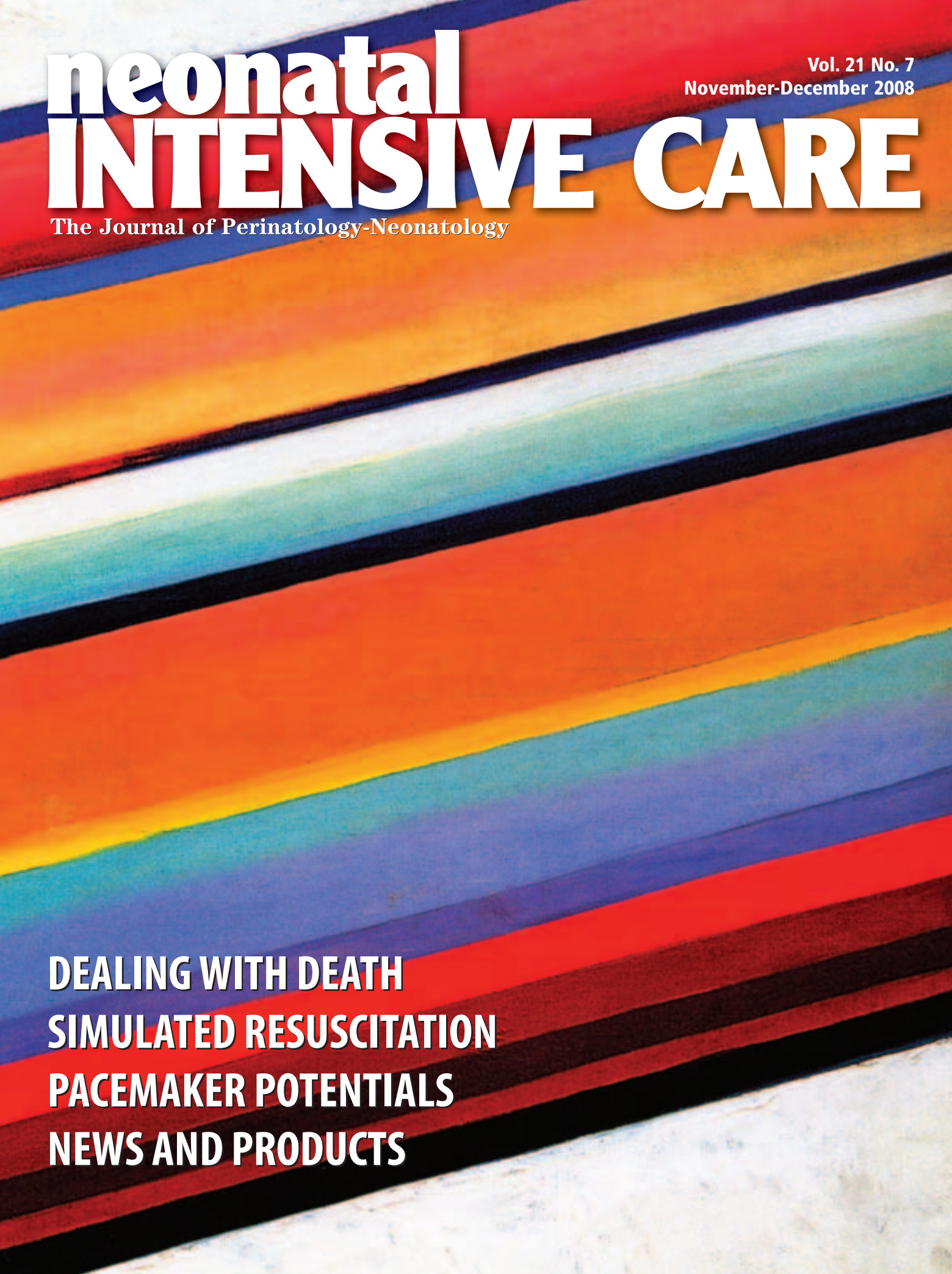
Vol. 21 No. 7
November-December 2008

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology



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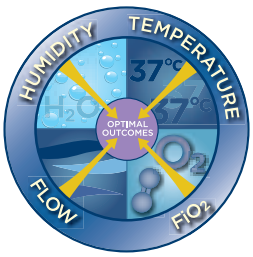

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Vol. 21 No. 7
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Editorial

At Death Do Us Part

Les Plesko

Neonatal practitioners must confront death, and its result, grief, on a regular basis. As such, caregivers need to be aware of the effect of neonatal/perinatal death on their patients' parents and siblings, as well as its effect on them. In the paper The Anatomy of Sorrow, Ronald Pies writes about mapping the boundaries of depression, from King David's time to today, and calls for a broader understanding of "mood," in its clinical and day to day aspects. Pies writes, "That life brings with it certain unavoidable or at least 'expectable' sorrows is a concept found in Eastern religious thought," but not so well accepted by the West. And yet, neonatologists and the parents and siblings who deal with death, are well aware of mortality and its attendant griefs. Pies writes, quoting the theologian Rabbi Levi Yitzchak, There is despairing sorrow, and "…the other kind is the honest grief of a man who knows what he lacks." Pies adds, "it is not always easy to tell 'proper sorrows' from intense grief, 'pathological' grief, or clinical depression. Indeed, it is very doubtful that these are strictly delineated categories. Furthermore, the nature of the putative 'cause' or precipitating event is not a reliable predictor of where, on this emotional continuum, a given individual may end up. The loss of a loved one, for example, ordinarily provokes sorrow and a finite period of grief and mourning. Most mourners do not develop a severe, intractable clinical depression." Well, perhaps not. Yet the death of an infant may call for special pleading. Neonatology practitioners are constantly confronted with this unique kind of sorrow, their own and others. Pies article delineates the varieties of sorrow, as it were, such as the skewing of the sense of time, when it seems grief will last forever, morbid preoccupations with the self, and so forth. He also notes the ambivalence of sorrow, in what it can ultimately engender in the sufferer. Pies writes, "Sorrow... is dialectical: it generates an inward 'conversation' between hopeful possibility and foreclosure of hope... Indeed, we might say that depression is to sorrow as falling is to leaping. Put another way: we are overtaken by depression, but give ourselves over to sorrow. Sorrow, says Pies, can remove your attention from the active life and focus it on the things that matter most. Neonatologists, then, have to be alert to the distinguishing features of sorrow, versus clinical depression, in themselves and the parents of their patients. It is sometimes a short bridge from one to the other. Yet, Pies warns, it's a bridge that shouldn't be crossed too quickly. He notes that there has been a trend to "medicalize" sadness, "lumping normal, adaptive sadness in with clinical depression, by failing to appreciate the emotional context in which depression takes place... To be sure, the criteria for depressive disorders are almost certainly too inclusive, and are undoubtedly in need of refinement." The term "complicated grief" has been coined by psychiatrists to delineate a state many neonatologists might be familiar with. Its symptoms, which are said to last about six months after a death, are: a sense of disbelief regarding the death; recurrent intrusive images of the dying person; and avoidance of painful reminders of the death. Individuals in this state can't find satisfaction in ongoing life, feel angry and bitter, and estranged from friends and relatives. For all that, true depression also manifests chemically, for example, in abnormal elevations of serum cortisol and decreased metabolic activity in the brain's frontal lobes. In any event, there is now some evidence that normal sadness and clinical depression have differing neurobiological underpinnings. Pies concludes that studies of sorrow and depression need to synthesize insights from phenomenological, spiritual and neurobiological perspectives.[1]

The Literature

Neonatologists and neonatal caregivers can look to a number of studies about neonatal death and grieving. The paper "Neonatal death: grieving families," examines familial stress after neonatal death. Sixty-seven families who experienced 63 neonatal deaths and four post-neonatal deaths were studied during an interview

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Parental Grief

The following is from "Handling of death in special care nurseries and parental grief," M.P. White, B. Reynolds, T.J. Evans, British Medical Journal, Volume 289, 21 July 1984. The study involved 12 families. "Communication was good before death but less satisfactory thereafter, particularly with regard to postmortem results and advice concerning recurrence risk." The parents needed a lasting memory of their child and attached great importance to mementos. Half had what the authors termed "abnormally high grief" six months after the death. In the study, there were 18 deaths (including a set of twins) and 12 families agreed to take part in the study. One mother was separated and one single. Two mothers had a previous miscarriage, but none had a previous neonatal death or stillbirths. The mean birth weight of the babies was 670-4,300 g, mean gestation was 25-41 weeks. Five babies had congenital abnormalities, four were extremely premature, the other three had necrotizing enterocolitis, bronchopulmonary dysplasia and birth asphyxia, respectively. The parents were interviewed 2 to 13 months after the death of their babies. Ten families were satisfied with how the death was initially handled, two complained of poor communication. All the parents got to see the baby before death. Ten had the opportunity to touch the baby when it was alive; seven accepted. Eleven parents wanted to participate more in the care of the baby. After the death, ten parents were invited to touch or hold their infant, but only four accepted. Five families accepted a memento—a nametag or a piece of clothing. The parents' level of satisfaction with communication decreased after the death of the child. Consent for necropsy was given in 10 cases, but only four mothers received the results. Eight families received advice about the risk of recurrence, but the information was provided haphazardly; in two cases, the doctor entrusted with providing information didn't have the facts of the case at hand. Only two sets of parents were counseled by an obstetrician. Four mothers expressed anxiety about future pregnancies. All of the parents received some type of bereavement counseling, though it was uneven.

Five mothers had high grief scores; all six were married, one separated. Only two mothers had good support from a spouse. One of the pregnancies was unwanted. In two of the cases, the parents had never touched the baby. One baby was buried in an unmarked grave, which contributed to the mother's distress. One mother was taking antidepressants seven months after the death, and one at 13 months was severely depressed. One of the mothers, at 16 months after, required a hypnotic medication. One set of parents scored zero on all assessments. Their baby was born at 25 weeks gestation, required prolonged ventilation, and lived for seven months. A major neurological handicap was apparent, and the parents rarely visited over the last two months.

Implications

Parents stressed the importance of a postmortem exam to alleviate guilt and questions, but only 40% subsequently obtained the results of the postmortem. The lack of touch between parents and infants led to "a sense of unreality." A high level of grief was associated with poor marital support. Half the patients with high Leeds grief scores were still severely depressed seven to 16 months after the death. However, the authors pointed out that the score could be interpreted in various ways; ie, "a low grief score six months after the death might be a more serious prognostic sign than a high score." The authors suggested that the speed and quality of communication needs to be improved, and developed a quick-check system which had practitioners check off the following procedures: 1. spoken to parents; 2. offered time to be with and hold the baby; 3. offered memento; 4. consent for necropsy, informed regular physician, informed obstetrician; 5. funeral advice; 6. pamphlets provided; 7. bereavement counseling required; 8. follow up arranged.

…Editorial, continued from page 4

held eight weeks after the death. Predominant support for the parents was provided by each other (63%), their parents (33%), friends, many of whom had experienced a similar loss (16%), neighbors (15%) and religion (13%). Grief reactions were more commonly reported by mothers than by fathers and included: sleep disturbances (51%); depression or fits of crying (34%); anorexia or weight loss (33%); nervousness and anxiety (19%); social withdrawal (18%); morbid preoccupation (9%); and guilt, anger or hostility (9%). Grief reactions were graded on a scale of I (physically, psychologically and emotionally settled) to IV (serious symptoms that disturbed day-to-day functioning). Pathological grief reactions occurred in 21 families and correlated with a lack of parental support and contact with the critically ill infant and a severe initial grief state. There was no correlation with the type of initial grief reaction; the attachment to the baby, the age of the baby, the comprehension of the cause of death, the hospital care or the way that they were informed of the death. The loss of a newborn infant had a major pathological effect on 31% of the families that were studied.[2]

The article "Grief Response of Parents to Neonatal Death and Parent Participation in Deciding Care" stated, "We determined the grief response to neonatal death of 50 mother-father pairs by administering a questionnaire and conducting a semistructured interview during the infant postmortem review. As measured by a parent grief score, maternal grief significantly exceeded paternal grief. Parent grief was not significantly related to birth weight, duration of life, extent of parent-infant contact, previous perinatal loss, parent age, or distance from the hospital of birth to the regional center. However, the attitudes and behavior of family, friends, and healthcare personnel in the hospital of birth often adversely influenced parent grieving. Of 39 mother-father pairs whose infants required respirator support, 18 participated in a group decision with their physician to withdraw respirator support when the prospects of infant survival seemed hopeless. No significant differences in parent grief scores were found when the limited respirator care group was compared to those parents of infants who died despite uninterrupted respirator care. The data suggested that informed parents can participate as partners with their physician in difficult infant care decisions, even when death results, and adjust to their loss with healthy grieving."[3]

The article, "The mental health impact of stillbirth, neonatal death or SIDS: Prevalence and patterns of distress among mothers," noted the following: "Although stressful events have long been implicated in the onset of psychological disorder, available data suggest that the majority of individuals appear to escape serious impairment even following highly traumatic events. Related to this is the question of chronicity and whether those who do become impaired develop mental health problems of an ongoing nature." The paper documented the psychological adjustment of 194 women following the death of an infant due to stillbirth, neonatal death or SIDS. Anxiety and depression were measured on four occasions, at 2, 8, 15 and 30 months post-loss. For comparative purposes, the mental health of 203 mothers of a surviving infant was similarly assessed. The abstract of the paper stated, "The results demonstrate that bereaved mothers, as a group, manifest significantly higher rates of psychological distress than mothers of living infants for at least 30 months after their loss. Their impairment may be either acute or chronic in form. The majority of bereaved mothers appear not to develop

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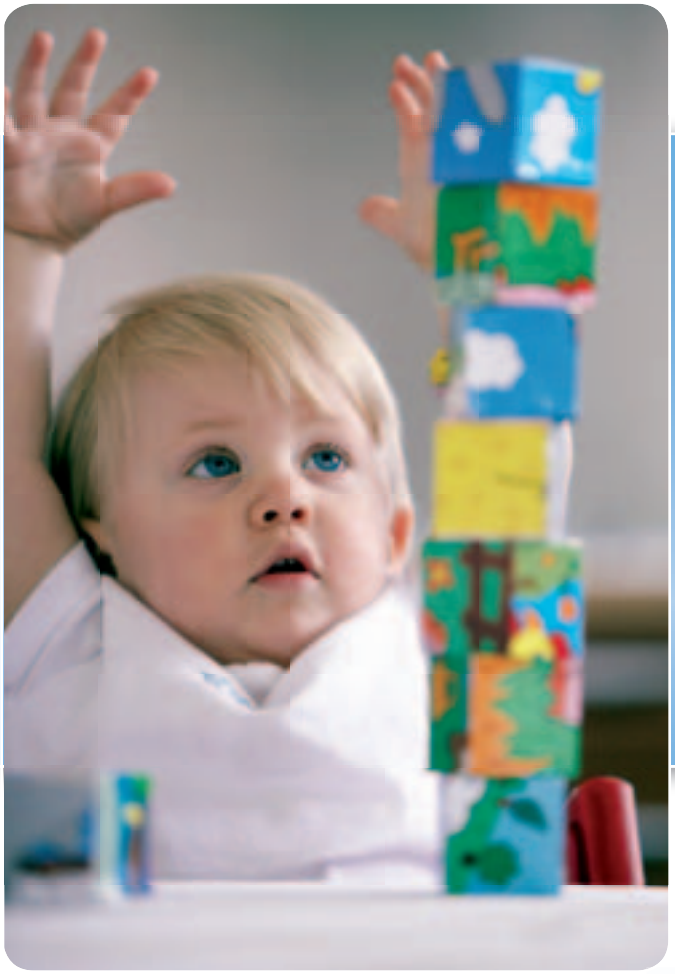

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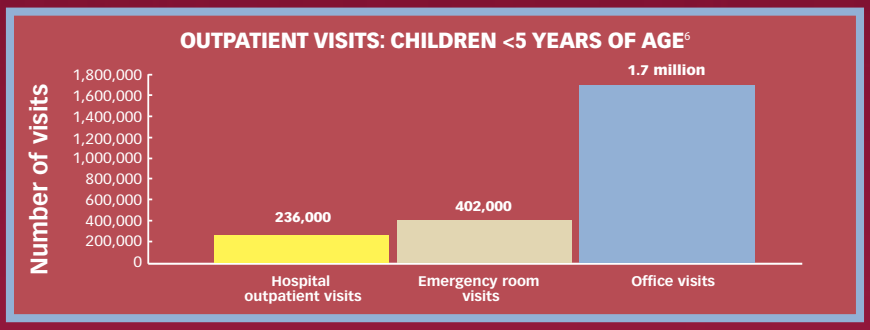
The unrecognized impact of RSV-associated lower respiratory tract infection in the inpatient and outpatient settings

Respiratory syncytial virus (RSV) is a common infection that infects virtually all children by 2 years of age[1]

- Up to 125,000 infants are hospitalized annually in the US as a result of RSV disease[2,3]
- 6.52 million outpatient visits in children younger than 1 year of age were associated with bronchiolitis, the most common cause of which is RSV[4]
- 70% of infants and children <5 years of age who presented in outpatient settings with wheezing and signs of lower respiratory tract infection, who had a positive viral culture, had RSV[5]

RSV is extremely prevalent across all outpatient settings[6]

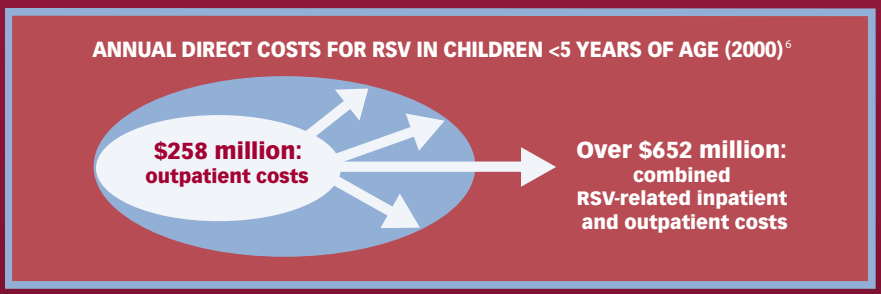


Adapted from Paramore LC et al. *Pharmacoeconomics*. 2004;22:275–284.

Estimated RSV-related visits (2000) in US children <5 years of age in several outpatient settings.

- RSV represents a substantial public health problem in outpatient settings, including hospital clinics[5]
- In fact, when infants and children present in the emergency department setting during RSV season with signs and symptoms suggesting lower respiratory tract infection, RSV is by far the most likely pathogen[7]
- In an 11-year study (1993–2004), emergency department visits for acute respiratory illnesses (ARI) in children <7 years old were estimated. Researchers found that the mean yearly rates of positive test results were 37.6% for RSV, 9.2% for influenza virus, 2.8% for parainfluenza virus, 4.6% for adenovirus, and 1.3% for enterovirus[7]

Outpatient costs represented 40% of all RSV-related costs in children <5 years of age in 2000[6]



"...[These] data underscore the enormity of the public health problem created by RSV."[5]

MedImmune: committed to ongoing research

MedImmune recognizes the need to help neonatologists continue to reduce the burden of RSV-related illness in hospital clinics and inpatient and outpatient settings and is dedicated to ongoing research in this field with the goal of helping infants live healthier lives.

References: 1. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child*. 1986;140:543–546. **2.** Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *J Pediatr*. 2003;143:S127–S132. **3.** Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980–1996. *JAMA*. 1999;282:1440–1446. **4.** Mansbach JM, Pelletier AJ, Camargo CA. US outpatient visits for bronchiolitis, 1993–2004. *Ambul Pediatr*. 2007;7:304–307. **5.** Fisher RG, Gruber WC, Edwards KM, et al. Twenty years of outpatient respiratory syncytial virus infection: a framework for vaccine efficacy trials. *Pediatrics*. 1997;99:e7. doi:10.1542/peds.99.2.e7. **6.** Paramore LC, Ciuryla V, Ciesla G, Liu L. Economic impact of respiratory syncytial virus-related illness in the US. *Pharmacoeconomics*. 2004;22:275–284. **7.** Bourgeois FT, Valim C, Wei JC, McAdam AJ, Mandl KD. Influenza and other respiratory virus-related emergency department visits among young children. *Pediatrics*. 2006;118:e1–e8. doi:10.1542/peds.2005-2248.

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imagination at work

…*Editorial, continued from page 8*
serious mental health problems in response to the loss or experience psychological impairment that is usually self-limiting. For a smaller group of women, the death of a baby may herald serious and ongoing distress. Bereaved mothers who were not distressed soon (2 months) after the loss were unlikely to become so later, but those who were still distressed at 8 months were likely to remain so subsequently."[4]

Postgraduate Medicine reports, in its paper, "Dying, death, and grief. Helping patients and their families through the process": When a patient has terminal illness and death is imminent, grief is a normal reaction. Primary care physicians can help patients and their families by talking with them about the five stages of grief (denial, anger, bargaining, depression, and acceptance), providing grief counseling and appropriate pharmacotherapy, and being supportive. Grief often manifests with features similar to those of depression, and it is critical for the clinician to distinguish between the two. "One distinguishing feature is that self-esteem in the grieving person is usually uncompromised, whereas a depressed person often has decreased self-esteem," the paper states. "Physicians should also watch for signs of mood disorders or abnormal grief. When grief is present more than 2 months after a loss, a diagnosis of major depression should be considered. Dysfunctional grief accompanied by severe depression and suicidal intent generally calls for psychiatric referral, hospitalization, or both."[5]

In the article, "Management of grief and loss: medicine's obligation and challenge," the author writes, "One of medicine's least taught and acknowledged areas is the physicians' obligation to the surviving families of patients who have died under our care. The uncomfortable feelings engendered by the death of a patient often lead to ending contact with the family of the deceased. However, this response fails to recognize the importance of the role that the treating physician continues to have for the surviving family. A phone call, letter, or attendance at the funeral has enormous meaning and value for the family. This role also provides the doctor with an opportunity to deal with the 'mini-grief' reaction that follows the death of a special patient, and it reduces the adverse effects of unacknowledged, cumulative losses that lead to burnout. Although the deaths of patients and our efforts to help their grieving relatives may be the dark side of medicine, this side can be among the most rewarding when it helps bereaved loved ones and ourselves to survive loss."[6]

The British Medical Journal, in the abstract of the article, "Handling of death in special care nurseries and parental grief," states, "The handling of death in a special care nursery and the needs of bereaved parents were studied in 12 families. Communication was good before death but less satisfactory thereafter, particularly with regard to postmortem results and advice concerning recurrence risk. Parents needed a lasting memory of their child and attached great importance to a tangible memento. Half had an abnormally high grief and Leeds scale score six months after the death, which seemed to be associated with poor marital support. All in the high scoring group favored bereavement counseling. Communication with general practitioners needed improvement. As a result of this study a protocol for the handling of death was designed."[7]

There is much more in the literature on this important subject, *continued on page 39…*

News

☐ November-December 2008

CORRECTION

Please note the following correction to our Buyers Guide: International Technidyne Corporation is now referred to as "ITC." The company purchased Diametrics Medical, so please delete Diametrics as a contact or reference. The correct street name for ITC is Olsen Avenue. Please note the following changes in the categories section of the Buyers Guide: Please replace Diametrics with ITC, Edison, NJ under the following categories: Gas Monitors, CO_2; Gas Monitors, saturation; Oximeters, oximetry; Tubes, capillary blood collection. Under Skin incision devices, change the name of the company to ITC. Please remove Diametrics from the following categories: Monitors, multi-modality; Point-of-care testing.

ETHICS AND PAIN

Researchers at the University of Turku, Finland, presented their latest findings about ethics in neonatal pain research in the July 2008 issue of Nursing Ethics. A literature review of 98 articles concerning clinical pain research in newborn infants was conducted to evaluate how researchers report the ethical issues related to their studies and how journals guide this reporting. The articles were published in 49 different scientific journals. The ethical issues most often mentioned were parental informed consent (94%) and ethical review approval (87%). In 75% of the studies the infants suffered pain during the research when placebo, no treatment or otherwise inadequate pain management was applied. Discussion about benefits versus harm to research participants was lacking. A quarter of the journals did not have any ethical guidelines for submitted manuscripts. The authors concluded that ethical considerations did not play a significant role in the articles studied and that lack of guidelines or superficial guidelines enabled authors to offer studies with fragile research ethics. See Ethics in neonatal pain research, Nurs Ethics 2008 Jul; 15(4):429-9.

SUDDEN DEATH

A Turkish hospital recently reported more than two dozen unexplained newborn deaths in a two week period from complications related to premature delivery. The Turkish Health Ministry was looking into the high number, though the hospital noted that most of the babies admitted to the hospital each year were premature, since it handled high-risk births.

FAILED FUNDING

Funding promised by the UK government to improve poor standards of care for mothers and newborn babies is failing to reach maternity units, according to the Times Online UK. An NHS survey revealed that nine out of ten units couldn't identify their share of the £330 million pledged for care by ministers. The Times noted that rising birth rates and a shortage of midwives

have put pressure on the system, meaning mothers are often left without care during labor. Of 85 trusts who responded to a survey, only eight claimed to have received additional funding for maternity this year. NHS spending on maternity in England was cut by £55 million in 2006-07, while the birthrate has risen 16% per cent since 2001. Forty percent of England's maternity units were rated "fair" or "weak" in quality of service by a government healthcare commission.

JOAN HODGMAN DIED

Dr Joan Hodgman, who helped define the field of neonatology and guidelines that improved the standards for newborn care, died early this August of ALS, Lou Gehrig's disease. She was 84. A resident of Arcadia, CA, she died at a family cabin in Oregon. She spent 60 years at County-USC hospital, and was director of its newborn division from 1957 to 1986. She played a central role in developing its intensive care unit for sick and premature babies, the first in Los Angeles and among the first in the nation, and led efforts that dramatically reduced the hospital's infant mortality rate. Dr Hodgman wrote and contributed to more than 300 articles and books, especially in the area of SIDS. She was also involved in debates about the limits of care. Hodgman entered Stanford University at age 16 and earned a BA in 1943, pursuing further medical education at UC San Francisco, where she was among its only women medical students. She organized County-USC's department for tiny babies before neonatology was even a subspecialty. In ten years, her efforts resulted in a 50% decrease in the hospital's infant mortality rate. In 1979, a watershed moment in the NICU convinced her to get involved with issues about the ethics of medical care for severely compromised infants. Hodgman was also a body-surfer and water skier into her 70s, and the winner of the 1999 Apgar Award from the AAP. She was widowed at 47, and never remarried. She was diagnosed with Lou Gehrig's disease in 2007 but continued to work through February of this year. Reported by Elaine Woo in the Los Angeles Times.

NURSES KNOW

The journal Pediatrics presented a study comparing pulse oximeter saturation limits targeted by nurses for extremely preterm infants during routine care with nurse opinions regarding appropriate pulse oximeter saturation limits and with policy-specified pulse oximeter saturation limits. The authors surveyed nurses in US NICUs with neonatal-perinatal fellowships in 2004. Data collected included pulse oximeter saturation limits targeted by nurses and by NICU policy when present, nurses' opinions about appropriate pulse oximeter saturation limits, and NICU and nurse characteristics. Among those eligible, 2,805 nurses in 59 NICUs responded. Forty (68%) of 59 NICUs had a policy that specified a pulse oximeter saturation target range for extremely preterm infants. Among 1,957 nurses at NICUs with policies, 540 (28%) accurately identified the upper and lower limits of their NICU's policy and also targeted these values in practice. NICU-specific SDs for individual nurse target limits were less at NICUs with versus without a policy for both upper and lower limits. Individual nurse opinions were cited as factors significantly associated with individual pulse oximeter saturation target limits. For each percentage point increase in individual opinion upper limit, the individual target upper limit increased by 0.41 percentage point at NICUs with a policy compared with 0.6 percentage point at NICUs with no policy. The authors concluded that the presence of policy-specified pulse oximeter saturation limits, nurse group opinion, and individual nurse opinion were independently associated with individual nurse pulse oximeter saturation target limits during routine care of extremely preterm infants. The presence of a policy reduced the influence of individual nurse opinion on targeted pulse oximeter saturation limits and reduced variation among nurse target limits within NICUs. See: Nurse opinions and pulse oximeter saturation target limits for preterm infants, Pediatrics 2008 May;121(5):e1039-46.

GOOD EARS

Mothers who give birth naturally are more responsive to the cry of their baby than those who choose to have a cesarean, according to researchers at Yale University. Brain scans on 12 new mothers soon after birth found more activity in areas linked to motivation and emotions in those who had a vaginal delivery. The Yale researchers said differences in the hormones generated by birth could be the key, because contractions trigger the release of oxytocin, which is thought to play a key role in shaping maternal behavior. C-section doesn't trigger this hormone release. The differences in brain activity were found in regions that not only appeared to influence a mother's response to her child, but also to regulate her mood. Since the study involved only women who had elective C-sections, it was conjectured that as such these subjects may have been in a group that weren't as good at bonding, or, because these women opted for C-sections, that they were slightly disengaged from the birth process. However, other researchers said this was poppycock.

BOY PRESSURE

Blood vessel changes linked to poor health later in life can be spotted within a few years in boys born small, according to researchers at Southampton University. Eight-year-olds who were smaller at birth were more likely to have vascular resistance, and the researchers said this could contribute to high blood pressure decades later. No such problem was seen in low birth weight girls. None of the 140 eight or nine year olds tested in the study showed any actual signs of heart disease, but scientists believe that even at this age, the arteries of these children may show differences which might raise the risk of problems decades on. In particular, they tested how a child's response to stress might affect vascular resistance. For the study, the children underwent a public speaking and mental arithmetic test designed to make them nervous and increase their heart-rate. Although all the children were in the normal range of birth weights, boys at the lower end of the scale were more likely to have higher vascular resistance than those born bigger. The difference in resistance levels between bigger and smaller birth weight boys was particularly strong half an hour after the test, suggesting some additional difference in the boys' ability to restore normal levels. Girls did not show this effect, but instead showed different levels of response in the part of their nervous systems linked to the fight or flight response. The researchers noted that the sex differences in these relationships were striking and may eventually lead to a better understanding of why men and women tend to develop high blood pressure and heart or vascular disease at different times in their lives. The study suggested that different underlying mechanisms for developing the same disorder may exist in the two sexes but have the same eventual result.

MORE MORTALITY

Data from the Centers for Disease Control and Prevention show that a nearly decade-long decline in infant-mortality rates has stalled, and that African-American children are twice as likely as white babies to die before their first birthday, according to a recent article in the Wall Street Journal. Blacks are 2.4 times

as likely to die when they're infants, compared with white newborns. Per 1,000 live births of black children, 13.26 died in infancy in 2005, according to the data, which is similar to infant-mortality rates in some developing countries. Among white children, the infant mortality rate rose to 5.73 per 1,000 live births in 2005, compared with 5.66 in the previous year. Overall, the US infant-mortality rate rose to 6.86 per 1,000 in 2005, from 6.78 in 2004. These slight increases followed years of generally steady declines during the 1990s and the early years of the current decade, especially among white infants. The CDC says the higher rates are largely attributable to low birth weight, shorter gestations and premature births. Higher rates of poverty, less access to healthcare and dietary differences were cited as reasons.

SEVEN UP

A 27-year-old Egyptian woman in Alexandria gave birth to septuplets. The newborns, four boys and three girls, weighed between 3.2 pounds and 6.17 pounds and were placed in incubators in four different hospitals with special premature baby units. The delivering doctor said this was something he had never witnessed in his 33 years as a physician. He decided to do a C-section at the end of the mom's eighth month of pregnancy due to the pressure on her kidneys. She already has three daughters, but took fertility drugs in an effort to have a son. The babies showed no deformities at birth. When the family found out about the septuplets, they said they thought about an abortion but felt it was religiously forbidden. Egypt's health minister said the seven babies would receive free milk and diapers for two years.

A FEW GOOD WO/MEN

The New York Times recently reported on the growing need for midlevel healthcare providers. In her article, Christine Larson wrote about the increasing opportunities, and lack of, qualified physician assistants, profiling Adam Kelly, who works in the neonatal unit of Hartford, CT's St Francis Hospital and Medical Center. Ms Larson wrote, "In an aging population, a shortage of doctors has created new demand for care providers like physician assistants and nurse practitioners—nurses with advanced training who can also examine and treat patients, make diagnoses and write prescriptions. From 2001 to this year, the number of nurse practitioners in the United States has grown to 125,000 from 82,000, and the number of PAs to 68,000 from 43,000." The average income of a full-time PA in clinical practice is $86,000; and $92,000 for an NP. Physician assistants practice under a physician's supervision, while nurse practitioners are licensed as independent healthcare providers, though some states require them to work under a supervising or collaborating physician. PAs are typically generalists, while NPs specialize. Ninety percent of PA schools now offer master's programs, and candidates have to pass a certifying exam. These programs cost about $46,000. Nurse practitioners are licensed by state boards of nursing, and are typically registered nurses who must then earn a master's in nursing science or a can earn a doctorate in nursing practice, a growing trend. Reported in the New York Times, August 9, in the column, "Fresh Starts."

ERT APPROVED

Enobia Pharma announced that the first patient in its clinical program for hypophosphatasia has been dosed. Enobia is investigating Enzyme Replacement Therapy with ENB-0040. Under two separate protocols, ENB-0040 will be evaluated in both adults and infants afflicted with hypophosphatasia in Canada and the USA. The first protocol is for adults. Under the second protocol, safety, tolerability, pharmacokinetics, and efficacy of ENB-0040 will be evaluated in a six-month open label study of up to six infants with particularly severe hypophosphatasia. Key efficacy outcomes include assessment of skeletal and respiratory manifestations of the disease. ENB-0040 is a fusion protein that includes the catalytic domain of human tissue non-specific alkaline phosphatase (TNSALP), and a patented peptide used to target the enzyme to bone.

BIG BABIES

The latest big baby birthing has taken place in Mexico, where Blanca Rosa de Leon Garcia gave birth to a boy who weighed more than 13 pounds. The baby's dad said, "We didn't expect this; now we have to buy bigger clothing because what we have is not going to fit." The baby was delivered by cesarean section [reported by MSNBC, © 2008 MSNBC Interactive]. For the record, other big babies of late include a boy born in December in Tasmania who weighed 13 pounds. Reports at the time said he had a larger head and longer body than the average newborn, and had thick, black, curly hair. The mom said, "I did have an epidural but apart from that it was naturally, and [the birth] was quite hard." This dad, too was fixated on clothes. The father noted, "The ones we had didn't fit him," and also said the couple had a four-year-old daughter, and that their family was now big enough. In the US, a 13 pound baby was born in Milwaukee in 2001, not even close to the record, a 24-pound boy born in Ohio in 1879, at 24 pounds. Nevertheless, the Milwaukee 13 pounder's mom said, "The second I had him, I lost 24 pounds. Just to get the baby out, believe me, it was the best Christmas present I ever had." The mom also said, "I couldn't believe his cheeks. He had the biggest ones I had ever seen." The mom had developed diabetes during the pregnancy, had to sleep in a recliner by her seventh month, and gained 30 pounds. The baby had an enlarged heart and underdeveloped lungs. The dad said he was really amazed but didn't mention clothes.

WRONG PLACE AND TIME

The Los Angeles Times reported that "microbes in the wrong place at the wrong time—a woman's amniotic fluid during pregnancy—may play a role in causing premature births," according to a study published in the online journal PLoS One. Rearchers at Stanford University School of Medicine found a greater quantity and variety of bacteria and fungi in a significant portion of women who gave birth prematurely. The more severe the infection, the earlier the women were likely to give birth. Up to now, the amniotic sac "has long been considered a protected, almost inviolable, site," according to the article's author, Mary Engel. The researchers used polymerase chain reaction and DNA sequencing to look for microbes in amniotic fluid samples from 166 women in preterm labor. Of these women, 113 went on to deliver prematurely and 53 carried their babies to full term. Evidence of infection was found in 15% of the samples, all from preterm women. The microbes found represented one fungal and 16 known bacterial species. Among these was Leptotrichia, commonly found in the mouth and vagina, and the researchers noted that both gum disease and bacterial vaginosis have been linked to premature delivery. The researchers also found a bacteria that hadn't been previously identified. The scientists used PCR to detect microbes, more effective in that it uses DNA and rRNA to differentiate types of bacteria. They also discovered that all the women whose samples were positive by either PCR or by culture had their babies prematurely.

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PRODUCTS & COMPANIES

CLINICAL CASE STUDY: Significant Apnea and Bradycardic Episodes in Premature Neonate Alleviated by Micropump Nebulizer, by Matthew Bolinsky RRT-NPS. The author is an NICU Respiratory Supervisor. This case study was provided by Aerogen.

Baby Doe was born prematurely at the age of 26 weeks gestation. She was intubated immediately in the labor and delivery suite and gently ventilated using a T-Piece resuscitator. She was transported to the NICU and placed on mechanical ventilation for her first 21 days of life. On day of life 21, she was placed on nasal CPAP of 7 cmH_20 and 30% oxygen. While the results of her blood gases remained within normal limits, her chest x-ray showed streakiness as seen with moderate bronchopulmonary dysplasia (BPD). The more disturbing element of her care was that of significant apnea and bradycardic episodes with moderate frequency. These episodes required physical stimulation as well as increases in oxygen concentration.

Baby Doe remained on NCPAP and was ordered Budesonide 0.25 mg twice daily by her neonatologist. After contacting our Aerogen representative, he brought the Aeroneb Solo into our institution for a trial. We began delivering the ordered Budesonide on the infant and the results were remarkable. Twice daily she was removed from the NCPAP unit and given the medication via T-Piece resuscitator. This allowed delivery of continuous distending pressures as well as medication delivery. Within 48 hours of use we began to wean both her NCPAP pressure and oxygen. More significant than the weaning of support were the marked changes in her episodic events of apnea and bradycardia. She began to become much more stable, requiring very infrequent increases in oxygen concentration. Much to the surprise of the medical staff, Baby Doe did wean completely off her oxygen and was able to be discharged without oxygen, treatments, or monitors. The respiratory staff was convinced that her positive outcome was attributed to the nebulizer treatments delivered via the Aeroneb Solo. We have since purchased a unit for our use and will continue to deliver our medications in this manner.

SURFIN' ALONG

Discovery Laboratories, Inc announced that it has made significant progress in addressing key remaining requirements identified by the US Food and Drug Administration (FDA) to gain marketing approval of Surfaxin (lucinactant) for the prevention of RDS in premature infants. Discovery Labs continues to conduct and finalize activities necessary to submit a Complete Response to the FDA Approvable Letter. The Approvable Letter did not require any additional clinical trials to gain Surfaxin approval. Prior to receiving that Approvable Letter, Discovery Labs and the FDA had agreed to a proposed Surfaxin package insert setting forth prescribing information. Also, the FDA had successfully conducted a pre-approval inspection PAI of Discovery Labs' manufacturing operations, and the company met with the FDA to clarify and reach agreement on addressing the key remaining requirements necessary to gain approval. The Preclinical Study results, together with data generated from the latest tests, support the comparability of Surfaxin drug product used in Discovery Labs Phase 3 clinical studies to the commercial manufacturing process for Surfaxin. The FDA requested and Discovery Labs agreed to augment the previously-generated data by conducting additional Surfaxin biological activity tests at a dose of 5.8 mL/kg, which is different than the dose of 8.0 mL/kg historically employed for Surfaxin release and stability testing. The data generated is being used to determine the final acceptance criteria for the biological activity test and to further confirm the comparability of Surfaxin drug product used in Discovery Labs' Phase 3 clinical trials to the commercial manufacturing process for Surfaxin, which is comprised of four active pharmaceutical ingredients (APIs); a novel peptide, a fatty acid and two phospholipids. At a recent meeting with the FDA, Discovery Labs discussed its approach to justify the levels of certain of the lipid-related impurities given their presence in the human lung at levels equal to or greater than those that exist in Surfaxin. At that meeting, the FDA requested additional information about the levels of these lipid-related impurities specific to the neonatal lung. In addition to reviewing scientific literature to satisfy the requirement that lipid-related impurities in Surfaxin's two phospholipids meet ICH guidelines, Discovery Labs has consulted with lipid-experts and has been working closely with its phospholipid suppliers to reduce lipid-related impurity levels to the ICH threshold limit. Based on recent analyses, Discovery Labs believes that it can satisfy the FDA requirements by either accepting the ICH threshold limits for certain lipid-related impurities and/or working with its phospholipid suppliers to further reduce impurity levels to the ICH threshold limits. Contact discoverylabs.com.

BUCKLE UP

Children's Medical Ventures, a subsidiary of Respironics, Inc, announced the introduction of its Car Seat Challenge initiative in support of car seat testing for premature and low birth weight infants. Developed in conjunction with the American Academy of Pediatrics guidelines as outlined in its article Safe Transportation of Premature and Low Birth Weight Infants, the Car Seat Challenge provides families and the NICU staff with a comprehensive program to perform car seat testing in the hospital prior to discharge. Research indicates that some infants, particularly those born at less than 37 weeks gestation, may be subject to transient episodes of bradycardia, apnea and oxygen desaturation when traveling in a standard car safety seat. As part of the Car Seat Challenge, ChMV has developed the Car Seat Challenge Knowledge Pack, which provides clinical resources, guidelines and testing protocols specific to this vulnerable population to ensure proper car seat positioning, as well as monitoring and analysis product solutions to help physicians better identify at-risk infants. Administered by a qualified clinician, the Car Seat Challenge involves properly positioning the baby in the car seat and then assessing heart rate, respiration and oxygen desaturation levels at periodic intervals for the length of the ride home or 90 minutes, whichever is longer. Based on these findings, NICU clinicians determine if it is safe to discharge the infant. Home monitoring or prescriptive medicine may be required as part of the discharge process, and it may be recommended that discharge be delayed for infants

who experience bradycardia, apnea or oxygen desaturation. The Car Seat Challenge Knowledge Pack includes the AAP's Safe Transportation of Premature and Low Birth Weight Infants reprint, a white paper titled Car Seat Safety: The Challenge, and a suggested car seat testing protocol and log sheet. Additional future components will include a Parent's Guide and a comprehensive, user-friendly web site. Combined with Children's Medical Ventures' SmartMonitor 2 PS and Synergy-E software monitoring and analysis products, the Car Seat Challenge provides a complete car seat testing program that supports both patient and clinical needs. Contact respironics.com.

HOT & HUMID

Vapotherm has received 510(k) clearance from the FDA for its Precision Flow, the first high flow humidification system to integrate gas blending, flow control and humidification technology into one device for the optimal conditioning of nasal cannula inspired gases. Precision Flow was developed with extensive input from clinical professionals in neonatology, pediatrics and adult respiratory care. The result is a device that combines performance, safety and ease of use for optimal patient outcomes. The new device offers high flow therapy benefits, with improved ease of use and performance features. With the FDA clearance, the company has initiated full-scale production. Vapotherm also announced that it has secured $20.5 million in new equity financing. The financing will support the company's growth plans including new product development, sales expansion and the launch of Vapotherm's newest acute care Precision Flow device. Contact vtherm.com.

GROUNDBREAKING

Siemens Healthcare broke ground recently on a new state-of-the-art training and service facility at its location in North Carolina. The event signalled the start of the company's expansion efforts due to greater demand for Siemens medical equipment and technologies. The new facility is a planned 143,000-square-foot, six-story office building. Scheduled to open in early 2010, it will house more than 500 technical and administrative support personnel. Siemens' commitment to the project includes a $57-million investment, as well as the addition of approximately 300 jobs over the next five years, in anticipation of the greater demand for training and technical support for Siemens' medical technologies. Currently, Siemens employs nearly 700 people in North Carolina. Siemens will be working in conjunction with the Leadership in Energy and Environmental Design's Certification process to ensure it uses environmentally safe products and processes in construction of the new facility. Siemens provides a variety of technical and application training for customers, Siemens Customer Service Engineers and application specialists, including both basic and advanced levels. The training offerings include class room training, web-based training, and virtual training. The company's UPTIME Services includes a national call center with technical and application specialists available around the clock, handling more than two million calls annually.

The company showcased its latest ultrasound solutions for ob/gyn, featuring innovative knowledge-based workflow and 4D imaging capabilities at the 18th World Congress of Ultrasound in Gynecology and Obstetrics (ISUOG) in Chicago. The ACUSON S2000 and ACUSON X300 ultrasound systems cover the complete range of obstetrical and gynecological imaging and advanced clinical applications, while the ACUSON P10 ultrasound system puts the power of an ultrasound in the palm of the hand. The ACUSON S2000 ultrasound system features innovative technologies and workflow-enhancing clinical applications which dramatically improve the efficiency of ultrasound exams. With applications, such as syngo Auto OB measurements, users can generate semi-automatic biometric fetal measurements. In addition, the ACUSON S2000 system features Fetal Heart STIC (Spatio-Temporal Image Correlation) imaging, which captures data over multiple heart cycles and creates a 3D fetal heart volume, allowing sonographers to view the fetal heart in multiple planes. The Siemens workflow solution for ob/gyn also encompasses sophisticated applications that were migrated from the high-end performance S Class into the X Class product series. The ACUSON X300 ultrasound system, Premium Edition (PE), for example, offers Advanced fourSight volume imaging technology providing a complete 3D/4D solution. It delivers streamlined, intuitive workflow and advanced acquisition, data rendering and post-processing functionality for all examinations, including 2D and Doppler. For the ACUSON S2000 system, the software also includes amnioscopic rendering, which provides a unique surface-rendering technique for stunningly realistic and detailed views of the fetus. Siemens also showcased the world's first pocket ultrasound system, the ACUSON P10 system. A little larger than a common PDA, the system weighs only 1.6 pounds, and fits easily into a lab coat pocket. The ACUSON P10 system is intended to deliver a quick and comprehensive overview on fetal positioning, anatomy, heartbeat, fluid levels and placenta location during labor or routine office visits. It can be used by physicians and medical personnel in a number of environments including intensive care units, ambulances and medevac helicopters. Contact siemens.com/healthcare.

FINDERS KEEPERS

SearchMedica.com was awarded the Silver Award for Outstanding Quality in the World Wide Web Health Awards, which are organized by the Health Information Resource Center and honor the best online health information. SearchMedica earned recognition in the category of Portal or Gateway site in the Professional class. SearchMedica provides free, open access to the web's most authoritative content for medical professionals, filtering out paid articles and consumer websites, making the research process more streamlined and productive. Contact searchmedica.com.

KIDNAPPED (NOT)

RF Technologies announced it has installed its Safe Place Pediatric and Infant Security Solution at Waukesha Memorial Hospital to help protect infants and children from abduction. The tertiary care hospital's staff delivers around 2,300 babies per year. How RF's system works is that a lightweight transmitter is placed around a child's ankle or wrist. This allows the staff to monitor the child's whereabouts within the protected area. The transmitter sends a signal to receivers placed throughout the hospital. If the band is tampered with or if the infant or child is too close to a doorway, an alarm will sound. Hospital doors also immediately lock down. Safe Place also allows the hospital's staff to generate a variety of customized reports to help reduce alarms and to be ready for Joint Commission reviews at the touch of a button. Contact rft.com.

PREEMIE PARTNERS

Draeger Medical Inc has announced its enhanced and exclusive partnership with Intensive Care On-Line Network (ICON) to provide 24x7 clinical and educational support for Draeger ventilation equipment now including the Babylog 8000+. ICON has supported Draeger Evita Series ventilator customers in

the US and Canada beginning in September 2001 and has since extended support to Savina and Babylog ventilator customers. ICON uses telephone and broadband technology to connect subscribers to their Critical Care Resource Center, which provides immediate live support for users of Draeger Evita, Savina and, now, Babylog 8000+ ventilators. ICON clinicians are certified and trained in the use of these Dräger ventilators and are available 24x7 to answer questions about the equipment, assist in troubleshooting alarms and help guide ICU staff through critical ventilation issues. ICON clinicians can even be contacted via live video, enabling uni- or bidirectional visual and audio interaction between ICU staff and the support team. ICON is staffed with a multi-professional group including intensive care physicians, pulmonologists, critical care nurses, respiratory care practitioners, critical care pharmacists, registered dieticians and information technology specialists. Draeger customers can receive around-the-clock support from ICON clinicians while continuing to manage patients at the bedside. ICON provides customer care packages through their website's "members only" section. Subscribers also have access to on-line clinical documents and case studies as well as educational web conferences, symposiums with continuing education units and respiratory care modules for RCPs and registered nurses. Support varies by level of customer care package. "This relationship enables Draeger to provide a detailed level of clinical assistance and support that is not typically available to customers. ICON provides the 24x7 clinical support, from simple troubleshooting to the most critical of issues" said Ed Coombs, MA, RRT, Senior Marketing Manager for Respiratory Care, Draeger Medical, Inc. ICON provides Draeger customers a support system and resource center that increases patient safety by reducing the number of errors that can occur in the ICU. Draeger is the only company among its ventilation competitors to offer this level of consultation. "It is necessary for us to have the best-in-class support ICON offers to go along with Draeger's innovative technology," said Coombs. Contact draeger.com.

KEEPING COOL

The Dickson Alarm Thermometer for use in safeguarding temperature-sensitive drugs and vaccines, features tamper-resistant audible and visual alarms. It can monitor both refrigerators and freezers simultaneously. The thermometer provides a visual display of alarm that remains on even if temperatures are no longer out of range, alerting the need for remedial action. The alarm is tamper-resistant, and displays refrigeration conditions every five seconds. It monitors temperatures in the -58 to +158°F range. Contact dicksondata.com.

EDUCATION PLUS

An AARC accredited continuing education program sponsored by Teleflex has attracted particiation from 10,000 RTs. Clinical Foundations offers modules focusing on a variety of respiratory diagnostic and treatment topics, including: mechanical ventilation and humidification, managing the difficult airway, trends in noninvasive respiratory support, continuum of care, technological advances in the clinical management of OSA, and preventing ventilator-associated pneumonia. Over 35,000 certificates of completion have been issued to RTs for these modules. Each edition of Clinical Foundations is accredited by the AARC for CRCE. Saxe Healthcare Communications provides the program and is supported by an education grant from Teleflex Medical, which makes the Hudson RCI brand of resipiratory products. In other Teleflex news, the company has received clearance from the FDA to market the Hudson RCI Neb-U-Mask, a respiratory device that allows for the concurrent delivery of aerosolized medication and a high concentration of medical gases to treat acute asthma exacerbations. The Neb-U-Mask allows the concurrent delivery of aerosolized medications and high concentrations of oxygen or heliox. The system is composed of a wye design, featuring a nebulizer connection and MDI adaptor, a non-rebreathing mask with a 750ml gas reservoir bag, and color coded tubing. This patented design promotes positive patient outcomes by avoiding therapy interruption. The nebulizer connection features a valved port, which maintains a closed system when a nebulizer is not in use. This closed system design allows for delivery of high levels of oxygen or heliox gas mixtures. For more on the foundation contact clinicalfoundations.org. For more on Teleflex, contact teleflex.com.

DISPOSABLE

Smiths Medical has announced the addition of the 10 mm disposable infant breathing circuit to its babyPAC ventilator accessories. The Pneupac babyPAC MRI transport ventilator is specially designed to deliver ventilation to small, fragile lungs of patients weighing 500 grams to 44 pounds. It has a sophisticated range of ventilation controls including CPAP, variable I:E ratio, and variable oxygen concentration. The babyPAC's internal CPAP and PEEP controls, with full blender or precise oxygen concentrations, allow the clinician the flexibility to ventilate delicate infant and neonatal lungs. The new 122006 Disposable Infant Breathing Circuit Kit comes with the circuit, and babyPAC expiratory diaphragm. Contact smiths-medical.com.

LOCK ON

UTMD, Utah Medical Products, Inc, is expanding its Nutri-Lok family of products to include two additional clinician-requested extension sets: Y-Connection Ext. Set and Gastrointestinal (GI) Ext. Set. The Y-Connection Extension Set has side ports that allow easy administration of medications and fluid delivery without disconnecting the system from the pump. The GI Ext. Set's stepped adaptor allows connection to various diameter gastrostomy tubes (G-tubes) for administration of nutritional fluids, including a side port. These new sets share the clinical benefits that apply to all UTMD enteral-only feeding catheters, extension sets, and oral dose syringes: • will not mate with a female luer IV line connector; • ensure a secure connection that will not accidentally slip apart; • they lock onto Utah Medical's oral dose Nutri-Cath catheters, but are compatible with other oral dose enteral feeding catheters via a slip fit connection. The entire Nutri-Lok system is sterile, DEHP-free, and patent pending. Contact utahmed.com.

Evaluating a Simulation-Based Neonatal Resuscitation Program

Daniel D. Woodhead, Robert D. Christensen

Introduction

The Neonatal Resuscitation Program (NRP) was introduced in 1987 as an educational collaboration between the American Academy of Pediatrics and the American Heart Association. NRP was designed as a standardized method of providing emergent assessment and care for newborn infants, and has been adopted by healthcare providers around the world.[1] In general, NRP instruction has been didactic, with practice sessions on resuscitation models used periodically throughout the classes.[2]

Simulation-based training has been embraced by organizations such as aviation, aerospace, police and fire departments, military service, and nuclear engineering.[3] A simulation-based environment can provide visual, auditory, and tactile cues unavailable in classical didactic learning.[4,5] Recent studies have shown that a simulation-based instruction in the healthcare profession can provide superior retention of essential skills.[6]

The Institute of Medicine and the Joint Commission on Accreditation of Healthcare Organization have recommended simulation-based medical training. On this basis, NRP simulation classes were begun in the northern region of Intermountain Healthcare in August of 2007. As part of introducing this new program, we performed two related studies. First, we sought to identify any specific skill-sets where performance after the class was seen to consistently be poor, so that additional education and training could subsequently be focused on strengthening those weak areas. Second, we sought to anonymously survey every class participant to identify the perceived strengths and weaknesses of the new NRP simulation-based program.

Methods

Seventy-seven health care professionals were enrolled in 11 NRP simulation classes, with a total of sixty-four scenarios. Class members included NICU respiratory therapists (n=14), NICU registered nurses (n=41), labor and delivery nurses (n=12), NICU nurse practitioners (n=1), neonatalogists (n=1), and third year Family Residents (n=8). These individuals had 2-22 years of prior NRP experience. Information was collected by a single observer (DDW) regarding whether each of the five skill-sets was performed properly. These five sets were: 1) drying, stimulating and removing wet linen, 2) suctioning mouth and nose, 3) thirty seconds of effective bagging was performed before chest compression started, 4) proper bagging rate, and 5) proper chest compression-bagging ratio. (Table 1) A Fisher Exact was used to compare the dichotomous variable (performed properly, yes vs. no) of each skill-set with the other four skill-sets.

At the conclusion of the NRP simulation class an evaluation form with a Likert Scale (1 through 5, with 5 indicating excellent and 1 indicating poor), was completed by each student. The evaluation form contained 11 questions comparing the standard NRP class with the simulation NRP class. These questions were: 1) relevance to my practice in the hospital, 2) ability to engage my intellect, 3) ability to develop my behavior skills, 4) ability to transfer behavioral skills to the real environment, 5) ability to develop my technical skills, 6) ability to transfer technical skill to real environment, 7) ability to develop critical thinking skills, 8) ability to transfer critical thinking skills to real environment, 9) builds confidence level in performing the steps of neonatal resuscitation, 10) would you recertify in a standard NRP course or a simulated NRP course and 11) overall, how would you rate the NRP simulation training? Responses were tabulated using means±SD and paired t-tests performed (Table 2). The study was approved by the Intermountain Healthcare Institutional Review Board.

Results

Of the five skill-sets evaluated, the one most often performed improperly was "suctioning of mouth and nose." The skill-set most commonly performed correctly was "proper chest compression-bagging ratio" (Table 1).

All 77 healthcare professionals completed the questionnaire. For each comparison, the simulation-based NRP classes were judged as superior to the standard classes (Table 2). All 77 participants responded that they would rather re-certify with the NRP simulation-based class than with the standard class.

The authors are with Intermountain Healthcare, Neonatal Intensive Care Unit, McKay-Dee Hospital Center, Ogden, UT. The authors would like to give a special thanks to Dr LP Halamek and "CAPE" (Center for Advanced Pediatric and Perinatal Education) at Stanford University and also to Teri Kiehn, RN and Mary Jane McGregor, RN of Intermountain Healthcare.

	n	Drying, stimulating and removing wet linen	Suctioning mouth and nose	30 seconds of effective bagging before chest compressions	Proper bagging rate	Proper chest compression-bagging ratio
Teams	64	64% (41/64)	51% (31/61*)	64% (41/64)	67% (43/64)	81% (51/63*)
P value		0.447	0.006	0.447	0.436	0.002

Table 1. Performance of NRP skill-sets by teams of 77 health care professionals. The numbers below represent the percentage (and actual numbers) where each of five skill-sets was performed properly, as part of a simulation-based NRP course. P values compare the performance of that skill set with performance of the four other skill sets.
*Scenarios were presented such that these elements did not always apply to all 64 teams.

Discussion

Since first introduced 22 years ago, NRP has served as a standard for resuscitation of newborn infants.[1] In each revision of the NRP program, an up to date evidence-based approach to resuscitation is taught.[2] Recent advances in NRP methodologies have been learner-focused, including incorporating simulation-based training into the curriculum.[7-11] Continued improvement of the NRP course depends, in part, on consistent re-evaluation of the performance of course participants. We recently introduced simulation-based NRP training into the northern region of Intermountain Healthcare, a health system including 18 hospitals with delivery services in the western United States. As part of this change, we sought to identify any consistently weak performance among the skill-sets taught in the classes. By using one evaluator to judge the performance of teams, we discovered that the suctioning of the nose and mouth was the procedure most often performed improperly. On the basis of that finding, we have added additional didactic and practice emphasis to this skill-set, as part of our next round of NRP classes.

A second part of our evaluative process, accompanying introducing simulation-based classes, involved learner evaluations, directly comparing the previous vs new simulation-based methods. The learners reported that simulation-based classes provided significantly better development of technical and cognitive NRP skills, improved communication, and facilitated teamwork.[12] In fact, without a single exception, the students all listed a preference to recertify in NRP using a simulation-based rather than a standard course.

Questions	Standard NRP	Simulation NRP	P value
Relevance to my practice in the hospital	3.23 + 0.79	4.95 + 0.21	<0.0001
Ability to engage my intellect	3.09 + 0.79	5.00 + 0.00	<0.0001
Ability to develop my behavior skills	2.64 + 0.80	5.00 + 0.00	<0.0001
Ability to transfer behavioral skills to real environment	2.56 + 0.79	4.98 + 0.13	<0.0001
Ability to develop my technical skills	2.83 + 0.85	4.97 + 0.18	<0.0001
Ability to transfer technical skills to real environment	2.66 + 0.84	4.97 + 0.18	<0.0001
Ability to develop my critical thinking skills	2.73 + 0.76	4.98 + 0.13	<0.0001
Ability to transfer critical thinking skills to real environment	2.80 + 0.78	4.98 + 0.13	<0.0001
Builds confidence level in performing the steps of neonatal resuscitation	2.78 + 0.74	5.00 + 0.00	<0.0001

Table 2. Evaluation of the Standard vs. Simulation-based NPR classes by 77 health care professionals, using a Likert Scale (1 through 5, with 5 indicating excellent and 1 indicating poor).

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The Fetal Pacemaker: Will It Ever Work?

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Introduction

Fetal hydrops is a non-specific entity from various fetal and maternal disorders that results in tissue edema and effusions in multiple cavities of the body. Approximately 50% of fetuses with hydrops fetalis die in utero with current medical care. (Matthew E. Abrams 2007) Hydrops is classically divided into immune and non-immune types. Immune hydrops is due to maternal hemolytic antibodies, while non-immune hydrops includes all other etiologies. The use of immunoprophylaxis and prevention of Rhesus disease has drastically declined the occurrence of immune hydrops, with the current majority of cases being of non-immune causes (>75%). This condition is associated with a high rate of fetal morbidity and mortality, with few treatment methods available (Matthew E. Abrams 2007).

Testing for maternal antibodies should take place within the first trimester of pregnancy and the fetal heart should be examined at 16 weeks with an echocardiogram. Current recommendations for abnormal findings such as increased PR interval, heart block. (Josephine Patricia Dhar 2006) The majority of fetal hydrops is currently caused by congenital heart problems (13.7%), abnormalities in heart rate (eg tachyarrythmias) (10.4%), twin-twin transfusions, congenital anomalies, chromosomal abnormalities, congenital viral infections, congenital anemia and congenital chylothorax (Matthew E. Abrams 2007).

A notable cause of hydrops is a complete atrioventricular conduction block that may be the result of autoimmune diseases such as systemic lupus erythematosus and Sjogren's syndromes. Neonatal lupus erythematosus is an isoimmune disease that occurs with passage of anti-Ro/SS-A and anti-La/SS-B antibodies through the placenta. These antibodies travel through the fetal circulation binding to fetal tissue causing congenital heart blocks and non-cardiac neonatal lupus. Lab studies in NLE show elevated liver enzymes and thrombocytopenia. Maternal antibodies have no effect on the fetus at 6 to 8 months of gestation and NLE subsides, however CHB still remains an important issue leading to significant mortality and morbidity.

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CHB occurs in 2% of cases, with incidence increasing to 20% in infants born to mothers with previous CHB due to anti-Ro/SSA and anti-La/SSA antibodies. CHB is a serious irreversible condition that is caused by anti-Ro/SSA and anti La/SSB antibodies that bind to cardiac tissue within the fetus resulting in myocarditis and fibrosis of the atrioventricular node. Cardiac injury occurs most often between 16-24 wks gestation and presumed to arise from transplacental passage of maternal IgG auto antibodies. Maternal antibodies bind to fetal Ro/SSA and La/SSB antigens that are expressed during the development of fetal cardiac conduction tissue. Once bound, inflammation ensues and apoptosis occurs extensively leading to scarring and ultimately fetal heart block. It has been shown that a disrupted calcium homeostasis induces death of the cardiomyocytes (Josephine Patricia Dhar 2006). The adverse effects of these antibodies can convert a normal rhythm into a complete heart block in as quickly as 7 days.

Diagnosis and Workup

Currently, ultrasound technologies are available for accurate recognition and diagnosis of fetal hydrops and are the cornerstone of fetal imaging. Sonograms of hydrops fetalis are likely to show fluid collection of the pleural, pericardial and peritoneal spaces. Polyhydramnios and an edematous thick placenta are often present. Diagnostic criteria for fetal hydrops includes: fluid accumulation in at least 2 serous cavities or 1 serous effusion and generalized anasarca. A single site of fluid accumulation may be sufficient to diagnose as long as there is a strong association with preexisting pathology. Ultrasonographic findings are subsequently used for follow-up imaging to observe progress of the disease in utero.

The workup of hydrops fetalis should be initiated if hydrops is suspected or if there is a history of previously affected fetuses. Maternal blood typing along with antibody screening by ELISA is recommended in immune related hydrops fetalis. The use of echocardiography to monitor fetal PR intervals is the current recommendation for antibody positive mothers. Monitoring should be weekly during 16 to 26 weeks gestation and biweekly from 26-32 weeks gestation. Furthermore, a high antibody titer should draw attention to a risk of hemolysis and anemia. Fetal anemia can now be safely analyzed by non-invasive doppler ultrasonography which is less tramatic than prior methods of

direct fetal blood sampling. Fetal anemia requires an ultrasound guided intravascular fetal blood transfusion

Nonimmune-related hydrops fetalis can result from numerous causes, and workup should be directed at the mother initially—specifically searching for hereditary or metabolic diseases, infections and medications. Blood tests should be performed to test for blood counts, thalassemias, G6PD deficiency, fetal-maternal transfusion and screening of TORCH infections. Furthermore, amniocentesis should be performed to obtain a fetal karyotype as well as cultures, AFP levels and lecithin-sphingomyelin ratios (Hamdan 2007).

Treatment

Treatment involves interventional fetal therapy that is focused on the etiology; however, modalities differ for both immune and non-immune hydrops fetalis. Initial treatment for immune-related hydrops fetalis should be aimed at correcting underlying fetal anemia. Fetal blood sampling and subsequent ultrasound guided in-utero blood transfusion is indicated for anemia that presents together with fetal hydrops. It has been shown that intravascular blood transfusions have a better prognosis than intraperitoneal transfusions because hypdrops interferes with peritoneal absorption. With IVT, 70-85% of fetuses with hydrops and 85-95% of fetuses without hydrops can survive.

Considering the complexity of treating non-immune hydrops fetalis, treatment is grouped into non-invasive and invasive. Non-invasive treatment includes the use of antiarrhythmic drugs, antibiotics, and correction of underlying maternal disease. Positive inotropic agents such as digoxin can be used in cases of fetal cardiac failure and SVT. Digoxin is transferred to the fetus transplacentally when given to the mother. Data is scarce regarding the use of antiarrhythmic agents in fetal arrhythmias; however, many options are available including quinidine, verapamil, amiodarone, adenosine, procainamide, sotalol, and flecainide. Loop diuretics (e.g.: furosemide) are used to treat fetal edema by promoting kidney excretion of excess water.

The use of glucocorticoids has been explored in cases of autoantibody-associated congenital heart block. A comparison study was conducted in which 28 of 50 pregnancies with fetal heart block were treated with fluorinated steroids while the remainder received no treatment. It was found that 100% of the third degree heart blocks were irreversible, and that there was no change in mortality, prematurity, degree of block, or need for pacing with the addition of steroids. There was however an improvement of effusions, ascites and hydrops in the steroid group. (Saleeb S. 1999) The use of maternal steroid therapy in fetal heart block still remains questionable due to associated complications. Dexamethasone was shown to cause oligohydramnios, intrauterine growth restriction, adrenal suppression, and poor brain development. (Breur 2004)

Invasive treatment that is available is usually reserved for severe cases of hydrops fetalis and outcomes depend on available resources and experience of the technician. Procedures include: amnioreduction, cord occlusion in cardiac twins, thoracocentesis of pleural effusions and vesicoamniotic drainage. These interventions hold a risk of complications and are not curative of hydrops fetalis. A new intervention utilizing intrauterine monolithic fetal pacemakers is currently being studied with promising results. (Hamdan 2007)

History of the Pacemaker

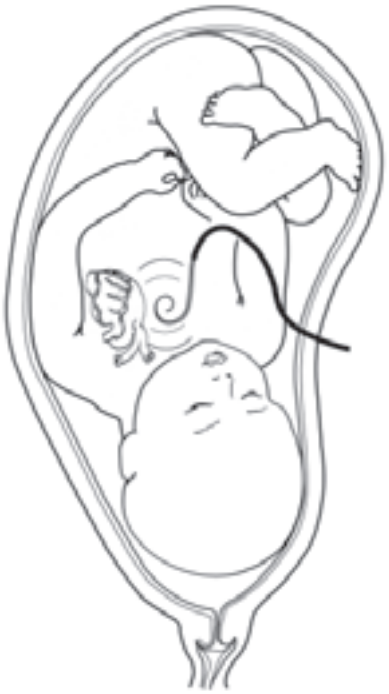
An artificial pacemaker is a device that uses electrical impulses via electrodes attached to myocardium to establish an adequate heart rate. The concept of pacing ones heart was reported as early as 1889 by J.A. McWilliam in the British Medical Journal in which an asystolic heart was ventricularly paced at a rate of 60-70 beats per minute. In 1928, Dr Mark C. Lidwell developed a technique of placing electrodes into a cardiac chamber, which was used to revive a still-born infant after ten minutes of pacing. Albert Hyman led the revolution in pacemaker history with the development of an electromechanical device that he coined as an "artificial pacemaker." During this time period much of the research on pacemakers was not published because of controversial views of interfering with nature by artificially stimulating the heart. The first external pacemaker design is attributed to John Hopps in the 1950s, which used a transcutaneous method of pacing. Early pacemaker designs were large, inconvenient, and were associated with patient discomfort. The development of the silicon transistor in 1956 allowed for the creation of the first wearable external pacemaker one year later. Advances led to the first clinical implantation of a pacemaker in 1958 via electrodes placed by thoracotomy. Transvenous pacing was subsequently studied in Sweden and France and became the mainstay of treatment. Although advancements had been made in technique, short battery life remained a large problem before the development of the lithium iodide cells in 1970. Current pacemakers offer adequate battery life, microchips that allow for external programming, and improved casing designs.

Pacemakers are currently being used for cardiac conditions such as sinus node dysfunction, bifascicular block, trifascicular block, third degree AV block, and Stokes-Adams conduction block. The success of pacemakers has been demonstrated in numerous studies in both adult and neonatal populations, however; the use of fetal pacemakers has not yet been applied. Neonatal pacemakers are being used for early intervention and treatment of congenital complete heart block with success. In a study led by Kelle in 2007, it was shown that "implantation of a dual-chamber epicardial pacemaker in neonates with congenital heart block is technically feasible and results in excellent outcomes in patients with structurally normal hearts and that system longevity at 6 years is excellent." (Kelle A. 2007.)

Currently, it is known that hydrops with a third degree heart blocks approaches a mortality of 100% despite treatment with steroids. The prospect of fetal pacing looks promising, and should be further explored as a treatment option for congenital complete heart block. Interventional pacing and heart rate support should theoretically correct the hemodynamic derangement and effectively clear the anasarca and pulmonary edema associated with CHB.

It has been shown that ventricular pacing should take place for a minimum of 2 to 4 weeks prior to delivery to achieve hemodynamic stability. This defines the necessary length of functionality needed for the fetal pacemaker system. In 2003, Dell'Orfano et al suggested the development of a prototype fetal pacemaker to be implanted via closed thorax over the wire deployment with ultrasound guidance, fetoscopy, or direct vision surgery. This fetal pacing system should avoid umbilical cord complications by bypassing umbilical vasculature and prevention of cord knotting or constriction by utilization of a low profile device. Another prerequisite entails in utero deployment with avoidance of thoracotomy or hysterectomy. The device

should be able to function for a minimum of 2 to 4 weeks or until delivery is plausible. A proposed method of delivery for an epicardial pacing is percutaniously via a subxiphoid incision—similar techniques have been used in adults. Additionally, unipolar electrical stimulation of the fetal heart is feasible due to the favorable conduction pathways. Electrical currents will pass through the high salt content of the amniotic fluid and through the fetal skin which has low electrical impedance due to underlying edema (Joseph Dell'Orfano 2003).



Fetal Pacemaker

A proof of concept article was published in 2003 showing successful use of the above described pacing system. In this study, complete AV block was artificially induced with ethanol in 11 Sprague rats. A J-wire was advanced through a 1cm subcostal incision and across diaphragm into the thorax. A pacing lead was then passed over the J-wire and positioned in close proximity to the mediastinum. Pacing was successful in 10 of the 11 rats, with ventricular capture and QRS widening. The mean QRS complex changed from 50.2ms pre-pacing to 95.1ms post-pacing. There were no complications caused by deployment, and the authors expect that fetal deployment will be associated with even less risk due to underlying pleural effusion that acts as a buffer against organ perforation during needle deployment. Movement of the fetus was also considered as a mode of deployment failure, but it is well known that a hydroptic fetus ceases to move thereby reducing the risk of dislodgment (Joseph Dell'Orfano 2003).

Some obstacles that must be taken into consideration were discussed by Fayn et al in 2005. These include the following 3 failure modes of the monolithic fetal pacemaker: primary positioning failure due to device length, angle of deployment and displacement due to somatic growth. The major finding in this study showed that the distance between the amniotic space and the pericardium has little variation in regards to gestational age. Data shows minimal changes in amniotic-to-pleural distance that followed a slope of 0.06 cm per week with a maximal change of 0.28 cm within 4 weeks—the time needed for resolution of the hydrops. This change is estimated to be much less in hydroptic fetuses with slower growth rates than healthy fetuses. Additionally, dislodgement of the electrodes due to somatic growth along with primary positioning failure was associated with minimal risk (Fayn E. 2005).

Conclusions

Hydrops fetalis that is associated with congenital complete heart block is a serious condition that has a poor prognosis. This condition leads to fetal mortality in 100% of cases. Unfortunately, current medical interventions are lacking and fail to address the underlying pathophysiology of the heart block. In utero pharmaceutical intervention with the use of steroids in previous studies showed no change in mortality, prematurity, degree of block, or need for pacing. Additionally, neonatal surgical intervention with dual chamber epicardial pacemakers has shown limited resolution of congenital complete heart block in regards to mortality and morbidity. Therefore, it may be assumed that intrauterine pacing should provide the greatest efficacy in reducing fetal demise from CHB. The monolithic fetal pacemaker holds the greatest potential for success in treatment of CHB, with positive results in prototypical lead designs. Recent studies in this field have recognized the importance of fetal pacemakers as an early intervention of hydrops associated with CHB. Further exploration of fetal heart pacing is imperative in regards to the future of interventional fetal medicine.

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Surfactant Replacement and Open Lung Concept—Comparison of Two Treatment Strategies in an Experimental Model of Neonatal ARDS

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Abstract

Background: Several concepts of treatment in neonatal ARDS have been proposed in the last years. The present study compared the effects of open lung concept positive pressure ventilation (PPVOLC) with a conventional ventilation strategy combined with administration of two different surfactant preparations on lung function and surfactant homoeostasis.

Methods: After repeated whole-lung saline lavage, 16 newborn piglets were assigned to either PPVOLC (n = 5) or surfactant treatment under conventional PPV using a natural bovine (n = 5) or a monomeric protein B based surfactant (n = 6).

Results: Comprehensive monitoring showed each treatment strategy to improve gas exchange and lung function, although the effect on PaO_2 and pulmonary compliance declined over the study period in the surfactant groups. The overall improvement of the ventilation efficiency index (VEI) was significantly greater in the PPVOLC group. Phospholipid and protein analyses of the bronchoalveolar lavage fluid showed significant alterations to surfactant homoeostasis in the PPVOLC group, whereas IL-10 and SP-C mRNA expression was tendentially increased in the surfactant groups.

Conclusion: The different treatment strategies applied could be shown to improve gas exchange and lung function in neonatal ARDS. To which extent differences in maintenance of lung function and surfactant homeostasis may lead to long-term consequences needs to be studied further.

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Background

In neonatal acute respiratory distress syndrome (ARDS)-like lung disorders different therapeutic approaches have been introduced in the last years. These include mechanical ventilation strategies as well as exogenous surfactant administration. Various animal studies have focused this topic and different regimes have been introduced into clinical practice although large clinical trials have not been performed yet.[1-3] As shown in experimental studies, the open lung concept (OLC) as an alternative ventilation strategy, improves gas exchange and reduces ventilator-induced lung injury in models of secondary surfactant deficiency.[4-5] These effects were seen while applying the OLC during high-frequency oscillatory ventilation an positive pressure ventilation.[4] Furthermore, histology and biochemical analyses of bronchoalveolar lavage specimen showed reduced signs of lung injury and pulmonary inflammation in OLC ventilated animals.[5] However, respiratory failure in term neonates is often accompanied by secondary surfactant deficiency, contributing to impairment of lung function in these infants. Thus, exogenous surfactant administration in neonatal ARDS-like lung injury is a clinically well established treatment option.[1,6,7] Even in meconium aspiration syndrome, leading to severe inflammatory-induced lung failure, exogenous surfactant administration is part of therapeutic concepts.[8] Experimentally, the restoration of pulmonary function and gas exchange as well as the amelioration of pulmonary inflammatory processes has been shown.[9] Nevertheless, it has not been extensively investigated whether surfactant therapy in neonatal ARDS attains different effects on gas exchange, lung function, surfactant homoeostasis or pulmonary inflammatory processes compared to the OLC without surfactant replacement, although these effects may lead to differences in short and long term pulmonary outcome following neonatal ARDS. Furthermore, there is still no consensus on ventilation strategy in these infants in combination or without surfactant administration until now.[10]

Concerning the choice of the surfactant preparation applied, surfactant preparations with altered protein and phospholipid

Table 1: Primer and TaqMan™ probes

Primer and Probe Description	Primer sequences for PCR (forward (F) and reverse (R)) Probe sequences for TaqMan™ analysis
Hypoxanthin-guanine-phosphoribosyl-transferase	F: 5'-TGGAAAGAATGTCTTGATTGTTGAAG-3'
	R: 5'-ATCTTTGGATTATGCTGCTTGACC-3'
	Probe: 5'(VIC)-ACACTGGCAAAAVAATGCAAACCTTGCT-(TAMRA)3'
β-Actin	F: 5'-TCATCACCATCGGCAACG-3'
	R: 5'-TTCCTGATGTCCACGTCGC-3'
	Probe: 5'(VIC)-CCTTCCTGGGCATGGAGTCCTGC-(TAMRA)3'
Interleukin 1 beta (IL-1β)	F: 5'-GGTTTCTGAAGCAGCCATGG-3'
	R: 5'-GATTTGCAGCTGGATGCTCC-3'
	Probe: 5'(FAM)-AAAGAGATGAAGTGCTGCACCCAAAACCTG-(TAMRA)3'
Interleukin 6 (IL-6)	F: 5'-GGGTAGGGAAGGCAGTAGCC-3'
	R: 5'-GAATCCCTCTCCACAAGCG-3'
	Probe: 5'(FAM)-CTTCAGTGGAGTCGCCTTCTCCCTAA-(TAMRA)3'
Interleukin 8 (IL-8)	F: 5'-TTCTGCAGCTCTCTGTGAGGC-3'
	R: 5'-GGTGGAAAGGTGTGGAAGTC-3'
	Probe: 5'(FAM)-TTCTGGCAAGAGTAAGTGCAGAACTTCGATG-(TAMRA)3'
Interleukin 10 (IL-10)	F: 5'-TTGGAGCTTGCTAAAGGCACT-3'
	R: 5'-CGGCGCTGTCATCAATTTCT-3'
	Probe: 5'(FAM)-CACCTCCTCCACGGCCTTGCTCTT-(TAMRA)3'
Surfactant protein B (SP-B)	F: 5'-TCC GCT GGT CGT TGA TCA C-3'
	R: 5'-GTT TGC ACA GGC CCA AGT G-3'
	Probe: 5'(FAM)-CAG AGC CAA ATG AAC CTG AAG GCC ATC-(TAMRA)3'
Surfactant protein C (SP-C)	F: 5'-CAC CTT CTC CAT TGG CTC TAG TG-3'
	R: 5'-ATA CTC TGC GGA GAC ATC TTC ATG-3'
	Probe: 5'(FAM)-TGA CTA CCA GCG GCT CCT GAT TGC C-(TAMRA)3'

contents compared to natural surfactant products have gained increasing interest in treatment of ARDS-like lung disorders[9,11,16-20] due to their potential resistance towards surfactant inactivation.[17] Thus, two different surfactant preparations have been chosen for surfactant replacement therapy in the present study: A natural bovine surfactant, frequently used in clinical treatment regimes for neonatal ARDS[18,19] and a modified monomeric SP-B based bovine surfactant, that had recently been demonstrated to improve biological activity of the surfactant preparation compared to standard preparations in a neonatal lung lavage model.[20]

The aim of the present study was to compare a treatment strategy applying the OLC without surfactant replacement with a treatment regime using exogenous surfactant administration under conventional ventilation for their effects on gas exchange and lung function variables in a piglet model of neonatal ARDS. Furthermore, different variables of the surfactant system have been assessed using molecular and biochemical analyses of surfactant proteins (SP) and phospholipid composition in order to obtain sensitive markers for lung injury processes. Regarding the impact of different treatment strategies on pulmonary inflammatory processes secondary to lavage-induced lung failure, histologic changes and pulmonary interleukin mRNA expression have been analyzed.

Methods

Anesthesia was performed in 16 newborn piglets, aged 6 ± 5 days and at a weight of 3.0 ± 0.5 kg (mean ± SD each) with ketamine and midazolam after an intramuscular bolus of ketamine as published previously.[9] The piglets were tracheotomized, a cuffed endotracheal tube (3.0 mm inner diameter; Rüsch, Kernen-Rommelshausen, Germany) was introduced into the trachea and connected to the Evita XL (Draeger, Lübeck, Germany).

Animals were ventilated using a pressure-controlled mode with a peak inspiratory pressure (PIP) of 9–12 cm H_2O, a positive end-expiratory pressure (PEEP) of 2 cm H_2O, and a respiratory rate of 25–30 cycles/min, a rate of inspiration to expiration of 1:2 at 100% oxygen (FiO_2 1.0). Under these conditions, normocapnia was observed. A neuromuscular block was induced with pancuromium bromide (0.5 mg/kg iv), followed by a continuous infusion with fentanyl (20 µg/kg/h), midazolam (0.3 mg/kg/h) and pancuromium bromide (0.3 mg/kg/h) to provide sedation, analgesia and muscular relaxation. The right common carotid artery was cannulated (20 G, Arrow, Erding, Germany) for continuous blood gas and blood pressure monitoring (Paratrend/ Trendcare, Philips Medical, Böblingen, Germany). A double-lumen central venous line (4.0 Fr, Arrow) was placed in the right femoral vein for infusion of fluids and medication. A continuous infusion of 5% dextrose was started (100 mL/kg/d) and all animals received one dose of cefotaxime (100 mg/kg). Body temperature was measured rectally and kept between 38° and 39°C.

Lavage procedure: Respiratory failure was induced by repeated saline lavage (50 mL/kg; 37°C) as described previously.[21] Lavage procedures were repeated at 3-min interval until partial arterial oxygen pressure (PaO_2) was below 10.7 kPa at the following ventilator settings: PIP/PEEP 25/5 cm H_2O; rate 40 breaths/min; I:E ratio 1:2 and FiO_2 1.0. A mean of 7 ± 3 lavage procedures were performed per animal and a mean recovery rate of 94% of the lavage fluid was achieved.

Experimental protocol: Within 10 min after the final lavage, animals were randomly allocated (T = 0 h) to one of the three study groups and ventilated for a period of 5 h. FiO_2 was kept at 1.0 during the whole experimental procedure. Animals that showed no recovery from lung lavage procedures in the different

Table 2: Gas exchange and lung function variables

a. Gas exchange and lung function variables at different time points

	Pa_{o2}	Pa_{CO2}	C_{dyn}/kg	VT/kg	Res	VEI	ΔP
Healthy (H)							
PPV_{OLC}	74.21 ± 16.75	5.67 ± 2.05	1.94 ± 0.89	16.0 ± 4.8	37.62 ± 8.09	0.29 ± 0.17	10.20 ± 0.45
mon SP-B	64.11 ± 34.10	3.75 ± 0.75	2.56 ± 0.50	20.4 ± 2.7	40.50 ± 8.63	0.35 ± 0.08	10.00 ± 0.00
nat SF	78.44 ± 15.09	5.29 ± 1.95	2.12 ± 0.87	19.2 ± 7.0	37.88 ± 7.43	0.29 ± 0.14	10.25 ± 0.50
Lavaged (T = 0)							
PPV_{OLC}	6.70 ± 3.04 **	6.95 ± 2.84	0.56 ± 0.23 *	11.3 ± 2.6	52.43 ± 13.53 *	0.10 ± 0.06 *	20.00 ± 0.00
mon SP-B	9.24 ± 0.79*	3.86 ± 1.64	1.21 ± 0.42 *	21.0 ± 5.0	63.28 ± 15.30 *	0.11 ± 0.02 **	20.00 ± 0.00
nat SF	8.16 ± 1.26 **	5.57 ± 1.35	0.88 ± 0.35 *	16.3 ± 5.4	50.25 ± 11.95 *	0.10 ± 0.04 *	20.00 ± 0.00
1 h							
PPV_{OLC}	9.68 ± 2.26	6.91 ± 2.07	0.57 ± 0.20	11.3 ± 4.5	47.50 ± 12.90	0.09 ± 0.04	20.00 ± 0.00
mon SP-B	38.60 ± 24.14	3.83 ± 2.84	1.52 ± 0.66	22.9 ± 8.4	58.55 ± 14.04	0.16 ± 0.09	19.50 ± 1.00
nat SF	56.86 ± 14.62	3.75 ± 1.13	1.50 ± 0.43	23.1 ± 6.2	53.98 ± 14.52	0.14 ± 0.05	20.00 ± 0.00
2 h							
PPV_{OLC}	71.45 ± 20.29	4.49 ± 1.97	1.03 ± 0.38	10.2 ± 2.2	34.34 ± 8.13	0.33 ± 0.20	12.60 ± 1.82
mon SP-B	64.87 ± 29.48	3.51 ± 0.91	1.53 ± 0.10	16.1 ± 7.0	47.80 ± 20.69	0.33 ± 0.27	13.75 ± 3.86
nat SF	75.18 ± 19.67	4.12 ± 0.41	1.39 ± 0.31	18.6 ± 4.0	45.20 ± 7.52	0.16 ± 0.02	17.75 ± 1.71
3 h							
PPV_{OLC}	74.08 ± 12.99	5.19 ± 2.35	1.13 ± 0.75	9.9 ± 3.0	34.76 ± 10.65	0.30 ± 0.19	12.40 ± 2.07
mon SP-B	59.05 ± 33.81	4.77 ± 1.11	1.23 ± 0.14	14.7 ± 4.1	50.63 ± 14.95	0.19 ± 0.12	14.00 ± 3.74
nat SF	72.32 ± 17.01	4.81 ± 0.55	1.15 ± 0.30	17.1 ± 5.0	43.85 ± 9.29	0.15 ± 0.04	17.00 ± 0.82
4 h							
PPV_{OLC}	70.09 ± 12.32	5.54 ± 1.67	1.11 ± 0.73	9.7 ± 2.4	35.46 ± 7.11	0.26 ± 0.15	12.60 ± 3.21
mon SP-B	60.05 ± 33.26	4.73 ± 1.28	1.21 ± 0.15	14.8 ± 3.4	53.70 ± 19.89	0.18 ± 0.11	14.50 ± 3.87
nat SF	56.53 ± 11.97	5.37 ± 0.53	1.05 ± 0.27	15.5 ± 2.8	44.18 ± 11.66	0.14 ± 0.04	16.50 ± 0.58
5 h							
PPV_{OLC}	71.61 ± 9.23	5.25 ± 1.01	0.97 ± 0.51	9.6 ± 3.2	35.78 ± 8.46	0.25 ± 0.14	12.80 ± 3.27
mon SP-B	60.38 ± 33.21	5.49 ± 1.17	1.04 ± 0.22	13.1 ± 3.7	51.93 ± 14.55	0.16 ± 0.08	14.0 ± 4.69
nat SF	48.94 ± 20.65	5.20 ± 0.52	1.01 ± 0.25	15.0 ± 2.2	50.55 ± 13.11	0.12 ± 0.04	17.00 ± 0.82

b. Overall differences in gas exchange and lung function variables (T5 - T0)

	Pa_{o2}	Pa_{CO2}	C_{dyn}/kg	VT/kg	Res	VEI	ΔP
T5 - T0							
PPV_{OLC}	64.90 ± 9.22	-1.71 ± 2.57	0.42 ± 0.40	-2.75 ± 0.96	-17.2 ± 5.43	0.19 ± 0.078 **/§**	-7.2 ± 3.27
mon SP-B	51.14 ± 33.47	1.63 ± 1.27	-0.18 ± 0.42	-8.0 ± 4.24 *	-11.35 ± 13.10	0.043 ± 0.07	-6.0 ± 4.69
nat SF	40.78 ± 20.49	-0.38 ± 1.71	0.13 ± 0.27	-1.25 ± 3.59	0.3 ± 5.91	0.02 ± 0.06	-3 ± 0.82

mean ± SD; open lung concept positive pressure ventilation (PPV_{OLC}; n = 5); surfactant treatment under conventional positive pressure ventilation: natural bovine surfactant (Alveofact®; nat SF; n = 4), monomeric surfactant protein B based surfactant (mon SP-B; n = 4). * $p < 0.05$; ** $p < 0.01$ vs initial values (healthy; H). Further levels of significance (two-way ANOVA) are given in detail in the text.
* $p < 0.05$ vs nat SF
§ $p < 0.05$ vs mon SP-B

treatment groups, indicated by a PaO_2 < 60 kPa, were excluded from further analyses.

PPVOLC group: In this group (n = 5), animals with an PaO2 below 13.3 kPa one hour after the whole-lung lavage procedure, were applied to pulmonary recruitment, that was attained according to the protocol previously published by van Kaam et al.[5] The ventilatory rate was increased to 80 breaths per minute with an I:E ratio of 1:1. These settings remained unchanged during the experiment. PEEP was increased up to 15 cm H2O and PIP was stepwise increased (5 cm H_2O each step) to open up the lung. Recruitment of previously collapsed alveoli during this procedure decreased intrapulmonary shunt and thus increased oxygenation.[4] Optimal alveolar recruitment was defined as PaO_2 levels ≥ 60 kPa.[4] The level of PIP needed to recruit the lung was accordingly defined the opening pressure (PIPO).

After this recruitment procedure, PIP and PEEP were simultaneously decreased in equal steps every 2 to 3 min until PaO_2 dropped below 60 kPa, indicating increased intrapulmonary shunting. The level of PEEP at this stage of alveolar collapse was called the closing pressure (PEEPC). PEEP was then raised to a level of 2 cm H_2O above PEEPC and PIP was momentarily raised to PIPO (about 19 s) to fully recruit the lung. Thereafter, the pressure amplitude was set to keep the partial arterial carbon dioxide pressure ($PaCO_2$) within the target range (4–6 kPa). PEEP only was decreased if there were signs of alveolar overdistension such as increasing $PaCO_2$, decreasing PaO_2 or decreasing blood pressure.

Surfactant group: In this group, animals were ventilated in the pressure-controlled mode, applying a conventional ventilation strategy, ie PIP/PEEP 25/5 cm H_2O; rate 40 breaths/min; I:E ratio 1:2 and FiO_2 1.0.

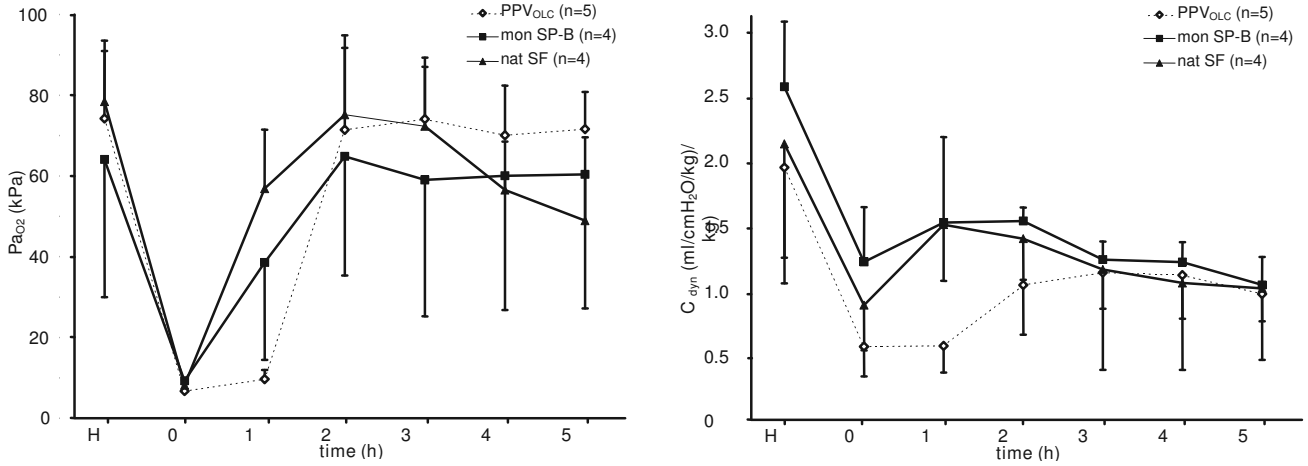

Figure 1
Gas exchange(Pa_{O2}) and lung function (C_{dyn}). Time course of Pa_{O2} (left panel) and dynamic compliance (C_{dyn}; right panel) over the observation period. Induction of lung injury by repetitive lavage procedures (T = 0) is followed by open lung concept positive pressure ventilation (PPVOLC; n = 5) or surfactant treatment under conventional positive pressure ventilation with a modified monomeric surfactant protein B surfactant (mon SP-B; n = 4) or a natural bovine surfactant (Alveofact®; nat SF; n = 4). Results are given as mean and standard deviation.

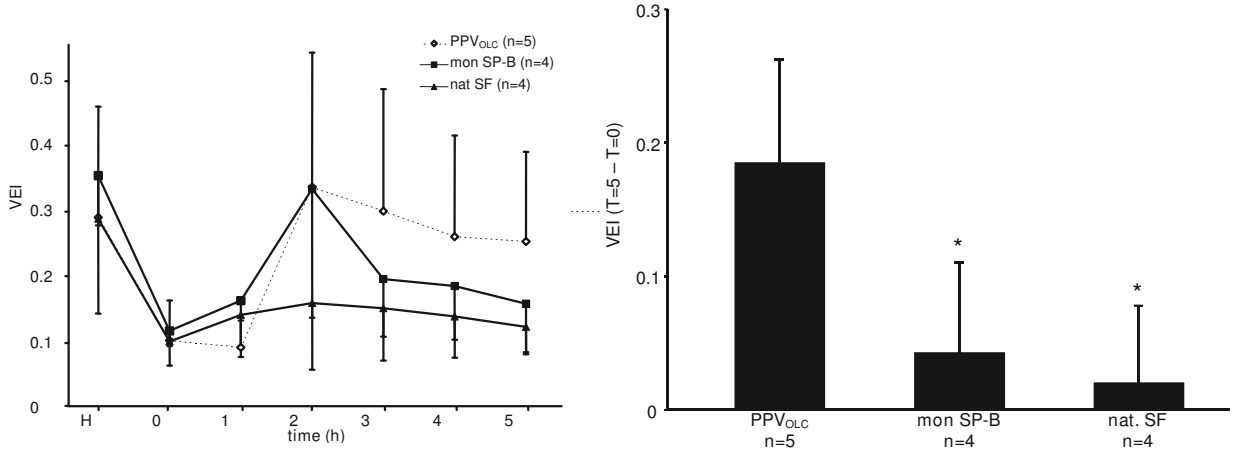

Figure 2
Ventilation efficiency index (VEI). *Left panel.* Time course of ventilation efficiency index (VEI) over the observation period. Induction of lung injury by repetitive lavage procedures (T = 0) is followed by open lung concept positive pressure ventilation (PPV_{OLC}; n = 5) or surfactant treatment under conventional positive pressure ventilation with a natural bovine surfactant (Alveofact®; nat SF; n = 4) or a modified monomeric surfactant protein B surfactant (mon SP-B; n = 4). *Right panel.* Difference of VEI over the study period (T5-T0). Study groups: open lung concept positive pressure ventilation (PPV_{OLC}; n = 5); surfactant treatment under conventional positive pressure ventilation with a modified monomeric surfactant protein B surfactant (mon SP-B; n = 4) or a natural bovine surfactant (Alveofact®; nat SF; n = 4). Results are given as mean and standard deviation. * $p < 0.05$ vs PPV_{OLC}.

Ten minutes after surfactant depletion with whole-lung lavage animals received either natural bovine surfactant (SF-RI1; Alveofact; n = 5) or a modified surfactant with a monomeric protein B (mon SP-B; n = 6) at a dosage of 100 mg/kg each. Details on surfactant preparations are given below. Surfactant preparations were administered as an intratracheal bolus under continuous chest movements and maintenance of PEEP. Again the pressure amplitude was set to keep the $PaCO_2$ within the target range (4–6 kPa) and PEEP was only decreased if there were signs of alveolar overdistension such as increasing $PaCO_2$, decreasing PaO_2 or decreasing blood pressure.

Mean arterial blood pressure, heart rate, ventilator settings, and lung function variables were recorded at the end of the instrumentation period, at the end of the lavage procedure and every 30 minutes thereafter. Although blood gas monitoring was available continuously to provide surveillance of ventilation, data were recorded at these same time points.

Therapeutic surfactant preparations: Alveofact (SF-RI1) is a chloroform/methanol extract of bovine lungs containing phospholipids, neutral lipids and the hydrophobic surfactant apoproteins SP-B and SP-C as described previously.[22]
The monomeric SP- B surfactant was prepared from SF-RI1 by selective reduction of dimeric SP-B by addition of mercaptoethanol (ME; 50 mg per 2 mL vial) at room temperature for 12 hours and subsequent removement of ME by vacuum extraction. Except for SP-B content subsequent analyses of

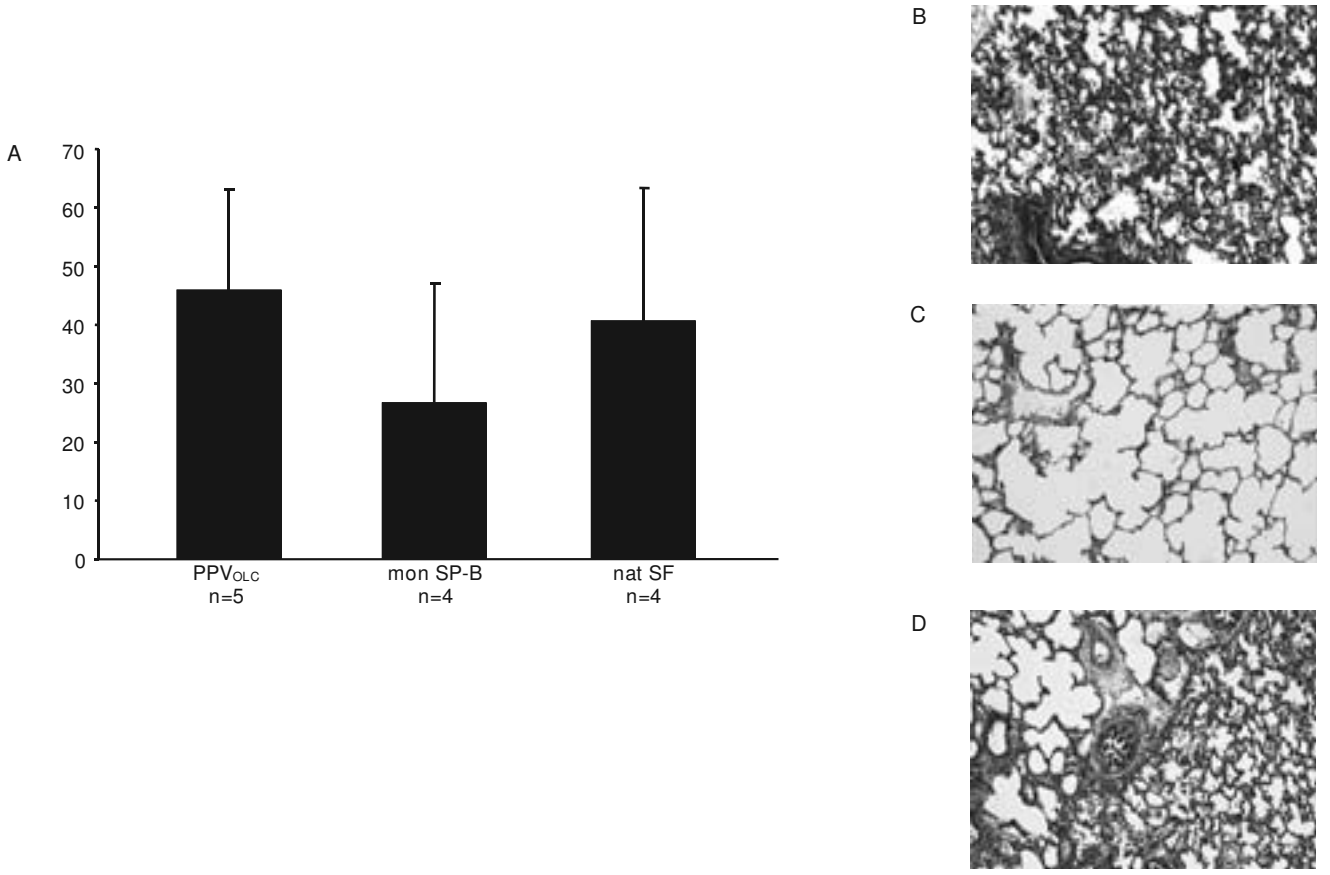

Figure 3
Histological sum scores (upper, middle and lower right lung lobe). Histologic sum scores (atelectasis, alveolar and interstitial inflammation, alveolar and interstitial hemorrhage, alveolar and interstitial edema, necrosis and overdistension) of upper, middle and lower right lung lobe using a four-point scale with no injury corresponding to 0 points and 4 points indicating maximum injury (**A**). Comparison of the groups showed no significant differences. Hematoxylin-eosin staining of exemplary histologic slides showing dystelectasis and neutrophiles in nearly all alveoli in the PPV_{OLC} group (**B**), regularly ventilated lung parenchyma in the monomeric SP-B group (**C**) and dystelectasis and neutrophiles in some of the alveoli in the natural SF group (**D**; hematoxylin-eosin, magnification 100×). *Study groups:* open lung concept positive pressure ventilation (PPV_{OLC}; n = 5); surfactant treatment under conventional positive pressure ventilation with a modified monomeric surfactant protein B surfactant (mon SP-B; n = 4) or a natural bovine surfactant (Alveofact®; nat SF; n = 4). Results are given as mean and standard deviation.

the obtained surfactant preparations showed no significant differences regarding their phospholipid and apo-protein profile. Both surfactant preparations were provided as lyophilized powder and resuspended in sterile saline 0.9% (Braun) to a final concentration of 60 mg/mL.

Lung function variables: Tidal volumes, resistance and dynamic compliance were measured by the Evita XL (Draeger, Lübeck, Germany) and related to body weight in order to compensate for different lung volumes. Ventilation efficiency index[23] and PIP-PEEP difference (ΔP) were further calculated.

Bronchoalveolar lavage: At the end of the experiment (T = 5 h) piglets were sacrificed by an overdose of phenobarbitone and bronchoalveolar lavage (BAL) was performed with physiological saline (3 × 50 mL/kg). The percentage of lung lavage fluid recovered was calculated and recovery of BAL fluid was comparable in all animals studied. Samples were centrifuged for 10 min at 300 × g at 5°C to remove cells and membranous debris and the supernatant was processed for analyses of surfactant protein and phospholipid concentrations.

Surfactant protein and phospholipid analyses; protein analysis: Total BAL proteins were calculated using a commercial assay (BCA assay, Pierce, Rockford, IL, USA). SP-B and SP-C were analyzed using ELISA techniques as described previously.[24,25]

Lipid analysis: Lipids were extracted from BALF with chloroform/methanol,[26] and the phospholipid content was determined by spectrophotometric measurement of phosphorus according to the method of Rouser et al.[27] Individual phospholipid classes were separated by high performance thin-layer chromatography and quantified using scanning densitometry as previously described.[28] Total fatty acids were analyzed by gas-liquid chromatography (Chrompack CP 9001, Varian, Darmstadt, Germany) following acid-catalyled transmethylation into fatty acid methyl ester (FAME) as previously described.[29] For characterization of relative content of large surfactant aggregates (LSA), BALF was centrifuged at 48,000 × g (1 h, 4°C), the pellet was resuspended in 0.9% NaCl and assessed for the PL-content. Recovery of PL in the pellet was used to calculate relative LSA content.

Histologic processing: After the end of the experiment following

Table 3: Phospholipid and surfactant protein analyses of lavage specimen

group	n (piglets)	PL [μg/ml]	PPQ	LSA [% PL]	SP-B/PL [% (w/w)]	SP-C/PL [% (w/w)]	PC [%]	PG [%]	PS [%]	PI [%]
PPV_{OLC}	5	48.65 ± 7.99	0.08 ± 0.01	47.7 ± 4.4	13.71 ± 3.08	3.06 ± 0.28	73.84 ± 5.57	3.59 ± 1.82	3.97 ± 2.44	6.87 ± 2.37
mon SP-B	4	131.10 ± 59.69	0.33 ± 0.16	62.7 ± 5.3	4.78 ± 2.01**	1.23 ± 0.45**	81.87 ± 1.38*	7.27 ± 2.25*	0.00 ± 0.00**	3.87 ± 1.94
nat SF	4	176.03 ± 68.91**	0.37 ± 0.21*	63.6 ± 6.2*	6.19 ± 1.73**	1.06 ± 0.62***	81.19 ± 1.43*	8.44 ± 1.10**	0.00 ± 0.00**	3.52 ± 0.79

group	n (piglets)	PE [%]	SPH [%]	PUFA [%]	Usat FA [%]	TL 16:0 [%]	Tlfa 20:4 (AA) [%]	Tlfa 20:5 (EPA) [%]
PPV_{OLC}	5	7.94 ± 3.63	3.80 ± 1.42	19.94 ± 1.39	40.34 ± 1.41	44.78 ± 1.73	5.54 ± 0.55	0.16 ± 0.03
monSP-B	4	4.99 ± 1.21	2.02 ± 0.85	12.16 ± 3.76**	33.19 ± 3.27**	52.97 ± 3.78**	3.03 ± 0.71**	0.15 ± 0.02
nat SF	4	0.47 ± 0.18	2.11 ± 0.81	11.52 ± 3.09**	35.76 ± 1.78*	50.24 ± 2.17**	2.58 ± 0.82***	0.29 ± 0.06**

PPQ (phospholipid-to-protein ratio); Phospholipid classes are given as percent (w/w) of all phospholipids. LSA = large surfactant aggregates, given as percent (w/w) of all BALF phospholipids. PC (phosphatidylcholine); PG (phosphatidylglycerol); PS (phosphatidylserine); PI (phosphatidylinositol); PE (phosphatidylethanolamine); SPH (sphingomyelin); Fatty acids were dermined in the BAL total lipid fraction and are given as percent (w/w) of all fatty acids. PUFA (polyunsaturated fatty acids in the total lipid fraction); TL 16:0 (palmitic acid in the total lipid fraction). AA = Arachidonic acid, EPA = Eicospentaenoic acid
* $p < 0.05$ vs PPV_{OLC}; ** $p < 0.01$ vs PPV_{OLC}; ***$p < 0.001$ vs PPV_{OLC}
§ $p < 0.05$ vs mon SP-B; §§ $p < 0.01$ vs mon SP-B

the lung lavage procedure, the right lung was perfused with 300 mL of a formaldehyde (4.6%)-glutaraldehyde (0.5%)-solution for approximately 10 minutes. Finally, the trachea was clamped at a PEEP of 10 cmH2O, right lungs were removed under maintenance of PEEP and submersed in the above mentioned solution for histomorphologic analyses. Tissue slides were obtained from dependent and non-dependent parts of the right lung. Four tissue slides were analysed from both the upper and lower lung lobe and two slides from the middle lung lobe, respectively. The slides were stained with hematoxylin-eosin (slides of 0.5 μm thickness). Lung histology was evaluated by a pathologist (M.E.), blinded to the animal's group assignment, according to a previously described histologic score.[30] Variables scored for histologic evaluation were atelectasis, alveolar and interstitial inflammation, alveolar and interstitial hemorrhage, alveolar and interstitial edema, necrosis and overdistension. The variables were scored using a four-point scale with no injury corresponding to 0 points and 4 points indicating maximum injury.

Measurements of interleukin and surfactant protein (SP) -B and -C mRNA expression by realtime PCR: Messenger RNA (mRNA) expression of interleukin (IL) -1β, IL-6, IL-8, IL-10 and SP- B and SP-C was measured in tissue of the left lung lobe using the real-time RT-PCR technique (TaqMan™). Samples were obtained from representative parts of the upper and lower lung lobe.

Primers and probes were designed using Primer Express software (Applied Biosystems, Foster City, USA) following a fixed set of recommendations as described previously.[9] Control PCRs showed no signal for genomic DNA, proving mRNA-specifity. Primers were purchased from Roth (Roth, Karlsruhe Germany), probes from Applied Biosystems, respectively. Lung tissue homogenization was performed in liquid nitrogen and total RNA was then extracted using the acid guanidinium thiocyanate-phenol-chloroform method (Roti Quick, Roth). Total RNA isolation, random primed reverse transcription and real-time PCR was performed following a standardized protocol as described previously.[9] Primer and TaqMan probe sequences are depicted in table 1. Relative quantification was performed using the ΔΔCt method, which results in a ratio of target gene expression and the expression of a housekeeping or reference gene.

For housekeeping genes β-actin (A) and hypoxanthin-guanine-phosphoribosyl-transferase (HPRT) were chosen and validated by variation analyses in all samples.

As β-actin showed both no differences between different experimental groups and the lowest variation in all samples, it was chosen as reference gene for further analysis.

Statistical analyses and data presentation: Results are given as mean and standard deviation (SD). Results of real-time PCR analyses are given in arbitrary units and were normalized to housekeeping gene expression. Data analysis was performed using SPSS for Windows Version 6.1.3. As normal distribution has been shown, two-way ANOVA with repeated measurements was performed for analysis of lung function variables over the time course. In order to compare outcome levels between the groups differences from T = 5 - T = 0 were calculated and one-way ANOVA was performed with posthoc Scheffé. Results of the histologic evaluation as well as from determination of lavage specimen and real-time PCR were analyzed using one-way ANOVA with posthoc Scheffé.

Results

All animals survived during the study period. There were no statistical significant intergroup differences in age, weight or number of lavages needed to induce the lung injury. No air leaks

Table 4: Pulmonary cytokine and surfactant protein mRNA expression (left lung lobe)

group	n *(piglets)*	IL-1β/A	IL-6/A	IL-8/A	IL-10/A	SP-B/A	SP-C/A
PPV_{OLC}	5	0.73 ± 0.51	1.27 ± 1.21	0.10 ± 1.3	0.34 ± 0.16	2.84 ± 2.17	0.82 ± 0.65
mon SP-B	4	0.35 ± 0.38	0.59 ± 0.78	0.03 ± 0.04	0.62 ± 0.32	4.05 ± 2.31	1.67 ± 0.87
nat SF	4	2.10 ± 1.77	3.96 ± 3.82	0.23 ± 0.22	0.67 ± 0.2	2.95 ± 1.27	1.09 ± 0.35

Normalization to β-Actin (A). Values are given as fold change ($2^{-\Delta\Delta Ct}$). Means were calculated from values of upper and lower lung lobe.

were observed within the study period. Blood gas values and lung function variables before and immediately after lavage were comparable in the three treatment groups (Table 2a). One animal of the natural surfactant group and 2 animals of the mon SP-B surfactant group did not recover after surfactant administration and required intensified ventilation (OLC) in order to reach PaO2 levels ≥ 60 kPa. As this alteration in treatment strategy was not comparable with the other study groups, these animals were therefore excluded from further analysis. Thus, 13 animals were available for analyses. No animal included for further analyses showed signs of hemodynamic compromise. Data on hemodynamics were not significantly different between the groups.

Gas exchange and lung function: After induction of lung injury, PaO_2, dynamic compliance and VEI were significantly reduced in all animals (see figure 1), whereas the resistance increased significantly. $PaCO_2$ remained largely unchanged. Mean opening pressure was 35 ± 4 cm H_2O, mean closing pressure 8 ± 3 cm H2O in the PPVOLC group.

After experimental intervention (OLC, surfactant administration), PaO_2, tidal volumes, difference of PIP-PEEP (ΔP), resistance, VEI ($p < 0.001$ each) and dynamic compliance ($p = 0.01$) significantly improved over the time course in each treatment group (two-way ANOVA; Table 2a).

Regarding differences between the treatment groups, two-way ANOVA testing revealed a significant difference with respect to PaO_2 ($p < 0.001$; figure 1) and $PaCO_2$ ($p < 0.05$) levels over the time course with declining effects in the nat SF group 3 hours after intervention. Comparing the relative change of the variables over the study period (T = 5 - T = 0), gas exchange variables showed a response to each experimental strategy and the overall change did not differ between the groups (Table 2b).

Comparable results were found for the development of the dynamic compliance and the ΔP over the study period with a significant difference between the study groups: Dynamic compliance could be shown to increase up to two-fold, with declining effects in the surfactant groups after 3 hours (figure 1), whereas ΔP could be decreased in all experimental groups during the observation period with most pronounced effects in the PPVOLC and the mon SP-B group ($p = 0.001$). Nevertheless, changes in dynamic compliance or ΔP over the study period (T = 5 - T = 0) were not statistically significantly different between the groups. Mean airway pressure was found to be significantly higher in the PPVOLC group compared to both surfactant treated groups ($p = 0.015$; data not shown).

The tidal volumes achieved under different ventilation strategies were significantly lower in the PPVOLC group over the whole study period compared to both surfactant groups ($p = 0.002$). Relative changes of tidal volumes (T = 5 - T = 0) showed a significant decline in the mon SP-B group when compared to the nat SF group ($p < 0.05$ vs nat SF).

Improved VEI were found in all treatment groups but differed in its time course between the groups ($p = 0.015$; figure 2). Most pronounced effects were seen in the PPVOLC and the mon SP-B group, although effects decreased in the mon SP-B group towards the end of the observation period (figure 2). The relative change of the VEI over the observation period (T = 5-T = 0) was found to be significantly greater in the PPVOLC group compared to the mon SP-B and nat SF treated group ($p < 0.05$; figure 2).

Lung histology: Lung histology was examined in tissue slices of the right upper, middle and lower lung lobes. All study groups revealed significantly higher histologic scores in the upper and lower lung lobe compared to the middle lung lobe ($p < 0.05$, data not given in detail). Figure 3 shows the histological sum score of the different treatment groups. Although there was a tendency towards lower sum scores in the mon SP-B group (27 ± 20) compared to the PPVOLC group (46 ± 17) and the nat SF group (41 ± 23) there was no significant difference.

Surfactant protein (SP) and phospholipid analyses: Total phospholipid and total protein content, phospholipid class profiles, total lipids fatty acid profiles, recovery of large surfactant aggregates and surfactant proteins (SP)-B and -C, were determined in cell depleted BAL specimen and are displayed in table 3. Total PL concentrations were elevated up to 3-fold in both surfactant groups with significant differences between the nat SF group compared to the PPVOLC group ($p = 0.012$; table 3). Total protein content was not different between the study groups, resulting in an increase of the phospholipid-to-protein ratio in both surfactant groups compared to the PPVOLC group (nat SF $p = 0.05$; mon SP-B $p = 0.09$). Regarding phospholipid composition, the relative content of phosphatidylcholine and phosphatidylglycerol was found to be significantly increased in both surfactant groups ($p < 0.05$ vs PPVOLC) and reached near normal levels. Accordingly, the relative content of phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine and sphingomyelin decreased in the mon SP-B and nat SF groups with significant effects for phosphatidylserine ($p < 0.001$ vs PPVOLC). Analyses of the total fatty acids revealed a significantly increased relative content of palmitic acid in both surfactant groups ($p < 0.01$ vs PPVOLC; table 3) whereas levels of polyunsaturated fatty acids and all unsaturated fatty acids decreased significantly ($p < 0.01$ vs PPVOLC). Levels of arachidonic acid decreased in both surfactant groups compared to the PPVOLC group, eicospentaenoic acid increased in the nat SF treated group ($p < 0.01$ vs PPVOLC).

The relative content of large surfactant aggregates was increased in the surfactant-treated groups compared to PPVOLC (nat SF $p = 0.06$; mon SP-B $p = 0.048$). Both, total SP-B and SP-C concentrations were not statistically different between the experimental groups. Nevertheless, levels were significantly lower in the surfactant groups compared to the PPVOLC group ($p < 0.001$) when normalized to the total PL content of each sample.

Interleukin and surfactant protein B and C mRNA expression analysis: Interleukin and SF mRNA expression was determined in the upper and lower left lung lobes. As there were no significant differences between the results obtained from the upper and lower left lung lobes, means were calculated and used for further analyses. Results normalized to β-Actin are represented in table 4. Normalization to the housekeeping gene HPRT confirmed the results.

Analyses of the pulmonary interleukin mRNA expression in the left lung revealed no significant differences between the study groups. Nevertheless, there was a tendency towards increased mRNA expression levels of the pro-inflammatory cytokines IL-1β, IL-6 and IL-8 in the nat SF group compared to mon SP-B

and the PPVOLC group (p = 0.1; table 4). Furthermore, mRNA expression of the anti-inflammatory cytokine IL-10 showed a tendency towards increased levels in both surfactant groups compared to the PPVOLC group (p = 0.1; table 4). Furthermore, SP-B and -C mRNA expression were found to be not significantly different. However, SP-C mRNA expression was shown to be tendentially increased in the mon SP-B and nat SF groups compared to the PPVOLC group (table 4).

Discussion

Respiratory failure often accompanies critical illness and determines morbidity in term neonates. Thus, evaluation of therapeutic strategies in neonatal ARDS-like lung disorders remains an important issue as demonstrated by a multitude of experimental and clinical studies.[19,31] Several concepts of treatment have been established in the last years. Under these, surfactant treatment is an established therapeutic option, as secondary surfactant deficiency may be causally related to the clinical picture and a potential cause for the impairment in lung function. Nevertheless, surfactant treatment is a very cost-intensive therapy and surely has its limitations due to adverse effects or the need for repetitive doses. Thus, conventional ventilation is often used as first-line management of the disease. If conventional ventilation strategies fail, further treatment regimes are searched for in order to minimize ventilator-induced lung injury.[32] Thus, ventilation following the open lung concept is often used as a rescue therapy. Nevertheless, there is still no consensus on ventilation strategy in these infants in combination or without surfactant administration until now.[10] Furthermore, different treatment regimes as exogenous surfactant administration under conventional ventilation or application of open lung ventilation strategies without surfactant replacement may result in differing effects on gas exchange, lung function, surfactant homoeostasis or pulmonary inflammatory processes and thus short and long term pulmonary outcome following neonatal ARDS.

In the present study, both treatment strategies investigated, administration of exogenous surfactant under conventional ventilation as well as application of the OLC, were found to be efficient in improving gas exchange and reconstituting lung function in neonatal ARDS. The effects on lung function and gas exchange have been confirmed for each treatment strategy in previous experimental studies.[4,7,18]

To experimentally assess the effects of exogenous surfactant administration in neonatal ARDS compared to the OLC, a standard treatment regime using natural bovine surfactant has been chosen. However, surfactant preparations with varying protein and phospholipid contents have gained increasing interest in treatment of ARDS-like lung failure.[11-13] As native SP-B in humans is secreted in the alveoli predominantly in its dimeric form, modification of the dimeric structure leads to differences in the function of SP-B and is currently under further investigation.[33,34] Recently, modification of a natural surfactant preparation (SF-RI1) into a monomeric SP-B content has been demonstrated to improve biological activity compared to standard preparations in vivo.[20] Thus, the monomeric SP-B surfactant has been chosen as an alternative surfactant treatment in the present model.

Regarding the effects of the different treatment regimes applied on lung function and gas exchange in detail, the decrease of PaO_2 levels in the natural surfactant group at the end of the study period might reflect the need for repetitive doses of surfactant to achieve sustained treatment effects and may be a consequence of surfactant inactivation in the alveolar compartment.[35] Furthermore, levels of dynamic compliance did not reach initial values during the observation period and treatment effects declined to the end of the study period in the surfactant treated groups. In line with our findings, van Kaam and colleagues have shown a dose-dependency of the surfactant effect whereas a time-dependency with declining effects over time could be shown in the present study.[36] Besides the need for repetitive or increased doses of exogenous surfactant the indicated effects may also be due to ventilator-induced lung injury under the conventional ventilation regime in the surfactant treated animals. Improvement of VEI over the study period was found to be most pronounced in the PPVOLC group, which may reflect the potential of this ventilation strategy to more equal recruitment of different parts of the lung. In contrast, surfactant is known to preferably reach lower lung lobes and its administration therefore often leads to inhomogenous recruitment and holds the risk of partial overdistension. However, P values could be reduced in all study groups possibly leading to a reduction of shear stress and therefore traumatic lesions in the lung in the experimental ventilatory setting.

In order to define the impact of the treatment strategies applied on lavage-induced lung injury, surfactant homoeostasis and inflammatory processes, histologic patterns, cytokine and surfactant mRNA expression as well as phosholipid profiles of BALF were investigated.

Regarding histologic patterns, the evaluated score comprising different variables indicating the degree of lung injury showed no significant differences between the groups. Nevertheless, analyses showed alterations to pulmonary tissue, reflecting the delay of structural recovery compared to reconstitution of lung function and gas exchange after induction of neontatal ARDS-like lung injury. The monomeric SP-B preparation revealed a tendency to improvement in lung structure, which may suggest the altered surfactant preparation to be effective in influencing surfactant homeostasis and thus the recovery in physiologic lung function.

Alterations to the surfactant system have been shown to closely reflect lung injury processes, especially alveolar type-II cell integrity and metabolism.[25,28,37] Furthermore, reconstitution of the surfactant system has been discussed as an important measure assessing different treatment regimes in ARDS-like lung disorders in children and infants. As expected, the phospholipid profile in BAL specimen showed a normalization of the phospholipid and fatty acid profile in both surfactant groups with an increase in concentrations of phosphatidylcholine and phosphatidylglycerol as well as the palmitic acid concentration in the total lipid fraction. In contrast, the phospholipid analyses of the PPVOLC group showed the typical profile for ARDS-like lung failure with a reduced recovery of phosphatidylcholine and phosphatidylglycerol, an increased relative content of polyunsaturated fatty acids, i.e. arachidonic acid and a decreased relative content of palmitic acid.[28,37] Furthermore, the relative content of large surfactant aggregates and the phospholipid-to-protein ratio in the BALF were significantly reduced in the PPVOLC group. These findings reflect a significantly reduced recovery of the surfactant system in the PPVOLC ventilated animals compared to the surfactant treated groups, potentially leading to short and long term consequences regarding lung

injury processes and pulmonary function. Regarding the surfactant protein concentrations in the BALF, levels were comparabel in all study groups. In the case of SP-C, this may suggest a stabilization of type-II cell integrity and surfactant homeostasis under the indicated treatment regimes as previous studies showed significantly reduced SP-C levels in BAL specimen from conventionally ventilated ARDS patients.[25] An early recovery of alveolar type-II cell integrity and metabolism after lavage-induced lung injury may be further indicated by tendentially increased SPC mRNA expression in the in the surfactant treated groups.

Nevertheless, the combination of both treatment strategies will gain increasing interest as shown by latest studies.[2,38] Here, open lung ventilations strategies after exogenous surfactant administrations allowed reduction of both the opening and the closing pressures after some hours, which may be explained by a higher alveolar stabilization after recruitment maneuvers in combination with the effect of surfactant administration. Furthermore, the present study showed the relative SP-B and SP-C concentration after normalization to the total PL content of each sample, to be lower in the surfactant-treated groups. This may be assigned to a higher rate of ventilator-induced lung injury in the conventionally ventilated, surfactant treated animals, where higher ΔP values and tidal volumes compared to the PPVOLC group may led to an increased rate of shear stress to the lung. On the other hand, a shift in the phospholipid-to-protein ratio may result from surfactant administration, as the indicated preparations contain relevant amounts of phopsholipids. Furthermore, limits of surfactant treatment in combination with a conventional ventilation strategy are demonstrated by cases with an absent response to exogenous surfactant administration as one animal in the natural surfactant and two animals in the monomeric SP-B group did not recover from lung failure and required an intensified ventilation regime.

In terms of pulmonary inflammatory processes, previous studies have been shown for the OLC ventilation to reduce signs of inflammation in BALF when compared to conventional ventilation strategies.[4] In the present study analyses of pulmonary pro-inflammatory cytokine mRNA expression showed no significant differences between the OLC and the surfactant treated groups. However, mRNA expression of the anti-inflammatory cytokine IL-10 showed a tendency towards increased levels in the surfactant groups compared to the PPVOLC group, possibly indicating anti-inflammatory or lung protective effects of exogenous surfactant. The tendency towards increased IL-1β, IL-6 and IL-8 mRNA expression in the natural surfactant group has also previously been shown in vivo for natural surfactant treated animals in a model of experimental meconium aspiration syndrome[9] and for endothelial cell activation in vitro[39] and may be explained by a higher concentration of arachidonic acid in the natural surfactant preparation.

In conclusion, we could show in a descriptive manner both treatment strategies, the administration of exogenous surfactant under conventional ventilation as well as the application of an intensified mechanical ventilation concept following the OLC to be efficient in improving lung function and gas exchange in neonatal ARDS. Nevertheless, administration of surfactant led to a more pronounced effect on gas exchange and compliance in the first hours, although improvement in oxygenation declined after 3 hours in the natural surfactant group. In contrast, improvement in VEI was found to be more evident in the PPVOLC group. Thus, differences between the surfactant and the PPVOLC groups regarding maintenance of the effects on lung function as well as surfactant homoeostasis and the pulmonary inflammatory balance may lead to pulmonary long-term consequences which should be addressed in further studies. Limitations of the study, that need to be addressed are the potential induction of lung injury processes by the initial phase of conventional ventilation, the induction of lung injury using repeated lavage procedures with each lavage volume potentially beyond total lung capacity leading to non-physiologic stretch as well as the application of relatively high tidal volumes in the PPVOLC group compared to previously published study settings applying OLC ventilation regimes. Changing ventilation strategies and modifying existing concepts reflect everyday clinical practice, but further studies are needed to address the impact of these variables on pulmonary outcome. As well clinical studies are needed in order to verify findings from animal studies. As the results indicate differing surfactant preparations to reveal distinct effects on lung function variables, further studies are needed to define an optimized surfactant composition.

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Do Not Resuscitate Order in Neonatology: Authority Rules

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Ethical dilemmas in medicine should be resolved in light of four essential principles. To specify and guide concrete actions, it is necessary to supplement these principles by certain other (substantive, authoritative and procedural) rules. The purpose of this paper is to establish and justify the authority rules regarding the order not to resuscitate newborns. The authority rules are intended to indicate who should decide, but they do not determine what should be chosen. Decision regarding newborn's treatment/letting die depends on medical and quality-of-life judgments. Parents, doctors, and society are considered to possess decisional authority in the matter. However, who in a given case should decide ought to be inferred from the reasoning which assumes, as its premises, the medical and quality of-life judgments. The logical syntax of this reasoning is presented in this paper.

When in the early 1970s bioethics emerged as a new, separate branch of knowledge, it was necessary to determine whether this discipline should have been grounded exclusively in the deontological tradition of medicine or in more general philosophical (ethical) theories.[1] The first option seemed to have special appeal to these bioethicists who had their formal education in medicine and very often practiced as physicians. The second option was preferred by philosophers who dedicated themselves to resolving the moral dilemma of the contemporary medicine. Although eventually 'the philosophical approach to medical ethics' has dominated bioethical discourse, it soon became evident that moral theories needed serious reconsideration to be useful for medical ethics. The classical ethical theories (in particular, utilitarianism and Kant's deontological ethics) proved to be so complex and awkward to be helpful in solving the moral problems of the medical practice and biomedical research. The four principles approach to medical ethics, called also principlism, could be regarded as the philosophically grounded bioethical theory which comes up to practically oriented bioethicists' expectations. Firstly, principlism seems to be enough simple, both in its conceptualization and application, to be effectively used to resolve moral dilemma in everyday medical practice.[1] Secondly, it is a sufficiently wide ethical theory to be used in the pluralistic society. And thirdly, the four principles approach to bioethics is in agreement with the dominant, at least within the Western world's intellectual culture.[2] Principlism reflects liberalism and individualism,[1] which seems to be still the mainstream of this culture and accepts the ways of reasoning which are appropriate for this culture.[3] No wonder this theory became the dominant ethical framework for resolving moral dilemma in medicine just in the 1980s, and the landmark book Principles of Biomedical Ethics by Tom L. Beauchamp and James F Childress was, as Callahan observes, "by far the most popular medical ethics textbook in the 1980s and 1990s for classroom use (and probably still is)."[1]

Principlism is based on the assumption that all ethical dilemma should be resolved in the light of nonabsolute (prima facie), middle-level principles which are derived mainly from so called considered judgment in the common morality. Respect for autonomy, nonmaleficence, beneficence, and justice constitute the four clusters of principles.

To specify and guide concrete actions it is necessary, however, that the cluster of four principles would be supplemented by certain moral rules, which could be divided in three groups: substantive, authority, and procedural rules.[2] Substantive rules could be considered as the rules which specify the abstract principles. The authority rules indicate who should perform a certain action. Among these types of rules one can distinguish: (i) rules of surrogate authority (who should decide in the name of an incompetent person); (ii) rules of professional authority (who is authorized to make decision whether the patients' decisions should be accepted or overridden); (iii) rules of distributional authority (who is the proper person to decide on the allocation of medical resources). It should be emphasized that substantive and authority rules interact in both theory and practice. For instance, authority rules are justified in part by how well they express substantive rules and principles.[2] The third group of rules, procedural ones, regulates distribution of medical resources, in particular, in the situations when both substantive and authority rules cannot help sufficiently. The main purpose of this article is to establish and justify the authority rules regarding to the do not resuscitate (DNR) order in neonatology. Taking into account that justification of authority rules assumes reflection on the proper, from a given point of view, substantive rules, the standard of "patient's best interest" will be discussed.

Methods

In this study, coherentism as a method of justification in ethics is accepted. This method consists of four essential steps: (i) identification of "considered judgment" in the domain of common

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morality; (ii) specifying and (iii) balancing it (if in conflict with other considered judgment(s)), and (iv) testing if the reflective equilibrium was yielded. It should be accentuated that considered judgments even if considered as 'fixed points' are always subject to change, and the obtainable reflective equilibrium is never complete, ie that in practice some degree of incoherence within reflective equilibrium should be allowed.

Results and Discussion

Undoubtedly, neonatal mortality in the developed countries has significantly decreased in the last decades.[4,5] Advances in obstetric and neonatal care together with the establishment of centers capable of providing highly sophisticated cure and care have greatly improved the survival chance of progressively smaller and less mature neonates.[4] Unfortunately, despite this impressive progress, outcomes for, in particular, extremely premature (gestational age ≤ 24 weeks) and incredible-low-birth-weight (ILBW; ≤ 750 g) infants are still very poor. They are at a significant long-term risk of chronic medical problems and neuron-developmental sequelae.[4, 6-8] It should not be forgotten that the medical procedures are often highly aggressive in their manner and are the source of iatrogenic pain, i.e., related to diagnostic and therapeutic processes (so called procedural pain), and to painful long-term results of medical treatment. Highly sophisticated procedures of contemporary neonatology unfortunately can serve as very clear examples of actions which cause both procedural pain and painful long-term follow-up results.[9-16] Moreover, it is worth noticing that in the case of neonates the procedural pain is experienced in the period of newborns' very intensive neurological development. This permits to assume that the experience of (procedural) pain itself would have potential long-term effects in the following babies' development.[16-19]

The question arises of whether the same categories of the newborns (ILBW, extremely premature) really benefit from progress in medicine, or rather they should be considered the victims of this process. Is it morally acceptable to withdraw or withhold newborn's treatment? Or is it an ethical duty to stop aggressive therapy?

The data obtained in empirical studies seem to reveal that during last decades the conviction that it is morally acceptable or even morally desirable to let extremely premature/sick infants die has gained acceptance in the different societies.[8,20] This conviction is in coherence with the well-known from the tradition of medical ethics maxim: Primum non nocere. This rule is closely associated with the principle of nonmaleficence, which is thought to be a considered judgment.[2]

The study carried out by Schulz-Baldes et al[8] which aimed at investigating the end-of-life practice in one of large perinatal centers in Germany clearly showed that 81% of neonatal deceases of newborns in delivery room and 83% in the neonatal intensive care unit were preceded by a decision to withdraw/withhold life-sustaining therapy. In 79%, death occurred as a direct effect of withdrawing the mechanical ventilation. DNR order seems to be the main means by which the end-of-life-decision is realized.

Decisions, especially end-of-life-decisions, regarding treatment of newborns are particularly difficult from the ethical point of view. The newborn is not and has never been competent person/patient. The surrogate decision is needed. However, it should be emphasized that the guidance rules for surrogate decision-making in the case of newborn are substantially different from rules used in the case of formerly competent patients. Different ethical and legal standards which can be applied in the case of actually incompetent patients who, however, were formerly competent (for instance: advance directives, substituted judgment) are simply inapplicable to the decision-making process regarding newly born babies' treatment.[2,21] De facto, the only option is to use the best interest standard in its form known as "Barber."[21] This standard assumes that when deciding whether treatment or withholding/withdrawing treatment (in particular acting according to DNR order) is in the newborn's best interest, five factors should be taken into account. "First, does the medical treatment offer relief of all suffering or does it merely prolong inevitable dying? Second, will medical treatment allow the infant to enjoy optimal functioning? Third, what quality of life can be predicted for the baby? Fourth, what is the predicted lifespan of the child? And last, how will medical intervention affect the parents and family of the baby?"[21] Beauchamp and Childress find the last factor objectionable. They agree that it is rather common that patients have an interest in their families' welfare; however, they simultaneously find unjustifiable "to impute altruism, a desire to relieve family of its burdens to the patient against his or her medical best interests."[2] In fact, the problem seems to be even more complicated. Even if most patients have an interest in the well-being of their families, it remains unclear and uncertain if the patients and the members of their families understand in the same way what constitutes "good" and what constitutes "evil" for a family's welfare.

The best interest standard can be considered as a substantive rule in light of which the authority rules (who should make a decision regarding newborn's treatment?) ought to be justified. Beauchamp and Childress[2] observe that a surrogate decision-maker should be characterized by four essential qualifications: 1. ability to make reasoned judgments (competence); 2. adequate knowledge and information; 3. emotional stability; 4. a commitment to the incompetent patient's interests that is free of conflicts of interests and free of controlling influence by those who might not act in the patient's best interests.[2]

The last of the above listed qualification seems to be particularly interesting. It should be accentuated that this qualification assumes partiality of surrogate decision-makers rather than their impartiality. It means that surrogate decision-makers should act as an advocate rather than as a judge. Although three previous qualifications seem to predispose a physician to be a decision-maker, the fourth qualification speaks in advocacy of parental right to be the primary decision-makers in the name of their children, including neonates. In fact, parents seem to be the persons who proved their engagement in favor of newborn by taking actions which ultimately resulted in the birth of the infant. Moreover, the common morality assumption permits to consider the parents as the people who seek their children's best interests in the highest degree. However, neither does it mean that a physician should be excluded from the decision-making process, nor that parents' decision has always to be honored. Taking into account that in this decision-making process human life is at stake, just another party, namely a state and its authorities, should be involved in this process. The primary purpose of a state is to protect its citizens, especially their right to life.

The first step in the decision-making process is based on deciding whether, taking into account medical condition of the newborn, a given treatment, in particularly resuscitation, should be

considered as indicated, optional or harmful/futile.[2] By medically indicated treatment, the treatment is understood which, in all probability, causes the amelioration of the lifethreatening condition of the neonate. 'Optional treatment' is defined as treatment which in fact only prolongs dying of an infant who is chronically and irreversibly comatose. This treatment ought to be neither painful nor particularly expensive. The fact that optional treatment is painless and relatively cheap differentiates it from harmful/futile treatment.

A physician seems to be the right person to undertake the decision about to which group a given treatment belongs. It is worth noticing, however, that the physician's decision is not 'purely' medical in its character. To classify a given treatment into one of the three groups, the physician always, in the more or less conscious way, presupposes the axiological dimension of medicine, in particular quality-of-life judgments.[2] The axiological judgments are justified on the basis of physician's outlook of life, accepted philosophical or religious convictions and not by purely scientific knowledge of medicine. In fact, it is highly doubtful whether 'purely' scientific judgments exist at all in the medical practice.[22]

It is physician's responsibility to check that parents fulfill the qualifications (indicated above) necessary for the surrogate decision-maker, namely whether they are competent, in possession of the adequate knowledge and information, emotionally stable, and able to act freely, ie without controlling influences that determine their action. It is physician's duty to convey to parents relevant and reliable information about their infants' medical conditions (to a degree they want to know) and to take care of parents' well-being. It is possible, however that despite all physicians' efforts, the parents do not posses necessary qualifications to be recognized as the right persons to make a surrogate decisions. In this case the doctor duty is to refer the case to the appropriate state's authorities.

The third step is also the last one in the majority of cases. Parents decide if the DNR order ought to be implemented. The available studies reveal that in the majority of cases parental decision is in agreement with physician's opinions, ie, parents decide that their infant should not be resuscitated when such treatment is defined by the doctors as harmful/futile, and when resuscitation is considered to be the medically-indicated treatment they authorize the physicians to resuscitate their infant.[8,20] If resuscitation is considered to be an optional treatment, the parents' decision should be always respected. It seems that it is the only one exception to these rules. The state has a moral power to decide how the scarce medical resources will be used. Beauchamp and Childress[2] indicate, as an example which appears in neonatal intensive care unit, the decision regarding withdrawing extracorporeal membrane oxygenation (ECMO) from a newborn with poorer prognosis in favor of another with a better prognosis. The state duty is to protect their citizens' lives by using the scarce resources in the most efficiently way.

When disagreement between the physician and the parents occurs it is necessary to introduce the additional authority rules (step four). As it was indicated above, such disagreement can take place only when the treatment is defined as indicated or harmful/futile. Firstly, the parents can decide to implement DNR order in the situation when the resuscitation is considered as the indicated medical treatment. Depending on the circumstance, the physician can refer to the state's authorities or, in emergency, act according to the standard of so called justified paternalism. Beauchamp and Childress, quoting the court decision (In re Estate of Dorone), observe: "The necessity to preserve life outweighed thirdparty judgments about what an unconscious patient would want. The court held that in emergency situations calling for immediate action, "nothing less than a fully conscious contemporaneous decision by the patient will be sufficient to overrule evidence of medical necessity."[2]

Secondly, it is imaginable that the physician who has decided that resuscitation is the medically indicated treatment, stands—against the parents' decision—to enter DNR order. In this situation, however, it is presumable that the physician is motivated by external and probably immoral reasons.

Thirdly, parents can decide to resuscitate their infant against the opinion of the physician who claims that, in a given situation, such treatment ought to be considered harmful or futile for the infant. The physician has moral right to refuse to undertake resuscitation. This right is justified by the judgment that none can be forced to do something against his/her conscience (right to the objection of conscience).

Fourth, it is possible that the physician opts for undertaking/continuing resuscitation even if it is considered harmful/futile treatment and against parental authorization to withhold/withdraw it. As Schulz-Baldes et al[8] show, the physicians seem to be prone to act according to a "wait until certainty" standard. In consequence, end-of-life decisions, including DNR order, are generally taken relatively late. It is quite likely that "wait until certainty" contributes to increasing and prolonging newborns' pain experiences. In order to avoid newborns' pointless suffering Young and Stevenson[6] propose an alternative, called an "individualized prognostic strategy" standard. When disagreement between the physicians and parents exists regarding which of these standards should be implemented, it seems useful to refer to the appropriate social or state's institutions: to the hospital's bioethics committee and/or to the court.

Conclusions

1 The progress in medical knowledge and practice has led to the situation in which patients become victims of medical success. It seems to be particularly obvious in the treatment of extremely immature and sick newborns.
2 The respect for newborns' human dignity obliges parents, physicians, and the appropriate state institutions to reconsider their attitude toward the end-of-life decisions in neonatology, including the DNR order.
3 The best interest standard should serve as a guidance rule for surrogate decision-making regarding the DNR order in neonatology.
4 The authority rules indicate the parties which ought to be involved in making end-of-life decisions: newborns, parents, physicians, and state authorities.
5 The primary decision-maker should be infant's parents.
6 State authorities could override the parental decision only in two cases: (i) when parents authorize the DNR order in the situation in which resuscitation is considered to be medically indicated treatment and (ii) when the problem of the allocation of the scarce medical resources arises.
7 The physicians' primary role in end-of-life-decisions is to be a parents' and state authorities' advisor.
8 Neither parents nor state authorities' decisions cannot deprive

physicians of their right to the objection of conscience.

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…Editorial, continued from page 14

and worth looking over, for the sake of clinicians and their charges.

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Use of Real Time Continuous Glucose Monitoring and Intravenous Insulin in Type 1 Diabetic Mothers to Prevent Respiratory Distress and Hypoglycemia In Infants

Dario Iafusco, Fabrizio Stoppoloni , Gennaro Salvia, Gilberto Vernetti, Patrizia Passaro, Goran Petrovski, Francesco Prisco

Abstract

Background: Pregnancy in Type 1 diabetic patients is a precarious condition, both for mother and fetus with increased the risk of prematurity and, immediately after delivery with risk of respiratory distress syndrome and hypoglycemia in newborns. A strict control and monitoring of diabetes throughout pregnancy is important in reducing the impact of the disease on the fetus and newborn. In recent years many new technologies have been introduced to ameliorate diabetes monitoring, where the last is the Real-time Continuous Glucose Monitoring System (RT-CGMS).

Methods: In the last three years, 72h continuous glucose monitoring system (RT-CGMS) (Medtronic, CA) was performed in 18 pregnant women with Type 1 diabetes in two moments of pregnancy: during treatment with betamethasone to prevent respiratory distress and during delivery. In both cases insulin was administered intravenous and the dose was changed on the basis of glycemia.

Results: The results present the use of this new technique during two topics moments of pregnancy of type 1 diabetes patients when is very important intensively to monitor diabetes and to obtain the well being of the fetus. No infant experimented hypoglycemia or respiratory distress syndrome at the moment and in the first hours after the birth.

Conclusions: We wish to stress the importance reducing glycemia during administration of betamethasone and during labor. It is conceivable that the scarce attention paid to monitoring glucose levels in diabetic mothers during labor in gynaecological world may be due to the difficulty in glucose monitoring with the devices until now available. Hopefully, our anecdotal account may prompt improvements with RTCGMS, and may lead to a better approach to the problem, thereby changing the prognosis of infants born to diabetic mothers.

Authors Iafusco, Passaro and Prisco are with the Department of Paediatrics, Second University of Naples; Stoppoloni and Vernetti are with the Maternal-Fetal Medicine Unit, and Salvia is with the department of Neonatology and the NICU, Buon Consiglio Fatebenefratelli Hospital, Naples, Italy; Petrovski is with the Clinic of Endocrinology and Diabetes, Skopje, Macedon. The authors wish to thank all the mothers with diabetes who collaborated in the study, Irene Iannitti for her collaboration and constructive comments, and Jean Ann Gilder for text editing. Reprinted from BioMed Central, BMC Pregnancy and Childbirth,

Background

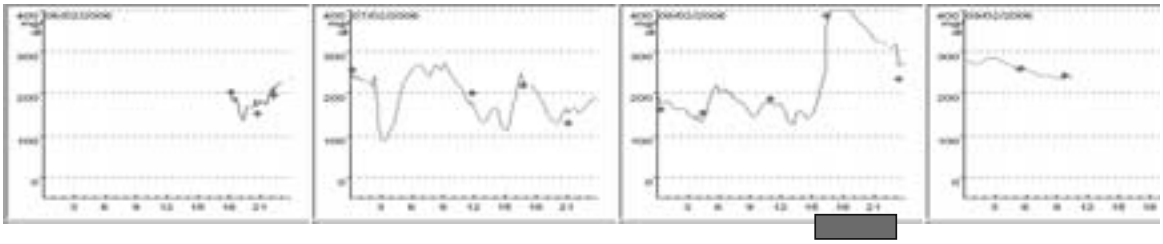
Infants born to type 1 diabetic mothers are at significantly greater risk for perinatal morbidity. Two conditions are very frequent at the birth: respiratory distress syndrome (RDS) and hypoglycemia. Strict maternal glycemic control during pregnancy complicated by diabetes mellitus reduces neonatal morbidity and mortality.

Infants of type 1 diabetic mothers are more likely to have respiratory symptoms in the newborn period from either RDS (surfactant deficiency) or retained fetal lung fluid (transient tachyp nea of the newborn) after operative delivery.[1] RDS occurs more frequently in IDMs (Infants of Diabetic Mother) because of later onset of maturity of the type II alveolar cells[2] and is secondary to pulmonary surfactant deficiency. Fetal hyperinsulinism is a key factor in the pathogenesis of RDS because insulin is believed to antagonize the physiological maturing effect of cortisol.[3] Hyperinsulinism is also responsible for polycythemia, a condition inducing persistent pulmonary hypertension which complicates the course of RDS.

Ideally, RDS is prevented by excellent maternal glycemic control during pregnancy.[2]Corticosteroids are strongly recommended to prevent prematurity complications in newborns of non-diabetic mothers in whom a rise in blood glucose levels in the two days following administration of betamethasone has been reported.[4] Due to the higher risk of RDS in infants from diabetic mothers administration of betamethasone to the mother is even more advisable then in non-diabetic mothers. On the other side the consequent rise in blood glucose levels[4] is expected to be more marked in diabetic than in non-diabetic mothers thus requiring a strict adjustment of the insulin therapy. This because the fetal hyperinsulinism consequent to the maternal hyperglycemic peak could block the beneficial effect of the administered betamethasone on fetal pulmonary maturation.

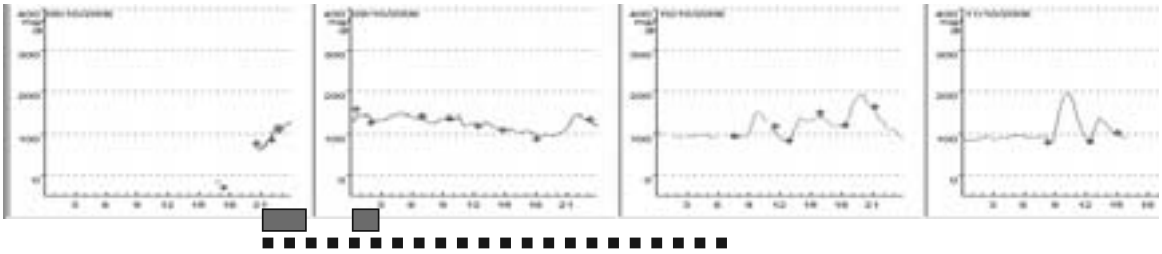
In the diabetic pregnant the stress during the labour usually

A



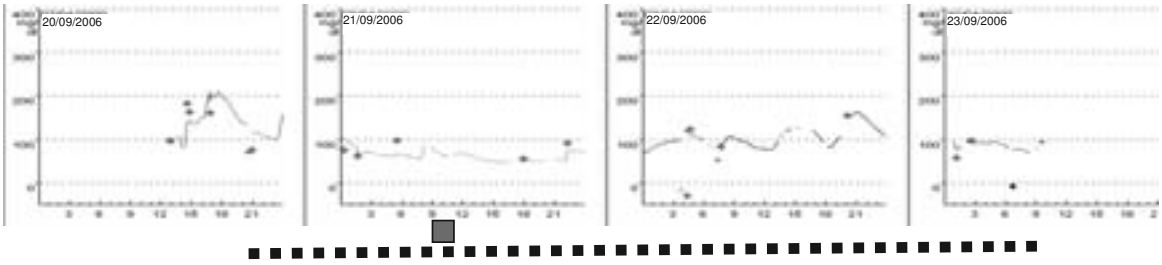
DM Stefania age 25 years, vaginal delivery, duration of gestation 32 weeks.
Infant birth weight kg 1.620 (50° pc), glycaemia at birth 56 mg/dl. No hypoglycaemic episodes during the first 72 hrs after birth

B



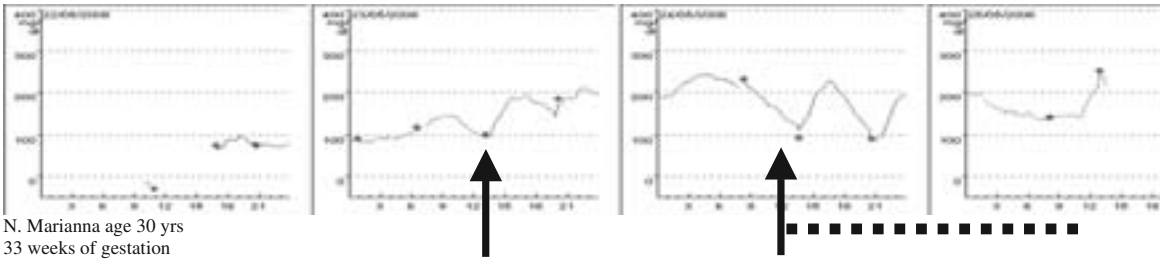
P Patrizia age 28 years, vaginal delivery, duration of gestation38 weeks
Infant birth weight kg 4.100 (97° pc), glycaemia at the birth 53 mg/dl.
No hypoglycaemic episodes during the first 72 hrs after birth

C



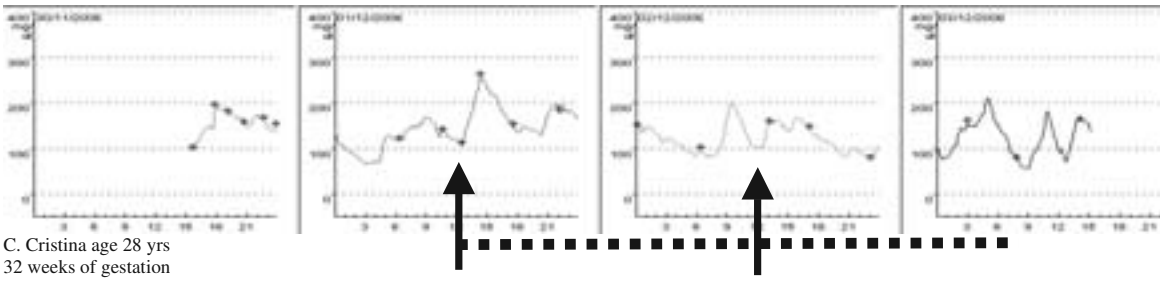
DM Daniela age 28 yrs caesarean delivery 34 weeks of gestation
Infant birth weight kg 3.520 (97° pc), glycaemia at the birth 50 mg/dl.
No hypoglycaemic episodes during the first 72 hrs after birth

D



N. Marianna age 30 yrs
33 weeks of gestation

E



C. Cristina age 28 yrs
32 weeks of gestation

Figure legend

Labor ▭ Insulin i.v . ▪▪▪▪▪ Betamethasone 12 mg i.m. ▲

On the x-axis are hours and every graph is a day. On the y-axis are glycemic values (mg/dl)
° The circle symbols represent glycaemia at the finger.

induces a further increase of blood glucose levels with a consequent rise of the fetal production of insulin and increased risk of hypoglycemia. Therefore, a close monitoring of blood glucose in the mother together with an appropriate insulin treatment during the last hours before delivery are needed.

Over the past years practitioners have sought to improve the outcome of diabetic pregnancies. In pregnancies complicated by type 1 diabetes, where excellent glucose control is desired to improve maternal and fetal outcomes, RT-CGMS, a novel well tolerated tool to assess 24-h glucose fluctuations, may have a role in fine-tuning management.[5] Its role may be crucial in two topic moments of pregnancy such as betamethasone therapy and labor.

Methods

Eighteen pregnant women (mean age 23.4 ± 2.5 yrs; range 18-28 yrs) with type 1 diabetes (mean age at the diagnosis 8.5 ± 3.3 yrs; mean duration of the disease 14.8 ± 2.9 yrs) were consecutively enrolled in the study in the last 3 years (2004-2007).

The research plan has been approved by the Ethics Committee of Department of Pediatrics of the Second University of Naples. An informed consent was signed by all mothers taking part to the study.

All patients wore Real Time Continuous Glucose Monitoring System sensors (RTCGMS), in two moments: during treatment with betamethasone and in the perinatal period and during labor. The glycemic profile was obtained with a continuous glucose monitoring system, not equipped for real-time visualization of the results (CGMS Medtronic), in the first 4 patients at the beginning of the study and with a Guardian Real Time CGMS (Medtronic) equipped for real-time visualization of the results in the others.

The CGMS unit consists of a glucose sensor, which is inserted into the subcutaneous tissue of the body and left in place for up to 72 hours. This sensor senses the interstitial fluid glucose levels electrochemically every 10 seconds, records an average value every 5 minutes and gives 288 values per day. The sensor of CGMS after 72 hours is removed and the data from the monitor are downloaded into a PC, which gives a continuous graph of the glucose values of the previous 3 days; Guardian Real Time CGMS (Medtronic) uses a continuous telemetry display of real-time glucose values. The RT-CGMS is an accurate tool for additional glucose monitoring in pregnant women with type 1 diabetes mellitus as previously demonstrated.[6]

Betamethasone was administered intramuscularly (12 mg/24 h for two days) between the 30th and 32nd week of gestation. Continuous intravenous infusion of insulin (between 0.02 U/kg/h and 0.06 U/kg/h), guided by glucose levels, enabled us to reach and maintain glucose levels constant between 100 and 150 mg/dl during treatment with betamethasone and during labor up to delivery in the vaginal delivery and between 80 and 100 mg/dl during the caesarean section birth.

Results and Discussion

At the beginning of the study after betamethasone administration we tried to maintain the multi-injection insulin therapy but it did not prevent an increase of glycemia despite of the increasing insulin dose.

Fig 1 D shows the continuous graph of the glucose values of a patient who received, the day after betamethasone, multi-injection insulin therapy at a dose of 0,9 Units/Kg/day in 4 administrations/day, which did not prevent an increase of glycemia monitored for about 24 h (around 200 mg/dl with a peak of 250 mg/dl after 15 h). After the second betamethasone injection, intravenous insulin was introduced reducing the degree and duration of hyperglycaemic peaks (<200 mg/dl).

Fig. 1E shows the graph of the first patient in which intravenous insulin was introduced after the first betamethasone dose resulting in an acceptable level of glycemia from the beginning and for all two days of treatment.

We wish to stress the importance of reducing glycemia and keeping blood glucose under tight control during administration of betamethasone not only for the metabolic status of the mother but to avoid hyperinsulinism of fetus that block the beneficial effect of betamethasone on pulmonary maturation.

No newborn from mothers of our study developed Respiratory Distress Syndrome after the birth.

Another period of high risk for babies from type 1 diabetic mothers is during delivery, when hyperglycemia could induce the newborns to produce high amounts of insulin with the consequence of hypoglycaemic status after the cut of the blood cord. The profile in Figure 1A, obtained with a continuous glucose monitoring system (CGMS; Medtronic USA) not equipped for real-time visualization of the results, shows that rapid, prolonged hyperglycemia can occur during labor and has provided opportunities to examine limitations of conventional monitoring of glycemia by intermittent finger-stick testing. Figure 1B and C (vaginal delivery and caesarean section) obtained with a Guardian Real Time CGMS (Medtronic) equipped for real-time visualization of the results shows that the continuous infusion of insulin (between 0.02 U/kg/h and 0.06 U/kg/h), guided by glucose levels, enabled us to reach and maintain glucose levels constant between 100 and 150 mg/dl during labor up to the vaginal delivery and between 80 and 100 mg/dl during the caesarean section birth. The mean glycemic values of infants immediately after birth was 84 ± 16 mg/dl and no hypoglycaemic episode was recorded during the first 72 hrs after birth.

Conclusions

Real-time CGMS is a very useful tool for obstetrics and diabetologists during the follow up of the pregnant type 1 diabetic patients in particular when the objective of the therapy is euglycemia. The sensor is useful because it permits a closer observation of the fluctuation of blood glucose levels. It would be impossible to measure blood glucose on capillary blood at the same frequency intervals mainly for the discomfort of the repeated punctures.

Therefore, we wish to stress the importance of reducing glycemia during administration of betamethasone and during the labor. It is conceivable that the scarce attention paid to monitoring glucose levels in diabetic mothers during labour in gynaecological worlds may be due to the difficulty in glucose monitoring with the traditional devices until now available. Hopefully, our anecdotal account may prompt improvements in CGMS, and may lead to a better approach to the problem, thereby changing the prognosis of infants born to diabetic mothers.

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Neonatal Group A Streptococcal Meningitis: A Case Report and Review of the Literature

Amer A. Lardhi

Abstract

Introduction: Group A streptococcus is a rare cause of neonatal meningitis. A review of the MEDLINE database since 1966 revealed only 15 documented cases of group A streptococcal meningitis in neonates.

Case report: A previously healthy 28 days old male neonate presented with a history of irritability, fever, and focal seizures. Cerebrospinal fluid analysis and culture confirmed the diagnosis of group A streptococcal meningitis. The clinical course was complicated by the development of brain abscess. The patient made full recovery following a surgical drainage of the abscess and a 6-week total course of antibiotics.

Conclusion: Although it is an uncommon organism, clinician should always consider group A streptococcal infection and its potential complications in the differential diagnosis and management of neonatal meningitis.

Background

Since the introduction of antibiotics, group A streptococcal infection has been an uncommon disease in neonates. Thirty-nine patients with severe neonatal disease caused by group A streptococcus (GAS) have been described since 1966.[1] Meningitis caused by GAS is reported in only 15 neonates during same period.[2-13] This case report describes a neonate with GAS meningitis seen at a university hospital and provides an overview of well-documented cases in the English-language literature over past 40 years.

Case Report

A 28 days old boy was presented to the Emergency Department with a history of fever, irritability, poor feeding of 1 week duration and right-sided focal seizures on the day of presentation. He was born after an uncomplicated pregnancy and delivery. An elder brother had developed symptomatic pharyngitis with fever, sore and congested throat 10 days prior to the neonate's disease. This pharyngitis, however, was not microbiologically investigated. He recovered after a one week course of antibiotic. Upon examination, the patient looked ill and irritable. Vital signs were stable. Anterior fontanel was normal and there was no neurological deficit. The peripheral blood white cells (WBC) were 33,600/mm3 with differential count 61% neutrophils, 18% lymphocytes, 6% monocytes and 10% eosinophils. C-reactive protein was positive.

Cerebrospinal fluid (CSF) was turbid and showed 23,520 WBC/mm3 with 82% neutrophils, 18% lymphocytes and 3 red blood cells /mm3. CSF protein was 502 mg/dl, glucose 5 mg/dl (simultaneous blood glucose 98 mg/dl). Latex antigen test was negative for Hemophillus influenzae B, Neisseria meningitides, Escherichia Coli, Streptococcus group B and Streptococcus pneumoniae. Gram positive cocci were seen in the deposit. He was treated with intravenous cefriaxone and vancomycin. The CSF culture yielded group A beta hemolytic streptococci. Sub- typing of the organism was not available. Vancomycin was discontinued after results of culture. Given the history of focal seizures, head MRI was performed on the seventh hospital day and showed a large lobulated abscess in the left parieto-occipital region. The patient underwent drainage of the abscess. No organisms grew in the culture of the pus (presumably owing to the preceding antibiotic treatment). The child was discharged after 6 weeks of treatment. At the age of 13 month, hearing test and neurological examination were normal.

Discussion

In the pre-antibiotic era, GAS was a major cause of neonatal sepsis and puerperal infections. Meningitis accounted for 10-20% of these infections with fatality rate of 95%. Since the advent of antimicrobial therapy, meningitis caused by GAS is rarely reported in adults or children, with less than 1% of all cases of bacterial meningitis.[6] Since the1980's an increase in the incidence of invasive infections caused by GAS has been noted. A review of GAS meningitis in children beyond the neonatal period describes only 31 well- documented patients in world literature in the past 30 years.[14]

The present case included a MEDLINE search from 1966 that revealed only 16 neonates with GAS meningitis. All but two

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Table 1. Group A streptococcal meningitis in neonates.

Case No.	Age/Sex	Associated Condition	Complication	Management	Outcome/Sequelae	Reference
1	6 days / M	Erysipelas	None	Penicillin + Kanamycin	Recovered/ NA*	2
2	1 Mo. / F	None	Seizures	NA	Died	3
3	8 days / M	None	Seizures	NA	Died	3
4	17 days / F	Umbilical sepsis	None	Penicillin	Recovered/ NA	4
5	3 days / F	Necrotizing fasciitis, septicemia	None	Penicillin	Recovered	5
6	14 days / F	Erysipelas	Seizures, D.I.C*.	Penicillin	Recovered	6
7	14 days / NA	None	None	Cefotaxime + Ampicillin	Recovered	7
8	26 days / M	Paronychiae, porencephalic cyst	Seizures	Penicillin + Cefuroxime+ Gentamycine	Recovered / Hydrocephalus	8
9	13 days / F	Cellulitis of both feet	Seizures, Hepatitis	Penicillin + Cefuroxime	Died	8
10	1 Mo. / F	None	Multiple brain abscess, seizures	Penicillin	Recovered/ NA	9
11	1 Mo. / F	Sepsis +RSV* Infection	Sepsis,Waterhouse-Friderichsen syndrome	NA	Died	10
12	33 days / F	Pneumonia	NA	Penicillin + Gentamycin	Died	11
13	34 days / NA	None	NA	Penicillin + Gentamycin	Recovered / NA	11
14	1Mo. / NA	NEC*+ Septicemia	NA	Penicillin + Gentamycin	Died	12
15	24 days / F	None	Seizures, brain abscess, cardiorespiratory Insufficiency	NA	Died	13
16	28 days / M	None	Seizures, brain abscess	Ceftriaxone + Vancomycin	Recovered	This case

***D.I.C**-Disseminated intravascular coagulation, **NA**-Data not available, **NEC**-Necrotizing entercolitis **RSV**-Respiratory syncetial virus

Figure legends

patients in the current review developed late onset (> 7 days of age) neonatal meningitis. Associated conditions included sepsis, erysipelas, necrotizing fasciitis, necrotizing enterocolitis, cellulitis, and respiratory infection. No associated or preceding illness was reported in 6 (40%) patients.

A 2004 review of GAS invasive infection in the neonates has described 39 patients since 1966 in the world literature.[1] Vertical transmission accounted for the majority of invasive early onset GAS disease in these neonates. Sixty percent of the mothers who delivered infants with early onset of GAS disease developed puerperal sepsis, toxic shock-like syndrome or both in the peripartum period. The mode of transmission in the majority of invasive late onset cases is unknown. Vertical transmission or postnatal acquisition of focal GAS infection such as pharyngitis and episiotomy abscess is a probable source of transmission. There was no recognizable underlying illness or predisposing factor of GAS meningitis in the present case. However, a family member had developed symptomatic pharyngitis 10 days prior to the onset of the disease, which may have been the source of infection.

GAS is sensitive to a variety of antibiotics administered either alone or in combination. Penicillin was the most commonly prescribed antibiotic for GAS invasive infection in children.[14,15] Burnett et al in his case series reported a favorable outcome when combind clindamycin with beta lactam penicillin.[15] In neonates with GAS meningitis penicillin was used in 77% of the cases. Other antibiotics used included amino glycosides, second and third generation cephalosporin, and vancomycin.

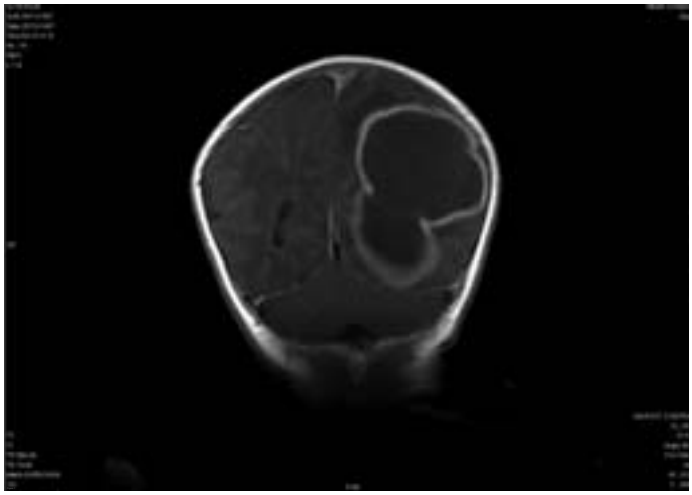
The choice of empiric antibiotic treatment for neonates with meningitis usually involves ampicillin and gentamicin, or ampicillin and cefotaxime. The clinical course of GAS neonatal meningitis was associated with major complications including seizures in 8 patients (60%) disseminated intravascular coagulopathy (DIC), cardio respiratory insufficiency, hepatitis, and Waterhouse-Frederichsen syndrome. Brain abscess developed in 3 patients.

Group A streptococcus is an uncommon cause of brain abscess in children and adults. Etiology of brain abscess in the reported cases includes meningitis, contiguous spread from a middle ear infection, facial furuncles and hematogenous spread from distant site. In neonates, brain abscesses are very rare. It usually occurs as complications of bacterial meningitis or bacteremia. Maternal factors include mastitis, and genitourinary tract infection can be an important source of neonatal brain abscesses. They are most often caused by gram negative organisms. The abscesses are often large and may be multiple. Symptoms of seizures, signs of sepsis and bulging fontanels are frequently seen in neonatal brain abscesses.

Eight (50%) patients with neonatal GAS meningitis died. This is higher than the mortality rate reported in neonates with meningitis caused by several other types of pathogens, and the mortality rate of GAS meningitis reported in children beyond the neonatal period.[14] No neurological sequelae were reported in 4 patients on whom follow up data is available.

Conclusion

GAS meningitis remains an uncommon but serious disease affecting mostly older neonates. Parent and siblings of the patients constitute the source of infection and may unknowingly infect the neonates. Since invasive infection is on the increase, clinicians should always consider GAS in the differential diagnosis of neonatal sepsis and meningitis. Prompt and appropriate treatment may reduce complications and mortality.



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Inadequate Prenatal Care and Its Association With Adverse Pregnancy Outcomes: A Comparison of Indices

Maureen I. Heaman, Christine V. Newburn-Cook, Chris G. Green, Lawrence J. Elliott, Michael E. Helewa

Abstract

Background: The objectives of this study were to determine rates of prenatal care utilization in Winnipeg, Manitoba, Canada from 1991 to 2000; to compare two indices of prenatal care utilization in identifying the proportion of the population receiving inadequate prenatal care; to determine the association between inadequate prenatal care and adverse pregnancy outcomes (preterm birth, low birth weight [LBW], and small-for-gestational age [SGA]), using each of the indices; and, to assess whether or not, and to what extent, gestational age modifies this association.

Methods: We conducted a population-based study of women having a hospital-based singleton live birth from 1991 to 2000 (N = 80,989). Data sources consisted of a linked mother-baby database and a physician claims file maintained by Manitoba Health. Rates of inadequate prenatal care were calculated using two indices, the R-GINDEX and the APNCU. Logistic regression analysis was used to determine the association between inadequate prenatal care and adverse pregnancy outcomes. Stratified analysis was then used to determine whether the association between inadequate prenatal care and LBW or SGA differed by gestational age.

Results: Rates of inadequate/no prenatal care ranged from 8.3% using APNCU to 8.9% using RGINDEX. The association between inadequate prenatal care and preterm birth and LBW varied depending on the index used, with adjusted odds ratios (AOR) ranging from 1.0 to 1.3. In contrast, both indices revealed the same strength of association of inadequate prenatal care with SGA (AOR 1.4). Both indices demonstrated heterogeneity (non-uniformity) across gestational age strata, indicating the presence of effect modification by gestational age.

Conclusion: Selection of a prenatal care utilization index requires careful consideration of its methodological underpinnings and limitations. The two indices compared in this study revealed different patterns of utilization of prenatal care, and should not be used interchangeably. Use of these indices to study the association between utilization of prenatal care and pregnancy outcomes affected by the duration of pregnancy should be approached cautiously.

Background

Prenatal care (PNC) is a frequently used health service that has the potential to reduce the incidence of perinatal morbidity and mortality by treating medical conditions, identifying and reducing potential risks, and helping women to address behavioral factors that contribute to poor outcomes. Prenatal care is more likely to be effective if women begin receiving care in the first trimester of pregnancy and continue to receive care throughout pregnancy, according to accepted standards of periodicity. The Society of Obstetricians and Gynecologists of Canada (SOGC) recommends that women receive PNC visits every 4 to 6 weeks in early pregnancy, every 2 to 3 weeks after 30 weeks' gestation, and every 1 to 2 weeks after 36 weeks' gestation, whereas the American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (ACOG) recommend that a woman with an uncomplicated pregnancy be examined every 4 weeks for the first 28 weeks of pregnancy, every 2 to 3 weeks until 36 weeks gestation, and weekly thereafter. Accurate measurement of PNC utilization is critical in monitoring trends and assessing the relationship between prenatal care services and pregnancy outcomes. At least four indices have been developed to measure utilization of PNC, each of which uses the month that care begins and the total number of visits adjusted relative to gestational age at delivery,

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Table 4: a – Odds ratios (OR) and 95% confidence intervals (CI) for association of inadequate/no prenatal care with preterm birth (< 37 completed weeks gestation)*b – Odds ratios (OR) and 95% confidence intervals (CI) for association of inadequate/no prenatal care with low birth weight (<2500 grams)*c – Odds ratios (OR) and 95% confidence intervals (CI) for association of inadequate/no prenatal care with small-for-gestational age (birth weight < 10th percentile for gestational age)*

a – Odds ratios (OR) and 95% confidence intervals (CI) for association of inadequate/no prenatal care with preterm birth (< 37 completed weeks gestation)*

Index	Unadjusted OR	95% CI	Adjusted OR**	95% CI
APNCU Index	1.3	1.2 – 1.5	1.2	1.1 – 1.3
R-GINDEX	1.1	1.0 – 1.2	1.0	0.9 – 1.1

b – Odds ratios (OR) and 95% confidence intervals (CI) for association of inadequate/no prenatal care with low birth weight (<2500 grams)*

Index	Unadjusted OR	95% CI	Adjusted OR**	95% CI
APNCU Index	1.4	1.3 – 1.6	1.3	1.2 – 1.5
R-GINDEX	1.2	1.1 – 1.4	1.1	1.0 – 1.3

c – Odds ratios (OR) and 95% confidence intervals (CI) for association of inadequate/no prenatal care with small-for-gestational age (birth weight < 10th percentile for gestational age)*

Index	Unadjusted OR	95% CI	Adjusted OR**	95% CI
APNCU Index	1.5	1.4 – 1.6	1.4	1.3 – 1.5
R-GINDEX	1.4	1.3 – 1.5	1.4	1.3 – 1.5

* Inadequate/no prenatal care was compared to the reference group of all other types of care (intermediate, adequate and intensive).
**Controlling for maternal age and parity, and adjusting for within-mother dependency. Maternal age was studied using categories of <20 years, 20–24 years, 25–29 years, 30–34 years, and 35+ years, with 35+ years as the reference group. Parity was studied using categories of first birth, 2nd-3rd birth and 4 or more births, with first birth as the reference group.

to assign women to categories such as inadequate, intermediate, adequate, and intensive PNC. However, use of the Kessner index and the graduated index of PNC utilization (GINDEX) have largely been abandoned because the restricted ninevisit coding limitation of these indices inaccurately classifies the PNC utilization of term and post-term pregnancies. The Adequacy of Prenatal Care Utilization (APNCU) index and the revised GINDEX (R-GINDEX) are both currently used to measure utilization of PNC.

Several studies using the PNC utilization indices have demonstrated an association between inadequate PNC and preterm birth or low birth weight (LBW). However, some investigators have questioned the use of these indices in determining an association with outcomes that are highly influenced by gestational age, such as preterm birth and LBW. Interestingly, the outcome of small for gestational age (SGA) infants has been explored in only a few studies, even though this outcome by definition is adjusted for gestational age.

Several studies in the United States have reported on rates of inadequate PNC, while other studies have compared two or more of the indices in monitoring utilization of PNC. In Canada, there are no national data on utilization of PNC, and only a few studies have examined rates of inadequate PNC. One study estimated that about 8.0 to 9.0% of pregnant women in Winnipeg, Manitoba received inadequate PNC in 1987–88, while rates ranged from 4.4 to 10.6% in 1987–88 in a British Columbia study. No studies have compared the PNC utilization indices in a Canadian context. Therefore, the objectives of this study were: to determine rates of PNC utilization in Winnipeg, Manitoba from 1991 to 2000; to compare the two most commonly used indices of PNC utilization in identifying the proportion of the population receiving inadequate PNC; to determine the association between inadequate PNC and preterm birth, low birth weight (LBW), and small-forgestational age (SGA), using each of these indices; and to assess whether or not, and to what extent, gestational age modifies the association between inadequate PNC and LBW or SGA.

Methods

We conducted a population-based cohort study of women having a hospital-based singleton live birth in Winnipeg, Manitoba over a ten-year period, from 1991 to 2000. Winnipeg is the capital city of the province of Manitoba, and had a population of 618,477 residents in 1996. Data sources for this study consisted of a linked mother-baby database constructed from hospital discharge abstract data and a physician claims file maintained by Manitoba Health. The project received approvals from the University of Manitoba Research Ethics Board and the Health Information and Privacy Committee of Manitoba Health.

There were 83,101 births to women residing in the city of Winnipeg from 1991 to 2000. After eliminating cases with missing or out-of-range gestational age (< 18 weeks or > 45 weeks), missing parity, maternal age less than 12 years, stillbirths or multiple births, and birth weight <400 grams but gestation >22 weeks, the final sample consisted of 80,989 births. Several mothers (37.6%) gave birth to more than one child during the ten years, and all these births were included in the analyses.

We combined two sources of data in order to estimate the number and timing of prenatal visits. We first recorded the gestational age at first visit and the total number of prenatal

Table 5: Odds ratios (OR) for association of inadequate/no prenatal care with SGA by gestational age category: Comparison of two prenatal care utilization indices.

Gestation	Total n	SGA n	APNCU OR	R-GINDEX OR
<27 weeks	263	57	ne*	ne*
27–28	177	22	0.82	1.84
29–30	186	20	1.31	0.92
31–32	403	38	0.23	0.25
33–34	865	78	0.27	0.77
35–36	2 926	321	0.81	0.89
37–38	16 024	1 352	1.40	1.38
39–40	45 115	4 515	1.48	1.47
41–42	14 964	1 552	1.80	1.64
43–44	66	9	2.71	1.73
Breslow-Day Test			p = 0.0001	p = 0.0154

*ne = not estimable.

visits from the linked mother-baby database. These data were abstracted from the prenatal record as part of the hospital discharge abstract data system. However, several limitations of these data have been documented, including a high percent of missing information and an underestimate of timing of the first prenatal visit and total number of visits. We therefore supplemented the information with data from the physician claims database. For women who received care from physicians billing on a fee-for-service basis, we determined the number of episodes of care by recording office visit tariff codes that were linked to an ICD-9-CM code indicating pregnancy, and any consultation visits linked to a physician code for obstetrician/gynecologist and an ICD-9-CM code indicating pregnancy. In addition, because many physicians billed for PNC using a global tariff during the time frame of this study, direct billing of in-office or laboratory diagnostic tests was used as a surrogate measure of a PNC visit, adapted from a method previously used and validated by Mustard. Finally, we determined the total number of prenatal visits by using whichever estimate of the number of visits was greater, and whichever estimate of gestational age at first visit was earlier, based on these two methods. Gestational age at delivery was determined from the newborn record. These three variables were then used to calculate the following indices of PNC utilization:

Table 6: Odds ratios (OR) for association of inadequate/no prenatal care with LBW (<2500 grams) by gestational age category: Comparison of two prenatal care utilization indices.

Gestation	Total n	LBW n	APNCU OR	R-GINDEX OR
<27 weeks	263	262	ne*	ne*
27–28	177	172	ne*	ne*
29–30	186	177	0.28	0.43
31–32	403	380	0.72	1.03
33–34	865	646	0.85	1.02
35–36	2 926	954	1.19	1.22
37–38	16 024	762	1.48	1.36
39–40	45 115	445	1.64	1.45
41–42	14 964	60	2.85	3.45
43–44	66	0	ne*	ne*
Breslow-Day Test			p = 0.0159	p = 0.0624

*ne = not estimable.

1. The Adequacy of Prenatal Care Utilization (APNCU) index, proposed by Kotelchuck, is comprised of two parts: the month in which PNC is initiated and the number of visits from initiation of care until delivery. Inadequate utilization is defined as either starting PNC after the 4th month of pregnancy or receiving less than 50% of expected visits based on the schedule of PNC visits recommended by ACOG. Intermediate care is care begun by month 4 and with between 50–79% of expected visits received; adequate care is that begun by month 4 and with 80–109% of expected visits received; intensive (adequate plus) care is begun by month 4 and with 110% or more of expected visits received.

2. The revised GINDEX (R-GINDEX), proposed by Alexander and Kotelchuck, has six categories of care: no care, inadequate, intermediate, adequate, intensive, and missing. The R-GINDEX is based on the full ACOG recommendation, rather than the flawed Kessner index coding strategy of a 9-visit limit. For example, at 40 weeks gestation, a woman who began prenatal care in the first 3 months and received between 13 to 16 visits would be categorized as having adequate care, whereas a woman who began care between 1 to 6 months of pregnancy and had less than 8 visits would be categorized as having inadequate care. The intensive care category includes women who have an unexpectedly large number of PNC visits, which may indicate potential morbidity or complications. Women whose number of visits is approximately one standard deviation above the mean number of visits for each trimester of initiation and gestational age at delivery are labeled as intensive care users.

Algorithms for calculating both of these indices have been published. Once the two indices were calculated, we then compared the proportion of cases assigned to each category by the indices from 1991 to 2000.

Differences in rates of inadequate/no PNC by maternal age and parity were calculated. SGA births (birth weight less than 10th percentile for gestational age) were determined using a population-based Canadian reference. Logistic regression analysis with generalized estimating equation parameter estimates (GEE) was used to determine the association between inadequate/no PNC, using both indices, and birth outcomes (preterm birth, LBW, and SGA) after controlling for maternal age and parity, and adjusting for more than one birth to the same mother (ie, within-mother dependency). Inadequate/no prenatal care was compared to the reference group of all other types of care (intermediate, adequate and intensive).

A stratified analysis was conducted to determine whether the association between inadequate/no PNC and LBW or SGA differed by gestational age. The Breslow-Day test of homogeneity was used to test the null hypothesis that the effect measure was uniform across strata.

Results

Only a small proportion of women (n = 293; 0.4%) received no care during the 10 years. The overall proportion of women assigned to the inadequate category varied slightly among the two indices, ranging from 7.9% for APNCU to 8.5% for R-GINDEX. The APNCU assigned a much higher proportion of women to the "intensive" care category (31.4%) than did the R-GINDEX (12.6%). Because of the small proportion of women receiving no care, the categories of inadequate and no care

were combined for most of the remaining analyses. Women aged less than 20 years had the highest rates of inadequate/no care (ranging from 21.1% to 21.6%) while women aged 35 years and older had the lowest rates. Women with the highest level of parity (4 or more births) had the highest rates of inadequate/no PNC (ranging from 24.3% to 26.4%) while women having their first birth had the lowest rates.

The proportion of preterm births and LBW by category of PNC varied among the two indices, with highest rates in the no PNC group (15.0%). Using the APNCU, the rate of preterm birth in the inadequate care group (7.2%) was approximately double that of the adequate care group (3.5%). However, this was not true of the RGINDEX, where the rate of preterm birth in the inadequate care group (6.1%) was lower than that in the adequate care group (8.8%). Using the APNCU, a high rate of preterm birth (10.8%) was also found in the intensive care category. The rate of SGA was more consistent across the indices, with the highest rate (18.8%) in the no care category and similar rates in the inadequate care category for the APNCU (13.0%) and the R-GINDEX (12.8%).

Table 4 reports the unadjusted and adjusted odds ratios (AOR) for the association between inadequate/no PNC care and pregnancy outcomes. Using the APNCU, the likelihood of preterm birth and LBW associated with inadequate or no PNC was significantly increased by 20% and 30% respectively. Using the R-GINDEX, there was no association between inadequate/no care and preterm birth and a weak association with LBW. In contrast, both indices yielded the same result for the outcome of SGA, with the likelihood of SGA being significantly increased by 40% among women with inadequate/no prenatal care.

The stratified analyses of the association between inadequate/no PNC and SGA and LBW are reported in Tables 5 and 6 respectively. The odds ratios varied widely across gestational age categories, with the association between inadequate/no PNC and both LBW and SGA increasing towards term. The Breslow-Day test of homogeneity was significant for the association between APNCU and both SGA and LBW, and between R-GINDEX and SGA, indicating the presence of heterogeneity (non-uniformity) across strata. The Breslow-Day test for the association between RGINDEX and LBW suggested a trend towards significance ($p = 0.06$) and the possibility of non-uniformity across strata.

Discussion

The proportion of cases assigned to PNC utilization categories varied using the two different indices. This finding is similar to the conclusions of Alexander and Kotelchuck and Kogan et al. Because the indices use different algorithms to define categories of PNC utilization, they yield different patterns of PNC use in a population and should not be used interchangeably. This emphasizes the need to use caution in comparing results across studies that use different indices. The proportion of women assigned to each PNC utilization category remained fairly stable over the 10 years for both indices, although it is noteworthy that the number of births steadily declined over the 10 years, from 9,093 births in 1991 to 7,124 births in 2000. This declining birth rate is consistent with that reported in a provincial surveillance report for Manitoba, 1989–1998.

The rates of inadequate and no PNC utilization among women in Winnipeg are lower than those reported in the United States, likely as a result of universal health care for residents of Manitoba. About 1.5 to 2.0% of pregnant women in the United States do not receive any PNC, compared to 0.4% among Winnipeg women in this study. Using the APNCU index, the rate of inadequate/no PNC in the United States declined from 12.8% in 1995 to 11.7% in 1999, but these rates are still considerably higher than the 8.3% of women in Winnipeg who received inadequate/no PNC from 1991 to 2000 based on the APNCU index.

The association between inadequate/no prenatal care and LBW varied using the two indices, with AOR ranging from 1.1 using the R-GINDEX to 1.3 using the APNCU. Caution needs to be used in interpreting these results because our analyses also confirmed the presence of effect modification by gestational age for both indices, with the association between inadequate/no care and LBW becoming stronger as gestational age increased. Koroukian and Rimm state, "Although adjusting the number of prenatal visits for gestational length is clearly important to assess the adequacy of prenatal care utilization, we must be mindful of the bias introduced by its use in an Index, because the gestational length is itself a birth outcome that is so strongly correlated with birth weight." Alexander and Kotelchuck suggest the use of different analytical approaches to examine the relationship between prenatal care use and birth outcomes, such as gestational age-specific, life table, survival, and two stage least squares analyses, to help control for the influence of gestational age. There is growing concern that the strength of the relation between PNC and LBW and preterm birth may be far less than previously assumed. This lack of association may result because PNC, in its present form, has limited ability to reduce the proportion of LBW and preterm births; however, some evidence suggests that PNC may make a difference in term LBW rates. This lack of association might also explain why efforts to prevent preterm birth and LBW through increased access to PNC have shown little benefit.

Of the three adverse pregnancy outcomes selected for this study, SGA may be the preferable outcome to study because by definition it adjusts for gestational age. However, our findings still showed some degree of effect modification by gestational age when studying the association between inadequate/no PNC and SGA, so the results should be interpreted with caution. After controlling for maternal age, parity, and within-mother dependency, women receiving inadequate/no PNC were up to 40% more likely to have a SGA birth compared to women receiving other categories of care. This result is consistent with the findings of a New Zealand study that less frequent attendance at PNC was associated with SGA. The reason for the observed association between inadequate PNC and SGA births is not fully understood. However, it is likely that women who do not receive adequate PNC are less likely to receive appropriate treatment or preventive care. SGA births are associated with several potentially modifiable risk factors, such as low pre-pregnancy weight, low gestational weight gain, cigarette smoking, and recreational drug use. Several of these risk factors may be mitigated or prevented with quality PNC.

As with most research, this study has limitations. First, administrative data are prone to a certain degree of coding errors and incomplete data, which may be random or contain systematic biases. The number and timing of PNC visits was estimated from hospital discharge abstracts and physician claims files, and the accuracy of our estimates may be affected by several factors, such as missing PNC records or receipt of PNC from non-physician providers. We were unable to

differentiate missing data from no care using this approach. As well, inaccurate ascertainment of gestational age may affect assignment to a PNC utilization category or determination of a preterm or SGA birth. We compared the rate of adverse birth outcomes among women with inadequate/no PNC to the remainder of the population. However, Kotelchuck suggests there is a U-shaped relationship between PNC and birth outcomes, in which women with both fewer and greater number of visits than expected are at higher risks of having poorer birth outcomes, so perhaps limiting the reference group to women with adequate care should be considered in future research. Our analysis was limited to singleton live births; therefore, multiple births were not represented. In addition, a limitation of both PNC utilization indices is that they only reflect the quantity of PNC; they indicate nothing about the spacing of visits or the content, clinical adequacy, or quality of PNC. These indices are based on the ACOG recommendations for number of visits for low risk pregnant women; the effectiveness of this standard has not been assessed through rigorous scientific testing, nor has adequacy of care for women with high risk pregnancies been operationalized. Last, selection bias is a major difficulty in assessing the impact of PNC on pregnancy outcomes, in that women who receive adequate PNC may be more likely to experience better pregnancy outcomes because of other characteristics which have independent influences on pregnancy outcomes. We were unable to control for maternal characteristics such as socioeconomic status, race/ethnicity, intendedness of pregnancy or health behaviors because information on these variables are not recorded in the databases.

Conclusion

The rates of no PNC and inadequate PNC are lower for women giving birth in Winnipeg, Canada, compared to rates reported for women in the US. The two indices compared in this study revealed different utilization patterns and resulted in varying degrees of association of inadequate PNC with adverse pregnancy outcomes. Selection of a PNC utilization index for research or program evaluation requires careful consideration of the methodological underpinnings and limitations of the chosen index. Although these indices remain useful for studying trends in PNC utilization or evaluating the effectiveness of programs to enhance access to care, we concur with other investigators that use of these indices to study the association between utilization of PNC and birth outcomes affected by the duration of gestation should be approached with caution due to effect modification by gestational age. In addition, "more refined future indices should incorporate parameters that reflect the qualitative aspects of PNC in addition to measuring number of visits." Future research should go beyond simply counting the number of visits and focus on studying the relationship between quality and content of PNC and pregnancy outcomes. There is a pressing need to develop a valid and reliable instrument to measure quality of PNC.

Homocysteine Levels in Preterm Infants: Is There an Association with Intraventricular Hemorrhage? A Prospective Cohort Study

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Abstract

Background: The purpose of this study was to characterize total homocysteine (tHcy) levels at birth in preterm and term infants and identify associations with intraventricular hemorrhage (IVH) and other neonatal outcomes such as mortality, sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia, and thrombocytopenia.

Methods: 123 infants < 32 weeks gestation admitted to our Level III nursery were enrolled. A group of 25 term infants were enrolled for comparison. Two blood spots collected on filter paper with admission blood drawing were analyzed by a high performance liquid chromatography (HPLC) method. Statistical analysis included ANOVA, Spearman's Rank Order Correlation and Mann-Whitney U test.

Results: The median tHcy was 2.75 µmol/L with an interquartile range of 1.34 – 4.96 µmol/L. There was no difference between preterm and term tHcy (median 2.76, IQR 1.25 – 4.8 µmol/L vs median 2.54, IQR 1.55 – 7.85 µmol/L, p = 0.07). There was no statistically significant difference in tHcy in 31 preterm infants with IVH compared to infants without IVH (median 1.96, IQR 1.09 – 4.35 µmol/L vs median 2.96, IQR 1.51 – 4.84 µmol/L, p = 0.43). There was also no statistically significant difference in tHcy in 7 infants with periventricular leukomalacia (PVL) compared to infants without PVL (median 1.55, IQR 0.25 – 3.45 µmol/L vs median 2.85, IQR 1.34 – 4.82 µmol/L, p = 0.07). Male infants had lower tHcy compared to female; prenatal steroids were associated with a higher tHcy.

Conclusion: In our population of preterm infants, there is no association between IVH and tHcy. Male gender, prenatal steroids and preeclampsia were associated with differences in tHcy levels.

Background

Intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) are significant causes of morbidity and mortality in the preterm infant population, yet aspects of the multifactorial pathophysiology leading to these CNS insults remain unclear. Petaja et al has suggested that thrombophilia may play a role in the etiology of IVH in preterm infants.[1] They identified 32% of infants with IVH as having abnormal prothrombotic factors.[1] Others have implicated activated coagulation factors in cerebral white matter damage; these activated factors are thought to cause injury by exacerbating inflammation rather than by occlusion of cerebral vessels.[2] Additionally, association has been found between hyperhomocysteinemia in term newborns and the risk of ischemic or hemorrhagic stroke.[3] The neonatal outcomes associated with abnormal coagulation factors and thrombophilia in preterm infants are not well understood. Homocysteine (Hcy), an important amino acid studied in adult thrombophilia, has not been extensively investigated as a possible contributor to preterm neonatal CNS pathologies.[4]

Hyperhomocysteinemia in adults is well known to be associated with a hypercoagulable state and cardiovascular disease.[4-6] Hcy also plays an important role in pregnancy.[7] Elevated maternal total homocysteine (tHcy) levels are known to be associated with preeclampsia, prematurity, and low-birth weight.[7-9] Furthermore, maternal hyperhomocysteinemia has also been reported to be associated with placental abruption, early recurrent fetal loss, and growth retardation, as well as neural tube defects.[7,10-12] Interestingly, the tHcy level measured in pregnancy is lower than in the nonpregnant state,[13,14] and maternal tHcy correlates directly with neonatal levels.[15,16] It has been suggested that tHcy levels in infants are dependent on gestational age at birth, postnatal age and neonatal diet.[17-20] Hongsprabhas characterized tHcy levels in 9 preterm versus 4 term infants and demonstrated lower levels in the preterm group.[17] Despite these documented effects of Hcy on a pregnancy and the fetus, very little is known of the role of Hcy in infants.

We theorized that an elevation of tHcy may promote thrombosis in the germinal matrix venules resulting in a post-infarction hemorrhage. We hypothesized that elevated levels of tHcy in preterm infants are associated with vascular complications, specifically IVH. The purposes of this investigation were to 1) characterize tHcy levels at birth in a preterm and term population and 2) determine if tHcy levels at birth are associated with IVH and other neonatal morbidities. This is an important investigation to undertake given that if an association exists between the neonatal tHcy levels and IVH or other neonatal morbidities, potentially modifying Hcy in pregnant mothers may affect neonatal outcome.

Methods

This was a prospective cohort study in which infants < 32 weeks gestation who were admitted to the level III Special Care Nursery

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Table 1: Patient demographics for all infants

	Term n = 25	Preterm n = 123
Gestational age (weeks)	37.9 ± 1.8	28.4 ± 2.4
Birth weight (g)	3343 ± 800	1188 ± 358
Male gender	20 (80%)	65 (57%)
Preeclampsia	1 (4%)	33 (27%)
Chorioamnionitis	3 (12%)	7 (6%)
Prenatal steroids	2 (8%)	74 (60%)

at Christiana Care Hospital from February 2002 to November 2002 were eligible. Patients were eligible regardless of family history of hematologic disorders or past pregnancy outcomes. Two blood spots were collected on filter paper specimens simultaneously with admission blood drawing. Samples were also collected for comparison on a convenience sample of term infants (≥ 37 weeks gestation) who were admitted to the Special Care Nursery during the same time period. Blood from both groups was drawn by either heel-stick procedure or arterial puncture if blood was being obtained for other purposes and was collected at < 24 hours of postnatal age. Written informed consent was obtained. The Institutional Review Board at Christiana Care Hospital approved this study.

Filter paper specimens were batched and refrigerated until transport to the Baylor Institute of Metabolic Disease where they were analyzed for tHcy by a method utilizing high performance liquid chromatography (HPLC) coupled to electrochemical (Coulometric) detection. This method of homocysteine analysis from newborn screening cards has been previously used and validated by others and ourselves.[21,22]

Clinical data, including all recorded diagnoses and platelet counts, were collected from the patient's chart. In addition to IVH, other common neonatal morbidities, such as cystic PVL and necrotizing enterocolitis, which are thought to involve inflammation or vascular compromise were chosen as measured secondary outcomes. Clinical chorioamnionitis was a clinical diagnosis made by the obstetrician using maternal symptoms of fever, uterine tenderness, or foul-smelling amniotic fluid. Neonatal sepsis was defined as culture positive; necrotizing enterocolitis was defined using Bell's staging criteria, stage II or greater.[23] Admission illness severity was documented using SNAP (Score for Neonatal Acute Physiology).[24] Bronchopulmonary dysplasia was defined as oxygen dependency at 36 weeks corrected gestational age. Thrombocytopenia was defined as a platelet count of less than 150,000. Infants were followed for all primary and secondary outcomes during their initial hospitalization until time of discharge.

All cranial ultrasounds were interpreted by a pediatric radiologist who was blinded to the infant's tHcy result. Cranial ultrasounds were obtained through the anterior fontanel using a 7.5 MHz transducer. The highest grade IVH as defined using Papile's classification was recorded.[25] Severe IVH was considered grade III and IV. Cystic PVL was defined as echolucent cysts in the periventricular white matter. Screening head ultrasounds (HUS) in our institution are typically performed in infants < 32 weeks gestation on the fourth postnatal day and at one month of age with additional ultrasounds done at the discretion of the neonatology team.

A sample size calculation determined 125 total preterm infants were necessary to enroll to show a 33% difference in tHcy in infants with IVH with a β of 0.8 and α of 0.05. We used the previously reported mean tHcy level of 3.8 ± 2.4 µmol/L reported by Hongsprabhas et al in preterm infants for calculations.[17] The historical incidence of IVH in preterm very low birth weight infants at our institution is approximately 25%. We enrolled 125 preterm infants but excluded two based on errors with the tHcy assay. Mann-Whitney U test and Spearman Rank Order Correlation were used to analyze data that was not normally distributed. ANOVA was utilized for normally distributed data. Levine's test for homogeneity was used to differentiate normally from non-normally distributed data. A p value of < 0.05 was considered significant. Results are reported as median and interquartile range.

Results

Patient demographics are represented in Table 1. The median tHcy was 2.75 µmol/L with an interquartile range of 1.34 – 4.96 µmol/L. 123 preterm infants were compared to a sample of 25 term infants. There was no difference between preterm and term tHcy (median 2.76, IQR 1.25 – 4.8 µmol/L vs median 2.54, IQR 1.55 – 7.85 µmol/L, $p = 0.07$). In the preterm infants, there was no association between tHcy and gestational age ($r = 0.15$, $p = 0.1$) or birth weight ($r = 0.14$, $p = 0.2$) using Spearman's Rank Order Correlation.

There was no statistically significant difference in tHcy in 31 preterm infants with IVH compared to those infants without IVH (median 1.96, IQR 1.09 – 4.35 µmol/L vs median 2.96, IQR 1.51 – 4.84 µmol/L, $p = 0.43$). Additionally, there was no significant difference in tHcy in the 16 infants with severe IVH compared to those infants without severe IVH (median 1.49, IQR 1.11 – 3.98 µmol/L vs median 2.83, IQR 1.42 – 4.8 µmol/L, $p = 0.26$). Cystic PVL was diagnosed in 7 patients and tHcy levels were not statistically significantly different in this group compared to infants without cystic PVL (median 1.55, IQR 0.25 – 3.45 µmol/L vs median 2.85, IQR 1.34 – 4.82 µmol/L, $p = 0.07$).

Male infants had lower tHcy compared to female (median 1.83, IQR 1.08 – 4.16 µmol/L vs median 3.26, IQR 1.95 – 5.54 µmol/L, $p = 0.01$). Prenatal steroids were associated with a higher tHcy (median 3.15, IQR 1.51 – 5.23 µmol/L vs median 1.82, IQR 1.14 – 3.29 µmol/L, $p = 0.03$) compared to infants born to mothers who did not receive steroids. Maternal preeclampsia also was associated with higher neonatal tHcy levels (median 4.32, IQR 2.31 – 6.28 µmol/L vs median 2.16, IQR 1.14 – 3.76 µmol/L, $p = 0.01$) compared to infants without maternal preeclampsia.

When tHcy was examined for association with other major morbidities of prematurity, there were no differences found in Hcy levels and mortality, sepsis, necrotizing enterocolitis, or bronchopulmonary dysplasia (data represented in Table 2). Table 2 also describes the tHcy levels in infants with thrombocytopenia during the first 3 days of life compared to infants without thrombocytopenia. There was no association with thrombocytopenia and tHcy level. There was also no correlation with platelet count at birth or during the 1st 3 days of life with tHcy (data not shown).

Discussion

In our population of preterm infants, there was no association between tHcy measured at birth and IVH. We cannot exclude an association between tHcy level beyond birth and brain injury

Table 2: Neonatal outcomes in 123 preterm infants versus tHcy

Neonatal outcome	Number of events	tHcy (μmol/L) median, (IQR)	tHcy (μmol/L) median, (IQR)	*p*
		yes	no	
Mortality	13	3.08 (1.83 – 4.98)	2.75 (1.25 – 4.77)	0.6
Sepsis	36	2.52 (1.09 – 3.40)	2.76 (1.42 – 4.85)	0.11
Necrotizing enterocolitis	8	2.20 (0.88 – 3.25)	2.83 (1.34 – 4.85)	0.25
Bronchopulmonary dysplasia	22	2.92 (1.14 – 5.23)	2.75 (1.42 – 4.8)	0.81
Thrombocytopenia, day of life 1	24	2.47 (1.38 – 4.37)	2.85 (1.34 – 4.85)	0.72
Thrombocytopenia, day of life 1–3	35	2.42 (1.12 – 4.29)	2.75 (1.17 – 5.19)	0.64

given that we measured values within the first 24 hours of life. Although an increased risk of other prothrombotic factors such as Factor V and prothrombin gene mutations in preterm infants with IVH was reported previously,[1] IVH does not appear to be associated with an elevated tHcy in our study population as we had hypothesized.

We were able to successfully measure tHcy levels in 148 mostly preterm infants from filter paper specimens and describe the normal distribution of tHcy in our study population. The tHcy level in our infants is similar to the mean of 3.8 μmol/L described by Hongsprabhas et al in 9 Canadian preterm infants.[17] Comparable values were also reported in a US study which described a mean tHcy level of 3.49 μmol/L from term umbilical arterial samples.[26] Others have documented varying tHcy levels at birth from 3.8 to 7.9 μmol/L;[13,16,27,28] some have suggested that these differences may be due to cultural variations or differences in fortification of foods.[29] Higher tHcy values have been described in the umbilical vein as compared to umbilical artery and this may account for some of the variation as well.[26]

Previous authors have suggested differences in Hcy based on gestational age with tHcy levels increasing with GA.[17] We did not identify any correlation of tHcy with gestational age in our population of infants. There also were no differences between preterm and term tHcy level. Our findings of increased tHcy in infants exposed to maternal steroids and preeclampsia may have elevated the tHcy in the preterm population contributing to our lack of difference between term and preterm tHcy. To our knowledge, our investigation examined the widest variation in GA (22–36 weeks) and the lowest mean gestation (29 ± 4 weeks) in relation to tHcy. Our data are consistent with Minet who found no correlation between tHcy and gestational age.[19] It has been previously described that elevated tHcy levels are associated with increased rates of prematurity while the natural history of maternal tHcy is to lower with pregnancy.[7,14] In 434 Chinese women, the risk of preterm birth was nearly 4-fold higher among women with preconception tHcy concentrations ≥ 12.4 μmol/L compared with women who had lower concentrations.[9] These opposing factors may also explain our lack of clear relationship between tHcy and GA.

We evaluated tHcy within the first day of life to negate any effects the neonatal diet may have. Based on our data we cannot comment on any association between tHcy levels in infants beyond the immediate postnatal period and IVH. The neonatal diet has been shown to clearly affect Hcy possibly through differences in intake of the essential vitamins necessary for folate metabolism.[13,18,19] Differences in maternal and neonatal Vitamin B12 levels account for much of the variation in tHcy. Preterm infants should not have received enteral nutrition or parenteral nutrient intake with folate or Vitamin B12 at the time of the blood draw. Therefore, the initial parenteral fluid should not have affected the tHcy value. Neonatal levels measured on the first day of life should predominantly be reflective of maternal levels and not influenced by diet or postnatal age changes.

We found lower tHcy in males as compared to females in our study sample. This has been described previously in newborn children by Refsum et al.[30] The opposite has been reported in adult males with some finding slightly higher tHcy values.[4] This finding in adults may be related to gender related differences in diet or hormonal influences which would be different in the postpubertal population compared to neonates. However, others have also reported no differences in tHcy related to gender; Minet found no difference in 123 term healthy infants as did Monsen et al in infants up to one year of age.[19,20]

Additionally, prenatal steroids were associated with higher tHcy values in our neonatal population. This is the first study to describe this effect. Analogous results of elevated tHcy levels have been documented in body builders using anabolic steroids.[31] In our neonatal population, this difference in tHcy associated with prenatal steroids did not appear to be related to differences in neonatal morbidities and therefore may not be clinically important in at least the short term management of infants.

There were several limitations to our study. We only measured tHcy within 24 hours after birth. Future investigations to exclude an association between tHcy and IVH or cystic PVL might characterize tHcy beyond 24 hours but during the first several days of life, which is the highest risk period for IVH. The majority of IVH in preterm infants is known to occur in the first three days of life. Due to the small number of cases of cystic PVL in our study population, our population may have been under powered to show small differences in tHcy with cystic PVL. We also did not measure other likely important variables such as folate, vitamin B12, or maternal tHcy. However, given our limitations, our findings are similar to those recently presented by Kenet et al.[32] Their group demonstrated no association in 166 preterm infants evaluated for multiple prothrombotic factors with neonatal complications. Importantly, most tHcy samples in their study group were measured in the first one to four weeks of life, but still demonstrated no association with IVH or PVL. Our current study differs largely in the timing of the measured tHcy; we obtained all tHcy samples within 24 hours, before the majority of IVH or cystic PVL occurs.

Conclusion

Homocysteine, while an important thrombophilic factor in

certain maternal and fetal morbidities, is not clearly associated with common neonatal morbidities, specifically IVH in our population of premature infants. It remains unclear if tHcy contributes to vascular compromise that may be important in other neonatal pathologies. Further investigations are essential to fully understand the role of tHcy in neonatal coagulation and its clinical consequences.

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