of a 30-year-old mother with a bicornuate uterus. Pregnancy was complicated by early intrauterine growth retardation; antenatal ultrasound assessment was otherwise reported as normal. Labor and delivery were spontaneous. The Apgar score was 9 and 10, respectively at one and five minutes. Birth weight was 2470 g (< 3rd percentile, small for gestational age), length was 46.7 cm (3rd to 10th percentile), head circumference 33.1 cm (10th percentile).

Authors Travan, Fertz, Brovedani and Demarini are with the NICU, Pecile and Fabretto are with the Department of Genetics, Institute for Maternal and Child Health, Trieste, Italy. Opitz is with the Department of Pediatrics, Human Genetics, Obstetrics and Gynecology, University of Utah, Salt Lake City. Reprinted from BioMed Central, Journal of Medical Case Reports,

At birth there was a marked trigonocephaly and other dysmorphic craniofacial features: micrognathia, upslanting eyelids, hypotelorism, depressed nasal bridge, low set ears. Cardiac and renal ultrasounds were normal. Computed tomography confirmed the early closure of metopic suture (Figure 1). Initially the baby was fed by nasogastric tube. At discharge after one week, he was fed completely by bottle.

At 40 wks post-conceptional age brain MRI showed a small area of hyper-intensity under the posterior horn of the left ventricle (interpreted as calcification of a periventricular hemorrhage) and a diffused alteration of white periventricular matter (Figure 2).

An auditory brain stem response (ABR) test performed at 44 weeks revealed an absent pattern on the left ear.

Clinical evaluation during the first four months of life did not show an evident psychomotor delay; however fidgety activity seemed absent.

Chromosome analysis showed a normal 46 XY karyotype. We also performed single-nucleotide polymorphism (SNP) array without any significant finding.

The baby died unexpectedly at five months of age during surgery performed to correct the craniofacial anomaly. Autopsy did not add anything to the clinical picture: specifically, there were no additional anomalies except for a double left renal artery. Some micro calcifications were found around brain vessels.

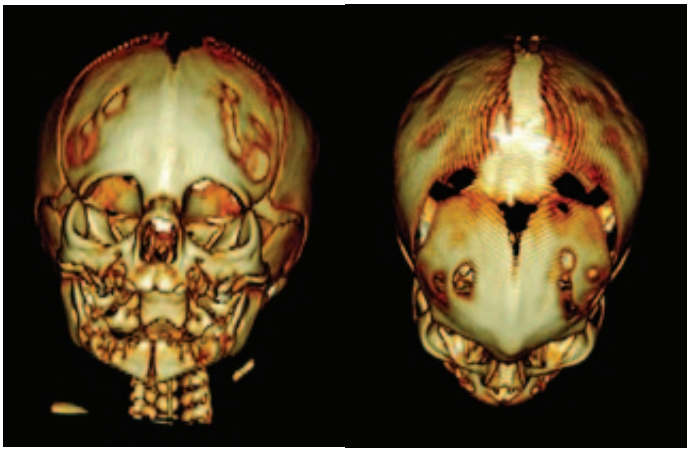


Figure 1. Three-dimensional computerized tomography. See the fusion of metopic suture.

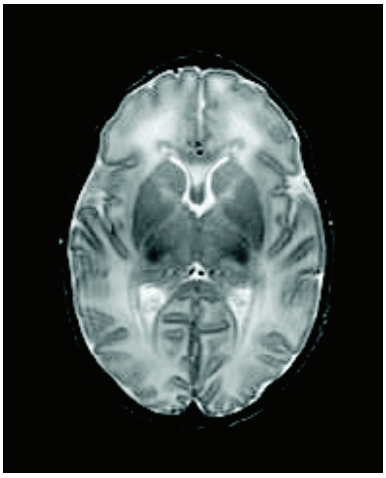


Figure 2. Cerebral MRI (whitened T2 sequences), showing diffuse white matter periventricular hyperintensity (hypointensity in T1 sequences).

Discussion

OTCS, first described in 1969 by Opitz[1] is characterized by trigonocephaly, mental retardation, short neck, typical facial appearance, joint and limb anomalies, up-slanting palpebral fissures, epicanthal folds, a broad depressed nasal bridge, small nose, abnormally low-set ears, and central nervous system and visceral anomalies, such as renal and heart anomalies.

OTCS is a heterogeneous genetic disorder which occurs sporadically, although familial cases have also been reported.[2,3]

A very high mortality rate has been described: almost 50% of patients with OTCS die within the first year of life.[3] Some patients, however, may have a good quality of life: Patient 2 of Lalatta[4] has normal IQ. She underwent multiple craniosynostectomies but she did well at the University and was also able to play the piano.

Our patient had many of the clinical and anatomic findings typical of OTCS: the dysmorphic face, white matter alteration, as described by Lalatta and by Azimi,[4,5] cerebral hemorrhage[3] and hearing loss as reported by Nacarkucuk et al and Zampino et al.[6,7]

We did not find any genetic abnormality either in the karyotype or in the region of CD96 gene, as recently described by Kaname.[8]

To the best of our knowledge this is the second case after patient 1 reported by Opitz who died after surgery for craniosynostosis repair. That patient, after the skull reconstruction, developed hematuria, cardiac arrhythmia and severe acidosis requiring cardiopulmonary resuscitation. Twenty minutes later, he developed a severe intra-vascular coagulation. After the autopsy, experts in genetics, immunology and rheumatology concluded that patient 1 of Optiz had a possible connective tissue abnormality and increased vascular fragility that started the catastrophic cascade that led to death.

Our patient died under the same circumstances as patient 1 described by Optiz. Autopsy did not find vascular malformation or connective tissue anomalies that could have explained death during surgery. However, as in Opitz's patient 1 the cause of death was an unexpected massive bleeding.

Conclusion

OTCS is a complex and heterogeneous condition that is still under-recognized and under-diagnosed. The fact that two children died as a consequence of craniofacial surgery may have clinical implications: diagnosing OTCS in trigonocephalic patients before surgery, may allow a better evaluation of risks and benefits of craniosynostosis repair.

References

1 Opitz JM, Johnson RC, Mc Creadie SR, Smith DW: The C syndrome of multiple congenital anomalies. In Birth Defects, Original Article Series. Volume 2. Edited by Bergsma D. New York: The National Foundation; 1969:161-166.

2 Antley RM, Hwang DS, Theopold W: Further delineation of the C (trigonocephaly) syndrome. Am J Med Genet 1981, 9:147-163. PubMed Abstract | Publisher Full Text

3 Opitz JM, Putnam AR, Comstock JM, Chin S, Byrne JL, Kennedy A, Frikke MJ, Bernard C, Albrecht S, Der Kaloustian V, Szakacs JG: Mortality and pathological findings in C (Opitz trigonocephaly) syndrome. Fetal Pediatr Pathol 2006, 25:211-231. PubMed Abstract | Publisher Full Text

4 Lalatta F, Clerici Bagozzi D, Salmoiraghi MG, Tagliabue P, Tischer C, Zollino M, Di Rocco C, Neri G, Opitz JM: "C" trigonocephaly syndrome: clinical variability and possibility of surgical treatment. Am J Med Genet 1990, 37:451-456. PubMed Abstract | Publisher Full Text

5 Azimi C, Kennedy SJ, Chitayat D, Chakraborty P, Clarke JT, Forrest C, Teebi AS: Clinical and genetic aspects of trigonocephaly: a study of 25 cases. Am J Med Genet A 2003, 117A:127-135. PubMed Abstract | Publisher Full Text

6 Nacarküçük E, Okan M, Sarimehmet H, Ozer T: Opitz trigonocephaly C syndrome associated with hearing loss. Pediatr Int 2003, 45:731-733. PubMed Abstract | Publisher Full Text

7 Zampino G, Di Rocco C, Butera G: Opitz C trigonocephaly syndrome and midline brain anomalies. Am J Med Genet 1997, 73:484-488. PubMed Abstract | Publisher Full Text

8 Kaname T, Yanagi K, Chinen Y, Makita Y, Okamoto N, Maehara H, Owan I, Kanaya F, Kubota Y, Oike Y, Yamamoto T, Kurosawa K, Fukushima Y, Bohring A, Opitz JM, Yoshiura K, Niikawa N, Naritomi K: Mutations in CD96, a Member of the Immunoglobulin Superfamily, Cause a Form of the C (Opitz Trigonocephaly) Syndrome. Am J Med Genet A 2007, 81:835-841.

Community Analysis of Bacteria Colonizing Intestinal Tissue of Neonates with Necrotizing Enterocolitis

Birgitte Smith, Susan Bodé, Bodil L. Petersen, Tim K. Jensen, Christian Pipper, Julie Kloppenborg, Mette Boyé, Karen A. Krogfelt, Lars Mølbak

Abstract

Background: Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in newborn neonates. Bacteria are believed to be important in the pathogenesis of NEC but bacterial characterization has only been done on human fecal samples and experimental animal studies. The aim of this study was to investigate the microbial composition and the relative number of bacteria in inflamed intestinal tissue surgically removed from neonates diagnosed with NEC (n = 24). The bacterial populations in the specimens were characterized by laser capture microdissection and subsequent sequencing combined with fluorescent in situ hybridization (FISH), using bacterial rRNA-targeting oligonucleotide probes.

Results: Bacteria were detected in 22 of the 24 specimens, 71% had moderate to high densities of bacteria. The phyla detected by 16S rRNA gene sequencing were: Proteobacteria (49.0%), Firmicutes (30.4%), Actinobacteria (17.1%) and Bacteroidetes (3.6%). A major detected class of the phylum Proteobacteria belonged to δ-proteobacteria. Surprisingly, Clostridium species were only detected in 4 of the specimens by FISH, but two of these specimens exhibited histological pneumatosis intestinalis and both specimens had a moderate to a high density of C. butyricum and C. parputrificum detected by using species specific FISH probes. A 16S rRNA gene sequence tag similar to Ralstonia species was detected in most of the neonatal tissues and members of this genus have been reported to be opportunistic pathogens but their role in NEC has still to be clarified.

Conclusion: In this study, in situ identification and community analysis of bacteria found in tissue specimens from neonates with NEC, were analyzed for the first time. Although a large variability of bacteria was found in most of the analyzed specimens, no single or combination of known potential pathogenic bacteria species was dominating the samples suggestive NEC as non-infectious syndrome. However there was a significant correlation between the presence of C. butyricum & C. parputrificum and histological pneumatosis intestinalis. Finally this study emphasizes the possibility to examine the microbial composition directly on excised human tissues to avoid biases from fecal samples or culturing.

Smith and Krogfelt are with the Statens Serum Institut; Jensen, Boyé and Mølbak are with the National Veterinary Institut; Bodé is with the Neonatel Department, Rigshospitalet; Petersen is with the Pathologic Institut, Ringshospitalet; Pipper is with the Faculty of Life Sciences, University of Copenhagen, Denmark. For the specific methodology of bacteria analysis, as well as technical information on bacterial analysis, please visit BioMed Central and type the full title of the article.

Background

Necrotizing enterocolitis (NEC) is an acute inflammatory disease that affect the intestinal tract of neonates. It remains one of the most common gastrointestinal emergencies in newborn neonates. Onset of NEC occurs within the first three months of life and neonates who are of low birth weight and under 28 week gestation are the most susceptible. The ileum and the proximal colon are the frequently affected although any segments of the gastrointestinal tract can be involved. The course of NEC is multifactorial and the most important elements is prematurity, enteral feeding, bacterial colonization and an inappropriate pro-inflammatory response. It is believed that immaturities of these functions due to age predispose the premature infant to intestinal injury and inappropriate responses to injury.

The bacterial role in NEC still needs to be clarified. Suggestions such as an imbalance of the gastrointestinal microbiota, overgrowth of potential pathogenic bacteria, and ischemia causing mucosal lesions that gives the bacteria systemic access have been followed but so far no specific pathogens have been identified. Correlation of NEC with bacteria has been suggested by analyzing fecal samples, however, this analysis of fecal samples is often far from the affected site and may not be representative. The use of formalin-fixed paraffin-embedded tissue samples give an opportunity to investigate a unique stock of archival disease-specific material. The method is challenged to access the limited and fragmented bacterial DNA present in the tissue. To characterize the bacterial population in the formalin-fixed NEC tissue laser-capture-micro-dissection (LCM) combined with fluorescence in situ hybridization (FISH), using a bacteria ribosomal RNA (rRNA)-targeting oligonucleotide probe, was used. The bacterial 16S rRNA gene was PCR amplified and sequenced by pyrosequencing. The bacterial distribution was verified and visualized within the lumen and mucus of the intestinal tissues with fluorescent in situ hybridization (FISH) with group and species specific probes targeting individual microbial cells. The aim of this study was to investigate the microbial composition and the relative number of bacteria in affected intestinal tissue samples surgically removed from

neonates diagnosed with NEC and to relate this with the patient data such as antibiotic treatment.

Result

Twenty-four neonates with different gestational age were enrolled in this study because they all had intestinal tissues surgically removed. Sections from the small intestine were removed in 15 neonates, from both the small intestine and the large intestine for 6 neonates, and only from the large intestine in 3 neonates. Eight of the 24 neonates died but there was no correlation between NEC-score and death. In summary, three neonates were full-term; two of these had heart disease and one feto-maternal bleeding. Three neonates were small for gestation. Nine neonates had pneumatosis intestinalis and 11 neonates had free air in the stomach as observed by x-ray. For 21 of the neonates information regarding enteral feeding was available. Mothers' breast milk or bank milk was introduced between day 1 and day 5, and supported with either 5% or 10% glucose. If the neonate was not able to reach the level of enteral feeding after day 5, support by parenteral nutrition was initiated; median 8 day SD 8.9 (n = 13). All neonates were treated with antibiotics for different time spans before the surgery. The standard treatment for children <7 days was iv injection of ampicillin, gentamicin and metronidazole; standard treatment for children >7 days was iv injection of cefuroxim, gentamicin and metronidazole. The antibiotic treatment will influence the general bacterial colonization but to the best of our knowledge there is no study about how it influences the bacterial composition and load of the NEC affected intestinal tissues in humans.

Detection of bacteria in tissue samples by fluorescent in situ hybridization (FISH): Bacteria were detected in 22 of the 24 examined specimens, and of these 71% had a moderate to a high density of bacteria. In 17 (70%) of the 24 specimens Enterobacterieceae were detected by a group specific FISH probe (Figure 1a) and a significant correlation was seen between this hybridization and the general bacterial probe based on the scoring system ($p = 0.02$).

In 4 specimens Clostridium species were detected by using a mixed Clostridium spp. probe targeting C. perfringens, C. difficile, C. butyricum and C. paraputrificum. Two of those specimens were by histological examinations observed to exhibit pneumatosis intestinalis and a significant correlation ($p < 0.05$) was found with the presence of the Clostridium spp even though the sample numbers are very small. In these two specimens C. butyricum and C. parputrificum were detected in high densities, C. perfringens was detected in one of the specimens whereas C. difficile was not detected in any of the slides. Nevertheless, no correlation was found between diagnosed neonates with pneumatosis intestinalis by x-rays and the specimens colonised with Clostridium spp. Finally, there was no correlation between the presence of bacteria by FISH and NEC score, type of nutrition, antibiotic usage, or death.

Characterization of bacterial composition in tissues removed surgically from neonates with NEC: Eight neonates were selected for further characterization of the bacteria located in the lumen and mucus layer of the inflamed tissues. Four of these neonates had received antibiotics for less than two days while the other four neonates had received antibiotics more than 10 days. A 16S rRNA gene library from each specimen was constructed. The individual tags (N = 364) were assigned to the closest mono-Phylogenetic group in order to obtain a Phylogenetic classification. In total, 41 consensus tags were identified. The frequencies of 16S rRNA gene sequences from all specimens were grouped according to their overall phylogeny and the phyla were Proteobacteria (49.0%), Firmicutes (30.4%), Actinobacteria (17.1%) and Bacteroidetes (3.6%). δ-proteobacteria was the major detected class of the phylum Proteobacteria. The Shannon diversity index was calculated based on the total library cloning sequences for each neonate. The Shannon diversity index revealed two distinct groups. The neonates p3, p6, p17 and p24 clustered together with a low Shannon diversity index and were dominated by more than 50% of one genera of either Escherichia spp or Enterococcus spp. In neonate p8, p20, p22 and p27, multiple bacterial genera were present with no single genus contributing with more than 30% of total bacteria (Figure 3). The differences in diversity could not be explained or correlated to clinical characteristics like NEC score, number of days with antibiotics, time of surgery, or gestational age.

The bacteria associated with the tissue in the individually neonates have the potential to reveal bacterial pathogens related to the pathogenesis of NEC. In the δ-proteobacteria group Escherichia/Shigella genera dominated with a frequency of 45% out of all δ-proteobacteria and were present in 5 of the 8 neonates with an average frequency of 24% (±36%). The Enterobacteriaceae group consisted of virtually one tag but it was similar to genera of Citrobacter, Enterobacter (Klebsiella) and Erwinia and was detected in 4 of the neonates. The taxonomic class Clostridia contained 10 different tags belonging to a variety of different genera, the two most prominent being Clostridium and Anaerococcus detected in four and three neonates, respectively. A tag matching the potential pathogen Finegoldia was found twice in two different neonates. One of the specimen characterized histologically exhibiting pneumatosis intestinalis was also observed to include the genus Clostridium. The most prevalent tag belonged to Ralstonia being present in 7 out of 8 neonates, with an average of 9% (±5%). R. detusculanense, R. pickettii and R. insidiosa were revealed with more than 99% similarity.

Discussion

The establishment of the microbiota early in life and the symbiosis with the human gastrointestinal tract has important consequences for human health and physiology. The interactions can have beneficial nutritional, immunological, and developmental effect or even pathogenic effects for the host. In this study the bacterial composition has been characterized for the first time directly on tissue samples from neonates with fulminate NEC. The specimens were collected from a single neonatal hospital unit with a consistent treatment and a similar environment over a period of 6 years. Even though, the study is naturally limited in number of patients this is the first description done in situ and not on surrogates in the form of fecal samples or experimental animals. FISH combined with laser capture microdissection ensured that only bacterial DNA from lumen and mucus was sampled and that no contaminations from the surrounding material or environment could occur. Furthermore, cloning and pyrosequencing used here has previously been shown to be efficient for the characterization of the intestinal microbiota. The presence of bacterial colonization in the small intestine and large intestine was documented and visualized by a general bacterial FISH probe and this method has previously been used to reveal bacterial spatial distribution in the intestine of experimentally colonized animals. In general, tissues with

disease were heavily colonized by bacteria but we could not correlate the bacterial colonization to NEC-score, days with antibiotics or type of antibiotics nor type of nutrition. This colonization might be because of resistance to or wrong choice of antibiotics or because the antibiotics do not reaches the bacteria because of stop of blood supply. It has recently been shown that antibiotics do not clear gut microbiota in neonates but reduce the diversity of bacterial species. We were therefore interested in finding which bacterial groups that colonized the surgical removed tissues.

The dominance of Proteobacteria could explain the susceptibility of preterm neonates to NEC or as a course of the antibiotic treatments that all neonates received in this study. From the 16S rRNA gene library the δ-proteobacteria was dominated by Escherichia-like organisms and to a lesser extent with Enterobacteria. It has previously been described by Wang et al that δ-proteobacteria dominated the bacterial composition in fecal samples from neonates with NEC but they also found a lower Shannon diversity for NEC patients compared to the control group. This could have been due to the antibiotic treatments. In this study there was no difference in the bacterial composition or Shannon diversity index after long term antibiotic administration (>10 days) compared to less than two days of antibiotic treatments. Furthermore, no difference in bacterial composition was found regardless of the type of antibiotics used for treatment, in contrast to the antibiotic selection seen by Gewolb et al. In general, a very high variation was observed in the bacterial composition of the specimens as well as different diversity indexes and if it had been possible to analyze more samples it would perhaps had been possible to correlate the different variables with the colonization. The colonization of the preterm intestine could have been speculated to be very homogeneous since the neonates were at the same hospital unit (environment) even though Palmer et al, showed that the composition and temporal patterns of the microbial communities in stool samples from term babies varied widely from baby to baby for their first year of life. However the composition of the intestinal microbiota in healthy pre- or term neonates present in the small intestine is not yet known due to the lack of samples.

Previous studies based on culture techniques have focused on single organisms as predisposing for NEC. Clostridium sp. and especially C. perfringens due to the fermentation of carbonhydrate substrates to hydrogen gas has been suspected. Very few neonates were colonised with Clostridium spp in this study but there was a significant correlation between a positive signal from the probes for Clostridium spp and pneumatosis intestinalis as verified by histopathology. It was specified that this Clostridium colonization was due to C. butyricum and C. parputrificum. A previous study has shown that these two lactose fermenting clostridium species can induce cecal NEC-like lesions in a gnotobiotic quail model and these lesions may be linked to short-chain fatty acid production. There was no correlation with pneumatosis intestinalis found by X-ray and Clostridium spp. and maybe pneumatosis intestinalis described on X-ray is different from the pneumatosis intestinalis described on tissue surgically removed. It seems therefore like C. butyricum and C. parputrificum are responsible for pneumatosis intestinalis when verified by histopathology, but because of the low frequency of Clostridium spp in our samples we believe that the pneumatosis intestinalis is a secondary effect of NEC and that these Clostridia are not the primary pathogens of NEC.

Ralstonia and Propionibacteria were detected in most of the specimens where laser capture microdissection was used. Ralstonia spp is a new genus including former members of Burkholderia spp. (Burkholderia picketti and Burkholderia solanacearum). Burkholderia spp has been described in children suffering of NEC and Ralstonia picketti has been reported to be a persistent Gram-negative nosocomial infectious organism. R. picketti can cause harmful infections and is mainly considered as an opportunistic pathogen of little clinical significance but R. pickettii isolates have been reported to be resistant or had decreased susceptibility to aminopenicillins, ureidopenicillins, restricted-spectrum cephalosporins, ceftazidime, and aztreonam.[31] The major conditions associated with R. picketti infection are bacteremia/septicemia and respiratory infections/ pneumonia. The bacteria has been isolated from patients diagnosed with Crohn's disease and cystic fibrosis from multiple sides including sputum, blood, wound infections, urine, ear swabs and nose swabs, and cerebrospinal fluid. Diversity in an ecosystem is important in establishing and preventing dominance by a single pathogenic species. In the samples with Ralstonia spp there were a relatively high diversity of different bacteria and if Ralstonia had had a primary effect we would expect a higher dominance of Ralstonia and a lower bacterial diversity. Therefore, we cannot conclude from this study whether Ralstonia has any effects, on the development of NEC and further studies have to elucidate this or/and if Ralstonia sp was present because of a higher resistance to the antibiotic treatment.

Propionibacterium spp have previously been described in fecal specimens. The presence of this genus has been reported to be the second largest on the adult body and predominant in sebaceous sites; it has probably been found in neonates' small intestine because of skin contact between the mother and the neonate. The reason why it has not been found in higher densities in many other gastrointestinal studies of the microbiota is a general underestimation of Actinobacteria created by the choice of primers and a dilution effect in feces.

Conclusion

This study emphasized the possibility to examine the microbial composition directly on excised human tissues to avoid biases from fecal samples or culturing. Although a large variability of bacteria was found in most of the analyzed specimens, no single or combination of known potential pathogenic bacterial species was dominating the samples suggestive NEC as non-infectious syndrome. However there was a general high presence of Proteobacteria and Ralstonia sp which may be due to the antibiotic treatment that all neonates received in this study and a significant correlation between the finding of C. butyricum & C. paraputrificum and the few histological pneumatosis intestinalis found in this study.

Maternal Markers for Detecting Early-onset Neonatal Infection and Chorioamnionitis in Cases of PROM

Thomas Popowski, François Goffinet, Françoise Maillard, Thomas Schmitz, Sandrine Leroy, Gilles Kayem

Abstract

Background: Accurate prediction of infection, including maternal chorioamnionitis and early-onset neonatal infection, remains a critical challenge in cases of preterm rupture of membranes and may influence obstetrical management. The aim of our study was to investigate the predictive value for early-onset neonatal infection and maternal histological and clinical chorioamnionitis of maternal biological markers in routine use at or after 34 weeks of gestation in women with premature rupture of membranes.

Methods: We conducted a two-center prospective study of all women admitted for premature rupture of membranes at or after 34 weeks of gestation. The association of C-reactive protein, white blood cell count, vaginal sample bacteriological results, and a prediction model at admission, for early-onset neonatal infection and maternal chorioamnionitis were analyzed by comparing areas under the receiver operating characteristic curves and specificity.

Results: The study included 399 women. In all, 4.3% of the newborns had an early-onset neonatal infection and 5.3% of the women had clinical chorioamnionitis. Histological chorioamnionitis was detected on 10.8% of 297 placentas tested. White blood cell counts and C-reactive protein concentrations were significantly associated with early-onset neonatal infection and included in a prediction model. The area under the receiver operating characteristic curve of this model was 0.82 (95% CI [0.72, 0.92]) and of C-reactive protein, 0.80 (95% CI [0.68, 0.92]) ($p = 1.0$). Specificity was significantly higher for C-reactive protein than for the prediction model (48% and 43% respectively, $p < 0.05$). C-reactive protein was associated with clinical and histological chorioamnionitis, with areas under the receiver operating characteristic curve of 0.61 (95% CI [0.48, 0.74]) and 0.62 (95% CI [0.47, 0.74]), respectively.

Conclusions: The concentration of C-reactive protein at admission for premature rupture of membranes is the most accurate infectious marker for prediction of early-onset neonatal infection in routine use with a sensitivity > 90%. A useful next step would be a randomized prospective study of management strategy comparing CRP at admission with active management to assess whether this more individualized care is a safe alternative strategy in women with premature rupture of membranes at or after 34 weeks.

Background

Premature rupture of membranes (PROM) occurs in 8% of pregnancies, 3% before and 5% after 37 weeks of gestation. Accurate prediction of infection, including maternal chorioamnionitis and early-onset neonatal infection (EONI), remains a critical challenge in these cases. EONI, generally acquired prenatally in pregnancies with PROM, is the most serious consequence of maternal infection and is associated with increased neonatal morbidity and mortality.

Numerous studies in recent years have failed to identify a satisfactory prenatal marker of infection to predict maternal chorioamnionitis and EONI. For these reasons, guidelines for the management of women with PROM do not take prenatal markers of infection into account but are usually based on the gestational age at which PROM occurs.

Many obstetricians therefore consider active management, usually defined as the induction of labor in the 12 hours after PROM, as the best strategy for preventing chorioamnionitis and EONI in cases of PROM at or after 34 weeks. Although a few studies have found systematic active management at or after 34 weeks to be advantageous for infectious outcomes, the choice between active or expectant management at 34 to 36 weeks continues to be controversial because this strategy may increase early delivery, which has been associated with increased neonatal morbidity, behavioral disorders, and healthcare costs. Furthermore, regardless of gestational age, induction of labor is sometimes contraindicated for various reasons or situations, including previous cesarean delivery and breech presentation. Active management in these cases would increase the rate of cesarean delivery.

The use of maternal laboratory markers at or after 34 weeks

Authors Popowski, Goffinet, Maillard, Leroy and Kayem are with the Epidemiological Research Unit on Perinatal and Women's Health, INSERM, Paris; Goffinet is also with the Department of Obstetrics and Gynecology, Maternity Port-Rohal, Cochin-Saint Vincent-de-Paul Hospital. Schmitz is with the Department of Obstetrics and Gynecology, Hôpital Robert Debre. Leroy is with the Centre for Statistics in Medicine, University of Oxford, UK; and Kayem is also with the Department of Obstetrics and Gynecology, CHI Creteil, France.

of gestation would help to distinguish women at risk from those who do not require active management, that is, for whom pregnancy can safely be prolonged. Their use might make it possible to await spontaneous labor and vaginal delivery and thus avoid cesareans when induction is contraindicated or unsuccessful but vaginal delivery remains appropriate. Prenatal maternal markers of infection at or after 34 weeks have, however, been insufficiently studied. Those that might be easily used in routine care are serum C-reactive protein (CRP) levels, white blood cell counts (WBC count), and bacterial analysis of vaginal samples. No study has included enough women at or after 34 weeks of gestation to allow the predictive values of these markers to be estimated.

Thus, our main objective was to investigate the predictive value for EONI and maternal histological and clinical chorioamnionitis of CRP, WBC count, and the bacteriological analysis of vaginal samples in routine use at or after 34 weeks of gestation in women with PROM and thus provide a safe alternative to systematic active management.

Methods

This prospective hospital-based study conducted from January 2004 through February 2006 in two French tertiary university referral centers investigated the predictive value of maternal serum and vaginal markers for clinical and histological chorioamnionitis and for EONI. This analysis included all women with PROM at or after 34 weeks of gestation in singleton pregnancies, except those in spontaneous labor at admission and those who gave birth more than 72 hours after admission. These women were excluded to preserve the physiological temporal effect between infectious markers at admission and maternal-fetal infection. Clinical PROM was confirmed by an immunochromatographic dipstick test that uses monoclonal antibodies to detect IGFBP-1 from amniotic fluid.

A standardized form was used to collect data prospectively at admission and thereafter. The attending physician obtained informed consent from all participants. The study was approved by the relevant institutional review board (CPP Ile de France).

Maternal serum samples were taken at admission from all women. Antibiotic treatment was started at admission for women if the third-trimester vaginal sample contained group B Streptococci, and they were not expectantly managed. Antibiotic treatment for all other women began 12 hours after PROM. Amoxicillin was administered except in cases of penicillin allergy, when erythromycin was used instead. Women with a clinical infection at admission were not included in the study. One center used active management, defined by induction of labor or cesarean delivery when induction was contraindicated, in the 12 hours after PROM. The other center used expectant management until 37 weeks, including clinical and laboratory monitoring for infection; it also used expectant management at or after 37 weeks for 48 hours after PROM, to promote spontaneous vaginal delivery when possible and not contraindicated.

Three infectious outcomes were studied: EONI, clinical chorioamnionitis and histological chorioamnionitis.

EONI was defined by the pediatrician as a neonatal infection within 72 hours after birth.[13] Confirmed neonatal infections were defined by a positive blood culture or a positive cerebrospinal fluid culture associated with clinical signs of infection. Probable neonatal infection was defined by clinical signs and a neonatal CRP ≥ 10 mg/L. The final diagnosis of EONI was determined after re-evaluation of the course of laboratory and clinical markers through discharge.

Clinical chorioamnionitis was diagnosed by the attending consultant physician responsible for management from admission through delivery, according to the following criteria: temperature greater than 37.8°C in a gravid patient without evidence of urinary, respiratory, or other localized infection, and any two of these other criteria: either uterine tenderness or foul-smelling amniotic fluid, maternal tachycardia greater than 120 beats per minute, and fetal tachycardia, greater than 160 beats per minute.

Acute histological chorioamnionitis was defined as mild or severe acute inflammatory changes in any relevant tissue sample (amnion, chorion, decidua, umbilical cord, or chorionic plate). For the histological analysis of the placenta, tissue samples from the umbilical cord, chorionic plate, and placental membranes were fixed in 10% neutral buffered formalin and embedded in paraffin. Sections of tissue blocks were stained with hematoxylin and eosin. The pathologists in each center, blinded to the clinical information, performed these examinations and classified acute inflammation as minor, mild, or severe, on the basis of the criteria of Salafia et al. The histological analysis of the placentas was standardized before the beginning of the study by developing a common analysis protocol.

Serum samples taken at admission were used to measure the maternal WBC count (expressed as cells × 10^9/L) and CRP concentration (expressed as mg/L, assessed by immunoturbidimetry). A vaginal swab sample was also cultured to detect the standard pathogenic genital bacteria according to groups II and III of a French classification.

Finally, we collected data about potential confounding factors, including gestational age (in weeks of gestation at admission), antibiotic prescription at admission, and type of management (expectant or active). Active management was defined as systematic delivery at admission, regardless of gestational age, infectious status, or medical history. Expectant management was defined as any other management, including close monitoring for infectious status, especially for women at 34 to 37 weeks of gestation.

We first described the population's characteristics and then analyzed the relations between each of the three infectious outcomes (EONI and clinical and histological chorioamnionitis) and all the predictive factors with a logistic regression model. When the relation between the outcome and continuous variables (CRP and WBC count) was not linear, the variables were transformed into fractional polynomials of the lowest possible degree. Binary variables were coded as follows: abnormal bacterial colonization of the genital tract: yes (1), no (0); antibiotic prescription at admission (1), no antibiotic (0); expectant management (1), and active management (0). Because the model was not convergent when gestational age was a continuous variable, it was dichotomized and coded as it usually is in the literature: (1) for gestational age at admission < 37 weeks gestation, (0) for ≥ 37 weeks. We first selected predictors that were significantly associated with infectious outcome in the univariate analysis, with a p value < 0.05. We then

used a backward stepwise technique, setting a p value > 0.1 for removal from the model and calculating maximum likelihood ratio estimates. The model's ability to discriminate between women with clinical chorioamnionitis, those with histological chorioamnionitis, and those with infants with EONI, compared with those without identified infection, was evaluated by the area under the ROC curve and compared with that of the continuous variables that remained significant in the multivariable analysis. We next transformed the continuous probability of the outcome given by the model into a binary test, choosing a threshold based on the area under the ROC curve that provided the best specificity with at least 90% sensitivity. The performance of the model was determined by calculating sensitivity, specificity, and positive and negative likelihood ratios.

Internal cross-validation of the final model was performed by bootstrapping (100 times), a computer-intensive statistical method and resampling technique based on random samples of observations to estimate error by systematically recomputing the statistics while omitting one observation at a time from the sample set.[19] Using the same pre-specified 90% sensitivity, we dichotomized continuous predictors into binary variables and used a paired χ^2 test to compare their discriminative abilities to those of the model.

Results

During the study period, 627 women were admitted for PROM, 434 of them at or after 34 weeks of gestation (Figure 1). Among the latter, 399 gave birth within 72 hours after admission and were therefore included in the final analysis; 57 (14.3%) had PROM before 37 weeks, 21 (5.3%) had clinical chorioamnionitis, and 32 histological chorioamnionitis (10.8% of the 297 women for whom histological analysis was available). EONI was diagnosed for 17 (4.3%) newborns, including six (35.3%) whose mothers had clinical chorioamnionitis and six (35.3%) whose mothers had histological chorioamnionitis (including one whose mother had both). Mean gestational age at PROM was 38.5 weeks. The characteristics of women and their babies are summarized in Table 1. Overall, 128 women (32.1%) had active management and 271 (67.9%) expectant management, that is, spontaneous deliveries. Among the latter, 211 (78%) took place within 12 hours after admission. Overall, only 57 of the 399 women (14%) were delivered at 34-36 weeks: one had clinical chorioamnionitis, five histological chorioamnionitis, and 2 had a neonate with an EONI. These figures are unfortunately too low to allow a useful statistical analysis for this subgroup.

As expected, spontaneous delivery rates differed according to center. In the center that provided an expectant management policy for 48 hours for women after 37 weeks, 76% of the women gave birth after spontaneous delivery, but only 56% of the women in the center with active management, all of those within the first 12 hours after PROM. Neither EONI (p = 0.12) nor clinical chorioamnionitis (p = 0.30) rates differed between the two centers. Histological chorioamnionitis was observed more often in the center with expectant compared with active management (p = 0.042). The cesarean rates were 18.0% (42/233) and 19.3% (32/166) (p = 0.75).

We observed no confounding factors; in particular, neither gestational age nor type of management was significantly associated with any of the three infectious outcomes. Because the association between WBC count and EONI was not linear (p = 0.004), we studied it by transforming the WBC count into a first-degree fractional polynomial function. In a univariate analysis, WBC count, CRP, and abnormal bacterial colonization of the genital tract were all associated with EONI. In a multivariable analysis after stepwise reduction, WBC count and CRP remained significantly associated with EONI (Table 2). The model fit was good (p = 0.54, Hosmer and Lemeshow test).

Using the coefficients assigned to each predictor in the logistic regression model, we derived a prediction model. Next, we used ROC curves to define the threshold corresponding to our pre-specified sensitivity of at least 90%, which allowed us to transform the continuous probability of EONI into a binary rule. A positive result according to this rule was significantly associated with EONI and had a sensitivity of 94% (77, 99%), a specificity of 43% (38, 47%), a positive likelihood ratio of 1.6 (1.5, 1.9), and a negative likelihood ratio of 0.1 (0.1, 0.7) for the prediction of EONI.

We applied the same pre-specified constraint of a sensitivity of at least 90% to dichotomize the only significant independent predictor, CRP, at a threshold of 5 mg/L. Elevated CRP (≥ 5 mg/L) was then significantly associated with EONI (OR = 14.7 [1.9, 112.2]), with a sensitivity of 94% (73-99), a specificity of 48% (43-53), a positive likelihood ratio of 1.8 (1.6, 2.1), and a negative likelihood ratio of 0.1 (0.0, 0.8) for the prediction of EONI. Lastly, the specificity of CRP alone was significantly higher than that of the prediction model (significant difference of 5% (2, 8%)). Internal cross-validation by bootstrapping showed that dichotomized CRP had a stable predictive value for EONI, with a sensitivity of 94% (82, 100%) and a specificity of 47% (42, 54%). The results for the prediction model were also stable after internal cross-validation, with a sensitivity of 94% (82, 100%) and a specificity of 43% (39, 47%).

CRP was the only factor significantly associated with both clinical and histological chorioamnionitis, and it was linearly associated with these outcomes. Areas under the ROC curves were 0.61 (0.48, 0.74) for clinical and 0.62 (0.47, 0.74) for histological chorioamnionitis. With a cut-off of 5 mg/L, the predictive values of CRP for clinical chorioamnionitis were 71% (48, 89%) (sensitivity) and 47% (42, 52%) (specificity), with positive and negative likelihood ratios of 1.4 (1.0, 1.8) and 0.6 (0.3, 1.2). For histological chorioamnionitis, sensitivity was 59% (41, 76%), and specificity 47% (41, 53%), with positive and negative likelihood ratios of 1.1 (0.8, 1.5) and 0.9 (0.6, 1.4).

Discussion

Of the routinely tested prenatal markers, a CRP concentration of 5 mg/L or more was the most accurate predictor of EONI, with a sensitivity of 94% and a specificity of 47%. Its predictive value was not improved by including it in a prediction model with WBC count. A CRP concentration of 5 mg/L or more was also associated with both clinical and histological chorioamnionitis, but its predictive values for both outcomes were low.

This study is, to our knowledge, the first to investigate prenatal markers in women with PROM at or after 34 weeks of gestation and the largest prospective cohort study of serum infectious markers in PROM. In a retrospective study including 90 women with PROM from 23 to 41 weeks of gestation, Yoon et al did not find that either CRP or WBC count had a high predictive value for histological chorioamnionitis.

The ability to predict EONI is a high priority for physicians

managing women with PROM, because it is the main cause of neonatal morbidity and mortality when PROM occurs at or after 34 weeks. We used a pre-specified high sensitivity because the aim of this study was to select a population with a very low risk of infection, who could safely avoid systematic active management. The negative predictive value of the test is important, regardless of its specificity. In fact, systematic active management is a strategy with 0% specificity; compared to it, a specificity of 47% is a good result, with nearly half the women safely able to avoid systematic active management.

The choice between immediate active or expectant management for women with PROM from 34 to 37 weeks of gestation remains controversial. Guidelines in many countries advocate active management, mainly because of the risk of neonatal infection. This strategy, however, may increase the rate of moderately preterm birth, which is associated with significant neonatal morbidity. It may also increase the cesarean rate among women for whom induction of labor is contraindicated (or unsuccessful). A survey, published in 2004 and including 508 specialists from all 50 of the United States and 13 other countries, showed that the gestational age at which expectant management is rejected in women with preterm PROM varied significantly between respondents: ≥ 34 weeks for 56%, ≥ 35 weeks for 26%, ≥ 36 weeks for 12%, and ≥ 37 weeks for 4.0%.8 Canadian and Australian surveys show a similar lack of medical consensus on management from 34 to 36 weeks.

A recent systematic review included seven randomized controlled trials (690 women) and compared expectant management with early delivery for women with preterm PROM before 37 weeks of gestation (from 25 to 36 weeks). It identified no difference in neonatal sepsis (RR = 1.3 (0.7, 2.5)) or neonatal respiratory distress (RR = 1.0 (0.7, 1.3)) but found that active management significantly reduced suspected neonatal infection (RR = 0.5 (0.3, 0.8)). Moreover, active management seemed to have no effect on clinical chorioamnionitis (RR = 0.4 (0.2, 1.1)) but was associated with a significant increase in the cesarean rate (RR = 1.5 (1.1, 2.1)). The authors concluded that there is insufficient evidence about the benefits and disadvantages of immediate delivery, compared with expectant management, for women with preterm PROM. Dare et al conducted a systematic review that finally included 12 randomized or quasi-randomized trials comparing planned early birth with expectant management in women with PROM at or after 37 weeks of gestation. They concluded that clinical chorioamnionitis was significantly less frequent among women with active management compared with those expectantly managed (RR = 0.7 (0.6, 1.0)), but they observed no difference for neonatal infection (RR = 0.8 (0.6, 1.1)). From our perspective, these findings underline the uncertainty related to PROM management after 34 weeks of gestation and emphasize the need for a predictive strategy to support individualized care based on the individual risk of infection.

Our methodology was selected to reduce bias as much as possible. We analyzed all continuous variables without dichotomizing them to reduce analytic bias. A bootstrap resampling procedure was used to reduce the over-fit of the statistical model on the study population. To prevent any bias related to gestational age, antibiotic prescriptions, or medical management, we adjusted for these factors in our multivariable model. A meaningful temporal relation between infectious markers and the primary outcome was preserved by including only those women who gave birth within 72 hours after admission. The 35 women who delivered more than 72 hours after admission (8.0%) were excluded from the study. This subgroup's characteristics did not differ significantly from those of women finally included in the study and no differences between the groups were observed for EONI (p = 0.69) or for clinical (p = 0.14) or histological chorioamnionitis (p = 0.06). Nonetheless, we did observe a trend to chorioamnionitis in this group with later deliveries, but lack of power prevented a definitive result. Our study shows that a CRP concentration of 5 mg/L or higher predicts EONI with high sensitivity. Measured routinely at admission, CRP may be useful for selecting a population among whom the risk of EONI contraindicates expectant management. In our study, consideration of CRP at admission would have led to active management of 215 women (54%); including 16 whose infants had EONI (94%). The remaining 184 women could have been managed expectantly: most of them (almost 90%) went into labor spontaneously within 72 hours, and only one neonate had EONI. Although the systematic active management in one center might be considered a limitation of this study, our results suggest that maternal serum CRP could be a safe alternative strategy to systematic active management, especially in cases of previous cesarean deliveries, or breech presentation, or in women with PROM near term. Given that the strategy of systematic active management has 0% specificity and in view of our findings, nearly half the cases could safely avoid systematic active management. Our results call for a randomized trial, to compare immediate systematic active management in PROM at and after 34 weeks of gestation with management according to maternal serum CRP.

Conclusions

Maternal serum CRP at admission is the most accurate infectious marker for predicting EONI that is currently in routine use. A useful next step would be a randomized prospective study of management strategy comparing CRP at admission with active management to assess whether this more individualized care is a safe alternative strategy in women with premature rupture of membranes at or after 34 weeks.

GUEST COMMENTARY

Epigenetics: Is There a Skeleton in Your Closet?

Jeffrey Karsdon, MD; Boris M. Petrikovsky, MD, PhD

Lamarckism may not be dead (not to be confused with Marxism which probably is dead). Jean-Baptiste Lamarck (1744–1829) believed an organism can pass on characteristics that it acquired during its lifetime to its offspring. This idea was opposed by Charles Darwin (1809-1882) and his belief in natural selection as the sole mechanism to pass on characteristics to the offspring (not to be confused with those creating today's use of Darwinism, which should be dead).

This is the classic nurture versus nature debate. It may be hard to join together these two opposing ideas of an offspring's characteristics as the result of those acquired during the parent's lifetime (nurture) or selected during the species evolution (nature). However, in the everyday science of life nothing is really black or white, (surely you are thinking of quantum physics), but usually shades of gray.

Epigenetics does seem to fill in this gray area and join together these two opposing ideas. Epigenetics is a new twist on the DNA double helix. Through the epigenetic process heritable characteristics are passed on to the offspring without changes in the DNA sequence but with changes to the gene expression or protein synthesis as a result of environmental influences.

So here we have the offspring's DNA selected by evolution (Darwin's nature) while the DNA is "tweaked" by the parents' characteristics influenced by their environment (Lamarck's nurture). This change can be diet or stress and is time dependent. This change causes primarily DNA methylation occurring in utero modulating the genes regulating protein synthesis, thus affecting the newborn and the disease process throughout its life.[1]

The joining of these two ideas has profound applications for fetal-neonatal medicine. The first epigenetic study was the result of one of the many examples of human resilience that came out of World War II. The Dutch Hunger Winter study[2] showed late effects of early stress.[3,4] Those who were exposed to the famine only during late gestation were born small and continued to be small throughout their lives, with lower rates of obesity as adults than in those born before and after the famine. However, those exposed during early gestation experienced elevated rates of obesity, altered lipid profiles, and cardiovascular disease.

The individual neonate can be affected by diet but also by stress before or during birth.[5] More clinically significant for the neonate is persistent pulmonary hypertension of the newborn, also thought to be an epigenetic response to stress.[6] Other neonatal epigenetic changes have been linked to some forms of cancer later in life.[7]

Jeffrey Karsdon is a Neonatologist and Boris Petrikovsky is Director, Maternal-Fetal Medicine, New York Downtown Hospital.

The epigenetic effects are not limited only to the exposed individuals, the influence of epigenetics is transgenerational. A study of the 19th century Overkalix, Sweden's population[8] showed the sex-specific effect of maternal or paternal famine on future generations, a connection between gender, diet and health...and perhaps a very important lesson even for today's families. In brief, if the grandparents had a good harvest and "pigged-out" their grandchildren had higher mortality rates. The possible mechanism is that environmental information was being imprinted on the egg and sperm at the time of their formation.

Another sex-specific epigenetic pathology is genomic imprinting where the father and mother contribute different epigenetic patterns to their offspring. The Angelman and Prader-Willi syndromes both can be produced by the same genetic mutation, chromosome 15q partial deletion, and the particular syndrome that will develop depends on whether the mutation is inherited from the child's mother (Angelman syndrome) or from their father (Prader-Willi syndrome). The Beckwith-Wiedemann syndrome is also associated with genomic imprinting, often caused by abnormalities in maternal genomic imprinting of a region on chromosome 11.

According to Barker, "fetal origins of adult disease hypothesis" proposes that fetal adaptation to a deprived intrauterine milieu leads to permanent changes in cellular biology and systemic physiology.[9] This combines Darwin's theory of natural selection, where selection entails a separation of the organism's DNA from its environment and Lamarck's theory of transformation arising from the organism's own experience of the environment, i.e. epigenetic changes to the organism's DNA.

Science is a living organism linked to the world and universe around it, not determined by dogma. Perhaps epigenetics can best be summarized by the Yogiism "it ain't over 'til it's over" (Yogi Berra, 1925–).

References

1 Xu XF and Du LZ. Epigenetics in neonatal diseases. Chin Med J. 2010;123:2948-2954.
2 Smith CA. Effects of maternal undernutrition upon the newborn infant in Holland (1944-1945). J Pediatr. 1947;30:229-243.
3 Lumey LH, et. al. Cohort Profile: the Dutch Hunger Winter Families Study. Int J Epidemiol. 2007;6:1-9.
4 Shultz LC. The Dutch Hunger Winter and the developmental origins of health and disease. Proc Natl Acad Sci USA. 2010;107:16757-16758.
5 Schlinzig T, et. al. Epigenetic modulation at birth – altered DNA-methylation in white blood cells after caesarean section. Acta Paediatr 2009;98:1096-1099.
6 Xu XF, et. al. Epigenetic regulation of the endothelial nitric oxide synthase gene in persistent pulmonary hypertension of the newborn rat. J Hypertens. 2010;28:2227–2235.
7 Tang WY, et. al. Persistent hypomethylation in the promoter of Nucleosomal Binding Protein 1 (Nsbp1) correlates with overexpression of Nsbp1 in mouse uteri neonatally exposed to diethylstilbestrol or genistein. Endocrinology. 149:5922-5931.
8 Pembrey ME, et. al. Sex-specific, male-line transgenerational responses in humans. Eur J Hum Genet. 2006;14:159-166.
9 Barker DJ. The fetal and infant origins of adult disease. Proc. R. Soc. Lond. 1995 262:37-43.

HAMILTON·C2

Intelligent Ventilation

Safe ventilation - now for the smallest patients

The new NEONATAL OPTION on the HAMILTON-C2 effectively supports your most fragile patient, the premature infant. Hamilton Medical has taken our 15 years of experience in advanced nasal CPAP systems, including the ARABELLA Infant NCPAP System, and incorporated this expertise into a new nCPAP-PS ventilation mode that supports even spontaneous breathing efforts.
With the addition of the NEONATAL OPTION, the HAMILTON C2, with its compact design, built-in batteries and ultra quiet turbine, is the first neonatal beside ventilator that can accompany the infant during hospital transports. The unique Ventilation Cockpit™ provides you with continuous patient status to ensure safe and effective ventilation therapy anywhere your patient goes.

For more information: www.hamilton-medical.com/C2 or call (800) 426-6331, Ext. 208.

Hamilton Medical, Inc.
4990 Energy Way, Reno, NV 89502
(800) 426-6331 (775) 856-5621
www.hamilton-medical.com/C2
info@hamilton-medical.com

HAMILTON MEDICAL

Endnote

Regarding our editorial in this issue, "Attention," The New Yorker's readers weighed in with their comments in the magazine's subsequent issue (Nov 21). One respondent wrote about her experiences with NICU holistic care: "Our daughter was born at 26½ weeks… In the NICU, amid all the 21st century technologies, I was encouraged to pump breast milk. Less than a week after her birth, my daughter was consuming my milk by tube, and at eight weeks she began trying to breastfeed. The NICU staff also urged my husband and me to do kangaroo care… Our daughter was extremely fortunate and simply needed a quiet, warm, controlled environment in which to grow."

Decisions

Another pair of respondents wrote: "As consulting psychologists to an NICU, we often see new moms and dads who, after their premature baby is born, are suddenly confronted with barely manageable uncertainty. Their situation can lead to miscommunication, anger, and accusations of blame, [such] acute anxiety can trigger PTSD and postpartum depression. Moreover, since developmental outcomes at NICU discharge are largely unknown, this sense of uncertainty often follows a family home. NICU policies also need to address the family's well-being."

Try again

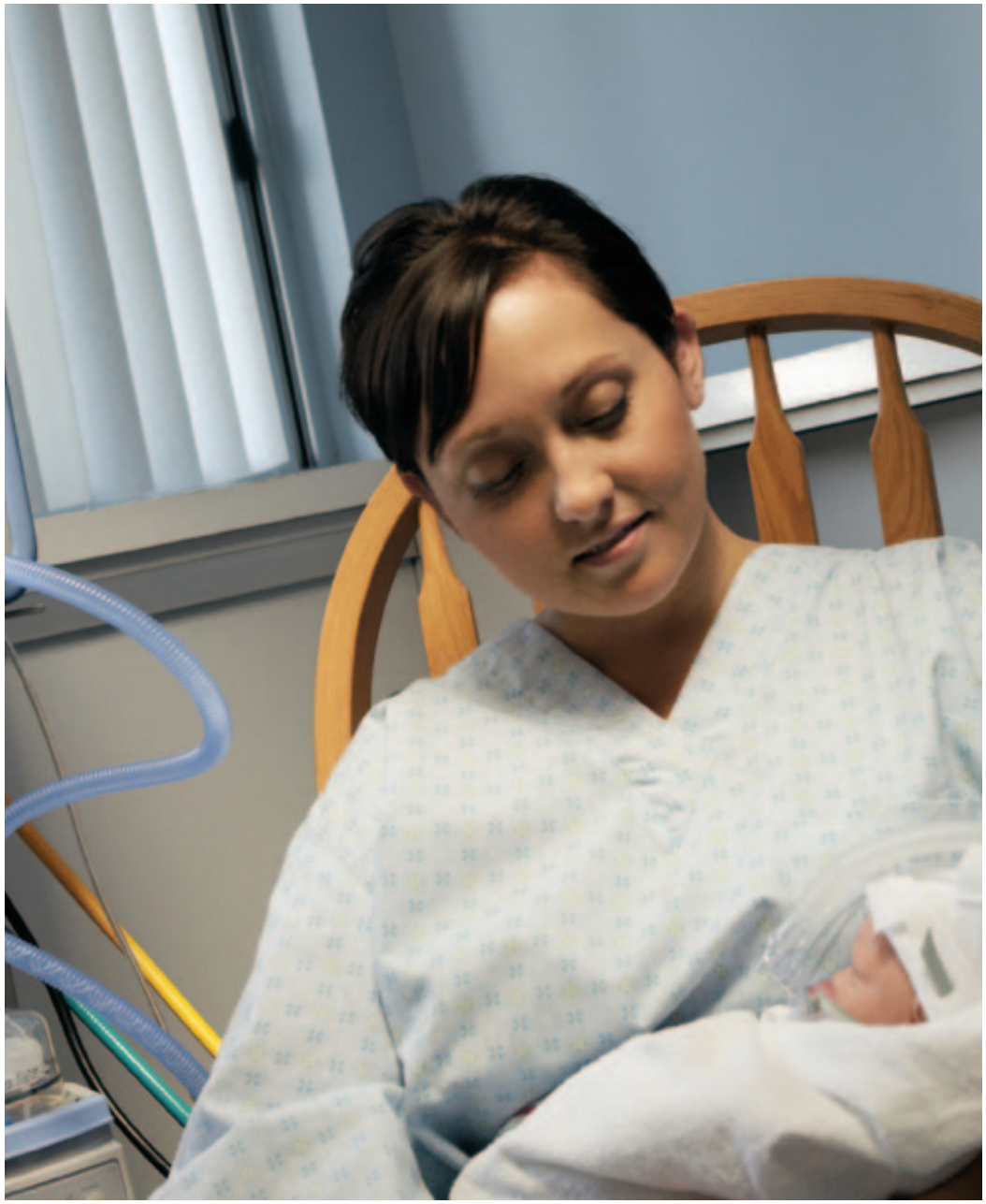
A mom reminded readers that many women who have a VLBW preemie can go on to have a full-term, healthy child, and noted that this was glossed over in The New Yorker article. "As the mother of twins born a generation ago at 32 weeks, I understand the anguish parents feel when confronted with decisions regarding the treatment of their child… When faced with such dire circumstances, the parents' decision-making process should include the knowledge that… there is every likelihood that they will have another, healthy baby. Despite the care and compassion so evident in the modern-day NICU, it seems that medical advances have clouded the ability to think in the broadest, most holistic terms."

Extreme intervention

One woman wrote, "It is difficult to read about the efforts now being made to keep even earlier preemies alive. Such extreme medical intervention prevents nature from aborting what is probably not a viable fetus. As a society, we hang on to life well beyond the point at which it is sane to let go. Until we learn to accept death, we will continue down this road of excessive sentimentalism."

Follow the money

Finally, a reader wrote that in all the books about preemies written in the US, there are warnings about what to do when the money runs out. She noted, "Twenty two years ago, when our daughter was born three months early… I was in the hospital for months and had two operations. [Our daughter] was in the ICU for 81 days, saw every type of specialist, and needed to have nine blood transfusions. When all was said and done, we paid five dollars for the birth of our daughter – to cover the parking… I am very grateful that she was born in Canada."



Advancing neonatal noninvasive ventilation for improved outcomes.

The Infant Flow® SiPAP System incorporates advanced technology for a complete noninvasive ventilation solution capable of helping to reduce ventilator days and extubation failures.

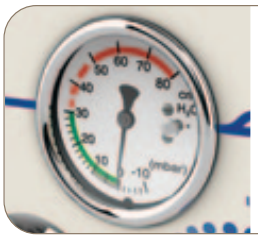
carefusion.com

3100A AVEA® AirLife™ Infant Flow®

CareFusion

F&P Neopuff™

Continuing to raise the standard of care in Infant **T-Piece Resuscitation**

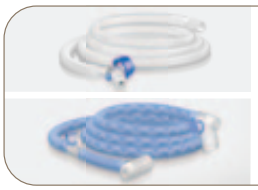


Accurate Pressure Control

- Superior manometer accuracy up to 80 cmH_2O
- Individually calibrated, ensuring pressures are displayed and consistently delivered
- Fast-acting needle and easy-to-read dial

Easy to Use and Versatile

- Easy-to-grip knob for adjustment of exact PIP pressures and larger carrying handle for ease in portability
- A range of mounting options is available for ideal placement in L&D, NICU, on transports and in other departments
- Availability of a complete range of accessories including gas supply line and full range of infant resuscitation masks



F&P Family of T-Piece Circuits

- A new and first-of-its-kind Ergonomic T-Piece Circuit with a Duckbill Port
- The only T-Piece device to provide a Humidified T-Piece circuit option

Cost Benefits

- Very affordable for any hospital regardless of the continuous enhancements made to the Neopuff

Since its introduction to the US in 1991, the **F&P Neopuff™** has established a proven track record in T-Piece resuscitation. Today, the Neopuff is used in over 120 countries around the world and has been included in over 10 years of clinical studies.

This is a testament to the depth of experience of Fisher & Paykel Healthcare in the neonatal setting and the Company's commitment to research and development, training and education.

To learn more about the F&P Neopuff Infant T-Piece Resuscitator, visit **www.fphcare.com**

Tel + 800 446 3908 or +1 949 453 4000

Fisher & Paykel HEALTHCARE