

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology

Vol. 24 No. 2
March-April 2011

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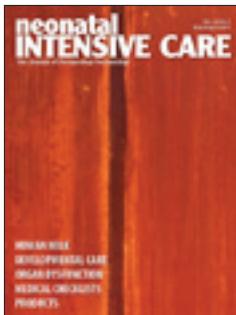
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neonatal INTENSIVE CARE

Vol. 24 No. 2
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Editorial

CONSIDERING EUTHANASIA

Should parental consent not be a prerequisite for neonatal euthanasia? Arguments are laid out in a blog by Tom Douglas, writing in Practical Ethics, a website about ethical issues published by the University of Oxford online. The article Douglas addresses, by Jacob Appell, in the Journal of Bioethical Inquiry, says parental consent should be dropped [see disclaimer].*

Could it be ethically permissible for medical staff to end the life of a child? Suppose that the only way to alleviate pain would be by permanently anesthetizing the child, which is not an option. Thus, the child would continue to experience unbearable pain for as long as he or she continues to live. Suppose further that letting the child die, without active killing, is also not an option because withdrawing treatment would not result in the infant's death, and withdrawing nutrition would unacceptably increase the child's suffering. Suppose that the parents have refused consent to euthanizing the child.

In this case, there seems to be a very strong moral reason for medical staff to euthanize the child: this would be in the child's interests. Or, plausibly, the child's future life was not one that would be worth living. However, there are also three plausible reasons not to euthanize the child: (a) that this would amount to killing a child; (b) that the child has not consented to euthanasia (not being competent to do so); and (c) that the parents have explicitly refused consent to euthanasia.

Suppose that the reasons to euthanize the child in his or her own interests could outweigh reasons (a) and (b) not to do so. The interesting question is whether, in such circumstances, reason (c) – the fact that parents have refused consent – provides a conclusive reason not to euthanize. It is not clear that it does.

Still, we often think that the best interests of a child can outweigh the wishes of the parents, eg, the case of a Jehovah's witness couple who have refused to consent to their child receiving a life-saving blood transfusion. Why not think that a similar situation could arise with neonatal euthanasia?

Consider, next, the public policy question of whether, given that a state allows neonatal euthanasia, it should legally require parental consent. Consider the analogy with life-sustaining treatment, noting the emerging legal consensus in many countries that medical staff may provide treatment to a child when they believe it to be in that child's best interests, even though the parents do not consent. There are legal precedents for withdrawing treatment without parental consent.

Reasons against permitting neonatal euthanasia without consent may include: 1. Doing so might deter parents from seeking medical help for their child. 2. Doing so might undermine the fragile policy of allowing neonatal euthanasia at all. 3. Doing so might lead to the abuse of euthanasia by the medical establishment or state. The first consideration seems to apply just as strongly to cases involving the provision of life-saving treatments or withdrawal of treatment without parental consent. It seems plausible that 2 and 3 don't apply equally in analogous cases. For example, in the case of providing life-sustaining blood transfusions to the children of Jehovah's Witnesses without parental consent, there is no concern about undermining the policy of providing blood transfusions in general. On the other hand, there may be a societal incentive to euthanize children who are likely to be a burden on society.

The analogy with withdrawal of treatment may be on stronger ground. Perhaps policies permitting treatment withdrawal are less open to abuse since, in any case, there are only limited circumstances in which withdrawal of treatment will actually lead to a child's death, whereas any child would be "at risk" from active euthanasia.

Of course, none of this is to say that concerns about abuse or undermining policy do *Continued on page 22...*



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Published seven times each year by
**Goldstein and
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10940 Wilshire Blvd., Suite 600
Los Angeles CA 90024
Phone: 310-443-4109
Fax: 310-443-4110
E-mail: s.gold4@verizon.net
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**Design, Typography, Prepress and
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Reference: 1. Chan GM. J Perinatol. 2003;23:620-623.

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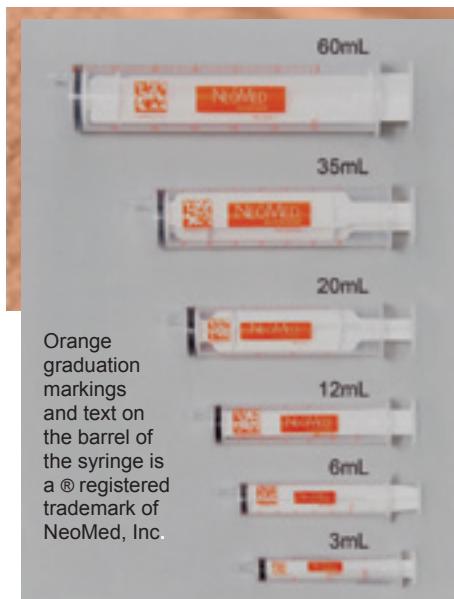


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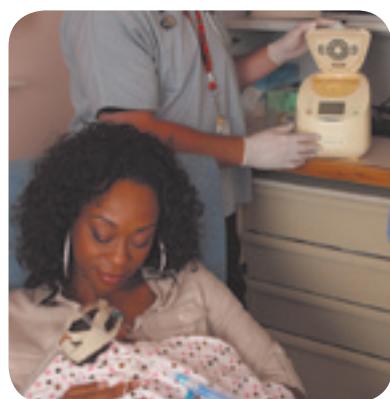
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Recommendations of CDC and Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR, 52(RR10):1-42.

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News

□ March-April 2011

FALLUJA FALLOUT

A study examining the causes of a dramatic spike in birth defects in Falluja, Iraq concluded that genetic damage could have been caused by weaponry used in US assaults that took place seven years ago. The study confirmed a rise in cancers and chronic neural-tube, cardiac and skeletal defects in newborns. The report by Falluja General Hospital found that malformations are close to 11 times higher than normal rates, and rose to unprecedented levels in the first half of 2010, a period that had not been surveyed in earlier reports. This follows on the heels of two earlier studies which noted a 15% drop in the births of boys since the US invasion. It's surmised that the defects are caused by depleted uranium rounds, which contain ionizing radiation. Battlefield residue in the form of dioxins may also be responsible. The latest study, published by the *Guardian*, surveyed 55 families with seriously deformed newborns between May and August. In May, 15% of the 547 babies born had serious birth defects and 11% of babies were born at less than 30 weeks, while 14% of fetuses spontaneously aborted. Researchers said this figure is likely lower than actual rates, since many Falluja babies are born at home and the parents don't seek help. In one case, a mother and daughter both gave birth to babies with severe malformations, as did the second wife of one of the fathers. The researchers noted that under normal conditions, the chances of such occurrences were virtually zero. The city's obstetricians have been complaining that they're overwhelmed by the number of serious defects. The US says it's not its fault, in Fallujah or anywhere else the occupation forces have been fighting, and said, "Iraqis who want to file complaints are welcome to do so." According to the *Guardian*, many have, but no one responded. No other Iraqi city has similar rates of abnormalities, which are 11 times the world average. Reported in the *Guardian*.

GENE GENIUSES

According to researchers at the Center of Genomic Regulation, the gene ZRF1 carries out a crucial role in the activation of other genes related to the cellular destination of stem cells. During embryonic development, cells undergoing multiplication have to decide what type of cells they will become. As such, it is as important for the cell to understand what it should become as opposed to what it should not become, and therefore a tight control of gene expression is required. In order to coordinate and direct the destiny of the stem cells, certain genes are responsible for activating and deactivating other genes that define their specialty during development and that also may be involved in cellular renewal for tissue and organ maintenance. ZRF1 is one of the genes that coordinate this regulation in embryonic development. The researchers said that genes like ZRF1 are essential for controlling cellular destiny and memory. When ZRF1 is removed, the "destiny" of the cell it's acting on is up for

grabs. It is hoped that learning about the gene differentiation process will lead to more knowledge about various pathologies.

NO CHOICE, PLEASE

Australians don't think a hypothetical blue or pink pill to select the sex of a child should be legal, according to researchers at the University of Melbourne, who analyzed responses from 2,500 people about social attitudes. Sixty nine percent of the respondents disapproved of the use of IVF for sex selection, with the disapproval rate increasing to 80% for sex-selective abortions. Previous Australian studies had said that most parents wanted a family with at least one son and one daughter. The study is said to be timely because the country's national health council is reviewing a current ban on sex selection.

PREGNANT WARRIOR

Pregnancy among women veterans who served in Iraq and Afghanistan increases their risk for mental health problems, according to a study published in the *Journal of Women's Health*. The author, Kristin Mattocks, PhD, reviewed the records of more than 43,000 women vets who served in Iraq or Afghanistan and completed their military service between 2001 and 2008. The article emphasized the importance of identifying and providing appropriate diagnosis and treatment services for this at-risk population.

PREGNANT PRISONERS

Throwing pregnant women in jail or into institutions for alcohol and drug problems doesn't work, according to an ACOG committee. Currently, fifteen states consider substance abuse during pregnancy to be child abuse and three consider it grounds for involuntary commitment to a mental health or substance abuse treatment facility. Some states consider alcohol use by pregnant women to be child neglect. Laws that incarcerate pregnant women haven't reduced alcohol or drug abuse among these women, the committee said. It noted that these women, if they're seeking healthcare, often risk being jailed or committed, thus losing custody of their children.

THE WORM TURNS

Routine treatment of worms (helminths) during pregnancy has no effect on improved infant survival or on the occurrence of infectious diseases or anemia, according to a study by the London School of Hygiene and Tropical Medicine. The finding is in opposition to the World Health Organization's policy of antenatal deworming in poor countries. The study described the effects of deworming on about 2,500 Ugandan women in the second or third trimester, of whom 1,693 were infected with worms. The women were randomly assigned a dose of albendazole plus praziquantel, or various placebo-treatment combinations. Newborns were followed up until 12 months. No effect was recorded for either anti-worming treatment on the incidence of infectious diseases during the first year of life or on vertical HIV transmission. The authors concluded that "one effective anthelmintic intervention given in the second or third trimester of pregnancy is insufficient to alter any effect of maternal worms on infectious disease outcomes in infancy."

NOT THE SAME

The human fetal immune system is different from the adult system, and is more likely to tolerate than fight foreign substances, according to UCSF researchers. Up to now, the fetal immune system was thought to be merely an immature version of the adult system. The new research has unveiled an entirely

different immune system in the fetus at mid-term that's derived from a completely different set of stem cells. The researchers said they found a fetal immune system that teaches the fetus to tolerate "everything it sees," including the mom and its own organs. After birth, a new immune system is generated from a different set of stem cells that fights everything foreign. The researchers gauged cell exposure to environmental assault, and noted the much higher tolerance to such exposure among fetal cells. They realized that there were two types of stem cells at work, with the fetal ones giving rise to T cells that were tolerant.

NOT SO SWEET

Diabetes was diagnosed in more than 250,000 pregnant women who delivered in 2008, either pre-existing or gestational, according to the Agency for Healthcare Research and Quality. Sixty-four percent of diabetic moms were likely to have cesareans, compared to 32% in the general mom population. Hospital costs for diabetic moms were pegged at 55% more for women with pre-existing diabetes and 18% more for gestational diabetes. The total cost for all pregnant moms with diabetes was set at \$1.5 billion, which was 8.5% of overall maternal hospitalization costs.

THEY'RE BOTH COVERED

Vaccinating pregnant moms for influenza also prevents 90% of their kids from being hospitalized with it during their first six months, according to researchers at the Yale School of Medicine. Since babies under six months can't get flu shots, researchers said this was a good way to keep them from getting influenza, and at a two-for-one rate.

GOOD VALUE

Neonatal intensive care provides substantial population health benefits in Mexico relative to its costs, even for very premature babies, and as such offers exceptional value within the country's Popular Health Insurance (Seguro Popular) program, which offers free access to a specific set of healthcare interventions. Researchers from Baylor College of Medicine and Harvard used an analytic model to show that compared to no intensive care, NIC for infants born at 24-26, 27-29, and 30-33 weeks gestation prolonged life expectancy by 28, 43, and 34 years respectively, and averted 9, 15, and 12 DALYs (disability-adjusted life years; one DALY represents the loss of a year of healthy life), at incremental costs of \$1,200, \$650, and \$240 for each DALY averted, respectively. The authors concluded that improving the survival of infants above 30 weeks gestation provides the greatest overall population health benefits, and at the highest value for money, intervention among all preterm infants above 24 weeks gestation should be considered as a cost-effective use of healthcare resources. For the full study, go to PLoS Medicine, "Clinical Benefits, Costs, and Cost-Effectiveness of Neonatal Intensive Care in Mexico," Profit et al.

DRINK UP

Elsevier's journal, *Alcohol*, published a special year-end double issue on Fetal Alcohol Spectrum Disorders (FASD). The issue features 15 articles covering new ways to identify pregnancies at risk for FASD using existing maternal self-report tools; the development of biomarker methods to help improve early identification and diagnosis of at-risk exposure to alcohol; the use of animal models to develop new diagnostic and intervention strategies; and a new framework to improve outcomes for children affected by prenatal alcohol-induced brain damage. Also included are three articles from the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), a consortium of international researchers currently in the process of collecting the largest set of integrated clinical data on FASD ever compiled. You can see the issue on a subscription or pay-per-view basis via ScienceDirect.

BETTER THAN METH(ADONE)

Babies do better withdrawing from drugs if their addicted moms receive buprenorphine instead of methadone during pregnancy, according to researchers at Vanderbilt, who conducted an eight-site, international, double-blind, double-dummy, flexible-dosing randomized controlled trial. Buprenorphine is currently prescribed for opioid addiction, but hadn't been studied in terms of pregnancy. Babies of mothers who received buprenorphine compared to those who received methadone needed significantly less morphine to treat their neonatal abstinence syndrome, had shorter hospital stays (10 days vs 17.5 days), and shorter duration of treatment for neonatal abstinence syndrome (4.1 days vs 9.9. days).

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STRESSED OUT

Stress hormones in depressed moms mean stress hormones in their babies at birth, according to researchers at the University of Michigan Medical School. The researchers found that two-week-old children of depressed moms had decreased muscle tone compared to other kids, though they achieved the proper level of neurological maturity. The researchers said the hormonal environment in the uterus may act as a catalyst that alters gene expression, with the ultimate result of later behavioral and psychological disorders. Researchers took samples of umbilical cord blood right after birth and found elevated levels of ACTH in babies born to mothers with depression. However, cortisol levels were the same in the babies of depressed and undepressed moms, meaning that the stress of birth wasn't the issue. Previous studies have shown that babies born to women with severe depression may be more likely to be born prematurely or underweight, have diminished hand-to-mouth coordination and "be less cuddly," according to the report published by Medical News Today.

SCANNERS

Researchers at the Chinese University of Hong Kong have developed new technology that scans the whole genome of a fetus using cell-free fetal DNA found in the mother's blood. Since this merely requires a sample of the mom's blood and the dad's DNA, it's a step toward a single noninvasive test for multiple fetal genetic disorders. Researchers used blood sampled from a pregnant woman from Southeast Asia. First they had to determine that the whole fetal genome was present in the fetal DNA molecules in maternal blood plasma, which went fine except that the DNA was highly fragmented. The lead researchers said solving the problem was like "trying to assemble a jigsaw puzzle that has millions of pieces and adding in tens of millions of pieces from another jigsaw puzzle and then trying to re-assemble the first one." The researchers sequenced 4 billion fragments and looked for sequences that carried the father's DNA signature, exclusively. From this, they created a map of the fetal genome that came from the dad. Next, they had to "draw" a non-contaminated fetal inheritance map from the mom – tough to accomplish, too, since fetal DNA is only 10% of maternal plasma. Without going into a lot of details here, they did it, and then created the genome map that the fetus had inherited from the mother, added it to the one from the father, and assembled the fetal genome. The completed map showed that the fetus of the woman in the experiment carried beta-thalassaemia, a blood disorder common in Southeast Asia. Thus, the study showed the feasibility of using genome-wide scanning to diagnose fetal genetic disorders prenatally in a noninvasive way. The above news item is edited from Medical News Today. The original article was written by Catharine Paddock, PhD, copyright Medical News Today.

THE GATESES GIVE

The University of British Columbia has received a \$7 million grant from the Bill & Melinda Gates Foundation to test new strategies for the monitoring, prevention, and treatment of pre-eclampsia. The grant will support a four-year international research and community-level intervention project called PRE-Eclampsia Monitoring, Prevention and Treatment (PRE-EMPT), comprising researchers, physicians and community health professionals from Canada, the US, Africa, Asia, Oceania, the UK and the WHO, who will study, develop and implement a set of clinical guidelines tailored for lower- and middle-income countries.

YOU KNEW THIS WAS COMING

Pregnant moms who regularly use mobile phones may be more likely to have kids with behavioral problems, especially if those kids use mobile phones, too, according to research revealed by the Danish National Birth Cohort study. Researchers enrolled 100,000 pregnant moms over six years and tracked their kids. About a third of the seven year olds used a mobile phone. Children exposed to mobile phones before and after birth were 50% more likely to have behavioral problems. Those exposed to mobile phones before birth only were 40% more likely to have behavioral problems, while those with no prenatal exposure but with access to phones by the time they were 7 were 20% more likely to exhibit abnormal behaviors.

EPILEPSY AND SPINA BIFIDA

Women with epilepsy who are taking carbamazepine have a higher chance of having an infant with spina bifida, according to researchers at the University of Groningen. Spina bifida was the only specific major congenital malformation significantly associated with exposure to carbamazepine monotherapy, and spina bifida was 2.6 times more likely in infants of women who had taken the drug compared to those who'd taken no antiepileptic drugs. The risks were even higher for epileptic moms taking valproic acid. Carbamazepine is the most commonly prescribed anti-epilepsy drug prescribed to women of reproductive age in Europe. Women on valproic acid are six times more likely to have a pregnancy outcome with spina bifida and seven times more likely to have an outcome with hypospadias. Of all the anticonvulsants, carbamazepine is associated with the lowest rate of morphological defects. In any event, for many, discontinuing antiseizure drugs isn't an option.

OVERHEARD

The following exchange (and many others) can be found on Overheardinnewyork.com:

A hospital cafeteria:

Nurse #1: I know, I still can't believe she signed that name on the birth certificate.

Doctor: What name?

Nurse #2: When Dr Smith delivered the afterbirth, this mom said, "Oh my god, what is that?" and Dr Smith said, "That's the placenta."

Nurse #1: Yeah, and then the freakin' idiot says, "That's the most beautiful name I ever heard! I'm gonna name my baby Placenta."

Doctor: No, don't tell me...

Nurse #2: Yep.

Doctor: I'm sorry I asked.

SMELL, EAT, DRINK

A study at the University of Colorado showed that a pregnant mother's diet not only sensitizes the fetus to the smells and flavors the mom ingests, but also changes the brain, thus influencing what the kid will eat and drink in the future. The authors logically inferred that if the mom drinks booze, the kid may too, and the same for eating fast food and lots of candy. Researchers used mice pups to track changes in their olfactory glomeruli. They fed one group of pregnant and nursing mice a bland diet and another a flavored diet. At weaning age, the pups from mothers on the flavored diet had significantly larger glomeruli than those on the bland diet. They also preferred the same flavor their mother ate, while the other pups had no preference. Information for the above is from Medical News Today, copyright Medical News Today.

EPIGENETIC

Researchers at Keele and Nottingham Universities and other UK institutions have identified a link between changes in the DNA of newborn babies, folic acid supplementation during pregnancy, and birth weight. This epigenetic study showed that the levels of homocysteine in newborn blood is linked to modifications of DNA methylation in key genes and that such modifications might be used to predict birth weight. Researchers examined the relationship between folic acid supplementation and its metabolites on DNA methylation in human blood from the umbilical cord, using microarray techniques which simultaneously examined methylation at 27,578 sites in the DNA. This study was the first to suggest that methylation of particular genes in the baby's DNA may be the key to unlocking the secret of the action of folic acid.

PRODUCTS

DANNY TIES

The new Danny Ties tracheostomy holder from B&B Medical minimizes skin irritation under the collar and offers a softer and more comfortable fit around the patient's neck. Danny Ties securely hold the artificial airway in place while maximizing comfort for infant, pediatric and adult patients. Danny Ties are made of a soft, absorbent cotton that lays smooth at the edges of the collar and significantly minimizes skin breakdown beneath the collar. Available in three sizes, the contoured collar holds its shape, does not fold in half around the neck and does not stretch when it absorbs moisture. The patent-pending design of the Danny Ties evenly distributes the padded collar material around the neck to minimize pressure points on the skin. The Danny Ties collar is easy and quick to apply, and is hypoallergenic and latex-free. If soiled, the Danny Ties may be washed, dried and reused for the same patient for up to 28 days, per institutional policy. Also available from B&B Medical Technologies are the Sil.Flex Stoma Pad and TrachStay, which may be used in combination with the Danny Ties. Sil.Flex Stoma Pads enhance patient comfort with all brands and styles of tracheostomy tubes. The TrachStay prevents accidental disconnects from the ventilator circuit. Contact www.BandB-Medical.com.

EMBRACEABLE

GE Healthcare announced a global partnership with Embrace to distribute a low-cost infant warmer that looks like a small sleeping bag and can help keep an infant warm for hours. This product will be distributed in India initially to improve rural infant care as an

alternative to more expensive warmers. The warmer comprises a sleeping bag, a sealed pouch of wax and a heater. The warmer swaddles the baby and a heated pouch of wax is placed in an adjacent compartment. The pouch can be heated via an electrical heater. Unlike traditional incubators that cost up to \$20,000, the Embrace Infant Warmer costs less than \$200, and works without a constant supply of electricity. Embrace was founded by a team of engineers and MBAs from Stanford and Harvard University. Contact gehealthcare.com.

WINNERS

The winners of Medela's November Virtual Breast Milk Collection campaign were Tampa General Hospital, Memorial Hospital at Gulfport, MS; Altru Health Systems, Grand Forks,



Focus on patient care, not the device.

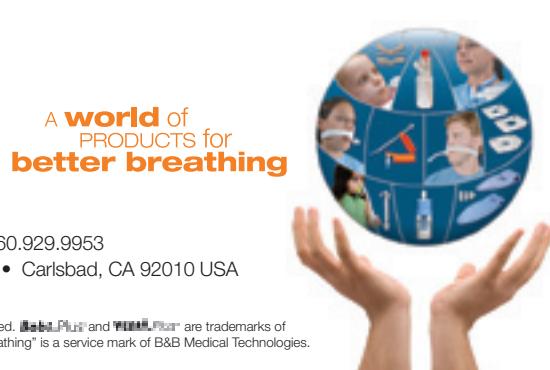
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ND; DuBois Regional Medical Center, PA; Children's Hospital of Wisconsin, and the University of New Mexico Hospital, Albuquerque. The winning hospitals were chosen by the 4,750 people who participated in the campaign and voted for their preferred Neonatal Intensive Care Unit. Each winner receives \$5,000 in neonatal human milk support products from Medela. Contact medela.com.

BE ETHICAL

The book *Medical Ethics for Dummies* from Wiley offers an affordable course supplement for those studying medical ethics. It includes discussions of basic principles, and common controversies, informed consent, distinctions between ethics and morality, ethical challenges, disclosing errors, and daily challenges. The authors are Jan Runzheimer, MD, a family physician and ethicist, and Linda Johnson Larsen, who has written 24 books on health. The book is \$24.99, through Amazon or from Wiley Publishing.

ROOMERS

The Ceilings & Interior Systems Construction Association (CISCA) has released a free extensive white paper "Acoustics in Healthcare Environments," which is an invaluable tool for architects, interior designers, and other design professionals who work to improve healthcare settings for all users, including NICUs. This white paper serves as a comprehensive introduction to the acoustical issues commonly confronted on healthcare projects. The white paper covers the current state of acoustics, understanding acoustic issues, design strategies, minimizing noise, and specific information about NICUs and emergency departments. Contact cisca.org.

NEW PLATFORMS

Covidien announced that three new platforms for its Puritan Bennett 840 ventilator – the Puritan Bennett 840 Neonatal ventilator, the Puritan Bennett 840 Universal ventilator and the Puritan Bennett 840 Pediatric-Adult ventilator – are now available in the United States. The Puritan Bennett 840 Neonatal ventilator helps clinicians safely deliver, manage and monitor a ventilation regimen tailored for even the smallest and most critically ill neonatal patients. It offers the ability to set a tidal volume as small as 2 mL for neonates weighing as little as 300 grams without having to change to another ventilator. The Puritan Bennett 840 Universal ventilator for every patient type, from neonatal to adult, includes a neonatal CPAP mode that enables clinicians to flexibly deploy noninvasive ventilation in neonates. It supports patient-ventilator synchrony, which has been shown to facilitate spontaneous breathing. The ventilator includes features that effectively match the patient's respiratory demand and adapt to changes in patient condition. The Puritan Bennett 840 Pediatric-Adult ventilator for pediatric to adult patients helps clinicians provide improved levels of ventilatory support by offering multiple therapies of ventilation, including invasive and noninvasive methods, as well as more advanced modes of ventilation.* [* Xirouchaki N, Kondili E, Vaporidi K, et al. Proportional assist ventilation with load-adjustable gain factors in critically ill patients: comparison with pressure support. *Intensive Care Med.* 2008; 34(11):2026-2034; Alotaibi G, Kacmarek R, Scanlan C. Comparison of dual mode ventilation among selected adult critical care ventilators using a programmable lung simulator. *Respir Care.* 2004. (Abstract).] Contact www.covidien.com.

GOING GREEN AND MORE

Masimo recently debuted product enhancements to its Radical-7 and Patient SafetyNet, and presented a clinical review of real-world use of the SafetyNet. A new clinical study offered results of Masimo's Acoustic Respiration Rate technology (Accuracy of Acoustic Respiration Rate Monitoring in an Acute Nursing Unit, Jim Kumpula, Respiratory Care, Swedish Medical Center, Seattle, WA.) In other Masimo news, Kaiser Permanente recently converted its entire health system of 37 hospitals to Masimo oximetry technology, via Masimo Rainbow SET Pulse CO-Oximetry. Masimo is also actively going green. The company's ReSposable Sensor solution has helped hospitals reduce sensor waste by more than 90%. The ReSposable Sensor system combines features of the LNOP, RNCS and Rainbow sensors into a design that allows the portion of the sensor that connects to the patient cable to be used on multiple patients, while the portion that attaches to the patient is used only once before disposal. The sensors measure hemoglobin, oxygen content, PVITM for fluid responsiveness, and methemoglobin, as well as oxygen saturation, perfusion index, and pulse rate – at a savings of 50% compared to single patient adhesive Rainbow sensors. In line with Masimo's Green Initiative program, as part of Masimo's manufacturing process, sensor and device packaging is made from 100% recycled material where applicable, cardboard waste is recycled, confidential documents are shredded on-site and recycled. Also recycled are batteries, CRTs and LCD displays, electronics, fluorescent lamps, metals and cables, plastic housings, and drink containers. The company is in the process of implementing ISO 14001 in its California facilities. Contact masimo.com.

TWO FROM SMITHS

The babyPAC emergency and transport ventilator from Smiths Medical is MRI compatible and allows for precise oxygen concentrations. Its variable gas mixing system extends cylinder life and allows precise selection of oxygen concentration. Calibrated inspiratory pressure control provides continuous adjustment of the end inspiratory pressure. Separate controls provide careful management of inspiratory/expiratory times and pressure to suit patient breathing requirements. It has four operating modes: CMV+PEEP, CMV+Active PEEP, IMV+CPAP and CPAP. Adjustable pneumatic pressure relief with alarm provides a wide range of options. Dual function PEEP/CPAP control allows continuous adjustment of pressure... The Pneupac VR1 emergency ventilator offers a single control for setting the frequency and tidal volume, including a clock-stop setting at the recommended adult position. This portable ventilator enables rapid setup in demanding circumstances. Auto/manual controls, a patient demand system, MR compatibility, and other features provide the means to manage respiratory emergencies. Its oxygen powered unit eliminates the need for electricity. Linked manual controls allow it to be used in a variety of chest compression and ventilation options in cardiac life support. MR compatibility provides maximum flexibility for transport within the hospital. Contact www.smiths-medical.com/pneupac.

Best Practices for Warming Human Milk in a Hospital Setting

Jean Rhodes, PhD, CNM, IBCLC

Introduction

Breastfeeding is the gold standard for feeding and nourishing the human infant. But when infants are unable to feed at breast – as in the case of hospitalized preterm or compromised infants – mother's milk feedings via enteral feeding systems, bottles or special feeding devices are undeniably the next best option.

The science of human milk feeding in the neonatal intensive care unit is constantly evolving. While the majority of research related to NICU breastmilk feedings has focused on storage of human milk, enteral feeding processes and fortification of human milk, surprisingly little research has explored the clinical process of milk preparation for feeds. For example, according to the Human Milk Banking Association of North America (HMBANA),¹ there are no studies on the optimal method of some of these basic processes such as thawing human milk for feedings. The 2006 HMBANA Guidelines for Best Practice for Expressing, Storing and Handling Human Milk in Hospitals, Homes and Child Care Settings are based on research evidence, are inferred from Food Safety Guidelines or, in the absence of scientific evidence, are based on reasoned opinions of experts. Gaps in the literature, particularly related to handling human milk in the NICU setting, should be re-examined in the light of new evidence and current technology. This article will summarize the science of human milk feedings in the hospital setting and propose a new standard of care with a waterless milk warmer. Key points are emphasized, including:

- delivering the maximum benefit of human milk to the hospitalized infant by safely thawing and warming milk.
- eliminating the possibility of water bath associated nosocomial infections.
- standardizing the temperature of infant feedings to the most physiologic temperature range (body temperature).
- reducing process variation and guesswork commonly associated with feeding preparation.
- maximizing clinical time at the bedside.

Benefits of Human Milk

In addition to species-specific macronutrients, human milk contains multiple immunologic factors such as secretory IgA (sIgA), lactoferrin, lysozyme, leukocytes and the bifidus factor that protect the fragile newborn from bacterial, viral and fungal

infections.²⁻⁴ Human milk – rich in antioxidants, prostaglandins, cytokines, epidermal growth factors, sIgA and lysozyme – is also capable of suppressing potentially devastating inflammatory processes in the preterm or sick infant. Inflammation originating in the infant's intestinal tract can predispose the infant to both feeding intolerance and the potentially devastating disease, necrotizing enterocolitis (NEC).⁵ Inflammation can damage other organ systems of the preterm infant, increasing the risk of chronic lung disease, retinopathy of prematurity and adverse neuro-developmental outcomes.⁶ Preterm infants fed mothers' own milk are shown to have decreased risks of both feeding intolerance and NEC when compared to preterm infants fed infant formula.⁷⁻¹¹

The benefits of human milk accumulate in a dose response manner: the greater the overall quantity of milk an infant receives, the greater the benefit to the infant. The concept of dose response is relevant not only to the percentage of human milk feeds, but also to the duration of human milk feeds over days, weeks and months. Thus the longer an infant receives mother's milk, the greater the overall benefit. Specifically, studies suggest that the more mother's milk a preterm infant receives during the NICU stay, the lower the infant's risks are of NEC, late onset sepsis and enteral feeding intolerance.^{9,12} In extremely low birth weight infants, intakes of higher amounts of human milk during the NICU stay result in lower risks of rehospitalization after discharge as well as higher Bayley mental developmental index scores and Bayley behavioral score percentiles for up to 30 months' corrected age.^{13,14}

At body temperature, 37°C (98°F), fresh human milk is an intricate living bioactive fluid with all essential properties – including macronutrients, anti-infective and anti-inflammatory components – intact. While fresh human milk is ideal for infant feeds it is not always available for hospitalized infants. Therefore, optimal handling and storage are critical in the NICU setting.

Temperature Effects of Human Milk

Human milk is sensitive to the effects of temperature changes.¹⁵⁻¹⁸ In the NICU, the separation of mothers and infants dictates milk storage in refrigerators or freezers; however, the process of freezing human milk inactivates some of its anti-infective properties.¹ Preparation of human milk for feedings involves additional processes – thawing, fortification and heating – that can also alter human milk composition.^{15,19-22} As previously mentioned, research on the actual processes of

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preparing human milk for feedings is incomplete. While there are no studies of the best process for thawing frozen human milk, there are studies of the impact of heat on human milk. Studies on pasteurized milk (heated to 62°C/144°F for 30 minutes) demonstrate measurable heat related changes: immunologic and anti-inflammatory components such as SIgA, lactoferrin, and lysozyme are decreased and beneficial probiotic bacteria and white blood cells are destroyed.^{4,23}

Temperature can affect not only the beneficial components of human milk but also the preterm infant's ability to tolerate feeds. A study by Gonzalez and associates²⁴ demonstrates this sensitivity of very low birth weight preterm infants to feeding temperatures. In this study, infants were fed milk prepared at 3 different temperatures: cool temperature (10°C/50°F), room temperature (24°C/75°F) and body temperature (37°C/98.6°F). The authors found that preterm infants fed milk at body temperature had the least amount of gastric residuals and greater feeding tolerances. Conversely, infants fed milk at cool temperatures had the highest milk residuals and the greatest incidence of feeding intolerance. The authors concluded that warming milk to body temperature might promote greater feeding tolerance in very low birth weight (VLBW) preterm infants.

Current Practice Standards

The 2006 HMBANA Guidelines for Best Practice for Expressing, Storing and Handling Human Milk in Hospitals, Homes and Child Care Settings recommends specific processes with rationale for the safe handling of human milk. Guidelines for thawing frozen milk include:

- Thawing milk quickly in a container of warm water not to exceed 37°C/98°F
- Avoiding milk contamination from water getting on or under the container lid
- Refrigerating milk before it is completely thawed and while ice crystals are still present.

HMBANA guidelines for warming human milk for feeding include:

- Warming individual feedings in a container of warm water or under running warm water
- Protecting the container from contamination in the water
- Noting that communal warming systems may not have clean water.¹

HMBANA guidelines are often recognized as the standard of practice recommended by professional organizations and practitioners. However, in NICU settings, human milk is thawed and warmed through a variety of methods not always in compliance with HMBANA recommendations. Human milk is often heated in cups of warm-to-hot tap water, in containers of water from instant heat faucets or in water-based feeding warmers. Water from instant heat faucets can reach 87°C (189°F), well above the HMBANA recommendation and at a point of potentially de-activating anti-infection properties in human milk.

Thawing and warming of milk with water involves a complex interplay of several factors including the milk volume, milk temperature at the beginning of the warming process, size of the milk container and the water temperature. Determining the exact point of thaw to include the presence of small amounts of ice crystals requires constant oversight of the warming

process. Determining when milk is at a desired temperature is inexact, often subjective and can be time consuming. Therefore, oversight of the thawing and warming of human milk can reduce nursing time for clinical care in the NICU.

Contamination of Hospital Tap Water

For 40 years, hospital tap water has been identified as a potential source of nosocomial infections from bacteria and other contaminants including Cryptosporidium parvum, Legionelle spp, E Coli and Pseudomonas aeruginosa.²⁵⁻²⁹ Patients at high risk of infection due to waterborne pathogens include AIDS patients, organ transplant recipients, oncology patients and neonates.³⁰ Healthcare-associated infections from water supplies have been identified in hospital nurseries. As recently as 2009, 23 strains of Pseudomonas aeruginosa were found in the water supply of a children's hospital in the US.³¹ In another report Buyukayvuz, et al,²⁶ identified *Staphylococcus* and *Klebsiella pneumoniae* in hospital tap water used to heat infant milk. These bacteria were determined to be directly responsible for an outbreak of septicemia in the hospital's neonatal intensive care unit.

Squier²⁸ and Angelbeck³⁰ have explained the process of microbial contamination of hospital tap water. A slime layer or biofilm containing microorganisms adheres to the lumen of pipes and fixtures in municipal and hospital plumbing systems and in hospital water tanks. Patient exposure to waterborne microorganisms can occur through any exposure to tap water including bathing, drinking, contact with medical equipment wet with water or health care provider hands rinsed in water. When tap water is used to warm infant feedings, there is potential for contamination of not only the container and the milk but also the nurse's hands. Squier recommends using dry-warming devices to heat fluids that come in contact with patients. In concurrence, the CDC in their 2003 Guideline for Infection Control in Health-Care Facilities,³² suggested facilities remove sources of contaminated water whenever possible. These guidelines clearly recognize that moist environments and water-based solutions can serve as reservoirs for waterborne microorganisms in hospital settings.

The Medela Waterless Milk Warmer

The Medela Waterless Milk Warmer eliminates the possibility of contamination caused by tap water by using forced dry convection heat instead of water to thaw and/or warm milk. The Waterless Milk Warmer uses a fan that circulates air over heated coils found in the lid of the device. The heating profile is controlled by a software program and maintained with safe operating limits through a series of thermal sensors and safety shutoffs, eliminating the guesswork involved in heating human milk to an optimal range. The Waterless Milk Warmer safely thaws frozen milk to 4°C in less than 30 minutes. (Temperatures may vary depending on the container used.) Thawed milk will contain small amounts of ice crystals, per HMBANA guidelines, indicating the milk has not been over-heated. The Waterless Milk Warmer also warms milk quickly and efficiently to body temperature range of 30 to 38°C (86 to 100°F). At the end of its operating cycle, the milk warmer alerts staff by a visual indicator and a low volume alarm but will continue to keep milk temperature stable for 30 minutes.

The Waterless Milk Warmer is easy to keep clean because of the use of disposable liners. Liners fit in the compartment that holds the milk container or syringe. Each liner is assigned

to a particular patient and can be labeled with the patient's information, date and time.

The Waterless Milk Warmer can be used with a variety of containers. As previously noted, the benefits of human milk are proportional to the amount an infant receives over time. In the early days of expression, mothers may produce very small quantities of colostrum or milk. During this time, preterm infants may receive very small tropic feeds to stimulate gut maturation, foster gut motility and support the infant's immune system. The Waterless Milk Warmer accommodates these small amounts of milk in syringes ranging from 1-60 mL. As feeding volumes increase, the warmer will handle containers or bottles from various manufacturers up to 250 mL.

In summary, human milk feedings in the hospital setting involve a complex matrix of issues related to the intricate nature of human milk and the potential hazards of milk storage and preparation. Through the use of innovative technology, and with effective clinical implementation, the Medela Waterless Milk Warmer may help maintain the optimal integrity of human milk feeds for hospitalized infants.

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Developmental Care in the Neonatal Intensive Care Unit – New York City Health and Hospitals Corporation (HHC)

Consuelo U. Dungca, EdD, RN; Marlene Allison, MPH, RN; Gloria Watson, MPH, RN, HHC

New York City Health and Hospitals Corporation (HHC) is the largest municipal health care system in the nation and serves mostly disadvantaged and vulnerable patient populations who are predominately low income, uninsured, undocumented, multi-ethnic and multi-culture. Each year, over 23,000 babies are delivered in the 11 HHC hospitals with 5,520 (24%) admitted to the Neonatal Intensive Care Units (NICU) due to low birth weight (7%), very low birth weight (2%), and other conditions requiring intensive care.¹

Developmental care in the NICU

In the past, HHC's NICUs, like most, were very busy, with bright lights and loud noises from beepers, telephones, overhead pagers, alarms, staff voices, and even radios. Clinicians provided optimum care to these delicate newborns in an efficient and protective manner, placing them in positions of perceived comfort and oftentimes using bed linen as boundaries to position them.

In 2009, two years after implementation of developmental care, the HHC NICUs are still very busy but the bright overhead lights are now dimmed, spotlights are used during procedures, and window shades limit the amount of sunlight entering the units. Modifications have been made to soundproof the ceilings and floors, sound alarms have been changed to light, and overhead pagers are now turned off. Preemies are appropriately positioned in state-of-the-art incubators with covers that further protect them from light exposure. Linen rolls have been replaced with positioning aids like the SnuggleUp, gel pillows and Bendy Bumpers and neonates enjoy the benefit of kangaroo care 24/7 with their parents.

Implementation

In 2005, the neonatology directors from two HHC regional perinatal centers (Bellevue Hospital Center in Manhattan and Jacobi Medical Center in the Bronx) recommended implementation of developmental care to enhance care practices and performance of NICU physicians and nurses. The idea at first seemed preposterous, radical, inhibitive, and even impossible,

since the concept of developmental care was new and not understood by the majority of providers. HHC prides itself on being at the forefront of quality, using current therapeutic modalities, technology, and implementation of evidence-based best practices. After extensive research reviews, and a formal proposal and presentation made to the HHC leadership, the Corporation made a unanimous decision to adopt the developmental care concept in all 11 NICUs.

Used synonymously with family-centered care, developmental care is an evidence-based practice model for delivering care to hospitalized, premature and critically ill neonates.² Care practices include modification of the environment to reduce light and sound levels, provision of individualized care based on neonates' cues, involvement of family, and utilization of developmentally supportive care giving, handling, and positioning techniques.³ Research evidence demonstrates that this concept of care fosters normal development of the premature brain, minimizes stress-related complications such as apnea and bradycardia, decreases position-related complications such as plagiocephaly (flattening of the head), torticollis (twisted neck due to shortening of neck muscles), and other flexion deformities, as well as allowing for quicker weight gain and earlier discharge.^{4,5}

With funding secured through a generous donation of the Corporation and a private foundation, modifications of the NICU environments were undertaken. Initial assessment of the 11 NICUs' physical structures showed light readings ranging from 1 to 139 foot-candles and sound levels as high as 114 decibels. These levels exceeded the American Academy of Pediatrics recommendations for light measurements of 1 to 60 foot-candles and maximum sound level of 45 decibels (average IV pump alarms at 61 to 78 decibels and normal human voice at 58 to 64 decibels).^{6,7} Unit modifications included replacing ceilings and floors with soundproof materials, installing dimmer switches, eliminating overhead paging, lowering telephone ring tones, replacing sound to light alarms, and changing garbage containers and linen carts from metal to rubber.

Operationalizing developmental care practices

In addition to the modification of the environment, staff performance and practice also required change. To actualize these changes, knowledge, understanding, commitment and hands-on training on concepts and the practice of developmental care were imperative. The Corporation contracted the services of Philips Children's Medical Ventures (PChMV/Wee Care program)

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to educate and assist the staff to operationalize these concepts in their daily performance and practice. PChMV conducted a baseline assessment of the 11 NICUs from a developmentally supportive, family-centered perspective, including a tour of each NICU and observations and discussions with staff on all shifts to gather information and elicit any preconceived notions or beliefs relating to developmental care. Thereafter, intensive staff education was provided through a series of leadership summits, classroom and onsite training, and follow-ups. The educational funding for the project was supported through the New York City Department of Health (NYSDOH) Regional Perinatal Center.

A major pre-site assessment finding showed that more than 90% of neonates' positioning was not in compliance with the developmental care concepts of flexion, containment, and alignment.⁸ However, from the nurses' perspective, these infants were in positions of comfort.

Given the importance of correct positioning, this aspect of training was a major focus and a challenge requiring the patience, understanding and support of the trainers. Staff gained competence and mastery in correct developmental care positioning through role play and practice sessions using adult-sized positioning devices and demonstrations in positioning, experiencing themselves the comfort of correct, supportive positions. Follow-up clinical visits at the bedside, and use of the Infant Position Assessment Tool (IPAT) as a guide to monitor head and neck positions, shoulder status, hand location, hip position, and orientation of knees, ankles and feet, further reinforced correct positioning. In the months that followed, staff amazingly embraced the developmental care concepts as evidenced in positioning of their neonates, their practice and performance.

Developmental care committee

A corporate developmental care committee was formed to monitor and ensure sustainability of the project through compliance with quality indicators, positive outcomes, continuous education, support, and implementation of new changes. The committee also sponsors a yearly symposium for the NICU staff to showcase successes and to address and resolve any challenges, as well as network with other staff. In addition, each NICU has established its own developmental care committee to discuss progress goals and identify opportunities for improvement. Both the corporate and the hospital committees are focused on the sustainability of developmental care, maintaining the gains, and identifying further opportunities for growth.

More recently, the Corporation hired a Developmental Care Coordinator (DCC) to conduct quarterly site visits to all the NICUs. The DCC conducts education on developmental care, monitors progress, assists in resolving issues and challenges, identifies opportunities for improvement, and provides positive feedback for accomplishments. Health and Hospitals Corporation is proud of its Neonatal Intensive Care Units' staff and their continuing quest for quality through achievements in the implementation and sustainment of developmental care.

Resources

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Induced Multiple Pregnancies and Neonatal Outcomes: Toward a Bioethical Issue

Antonio A. Zuppa, Giovanni Alighieri, Piero Catenazzi, Antonio Scorrano, Costantino Romagnoli

Abstract

Assisted reproductive technology has made great progress during the last three decades. After the initial enthusiasm, many ethical, legal and social issues related to the application of these procedures began to evolve. Multifetal pregnancy and fetal reduction, embryo cryopreservation, preimplantation genetic diagnosis, risks of birth defects and other adverse outcome associated with assisted reproductive technology are issues that have to be addressed building future collaborative studies and continuing the debate on related ethical issues.

Summary

The rapid evolution of ART has revealed certain ethical issues that have to be addressed such as multifetal pregnancy and fetal reduction, embryo cryopreservation, preimplantation genetic diagnosis, risks of birth defects and other adverse outcome associated with assisted reproductive technology. Advances in human reproductive biology during the last three decades enabled the increased use of ovulation induction and the introduction and rapid progress of assisted reproductive techniques (ART), defined as any procedure that entails the handling of both eggs and sperm or of embryos for the purpose of establishing a pregnancy (ie, in vitro fertilization -IVF-, intracytoplasmatic sperm injection -ICSI-).¹

As consequence, the incidence of multiple pregnancies has increased: twin births have doubled and the number of triplet births has tripled.² In the 1990s, the ART and non-ART technologies were responsible for at least two thirds of all multiple pregnancies, and for the majority of high order multiple pregnancies.³ Because of pressure from politicians and international societies it is hard, in Europe, to find countries with the same rules regarding medically assisted reproduction.⁴ International studies in the last ten years have continued to show an increased incidence of preterm birth (<37 weeks' gestation), low birth-weight (<2500 g) and associated adverse neonatal outcomes in ART births compared with naturally conceived births.^{3,5-8}

In an interesting review it was found a difference in singleton pregnancies outcomes between natural and assisted conceptions

with a worse perinatal outcome in the second one. It was not similarly observed in assisted twin pregnancies that seem to have outcomes that are either similar to or slightly better than those conceived naturally. But this is poor consolation for the much greater risks of twin pregnancy overall. Virtually all perinatal and infant morbidity occurs more frequently in twins than in singletons. One of the most results of this study is that there is an increased perinatal mortality in singleton and twin pregnancies after assisted conception than in natural conception.⁹

In our cohort study we compared 228 neonates from spontaneous twin pregnancies with 32 neonates from induced twin pregnancies, showing a significantly higher incidence of prematurity, low birth-weight, severe depression at birth and respiratory disease in the latter.¹⁰

More recently, we conducted another cohort study comparing 6 spontaneous triplet pregnancies with 18 induced triplet pregnancies.¹¹ In spite of the lack of significant differences between the two groups, the assisted reproduction group showed more complications. According to international data, the results suggest that the incidence of major neonatal morbidity (i.e., neonatal malformations) might increase due to assisted reproduction.

Additionally, there has been a suggestion that ART births have a small but significantly increased incidence of birth defects. Rates of ART-associated birth defects are 1.4 to 2.0 fold higher than the overall rate of 3% to 4% of births in general.¹² A large study from Western Australia examined 301 IVF infants, 837 ICSI infants, and 4,000 naturally conceived controls.¹³ The authors found an unadjusted odds ratio of developing congenital birth defects of 2.2 (1.3 to 3.3) for ICSI and 2.6 (1.7 to 3.0) for IVF compared with controls. On adjustment for multiple gestations and maternal age and parity, the odds ratios remained significantly elevated at 2.0 (1.3 to 3.2) and 2.0 (1.5 to 2.9) for ICSI and IVF, respectively. Some authors have reported in infants conceived with ART small increases in specific birth defect rates, such as neural tube defects, omphaloceles and hypospadias.¹⁴

ART births are also associated with an increased incidence of chromosomal abnormalities and imprinting defects, as Beckwith-Wiedemann Syndrome, Angelman Syndrome, Silver-Russel Syndrome, Maternal Hypomethylation Syndrome and Retinoblastoma.¹⁵ Regarding to chromosomal abnormalities, a meta-analysis compared ICSI conceived fetal karyotypes with those in the normal neonatal population and documented an

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increased risk of de novo anomalies and inherited chromosomal defects, usually from an infertile father.¹⁶ This risk estimates among women receiving ART is readily confounded by overlapping risk factors including multiple pregnancies, underlying causes of infertility and factors associated with ART themselves (i.e., the avoidance of natural selection mechanism of sperm during the course of a natural conception, the delayed fertilization of the oocyte, the freezing and thawing of embryos).^{17,18}

As regards imprinting defects, ART procedures including ovarian stimulation and the manipulation of preimplantation embryos occur during critical developmental periods when genomic imprints have been shown to be vulnerable in animal studies. The defect more frequently observed involves DNA methylation, especially loss of maternal methylation that seems to be due to underlying subfertility or ovarian stimulation without subsequent in vitro procedures.^{15,19}

However, these findings require further confirmation because it would be very difficult to design randomized controlled trials to study the effects of ART and non-ART technologies with natural conception. Much of the information relies on observational studies or small cohort studies that may not have significant power.

Developments of the ART over the last thirty years have created unexpected public interest in certain aspects of human reproduction. After the initial enthusiasm, many ethical, legal and social issues related to the application of these procedures began to evolve, which led to serious discussions and often disagreements among the involved physicians, public and the state itself: multifetal pregnancy and fetal reduction, embryo cryopreservation, preimplantation genetic diagnosis, genetic material donation and surrogacy.²⁰

Legislations and guidelines for infertility clinics have been outlined, along with strategies to limit the number of embryos transferred to achieve a lower risk of multiple births. Since 1997, a decrease has occurred in the number of embryos transferred and the percentage of gestation with three or more fetuses.²¹

The common practice of physicians is to transfer to the uterus only two or three embryos in any cycle, although many embryos are produced during a single IVF cycle. Then human embryo cryopreservation has become integral part of ART and there is little knowledge about the limits of storage period and the possible effects of long term storage.

Until advances in assisted reproductive technology eliminate the iatrogenic cause of multiple gestation, fetal reduction offers hope for a good outcome in an otherwise adverse situation, such as a multiple pregnancy where its continuation represents a threat to the life or health of the mother.

The recent advances in genetic disorders have made possible to diagnose the genetic conditions in the embryos before implantation in a setting of in vitro fertilization. Polymerase chain reaction and fluorescence in situ hybridization are the two common techniques employed on a single or two cells obtained via embryo biopsy.²²

It is our view that several approaches are needed to better address real risk for ART complications: guidelines on the

number of embryos that should be transferred, detailed information on the use of specific ART techniques on birth certificates, ART registry data, the linkage of the latter to birth defects registry data, prospective studies of ART births.

Obstetricians and pediatricians need to become sources of such information. Couples who want to use ART should be counseled about the risk/benefit associated with these techniques. An educated counsel is needed because evidence reveals that the diagnosis of infertility itself may increase the risk of perinatal complications.

In spite of the developments in reproductive medicine and the changes that have taken place to the structure of the society, a number of medical and ethical issues still remain unresolved.

Furthermore socioeconomic concerns are also important if we consider the remarkable use of human and technological resources needed to guarantee a good outcome in an induced multiple pregnancy.

In a pluralistic society it is more problematic to reach consensus on universal policy about assisted reproduction.

Would be acceptable to set the limits for the provision of these very useful treatments? This open question must be addressed building future collaborative studies and continuing the debate on related ethical, legal and social issues.

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justify the parental consent requirement on neonatal euthanasia. It is simply to point out that, at the level of public policy, drawing a parallel with cases of life-sustaining treatment or treatment withdrawal may not be straightforward.

An anonymous reader commented on Douglas's blog as follows: Firstly, although there are legal precedents for treatment withdrawal without parental consent – in practice this largely occurs following judicial review. In a setting where a child were suffering interminably and parents refused to agree to euthanasia the doctors might seek explicit court approval to euthanize the child...Defending neonatal euthanasia without consent plays directly into the hands of those who oppose it. It is a clear example of the type of slippery slope that opponents of euthanasia refer to. Even raising publicly the question of whether it would be permissible to end the life of a newborn without parental consent might undermine any attempt to have non-voluntary euthanasia seriously considered.

* The preceding is taken directly from Douglas's blog, and substantially edited. It comprises direct quotes and paraphrase. The copyright to the original article is held by the University of Oxford. Tom Douglas, Practical Ethics, Ethics in the News, University of Oxford, Copyright © the University of Oxford; 2011. All Rights Reserved. The article referenced by Douglas is: Appel JM. Neonatal Euthanasia: Why Require Parental Consent?, in the Journal of Bioethical Inquiry.

Differences in Organ Dysfunctions Between Neonates and Older Children

Nawar Bestati, Stéphane Leteurtre, Alain Duhamel, François Proulx, Bruno Grandbastien, Jacques Lacroix, Francis Leclerc

Abstract

Introduction: The multiple organ dysfunction syndrome (MODS) is a major cause of death for patients admitted to pediatric intensive care units (PICU). The Pediatric Logistic Organ Dysfunction (PELOD) score has been validated in order to describe and quantify the severity of organ dysfunction (OD). There are several physiological differences between neonates and older children. The objective of the study was to determine whether there are differences in incidence of ODs and mortality rate between full-term neonates (age <28 days) and older children.

Methods: In a prospective, observational study, 1,806 patients, admitted to seven PICUs between September 1998 and February 2000 were included. The PELOD score, which includes six organ dysfunctions and 12 variables, was recorded daily. For each variable, the most abnormal value was used to define the daily OD. For each OD, the most abnormal value each day and that during the entire stay were used in calculating the daily PELOD and PELOD scores, respectively. The relationships between OD, daily OD, PELOD, daily PELOD and mortality were compared between the two strata (neonates, older children) based on the discrimination power, logistic and multiple regression analyses.

Results: Of the 1,806 enrolled patients 171 (9.5%) were neonates. Incidence of MODS and mortality rate were higher among neonates than in older children (14.6% vs. 5.5%, $P < 10^{-7}$; 75.4%, vs 50.9%, $P < 10^{-4}$, respectively). Daily PELOD scores were significantly higher in neonates from day 1 to day 4. Daily cardiovascular, respiratory and renal dysfunction scores from day 1 to day 4 as well as the PELOD score for the entire pediatric intensive care unit stay were also significantly higher in neonates. Neurological, cardiovascular, and hepatic dysfunctions were independent predictors of death among neonates while all ODs significantly contributed to the risk of mortality in older children.

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Conclusions: Our data demonstrate that incidence of MODS and mortality rate are higher among neonates compared to older children. Neurological, cardiovascular, and hepatic dysfunctions were the only significant contributors to neonatal mortality. Stratification for neonates versus older children might be useful in clinical trials where MODS is considered as an outcome measure.

Introduction

Multiple organ dysfunction syndrome (MODS) is a major problem in the pediatric intensive care unit (PICU).^{1,2} Several studies have shown that mortality increased with the number of organ dysfunctions (ODs) in critically ill children. Two MODS scores have been developed to describe and quantify the severity of OD in critically ill children: the pediatric logistic organ dysfunction (PELOD) score and the pediatric multiple organ dysfunction score (P-MODS).³⁻⁵ The neonatal multiple organ dysfunction (NEOMOD) score provides information on ODs influencing mortality during the first 28 days of life among critically ill premature babies.⁶

There are several physiological and immunological characteristics that may differentiate the neonatal population.⁷⁻¹¹ For example, neonates are especially vulnerable to sepsis and nosocomial infections,¹² which represent a well-known cause of MODS.¹³ Human and animal studies have shown differences in organ response to injury between neonates and adults.^{14,15} Recently, Typpo and colleagues¹⁶ described the epidemiology of MODS at day 1 in patients older than 1 month across PICUs in the US. There was differential PICU mortality based on age. Infants had the highest overall PICU mortality compared with other age groups, and their increased mortality was supposed to be linked to the increased incidence of MODS.¹⁶ No similar study has considered neonates as an independent age group in comparison with the rest of the pediatric population. The aim of the present study was to determine whether there are differences in mortality, OD incidence estimated by the PELOD score, and OD contribution to mortality, between neonates on one side and older children on the other side.

Materials and Methods

Population: We included all consecutive patients admitted to seven multidisciplinary tertiary-care PICUs of university-affiliated hospitals (two French, three Canadian, and two Swiss) between September 1998 and February 2000. Exclusion criteria were the following: age of 18 years or older, prematurity, pregnancy, PICU length of stay of less than 4 hours, admission

Table 1. Description of the study patients

Characteristics	No. (%)	
	Neonates	Older children
Male to female ratio	1.16	1.22
Surgical patients	81 (47.4)	801 (49.0)
Ventilated patients**	115 (67%)	806 (49%)
PRISM score, median (Q1-Q3)**	10 (5-16)	5 (2-10)
Administrative length of stay in PICU in days, mean; median (Q1-Q3)**	8.0; 6 (3-6)	5.5; 3 (2-6)
Organ system of primary dysfunction on admission*		
Respiratory	63 (36.8)	568 (34.7)
Neurologic	16 (9.4)	319 (19.5)
Cardiovascular	60 (35.1)	425 (26.0)
Hepatic	1 (0.6)	33 (2.0)
Genitourinary	4 (2.3)	31 (1.9)
Gastrointestinal	20 (11.7)	71 (4.3)
Endocrine	1 (0.6)	21 (1.3)
Musculoskeletal	0 (0.0)	68 (4.2)
Hematologic	1 (0.6)	23 (1.4)
Miscellaneous/undetermined	5 (2.9)	76 (4.7)
Primary category of illness on admission		
Infection	34 (19.9)	405 (24.8)
Trauma**	1 (0.6)	174 (10.6)
Congenital disease**	102 (59.7)	561 (34.3)
Chemical injury	0 (0.0)	25 (1.5)
Drug	1 (0.6)	11 (0.7)
Cancer*	1 (0.6)	59 (3.6)
Diabetes	0 (0.0)	18 (1.1)
Allergic/Immunologic diseases*	0 (0.0)	42 (2.6)
Miscellaneous/undetermined	32 (18.7)	340 (20.8)
Deaths**	25 (14.6)	90 (5.5)

Q1-Q3: first and third quartile; *: p<0.05; **: p<10⁻⁴

in a state of continuous cardiopulmonary resuscitation without achieving stable vital signs for at least 2 hours, transfer to another PICU, and admission for scheduled procedures normally cared for in other hospital locations. Children with a history of prematurity were not excluded. Ethics committees of all participating hospitals approved the study. The requirement for consent was waived since the study was strictly observational.

Procedures: Data on PELOD score, which considers six ODs (cardiovascular, respiratory, hematological, neurological,

Table 2. Relative statistical contribution to mortality of each organ dysfunction (logistic regression) and of the PELOD score (multiple regression) in neonates and older children

Dysfunction	Logistic regression, odds ratio (95% CI)		Multiple regression, partial r^2	
	Neonates	Older children	Neonates	Older children
Neurological	1.118 (1.052-1.188)	1.156 (1.124-1.190)	0.46	0.34
Cardiovascular	1.211 (1.040-1.411)	1.116 (1.048-1.189)	0.28	0.47
Renal	0.970 (0.867-1.086)	1.099 (1.034-1.168)	0.19	0.12
Respiratory	1.126 (0.971-1.307)	1.172 (1.096-1.253)	0.06	0.05
Hematological	1.604 (0.956-2.690)	1.156 (1.019-1.312)	0.01	0.02
Hepatic	3.020 (1.012-9.011)	2.003 (1.115-3.599)	0.001	0.001

PELOD: pediatric logistic organ dysfunction; CI: confidence intervals.

hepatic, and renal dysfunction) and 12 variables, were recorded daily. For each variable, the most abnormal value was used to define the daily organ dysfunction (dOD). For each OD, the most abnormal value each day and that during the entire stay were used in calculating the daily PELOD (dPELOD) and PELOD scores, respectively. The distribution of the day 1 PELOD according to the outcome was analyzed by logistic regression and identified three classes of d₁PELOD score: low (fewer than 10 points), medium (10 to 19 points), and high (at least 20 points).

As the mortality rate decreased after 7 days, daily analyses were limited to data collected during the first week. Thus, only patients who stayed at least 7 days were included in the analysis of the dPELOD score on day 7, those who stayed at least 6 days were included in the analysis of the dPELOD score on day 6, and so on. The dependent variable was survival at PICU discharge.

Statistical analyses: Two distinct strata were considered: neonates (age of fewer than 28 days post-term) and older children. The descriptive analyses and comparisons of OD, dOD, PELOD, and dPELOD scores between the two strata were performed. Comparisons were performed with Mann-Whitney test (continuous variables) and chi-square or Fisher exact tests (categorical variables). Kaplan-Meier analysis at PICU discharge and log-rank test were used to compare the survival curves between neonates and older children. The relationships between OD, dOD,

PELOD, dPELOD, and mortality were compared between the two strata on the basis of the discrimination power as well as logistic and multiple regression analyses.

Based on the expected probability of death, discrimination describes the power of models to distinguish patients who died from those who survived. To estimate the discrimination of the PELOD and dPELOD scores, we used a receiver operator characteristic curve for each strata and calculated the area under the receiver operator characteristic curve (AUC). It is generally accepted that an AUC of at least 0.7 is acceptable, at least 0.8 is good, and at least 0.9 is excellent.¹⁷ Comparison of AUCs was performed when appropriate.¹⁸

To evaluate the relative weight of the ODs within each strata, a logistic regression model was developed. Independent variables were ordinal variables of each OD, and the dependent variable was PICU mortality. Second, a stepwise multiple regression analysis was developed for each strata, using the PELOD score as the dependent variable. All statistical analyses were

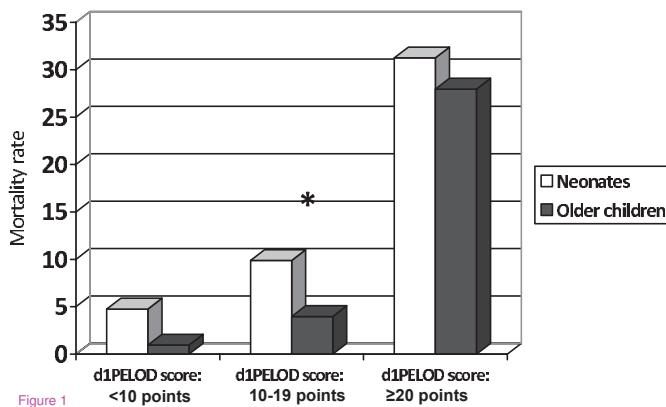


Figure 1

Figure 1. Pediatric logistic organ dysfunction (PELOD) score values on the first day (d1PELOD score) and mortality rate in neonates and older children. * $p<0.04$

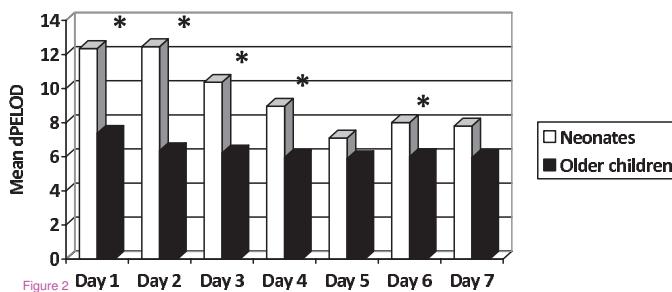


Figure 2. Mean daily Pediatric logistic organ dysfunction (PELOD) score values (mean dPELOD) in neonates and older children. *Significant difference between the two strata.

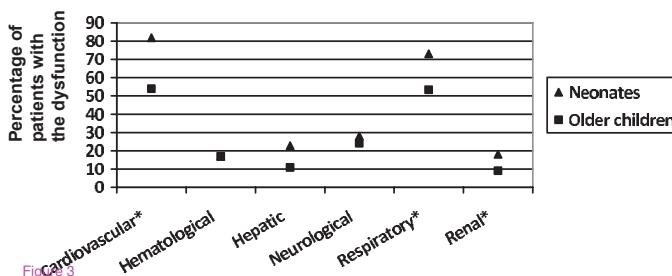


Figure 3. Incidence of organ dysfunctions during the pediatric intensive care unit stay in neonates and older children. *Significant differences between the two strata.

done with SAS software (SAS Institute, Inc., Cary, NC, USA). P values of less than 0.05 were considered significant.

Results

There were 2,021 consecutive admissions between September 1998 and February 2000. We excluded 215 patients for the following reasons: admission to the PICU for scheduled procedures normally cared for in another hospital location (117), prematurity (55), PICU length of stay of less than 4 hours (13), incomplete records (13), age (12), still cared for in the PICU at the end of the study (2), palliative care (2), and transfer to another PICU (1). Therefore, we enrolled 1,806 patients, including 171 (9.5%) neonates and 1,635 (90.5%) older children (525 infants: 1 month to less than 1 year; 853 children: 1 to less than 12 years; 257 adolescents: at least 12 years). Neonates were more frequently ventilated and had a higher PRISM (pediatric risk of mortality) score than older children. Organ systems of

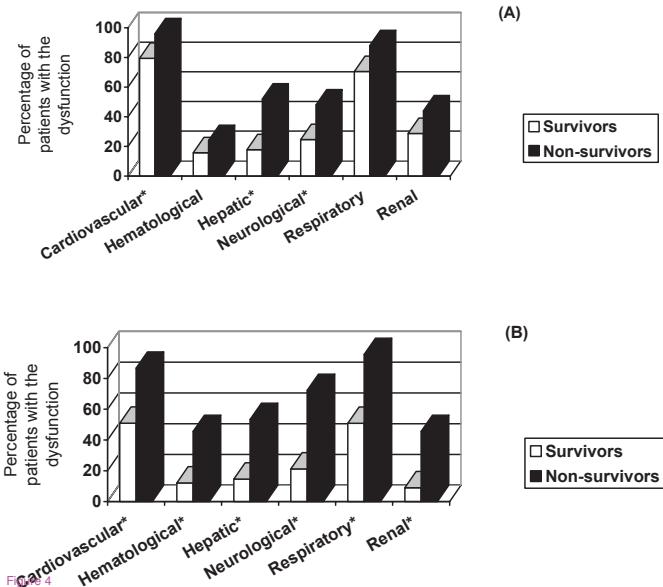


Figure 4. Frequencies of organ dysfunctions during the pediatric intensive care unit stay among survivors and non-survivors: in neonates (A), and in older children (B). *Significant difference between survivors and non-survivors.

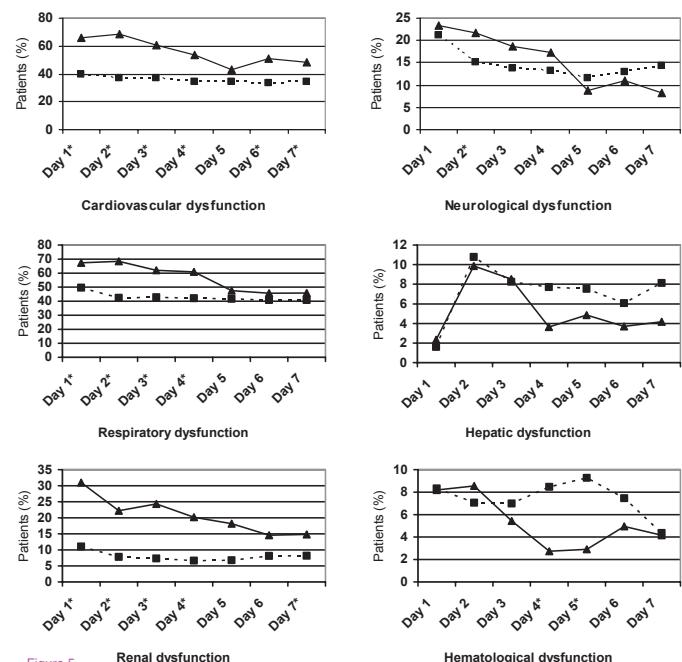


Figure 5. Incidence of daily organ dysfunctions in neonates (black triangular) and older children (black square). *Significant difference between the two strata.

primary dysfunction on admission were different between the two strata. The population characteristics are presented in Table 1. Neurological primary dysfunction was more frequent in older children compared with neonates, whereas cardiovascular and gastrointestinal primary dysfunctions were more frequent in neonates compared with older children. Trauma, cancer, and allergic/immunologic diseases were more frequent in older children, whereas congenital diseases were more frequent in neonates (Table 1).

The global case-fatality rate was 6.4% (115 deaths). Mortality was higher among neonates compared with older patients (14.6% versus 5.5%, $P < 10^{-7}$). Given different age subgroups of older

children (infant: 1 month to 1 year), toddler and preschool (2 to 5 years), school-age child (6 to 12 years), and adolescent and young adult (13 to 18 years), mortality rate was not different (6.6%, 4.6%, 4.8%, 5.8%, respectively; $P = 0.48$). Kaplan-Meier analysis at PICU discharge showed that the mortality rate was significantly higher in neonates compared with older children (log-rank $P = 0.003$). MODS was also significantly more frequent in neonates compared with older children (75.4% versus 50.9%, $P < 10^{-4}$).

PELOD and daily PELOD scores: The median PELOD score was higher in neonates than older children (5 versus 3, $P < 10^{-4}$). The discriminative capacity of the PELOD score was acceptable in neonates ($AUC = 0.78$) but was excellent among older children ($AUC = 0.93$); the difference was significant ($P = 0.008$). Within each strata, the mortality rate increased from one class to the other of d₁PELOD score values (Figure 1). A significant difference in mortality rate between the two strata was found in the medium d₁PELOD class only (Figure 1). The mean dPELOD scores were higher in neonates from days 1 to 4 (Figure 2). Discriminative values of the dPELOD score from days 1 to 7 were acceptable to excellent in neonates ($AUCs = 0.73$ to 0.94) but were good among older children ($AUCs = 0.84$ to 0.89).

Organ dysfunctions and daily organ dysfunctions: Over the entire PICU stay, neonates presented cardiovascular, respiratory, or renal dysfunctions more frequently (Figure 3). Moreover, cardiovascular, hepatic, and neurological dysfunctions developed more frequently among neonates who did not survive (Figure 4a), whereas all ODs were significantly more frequent among older children who died (Figure 4b).

From days 1 to 4, cardiovascular, respiratory, and renal dysfunctions were significantly more frequent in neonates than older children (Figure 5). In neonates, only cardiovascular, neurological, and hepatic dysfunctions were statistically related to mortality. In older children, all ODs were statistically related to mortality (Table 2). Neurological and cardiovascular dysfunctions accounted for 46% and 28% of the PELOD score variance in neonates and 34% and 47% in older children (Table 2).

Discussion

This study showed that the incidence rate and severity of MODS and mortality rate were significantly higher in neonates compared with older children. The median and mean dPELOD scores were significantly higher in neonates from days 1 to 4 after admission to the PICU. Cardiovascular, respiratory, and renal dysfunctions were also significantly more frequent in neonates from days 1 to 4. Only three ODs were statistically related to mortality in neonates, whereas all ODs contributed significantly to mortality among older children.

There are a few studies on the incidence of MODS in the PICU. Proulx and colleagues¹⁹ reported an incidence rate of 18%, but no distinction was made between neonates and older children. In the study by Typpo and colleagues¹⁶ ($n = 44,693$ patients; neonates excluded), the incidence of MODS on day 1 was 18.6%, and all ODs contributed to mortality. We found that MODS was more frequent in neonates; this suggests that a stratification for neonates versus older children might be useful in clinical trials in which MODS is considered an outcome measure.

Mortality rate of neonates in the present study, in which prematures were excluded, was higher (14.6%) than mortality

rate in neonates of all birth weights, admitted to Canadian neonatal intensive care units (4%).²⁰ In our study, the significant mortality difference found between neonates and older children could be attributed to the higher incidence of MODS and a higher PRISM score among neonates compared with older children. This may reflect different diseases leading to PICU admission among neonates compared with older children (Table 1). This difference in mortality might also be attributed to different physiological processes among neonates²¹ and the high frequency and variety of congenital anomalies.²²

Even though physiology does not change abruptly, studies have shown differences in organ response to injury between neonates and adults.^{14,15} In neonates with MODS, there is an early and prominent microvascular failure, characterized by a generalized capillary leak and anasarca, followed by renal and hepatic dysfunctions, while pulmonary dysfunction is the first to develop in human and animal adult MODS.^{14,15}

In our study, cardiovascular dysfunction significantly contributed to neonatal mortality. In neonates, cardiomyocyte differs from that in adults because of structural differences, functional alterations in proliferative activity, and excitation-contraction coupling.²³ Cardiac physiology is also quite different: the capacity to increase stroke volume is lower in neonates. These physiological abnormalities, coupled with the fact that the neonatal left ventricular myocardium already functions at a higher baseline contractile state, and the high dependence of left ventricle systolic performance on afterload increase the susceptibility of neonates to sudden cardiac deterioration in the setting of shock and vasoconstriction.²³ Severe congenital cardiac diseases might also explain why the hazard ratio of death attributable to cardiac dysfunction is so high in neonates.

Respiratory dysfunction did not significantly contribute to mortality in neonates but was significantly more frequent in neonates during the first 4 days only. This high frequency of respiratory dysfunction may explain the higher percentage of ventilated neonates compared with that of older children. The contribution of respiratory dysfunction to mortality could have been diminished by recent management development such as extracorporeal membrane oxygenation in newborns.²⁴

Renal dysfunction was significantly more frequent in neonates during the first 4 days but did not significantly contribute to mortality. This might be explained by the good efficacy of supportive treatment in most cases of neonatal acute renal failure.²⁵ Factors associated with neonatal mortality in case of renal dysfunction include multiorgan failure, hypotension, need for vasopressors, hemodynamic instability, and need for mechanical ventilation and dialysis.²⁶ This probably means that death in neonates with renal failure is seldom caused primarily by renal diseases.²⁷

Hepatic dysfunction significantly contributed to mortality in the two strata (odds ratios [ORs] 3.02, 95% confidence interval [CI] 1.01 to 9.1 in neonates and 2.00, 95% CI 1.12 to 3.60 in older children). However, hepatic dysfunction in neonates and older children had a relatively low incidence (22.8% and 16.8%, respectively). In the study by Tantaleán and colleagues¹ carried out on 276 patients (including 37 newborns) admitted to the PICU, hepatic dysfunction was infrequent (5.8%) and associated with the highest risk of mortality (OR 7.33, 95% CI 1.99 to 26.9).¹ In the study by Typpo and colleagues,¹⁶ hepatic dysfunction had

the lowest incidence (0.9%) and the OR of mortality (3.7, 95% CI 2.7 to 5.1) was close to that of the other ODs (from 2.8 [95% CI 2.5 to 3.2] for cardiovascular dysfunction to 5.5 [95% CI 4.7 to 6.5] for respiratory dysfunction).

Neurological dysfunction significantly contributed to mortality in neonates and older children. In the study by Flori and colleagues,²⁸ which included children and neonates who were more than 36 weeks of gestational age and meeting the 1994 American European Consensus Committee definition of acute lung injury (n = 328 admissions), neurological dysfunction contributed independently to an increased risk of death (OR 12.58, 95% CI 6.78 to 23.31). In our study, the ORs of 1.118 in neonates and 1.156 in older children corresponded to a variation of 1 point for the neurological OD score. In patients with severe neurological dysfunction (corresponding to 20 points), ORs were 9.31 in neonates (1.118²⁰) and 18.16 in older children (1.156²⁰). These values were close to the OR of 12.58 reported by Flori and colleagues.²⁸

Incidence of hematological dysfunction of the entire stay was the same in neonates and older children (17%). Hematological dysfunction was a significant contributor to mortality in older children only (Table 2). Similarly, in children excluding neonates, Johnston and colleagues²⁹ also showed that hematological dysfunction was a significant contributor to mortality (OR 3.10, 95% CI 2.78 to 3.46).

A limitation of this prospective study is the time elapsed since the period when data were collected (1998, 2000): there is a risk that the case mix of patients in the PICU has changed over this period. A second limitation is the possibility of a false association between the PELOD score and death rate in neonates. In fact, the AUC in this group was acceptable but lower (0.78) than in the older children group (0.93), suggesting a differential performance (discrimination) of the model between the two groups. Another limitation is that we considered only intensive care unit mortality and not hospital mortality. However, in hospital post-intensive care, mortality of critically ill children is not frequent. A study from a PICU, typical of US units, showed that among 341 survivors only three children (0.9%) died in the hospital after discharge from intensive care.³⁰ Otherwise, the PELOD score has been criticized, mainly because it does not assign risk on a continuous scale.³¹

Conclusions

The incidence and severity of MODS and mortality rate were significantly higher in neonates than in older children. Three ODs - neurological, cardiovascular, and hepatic dysfunctions - significantly contributed to mortality in neonates, whereas all ODs were significantly associated with mortality in older children. In our hands, the PELOD and dPELOD scores were higher in neonates and risk of death with similar PELOD scores tended to be higher in neonates than older children. These data suggest that an updated version of the PELOD score should take this into account; also, they suggest that it might be a good strategy to consider these two strata in randomized clinical trials involving critically ill children.

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One Life Ends, Another Begins: Management of a brain-dead pregnant mother

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Abstract

Background: An accident or a catastrophic disease may occasionally lead to brain death (BD) during pregnancy. Management of brain-dead pregnant patients needs to follow special strategies to support the mother in a way that she can deliver a viable and healthy child and, whenever possible, also be an organ donor. This review discusses the management of brain-dead mothers and gives an overview of recommendations concerning the organ supporting therapy.

Methods: To obtain information on brain-dead pregnant women, we performed a systematic review of Medline, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). The collected data included the age of the mother, the cause of brain death, maternal medical complications, gestational age at BD, duration of extended life support, gestational age at delivery, indication of delivery, neonatal outcome, organ donation of the mothers and patient and graft outcome.

Results: In our search of the literature, we found 30 cases reported between 1982 and 2010. A nontraumatic brain injury was the cause of BD in 26 of 30 mothers. The maternal mean age at the time of BD was 26.5 years. The mean gestational age at the time of BD and the mean gestational age at delivery were 22 and 29.5 weeks, respectively. Twelve viable infants were born and survived the neonatal period.

Conclusion: The management of a brain-dead pregnant woman requires a multidisciplinary team which should follow available standards, guidelines and recommendations both for a nontraumatic therapy of the fetus and for an organ-preserving treatment of the potential donor.

Background

Brain death (BD) as “coma dépassé” was first defined by Mollaret and Goulon in 1959,¹ and it remains the medically and legally accepted framework for the diagnosis of death. Death is

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pronounced on the basis of well-defined clinical examinations followed by confirmatory technical tests. Recent improvements in life support technology and critical care management make it possible to maintain the patient’s vital functions after BD. The question whether to offer life support to brain-dead patients and how long it should be provided has become a controversial ethical issue. The issue is still more complex when BD occurs during pregnancy. Of course, the incidence of BD in pregnant women is very low and there are only few case reports. As shown by Suddaby et al.,² of 252 brain-dead patients, only 5 (2.8%) cases involved pregnant women between 15 and 45 years of age.

When confronted with BD in a pregnant woman, physicians must primarily focus on saving the life of the fetus, and therefore the treatment protocol should give special recommendations on how to support the mother in a way that she can deliver a viable and healthy child. After delivery, brain-dead pregnant women may also be candidates for organ donation. Therefore, two aspects must be considered in case of maternal BD: supporting the fetus until successful delivery and, if possible, supporting the brain-dead mother as an organ donor. Hence, if the mother and the fetus are regarded as two distinct organisms, maintaining the vital functions of a brain-dead pregnant patient may be ethically justifiable to support both the birth of a child and possible organ donation. In such a situation, various clinical disciplines such as neurosurgery, intensive care medicine, obstetrics, neonatology, anesthesiology, transplantation surgery and an ethics committee should work together to minimize maternal and fetal morbidity as well as mortality.

Since only a few reported cases are to be found in the medical literature, most approaches to managing a brain-dead mother remain experiential and relatively little publicized. In this article, we review the available cases of prolonged somatic support in brain-dead pregnant women and analyze when and under which circumstances the pregnancy should be maintained and what challenges are to be faced. To present a protocol to support such patients, we discuss the management of the brain-dead mother and fetus, related recommendations and legal and ethical issues.

Methods

Search strategy: We performed a systematic review of Medline (1975–2010), EMBASE (1982–2010) and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 2010) for relevant citations. Key words used in electronic searching included “maternal brain death,” “pregnancy,” “brain

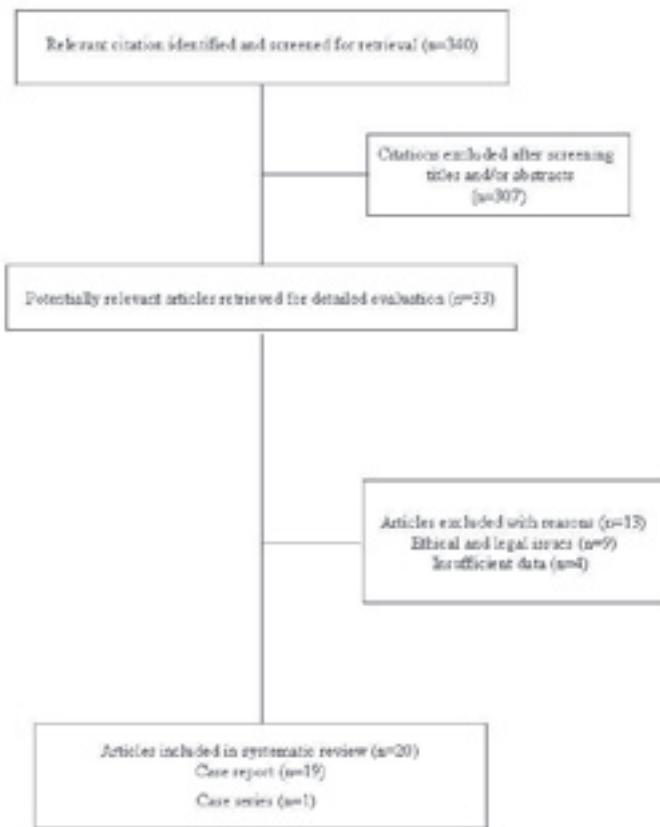


Figure 1. Flow chart of abstracts and articles identified and evaluated during the review process.

death," "management of brain death" and "fetal monitoring." Reference lists of retrieved relevant articles were screened for other studies. Additionally, to include all existent studies, we also contacted experts in the related fields of brain death and pregnancy.

Study selection and data extraction: All studies which reported at least one case of maternal brain death during pregnancy were eligible for inclusion. We excluded studies dealing with pregnancy in a persistent vegetative state because brain death adds complexities to pregnancy that are very different from a persistent vegetative state, calling for different medical management and obstetric strategies, as well as other legal and ethical considerations. Furthermore, we excluded studies which only discussed ethical and legal issues and studies providing insufficient data. There were no language restrictions. One reviewer (ME) screened all titles and abstracts to assess whether they were potentially eligible for inclusion and whether full text was required. Then abstracts and full texts for all potentially eligible studies were reviewed by two researchers (ME and EK), who independently evaluated these articles and extracted their data. Any disagreement during study selection and the data extraction process was resolved by discussion with a third author (AM). According to our search of the medical literature, 30 cases of maternal BD (19 case reports and 1 case series) were reported between 1982 and 2010. The collected data included the age of the mother, the cause of BD, maternal medical complications, gestational age at BD, duration of life support and gestational age at delivery. In addition, we evaluated the indication of delivery, mode of delivery, neonatal outcome and organ donation by the mothers, as well as the transplant outcome. In our analysis, we particularly focused on the critical care management of brain-dead mothers such as respiratory and

cardiovascular support, endocrinology and thermoregulation, nutritional support and organ donation, as well as aspects of obstetric management, including fetal monitoring.

Statistical analysis: The statistical analysis was performed using SPSS 14.0 software for Windows (Stata Corp., College Station, TX, USA). All statistical data regarding maternal age, duration of maternal support, gestational age and fetal birthweight were expressed as means.

Results

Figure 1 summarizes the process of literature identification and selection. According to our search, between 1982 and 2010, 19 case reports and 1 case series were published. In Table 1, we summarize the 30 reported cases of extended maternal life support after BD with pregnancy and the resulting neonatal outcomes.

Maternal and obstetric outcome: In the 30 reported cases, the maternal mean age at the time of BD was 26.5 years. Only three mothers were in the high-risk pregnancy category (age <18 or age >35 yr) with respect to their age. Two mothers were 18 years old and a third one was 40 years old at the time of pregnancy. Trauma was the cause of BD in 4 of 30 mothers, and the other 26 died of nontraumatic brain injuries. The mean duration of maternal support was 38.3 days (range, 2-107 days). In two cases, children were delivered on the second day after BD was diagnosed. Conversely, in two reports, mothers were supported for more than 100 days before delivery. The mean gestational age at the time of BD was 22 weeks (range, 1-40 wk). In 10 of 19 reported cases, the baby was delivered later than week 28. The mean gestational age at delivery was 29.5 weeks (range, 26-33 wk). During extended life support, patients developed several complications, including infection, hemodynamic instability, diabetes insipidus (DI), panhypopituitarism, poikilothermia, metabolic instability, acute respiratory distress syndrome and disseminated intravascular coagulation (Table 1). The indications for delivery in all reported cases were maternal or fetal difficulties, including maternal hemodynamic instability (seven cases), fetal distress (three cases), oligohydramnion (two cases), intrauterine growth retardation (one case) and abnormal pattern of the placental structure (one case). In two cases in which maternal BD began at week 13 of gestational age, spontaneous abortion occurred at weeks 13 and 19. In four cases, there was intrauterine death. A cesarean section was the mode of delivery in all cases which resulted in live-born fetuses (Table 1).

Fetal and neonatal outcome: In 12 (63%) of 19 reported cases, the prolonged somatic support led to the delivery of a viable child. We did not find any information about the fate of the fetuses in the published case series. Children who were born included 1 female and 10 male infants. No information regarding sex was given about one infant. The average birthweight was 1,384 g (range, 815-2,083 g), and the mean Apgar score was 7 and 8 at 1 and 5 minutes, respectively. Congenital defects were reported for only one infant, who was diagnosed with fetal hydantoin syndrome resulting from previous chronic phenytoin usage by the mother. Four infants required temporary mechanical ventilation because of neonatal respiratory distress syndrome or pneumonia. Fungemia was diagnosed in one infant, and he was treated with amphotericin B. However, not every infant was sufficiently followed to determine the long-term effects of prolonged maternal life support. Postnatal follow-up up to 24 months was available only for six infants. All of them

Table 1. An overview of the reported cases of extended maternal somatic support after brain death (BD) including neonatal outcomes*.

Study	Year/ country	Age of mother (yr)	Cause of BD	Gestational age at BD (wk)	Duration of life support (days)	Maternal medical complications	Indication for delivery	Gestational age at delivery (wk)	Mode of delivery	Neonatal outcome	Organ procurement	Transplant outcome
Dillon <i>et al.</i> [48]	1982/ USA	24	Meningitis	23	24	Thermovariability, DI	Fetal distress	26	C/S	Female, 930 gr, Apgar 8/8, IRDS	No	-
Heikkinen <i>et al.</i> [49]	1985/ Finland	31	ICH SAH	21	71	Thermovariability, pneumonia, hypotension, DI, bacteremia, panhypopituitarism	Maternal blood pressure fluctuation	31	C/S	Male, 1600 gr, Apgar 6/7, IRDS Normal at 8 mo.	No	-
Field <i>et al.</i> [14]	1988/ USA	27	CNS mass	22	63	Thermovariability, hypotension, panhypopituitarism, DI, ARDS, UTI, bacteremia	Septicemia, Growth retardation	31	C/S	Male, 1440 gr Apgar 8/8, IRDS, normal at 18 mo.	No	-
Bernstein <i>et al.</i> [33]	1989/ USA	30	Traumatic brain injury	15	107	Thermovariability, panhypopituitarism, pneumonia, DI	Suspicious for fetal distress	32	C/S	Male, 1555 gr Apgar 6/9, Mild hyperbilirubinemia, Normal at 11 mo.	No	-
Antonini <i>et al.</i> [50]	1992/ Italy	25	ICH	15	49	Panhypopituitarism, Pneumonia UTI, Hemodynamic instability Hyperglycemia anemia	Maternal death due to progressive hypotension	Not applicable	Not applicable	Intrauterine death	No	-
Nettina <i>et al.</i> [51]	1993/ USA	31	ICH	27	44	hypothermia; hypotension; decubitus ulcer, DI, pneumonia	Maternal hypotension	33	C/S	Male, 2083 gr Apgar 9	Yes	N.A.
Anstotz [52]	1993/ Germany	18	Accident	13	38	Severe infection	Not applicable	Not applicable	Not applicable	Spontaneous abortion at 19 weeks (autopsy refused)	No	-
Bequin [53]	1993/ Switzerland	20	ICH	20	3	No complication	Not applicable	Not applicable	Not applicable	Intrauterine death	Yes	N.A.
Wuermerling [54]	1994/ Germany	18	Traffic accident	14	N.A.	infection	N.A.	N.A.	N.A.	Intrauterine death	N.A.	-
Iriye <i>et al.</i> [55]	1995/ USA	35	ICH after cocaine	30	2	hypotension	Maternal blood pressure fluctuation	30	C/S	Male, 1610gr, Apgar 7/8	No	-
Vives <i>et al.</i> [56]	1995/ Spain	25	Meningitis	27	1,5	Hypotension, sepsis, DIC, cardiac arrhythmia	Maternal hypotension	27	C/S	Male, 1150 gr, Apgars 7/10, IRDS, normal at 14 mo.	No	-
Catanzarite <i>et al.</i> [32]	1997/ USA	25	ICH	25	25	Hypotension, ARDS, DI, panhypopituitarism, pneumonia,	Fetal distress	28	C/S	Male, 1315 gr Apgar 3/7 fungemia	No	-
Lewis <i>et al.</i> [42]	1997/ USA	20	SAH	25	54	Hypotension, DI bacteremia,	Sufficient fetal lung maturity	32	C/S	Not available	Yes	No complication after 1 year
Suddaby <i>et al.</i> [2]	1998/ USA	Range from 15 to 45 (11 cases)	5 cases: ICH 1 case: Hematoma 1 case: Aneurysm 1 case: Amniotic embolus 1 case: Glioblastoma 1 case: Cardiac arrest 1 case: Gunshot	Range from 2 to 40	NA	Hypotension DI Anemia Hypernatremia Hyperglycemia Hypocalcemia hyperchlormia	NA	NA	NA	NA	In five mothers	Of 25 donated organs (5 heart, 5 liver, 10 kidney, 5 pancreas), only one liver and one pancreas graft lost.
Spike [57]	1999/ USA	20	ICH	16	100	Panhypopituitarism, DI, Thermovariability Hypotension	Unusual pattern of the placenta in ultrasound	31	C/S	Male, 1440gr Apgar 8/8	No	-
Beca <i>et al.</i> [58]	1999/ Chile	26	ICH	17	5	Hemodynamic instability Fibrer	Maternal death due to resistance hypotension	Not applicable	Not applicable	Intrauterine death	No	-
Lane <i>et al.</i> [59]	2004/ Ireland	26	Cerebral venous sinus thrombosis	13	8	DI, pneumonia, Hyper- and hyponatraemia	Not applicable	Not applicable	Not applicable	Intrauterine death at 14 weeks	Yes	N.A.
Hussein <i>et al.</i> [60]	2006/ UK	33	ICH	26	14	Hypertension, bradycardia, Chest infection, Hyperglycemia, serum cortisol reduced	Progressive oligohydraminos	28	C/S	Male, 1285 gr, breathing difficulties Normal at 24 mo.	No	-
Souza <i>et al.</i> [61]	2006/ Brazil	40	ICH	25	25	Panhypopituitarism, hyperglycemia DI, hypotension, bradycardia, hypothermia, pneumonia,	Progressive oligohydraminos, brain sparing	29	C/S	Male, 815 gr Apgars:9/10 Normal at 3 mo.	Yes	N.A.
Mejia <i>et al.</i> [62]	2008/ Argentina	29	ICH	17	56	DI Panhypopituitarism, Pneumonia UTI, Hemodynamic instability	Maternal hypotension & Cardiac arrest	25	C/S	450 gr Premature Birth complication, Candida infection Died at day 30	No	-

*ICH, intracranial hemorrhage; SAH, subarachnoid hemorrhage; DI, diabetes insipidus; ARDS, acute respiratory distress syndrome; UTI, urinary tract infection; C/S, cesarean section; IRDS, infant respiratory distress syndrome; N.A: not available.



Figure 2. Recommendations for the management of maternal brain death. GA, gestational age.

developed normally and apparently had no problems related to their exceptional intrauterine circumstances (Table 1).

Organ procurement and transplant outcome: In three reported cases after successful delivery, organ donation from the brain-dead mother was carried out. In two cases, organ procurement was accomplished after the intrauterine death of the fetus. In yet another five cases, organ donation was performed, but no report about the status of the fetus was provided. In six patients, consent was given by the patient's family to donate heart, lung, liver, pancreas and kidneys. In four donors, no information was given concerning donated organs. The 1-year graft survival in the reported cases was excellent. Only one liver and one pancreas were lost in two patients owing to their primary nonfunction. Finally, in all cases, maternal somatic support was ended either after delivery or after organ donation (Table 1).

Discussion

Clinically, following the onset of BD, it is possible to sustain a brain-dead mother's somatic functions over a longer period. Manifold physiological changes occurring during pregnancy and brain death, as well as the prolonged hospital stay after BD, present enormous challenges, however, both for the treating clinicians and for the family. The important question is from which gestational age onward should the pregnancy be supported? At present, it seems that there is no clear lower limit to the gestational age which would restrict the physician's efforts to support the brain-dead mother and her fetus. As reported by Slattery et al.,³ a fetus born before 24 weeks of gestation has a limited chance of survival. At 24, 28 and 32 weeks, a fetus has approximately a 20-30%, 80% and 98% likelihood of survival with a 40%, 10% and less than 2% chance of suffering from a severe handicap, respectively. Therefore, depending on

maternal stability and fetal growth, the decision must be made on an individual basis. According to our findings, prolonged somatic support can lead to the delivery of a viable child with satisfactory Apgar score and birthweight. Such children can also develop normally without any problems resulting from their intrauterine conditions. Furthermore, after the delivery, mothers could be considered as potential organ donors. In Figure 2, we summarize the recommendations for the critical care management of brain-dead pregnant women. This schema is not a definitive guideline, because the technical support and the experience of the responsible medical team must also be taken under consideration. Also, the number of reported cases is too small to define the rate at which intensive care support of the brain-dead mother can result in a healthy infant. The percentage of successful cases cannot be determined, because there are no reports describing failure of intensive maternal support from all medical centers. Finally, it cannot be established whether a relative infrequency of cases such as those that we found in the published literature reflects the rarity of the event, perfect success in all prior situations, reluctance to initiate intensive efforts required to support the brain-dead patient or simply publication bias.

However, we maintain that the management of a brain-dead pregnant woman should follow the existent standards, guidelines and recommendations both for nontraumatic therapy for the fetus and organ-preserving treatment for the donor.⁴⁻⁶ What follows here is the summary of these guidelines and recommendations.

Cardiovascular support: In the initial phase of BD, tachycardia was detected in less than half of the patients.^{7,8} However, subsequently the heart rate slowed in all of these patients as factors such as hypothermia and subclinical myocardial hypoxia antagonized the sympathetic activation occurring during the initial phase of BD.⁷ Hypertension in this situation is a rare, usually self-limiting event. In prolonged hypertension, short-acting substances such as urapidil or nitroprusside were applied.^{9,10} Typically, at some point, BD patients also develop hypotension.⁹ The initial treatment for hypotension consists of aggressive fluid replacement, which is usually done with crystalloids such as lactated Ringer's solution in normal (0.9%) or half-normal (0.45%) saline solutions. Recent studies suggest that to keep intravascular volume and colloid oncotic pressure within physiological ranges,⁹ hydroxyethyl starch can also be applied in case of a negative effect on the renal graft function.¹¹ However, it must be kept in mind that low oncotic pressure and hypoalbuminemia can cause pulmonary edema.^{12,13} Field et al.¹⁴ recommended that in case of pulmonary edema a Swan-Ganz catheter be used to differentiate cardiogenic pulmonary edema from acute respiratory distress syndrome (ARDS) and to guide fluid management. In addition, extensive hemodynamic monitoring such as Pulscontour Continuous Cardiac Output (PiCCO) should be considered.^{4,15} Fluid-resistant hypotension can be treated using continuous intravenous dopamine receptor agonists, which should be titrated until a mean arterial pressure of 80 to 110 mmHg is reached.¹⁶

Respiratory support: In maternal BD, special attention needs to be paid to mechanical ventilation. To facilitate the elimination of carbon dioxide from the fetus and as a result of the progesterone effect on the respiratory center, the pregnant mother develops hypocapnia mediated by an increase in tidal volume and respiratory rate. Hypocapnia is compensated by an increase in

excretion of bicarbonates by the kidneys.¹⁷ Maternal carbon dioxide tensions, a tidal volume and respiratory rate should be maintained in the normal pregnancy range of 28 to 31 mmHg, 6 to 8 mL/kg and 10 to 12/min, respectively.¹⁸ The fraction of inspired oxygen should be kept in a range maintaining the arterial oxygen saturation above 90%.

Endocrine support: Seventy-eight percent of brain-dead patients who were kept alive for more than a few days developed central diabetes insipidus (DI) resulting from posterior pituitary gland failure.¹⁹ Administration of vasopressin and aggressive volume replacement should be performed for the treatment of DI.⁴ Howlett et al.²⁰ reported a decrease in serum triiodothyronine (T3) in 81% and in serum thyroxin (T4) in 29% of BD dead organ donors. Therefore, especially in brain-dead pregnant women T3/T4 substitution should be adjusted according to laboratory examinations. Adrenal insufficiency causes hypotension and should be treated with methylprednisolone. To avoid prolonged exposure of the fetus to glucocorticoids during maternal somatic support, prednisone or methylprednisolone should be used, as they do not readily cross the placenta.²¹ Furthermore, since hyperglycemia is also observed during BD as a result of stress-related peripheral insulin resistance, insulin substitution may be needed to achieve normoglycemia.¹²

Thermoregulation: According to Smith et al.,²² the majority of brain-dead patients develop hypothermia. It is recommended that the patient be rewarmed passively using warming blankets or by warming of fluids. Following infections, brain-dead patients might also develop hyperthermia. In general, the inability to maintain body temperature and poikilothermia (body temperature that is dependent on the environment's temperature) accompany brain-dead patients.^{23,24}

Nutritional support: The nutritional needs of a pregnant woman before and after BD are not the same. Basal energy expenditure (BEE) in pregnancy is $655 \text{ Kcal} + (9.6 \times \text{weight (kg)} + [1.8 \times \text{height (cm)} - 4.7 \times \text{age (year)}])$.²⁵⁻²⁷ A weight gain of 10 to 15 kg accompanies a normal pregnancy.¹² A brain-dead pregnant woman will expend about 75% of a healthy pregnant woman's BEE.²⁷ Nutritional support should be calculated by maternal serum alimentary values, the weight of the mother and the growth of the fetus. Owing to reduced motility of the gastrointestinal tract in brain-dead patients, special attention should be paid to the management of gastric reflux. Total parenteral nutrition (TPN) during BD in pregnant mothers needs to support a positive nitrogen balance, maternal weight gain, and normal fetal growth and birthweight.²⁸ The recommended daily allowance for protein during pregnancy is $0.8 \text{ g kg}^{-1} \text{ day}^{-1}$ (the normal intake for an average healthy adult) plus an additional 1.3, 6.1 or $10.7 \text{ g kg}^{-1} \text{ day}^{-1}$ for the first, second or third trimesters, respectively.^{29,30} In addition, 20-25% of nonprotein calories should be from fat.²⁹

Infection: There are three sources of infection which should be taken into account during prolonged somatic support: ventilators causing recurrent pneumonia, urinary catheters resulting in bladder and kidney infections and intravascular catheters as a source of septicemia.³¹ The majority of reported organisms were typical of nosocomial intensive care unit infections such as *Staphylococcus aureus*, *Actinobacter*, *Pseudomonas*, *Hemophilus influenza* and fungal pathogens.^{32,33} These infections are usually resistant to antibiotics, and their treatment is challenging. Maternal infections must be treated aggressively

with the most effective substances, rather than opting for using substances safe for the fetus, which in turn may not effectively treat the infection.³⁴⁻³⁶

Prophylactic anticoagulation: The risk of developing deep vein thrombosis is greater during pregnancy because of immobility and flaccid paralysis following BD. Recommended is prophylactic anticoagulation as it is efficacious for the mother and safe for the fetus. For venous thromboembolic disease treatment or prophylaxis during pregnancy, low molecular weight heparin appears to be as safe and effective as unfractionated heparin.³⁷

Obstetric considerations: In maternal BD, it is recommended to screen the mother's serum and to examine carefully the fetus by ultrasound to establish that there are no malformations or pathologic findings in the fetal development and no chromosomal abnormalities. In cases with uncertain findings, amniocentesis should be discussed with family members, since the results of these screenings may influence their decisions.¹⁷ In addition, laboratory tests including complete blood cell count, electrolytes such as Na^+ , Ca^{2+} , K^+ , creatinine, urea, liver enzymes, retinol-binding proteins, albumin, prealbumin, transferrin and urine analysis should be periodically performed. After 24 weeks of gestation, glucocorticoids should be administered for fetal lung maturation and prophylaxis of fetal respiratory distress syndrome.^{38,39} To prevent preterm uterine contractions, in particular in the early weeks of gestation when no fetal lung maturation is yet provided, tocolytic interventions may be needed. Calcium channel blockers and prostaglandin inhibitors are effective and well tolerated and are therefore preferred to -mimetic agents.^{37,40} A prolongation of the pregnancy should continue until at least 26 weeks of gestation with a possible second application of glucocorticoids. If maternal and fetal status remain stable, further prolongation of the pregnancy until at least 28 weeks of gestation should be attempted. According to the reported literature, after 32 weeks of gestation and under glucocorticoid-induced fetal lung maturity, no further prolongation of a pregnancy seems necessary. The optimal method of delivery in prolonged maternal somatic support is by cesarean section, as it ensures the least traumatic birth for the fetus. The optimal timing for a cesarean section can be estimated by amniocentesis assessing fetal lung maturity.⁴¹

Fetal and neonatal considerations: The gestational age and the condition of the fetus, above all lung maturity, are the two most important factors affecting fetal outcome. The majority of studies reported routine and complex fetal monitoring such as daily fetal heart rate monitoring using cardiotocography and nonstress testing. Serial ultrasound examinations to evaluate the fetoplacental unit, including biometric estimations as well as morphologic studies on the placental structure and the amniotic fluid, should be performed weekly to assess intrauterine fetal growth.^{39,42-44}

Organ donation and transplant outcome: After the delivery of the fetus, a brain-dead mother should be considered as a potential organ donor. Multiorgan instabilities and extensive critical care therapy lasting for weeks may have endangered the organs and caused complications in the recipients. Nevertheless, if one or more organs are still functioning at the time of delivery, the feasibility of organ donation in such catastrophic cases should not be ignored. As reported by Suddaby et al.² in a retrospective review of 252 brain-dead potential donors from

1990 to 1996, five of seven pregnant women functioned as organ donors for 20 transplant recipients. For all of those patients, excellent patient and graft outcomes were reported.

Ethical and legal issues: Many ethical and legal questions arise in cases of maternal BD. Although it was not the focus of this review, we briefly discussed various aspects of ethical and legal issues such as “the mother’s body as a cadaveric incubator,” “mother as the organ donor and fetus as the recipient” and the concern for “possible damages to the fetus.”^{31,45} Some professionals believe that it is not ethically acceptable to maintain the mother’s body after BD to use it as a “fetal container.” Such a decision should not be simply assumed, but it must be debated. If the mother is to be considered a “cadaveric incubator” with no autonomous rights, the rights of the fetus should legally prevail. Another argument claims that the prolonged somatic support itself is actually organ donation with the fetus as the recipient. In that case, if the mother had previously indicated a wish to donate her organs, it would be appropriate to proceed with the extended somatic support. Finally, some believe that strategies used to maintain maternal somatic function are still in the experimental stage. Not every adverse effect of medication used on the fetus during an extended somatic support is known. The next of kin must therefore be informed about the existing life maintenance strategies and the possible damages they may cause to the fetus. Psychological consultation should certainly be beneficial in this situation.

Since such catastrophic cases are so infrequent, the mother’s wish is in effect rarely known. For this reason, it is strongly suggested to engage the family in the planning of the care. The physician and transplant coordinator should not impose all available procedures against the wishes of the family. Sperling et al.⁴⁶ suggested that questions be answered on a case-by-case basis with the involvement of the hospital’s ethics committee. One also needs to consider that while nowadays somatic support in the case of maternal BD is technically possible, there is still no legal document which asks a pregnant woman about the fate of her unborn child in the event of BD. It is highly recommended that this question be added to the advance directives of any woman of childbearing age and routinely discussed in standard prenatal interviews.⁴⁷

Conclusions

At present, BD is a medically and legally accepted event allowing a pronouncement of death. Taking into account that in maternal BD two organisms are involved, the mother and the fetus, a decision whether to maintain the mother’s vital functions to allow fetal survival is also an ethical and legal issue. The goal of prolonged maternal somatic support is to deliver a viable and healthy infant with a beneficial long-term outcome. From the medical point of view, the management of a brain-dead pregnant woman should follow the common standards, guidelines and recommendations for organ-preserving therapy. In some situations, however, the mother needs special medical support and interventions which differ from somatic support in nonpregnant BD patients. Both after a successful delivery and in the case of fetal abortion, the mother can also be considered as an organ donor. In general, we recommend that there be no clear lower limit to the gestational age which would restrict the physician’s efforts to support the brain-dead mother and her fetus. A meeting of the neurosurgical, critical care, obstetric, neonatal, transplant and ethical staff, along

with the patient’s family, should collectively make a decision about future treatment steps. Since currently there are still only a limited number of cases describing the management of extended maternal somatic support after brain death, the current recommendations should be continuously reassessed and adapted along with the growing experience and knowledge. For such serious and rare cases as described here, it would be advisable from a clinical point of view to establish an international registry network of BD pregnant patients, which could help to gather further experience. We also think that from the practical point of view, it would be possible to establish such a registry and this network could become a part of routine clinical usage in all neurosurgery and intensive care centers.

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Congenital Myelomeningocele – Do We Have to Change Our Management?

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Abstract

Background: Eagerly awaiting the results of the Management of Myelomeningocele Study (MOMS) and with an increasing interest in setting up intrauterine myelomeningocele repair (IUMR), the optimal management of patients suffering from congenital myelomeningocele (MMC) has become a matter of debate again. We performed a cross-sectional study at our referral-center for MMC to determine the outcome for our expectantly managed patients.

Materials and methods: A computed chart review at our institution revealed 70 patients suffering from MMC. Forty-three patients were eligible for the study and analyzed further. A retrospective analysis was performed only in patients that underwent MMC repair within the first two days of life and were seen at our outpatient clinic between 2008 and 2009 for a regular multidisciplinary follow-up. Data were collected on: gestational age (GA) and weight at birth, age at shunt placement and shunt status after the first year of life, radiological evidence for Arnold-Chiari malformation (ACM) and tethered cord (TC), need for surgery for TC, bladder function, lower leg function and educational level. Data were compared to published results for IUMR and to studies of historical controls.

Results: Patients were born with MMC between 1979 and 2009 and are now 13.3 ± 8.9 (mean \pm SD) years of age. At birth, mean GA was 37.8 ± 2.3 weeks and mean weight was 2921.3 ± 760.3 g, both significantly higher than in IUMR patients. Shunt placement in our cohort was required in 69.8% at a mean age of 16.0 ± 10.7 days, which was less frequent than for historical controls. Amongst our cohort, radiological observations showed 57.1% had ACM II and 41.9% had TC. Only two of our patients underwent a surgical correction for TC. Clean intermittent catheterization was performed in 69.7% of our patients, 56.4% were (assisted) walkers and 64.1% attended regular classes, both comparable to historical controls.

Conclusions: With a close and interdisciplinary management by pediatric surgeons, neurologists and urologists, the long-term outcome of patients suffering from MMC can currently be considered satisfactory. With respect to the known drawbacks

of fetal interventions for mother and child, especially preterm delivery, the results of the MOMS trial should be awaited with caution before proceeding with a complex intervention like IUMR.

Background

Myelomeningocele (MMC) is a mostly isolated congenital disorder of the central nervous system that has a multifactorial etiology. Based on a prevalence of 10-15 per 10,000, more than 4,500 pregnancies are affected in the European Union each year.¹ Its prevalence can be reduced by 50-70% with maternal 400 µg folic acid supplementation before conception and during the first trimester.^{2,3} Myelomeningocele is characterized by a protrusion of the meninges and spinal cord through open vertebral arches which results in varying degrees of paralysis, mental retardation, bowel and bladder dysfunction as well as orthopedic disabilities.⁴ After surgical closure of the defect, many patients present with a hydrocephalus that requires the placement of a ventricular shunt to prevent additional cerebral damage, which again is associated with a high rate of complications like dysfunction and infection.⁵ Most patients are further affected by an Arnold-Chiari malformation (ACM) due to a downward movement of the hindbrain and obstruction of the normal egress of cerebrospinal fluid (CSF) from the fourth ventricle that increases the 5-year-mortality from 7.9% to 35%.^{5,6,8} A high number of patients also suffer from spinal cord tethering (TC), which progressively worsens neurological function and frequently requires surgical correction.⁹ In 1990, the two-hit-hypothesis for the pathogenesis of MMC was postulated by Heffez et al: A defective spinal development is followed by an intrauterine injury of the spinal cord due to the exposure to amniotic fluid, meconium and urine, as well as direct trauma and hydrodynamic pressure, thus causing loss of neural tissue due to a progressive cell toxicity over gestation.¹⁰⁻¹³

Spina bifida is nowadays diagnosed prenatally in 70-90% of cases mostly before 20 weeks of gestational age (GA) by routine ultrasound scan.^{14,15} If the ultrasound scan is positive, amniocentesis is performed to rule out genetic syndromes and to measure alpha-fetoprotein (AFP) levels. Mostly, parents are counseled to opt for expectant management or termination of pregnancy. In the United States, an intrauterine myelomeningocele repair (IUMR) can also be offered. The concept of IUMR is based on the hypothesis that an intrauterine protection of the exposed spinal cord as well as the reduction of continuous intramniotic leakage of CSF might prevent some of its secondary damage.^{16,17} Since the first intrauterine

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Table 1 Criteria for shunt placement

Criteria for Shunt placement (MOMS trial)	
At least two of the following:	Or:
An increase in the greatest occipitofrontal circumference adjusted for gestational age and defined as crossing percentiles	Head circumference > 95 th percentile for gestational age
A bulging fontanelle*, split sutures or sunsetting sign	Presence of marked syringomyelia (syrinx and expansion of spinal cord) and ventriculomegaly (undefined)
Increasing hydrocephalus on two consecutive imaging studies determined by an increase in ratio of biventricular diameter to biparietal diameter [§]	Ventriculomegaly (undefined) and symptoms of Chiari malformation (stridor, swallowing difficulties, apnea, bradycardia)
	Persistent cerebrospinal fluid leakage from the myelomeningocele wound or bulging at the repair site

Criteria for shunt placement as defined for the MOMP trial. *Bulging fontanelle: above the bone as assessed when the baby is in an upright position and not crying. [§]Defined by O'Hanlon *et al*, 1998 [34]. Table adapted from Tulipan *et al*, 2004 [35].

endoscopic repair in 1994, which was replaced by open surgical repair in 1997, about 400 open fetal interventions for MMC have now been performed worldwide.⁴ Preliminary results suggest a reversal of hindbrain herniation, a decrease in shunt-dependent hydrocephalus, an improvement in leg function and an unaltered bladder function after IUMR.^{4,18,19} However, the technique remains of unproven benefit and the reported findings might be explained by selection bias and changing management indications.²⁰ Therefore, the Management of Myelomeningocele Study (MOMP), a multicenter, prospective, randomized controlled trial of 200 patients (100 fetal repair, 100 postnatal repair), was set up in 2003 in the US (San Francisco, Nashville and Philadelphia) to primarily investigate death or the need for shunting by the age of one year with and without fetal intervention in MMC.

The objective of this study was to decide, whether it is time to offer IUMR at our institution to patients diagnosed prenatally with MMC. Therefore, we performed a retrospective data analysis on expectantly managed patients with MMC that attended our hospital and compared them to results obtained

after IUMR at other institutions and to historical controls as collected from the literature.

Methods

Patient recruitment: A computed chart review was performed in February 2010 to conduct a descriptive and retrospective study on information obtained from medical reports. Patients were recruited to the study if they suffered from an open spina bifida that was diagnosed pre- or postnatally and underwent surgical repair within the first two days of life to prevent further damage, eg by CSF leakage, local infection or scarred shrinking, as generally accepted.

Surgical repair of open spina bifida: After an ellipsoid incision of the zona cutanea, the zona epithelioserosa was dissected. The dura was mobilized completely and isolated from the fascia thoracolumbalis. The zona epithelioserosa was excised and the neural tube was reconstructed if possible using 10-0 absorbable single sutures. The dural layer was closed in craniocaudal direction using a 6-0 or 7-0 absorbable running suture, exceptionally inserting a dural patch. After the water-tight

Table 2 Characteristics of patients studied

Study Group	Reference	Publication Year	Study Site	Study Period	N patients	Level of lesion (%)			
						thoracic	lumbar	sacral	other
(1) Leipzig group			Leipzig, Germany	1979-2009	43	11.6	79.1	9.3	-
(2) IUMR group	Bruner [22]	1999	Vanderbilt, USA	1990-1997	29	median L4 (S-T12)			
	Tulipan [21]	2003	CHOP, Vanderbilt, USA	1983-2000	177	4.8	80.8	14.4	-
	Johnson [24]	2003	CHOP, USA	1998-2002	48	5	84	11	-
	Bruner [25]	2004	Vanderbilt, USA	1997-2003	116	4.3	81.9	13.8	-
	Brunner [23]	2005	Vanderbilt, USA	1997-2003	116	4.3	81.9	13.8	-
	Koh [27]	2006	Boston, USA	1979-2003	5	lumbosacral			
	Danzer [26]	2008	CHOP, USA	1998-2003	54	7.4	85.2	7.4	-
(3) Historical controls	Danzer [18]	2009	CHOP, USA	1998-2003	54	7.4	81.5	11.1	-
	Danzer [29]	2010	CHOP, USA	1998-2003	30	median L4 (T12-S1)			
	Bruner [22]	1999	Vanderbilt, USA	1990-1997	23	median L4 (S-T12)			
	Bowman [5]	2001	Chicago, USA	1975-1979	71	35.2	42.2	21.2	1.4
	Tulipan [21]	2003	CHOP, Vanderbilt, USA	1983-2000	189	18.5	60.3	21.2	-
Aguilera [15]	Koh [27]	2006	Boston, USA	1979-2003	88	-			
	Aguilera [15]	2009	Bristol, UK	1999-2007	74	10.8	41.9	44.6	2.7

Summarized characteristics of included studies sorted by study group.

Table 3 Summarized results and statistical comparisons

	(1) Leipzig group	(2) IUMR group	(3) Historical controls	Statistical comparison (p-value)		
				(2) vs (3)	(1) vs (2)	(1) vs (3)
Neonatal death (%)	0	4.5 [21]	NA	-	< 0.05	-
GA at birth (wk)	37.8 ± 2.3	34.6 [21]	37.0 [22]	-	< 0.0001	ns
		33.2 [22]	37.0 [22]	< 0.001 [22]	-	-
GA < 30th wk (%)	0	11.8 [23]	NA	-	< 0.05	-
Birth weight (g)	2921.3 ± 760.3	2512 [24]	3075 [22]	-	< 0.01	ns
		2171 [22]	3075 [22]	< 0.001 [22]	-	-
Shunt placement ≤ 1 y (%)	69.8	54.3 [25]	85.7 [21]	< 0.0001	ns	< 0.05
Age at shunt placement (d)	16.0 ± 10.7	21.2 [24]	-	-	< 0.05	-
	12.5 ^s	85.5 [22] ^s	5 [28] ^s	< 0.01 [22]	-	-
Incidence ACM II (%)	57.1	100 ^s	75.7 [15]	-	-	ns
Surgery TC (%)	11.1	29.6 [26]	32.4 [5]	ns	< 0.01	< 0.001
(Assisted) Walkers (%)	56.4 ^f	92.6 [18] [#]	59.2 [5] [#]	< 0.0001	< 0.0001	ns
Wheelchair users (%)	41.0 ^f	7.4 [18] [#]	40.8 [5] [#]	< 0.0001	< 0.0001	ns
Regular education (%)	64.1	NA	63.4 [5]	-	-	ns
CIC (%)	69.7	NA	84.5 [5]	-	-	ns

Summarized results of our data collection compared to published results for historical controls and IUMR applying the two-sided t-test or Fisher's exact test at $p < 0.05$. Data are presented in mean (\pm SD) or median and percentages. GA: gestational age, ACM: Arnold-Chiari malformation, TC: tethered cord, CIC: clean intermittent catheterization. NA: not applicable, ns: not significant. ^smedian; [#]ACM is one of the inclusion criteria for IUMR; ^fmean age 13.3 ± 8.9 years, [#]mean age 67.0 ± 18.2 months, ^{*}mean age 21.7 years.

closure of the dura, the defect was covered by a wing-flap plasty. The fascia thoracolumbalis was dissected and closed before the subcutaneous tissue and skin layer were sutured. A primary stainless skin closure is essential in cases with extremely large defects, for which we preferred longitudinal incisions with mobilization of the skin and temporary skin substitution if necessary. Postoperative monitoring consisted of frequent clinical investigation, measurement of head circumference and cranial ultrasound examination.

Shunt placement: A ventricular-peritoneal shunt was placed only in the case of symptomatic hydrocephalus, according to similar criteria to that listed in Table 1.

Patient follow-up: All included patients were regularly seen at our outpatient clinic for a multidisciplinary follow-up, including consultation with a pediatric neurologist, pediatric urologist, pediatric orthopedists and pediatric surgeon. The final follow-up was between 2008 and 2009 in order to assess the patients' current health status.

Data collection: Data were collected on: GA and weight at birth, neonatal death (defined as death within the first 28 days of life), shunt status at the first year of life and age at shunt placement, radiological presence of ACM and TC as assessed postnatally by ultrasound and/or magnetic resonance imaging, the need for surgery for TC, as well as bladder function, lower leg function and educational level. Satisfactory bladder function was defined as use of clean intermittent catheterization (CIC) and satisfactory educational level as regular attendance at kindergarten, school or job.

Comparison with published data: We performed computerized bibliographic searches using Pubmed and Embase databases to identify studies that report on outcome measurements after

IUMR ("IUMR group") and for postnatally-managed patients with spina bifida ("historical controls"). If applicable, studies on which the MOMS trial had been based were preferentially included as historical controls. After identification of matching studies, data extraction was performed for outcomes as listed above. If the same outcome was published several times, e.g. mean gestational age at birth, the cohort with the largest number of patients was used for comparison.

Study groups: The study consisted of three groups: (1) retrospectively assessed data on patients with open spina bifida that underwent MMC closure and follow-up at our institution ("Leipzig group"), (2) published data on patients that underwent IUMR elsewhere ("IUMR group") and (3) published data on patients that were operated postnatally and managed elsewhere, preferentially providing the basis for the MOMS trial ("historical controls") (Table 1).

Statistical analysis: Data collected from our cohort study ("Leipzig group") were analyzed assessing mean and standard deviation (SD) for continuous data (GA and weight at birth, age at shunt placement) and percentages for dichotomous data (neonatal death, birth before 30 weeks GA, shunt status at the first year of life, radiological presence of ACM II and TC, use of CIC, lower leg function and educational level). The collected results were compared to data published for IUMR and historical controls, respectively. For continuous data two-sided t-tests were applied to compare published means against sample means ("Leipzig group"). In none of the published articles were standard deviations presented. Therefore, similar standard deviations to our studies were used, assuming comparable distributions in similar populations. For nominal data contingency tables were generated from the total numbers of all study groups and tested applying two-sided Fisher's exact test. Regression analysis was further performed to test the correlation between birth year

and prenatal diagnosis of our population. All statistical analyses were performed using JMP 7 software (SAS Institute, Cary, NC, USA). Data are given in raw numbers, percentage or mean \pm SD if not indicated differently. Results were considered statistically significant at $p < 0.05$.

Results

Study population: The chart review revealed 70 patients suffering from spina bifida. Of those, two underwent IUMR elsewhere, five underwent MMC closure beyond the second day of life, 10 had not undergone surgery for MMC at our hospital or the operation date could not be identified and 10 patients were lost from follow-up. Therefore, data from 43 MMC patients that underwent surgical correction for MMC within the first two days of life and had been seen at our outpatient clinic between 06/2008 and 12/2009 were analyzed. All results are summarized in Table 3. The 43 patients were born between 1979 and 2009 and were on average 13.3 ± 8.9 y of age at the time of data analysis. 11.6% had thoracic, 79.1% lumbar and 9.3% sacral lesions (Table 2).

Prenatal diagnosis and birth: Only 37.2% of our patients had been diagnosed prenatally with MMC. However, the number of prenatal diagnoses significantly increased over time with a significant correlation between prenatal diagnosis and birth year ($p < 0.0001$). There were no neonatal deaths in our study population compared to 4.5% after IUMR ($p < 0.05$).²¹ Mean GA at birth in our population (37.8 ± 2.3 weeks) and of historical controls (37.0 weeks) was significantly higher than after IUMR (34.6 weeks; $p < 0.001$) without a significant difference between our population and historical controls.^{21,22} None of our patients but 11.8% of the children after IUMR were born before 30 weeks of gestation ($p < 0.05$).²³ Mean weight at birth in our group was 2921.3 ± 760.3 g, which was significantly higher than after IUMR (2512 g; $p < 0.01$) and not significantly different from historical controls (3075 g).^{22,24}

Shunt status

Among historical controls, median 85.7% of the patients required shunt placement within the first year of life, which was significantly different from median 54.3% after IUMR ($p < 0.0001$) and from 69.8% in our study population ($p < 0.05$).^{21,25} On the contrary, there was no significant difference for the need of shunting within the first year of life between IUMR and our population. However, the average age at shunt placement was significantly higher after IUMR (mean 21.2 days) than in our study population (mean 16.0 ± 10.7 days; $p < 0.05$). Likewise, median age at shunt placement was significantly higher after IUMR as compared to historical controls (85 vs. 5 days; $p < 0.01$).^{22,24}

Arnold-Chiari malformation and tethered cord: ACM II was radiologically diagnosed in 57.1% of our patients, one patient presented with ACM I. The incidence of ACM II was not different from historical controls (75.7%).¹⁵ Among our patients 18 (41.9%) presented with tethered cord and only two (11.1%) of them had to undergo surgery for TC so far, which is significantly less than after IUMR (29.6%; $p < 0.01$) and less than for historical controls (32.4%; $p < 0.001$), whereas the latter two did not differ significantly.^{5,26}

Quality of life: In our population 56.4% and in historical controls 59.2% were assisted walkers that ambulate most of the time, both of which are significantly different from 92.6% of the patients

after IUMR ($p < 0.0001$).^{5,18} Likewise, 40.8% of historical controls and 41.0% of our study population were reliant on a wheelchair, which is significantly more than after IUMR (7.4%; $p < 0.0001$). CIC was regularly performed in 69.7% of our population and similarly in 84.5% of historical controls.⁵ Conversely, all patients after IUMR but only 38% of historical controls showed detrusor overactivity, suggesting that IUMR is associated with a higher incidence of complete denervation of the external urethral sphincter and detrusor overactivity.²⁷ A similar proportion of patients in all three groups attended regular education, suggesting adequate intellectual development (64.1%, 76.7% and 63.4% for Leipzig, IUMR and historical groups, respectively).^{5,18} There was no significant difference between shunted and non-shunted patients for the attendance of regular education in our population (80% vs 58.6%). After IUMR, 67% of the patients had normal cognitive language and personal-social skills, 20% had mild and 13% significant delays at the age of two years, 23% were at risk for (significant) learning disabilities, with the majority (85.7%) shunted.^{28,29}

Discussion

Myelomeningocele is a congenital anomaly that affects about 1,500 infants per year in the US, of which recently more than 90% survive the first year of life and about 75% will reach adulthood.⁵ Even though MMC is a non-lethal birth defect, it is the associated life-long morbidity that motivates clinicians all over the world to examine the value of fetal therapy. The aim of IUMR is to improve postnatal morbidity and in particular neurological outcome by reduction of secondary injury to the spinal cord.³⁰ This should be achieved by coverage of the spinal defect to stop CSF leakage and to prevent secondary damage, which in turn might allow normal brain development. The initial fetoscopy approach failed to show convincing benefit due to a high rate of perinatal deaths, which could be ruled out when standard neurosurgical closure of the defect was performed prenatally via a hysterotomy.³⁰ Since then, in about 400 cases of IUMR a reversal of hindbrain herniation, a decrease in shunt-dependent hydrocephalus and an improved leg function as compared to historical controls have been suggested.⁴ Those results will be confirmed or rejected in the randomized controlled MOMS trial that was initiated in 2003 in three major centers for fetal surgery in the US to evaluate potential benefits after prenatal versus postnatal MMC closure. While keenly awaiting the results of the trial, we performed a retrospective analysis on patients from our referral center for MMC and reviewed the literature to compare the outcomes of MMC patients treated at our institution with published data from IUMR and historical controls.

Comparable to historical controls, mean gestational age at birth in our patients was 37.8 weeks and no prenatal deaths were recorded. In contrast, after IUMR, mean gestational age at birth was 34.6 weeks with 11.8% of the infants born before 30 weeks of gestation, both significantly different from historical controls and our findings.²¹⁻²³ Perinatal mortality after IUMR was 5.9%.²⁴ As Bruner et al stated in 2005, virtually all fetuses that underwent IUMR deliver preterm and more than 10% even before 30 weeks, thus risking major morbidity.²³ That prompts the question if the postulated benefits of IUMR on hindbrain herniation, shunt-dependent hydrocephalus and leg function justify the associated risks for mother and child when IUMR in turn may cause major morbidity and neonatal death due to preterm delivery in a condition that is usually non-lethal.²⁴ Lethal complications due to chorioamnionitis, placental abruption and preterm premature rupture of the membranes have been reported in particular for

endoscopic IUMR, diminishing a fetoscopic approach for MMC in the late 1990s.³⁰ To what extent surgical risks and preterm delivery due to open IUMR contributes to major morbidity and neonatal death cannot be estimated from the available data but might be answered by the MOMS trial.

The second main outcome of the MOMS trial, besides neonatal death, is the need for shunting. As compared to historical controls, the rate of shunting within the first year of life was significantly lower in our cohort and after IUMR, whereas the latter two did not differ significantly. This observation is backed up by the findings of others that reported shunt rates of 78% (n = 203) and 43.3% (n = 293), respectively, for postnatally-managed patients.^{31,32} One reason for the discrepancy in shunt rates might be the inconsistency in clinical criteria for shunting, suggesting that the criteria characterized for the MOMS trial should become generally accepted (Table 1).

Another important finding of our study was the discrepancy in the rate of assisted walkers and wheelchair users between our population/historical controls and IUMR, for which 92.6% (assisted) walkers and only 7.4% wheelchair users have been reported.¹⁸ At first glance this highly significant difference encourages the efforts of IUMR. However, the mean age of the study population was 21.7 years for historical controls, 13.3 years for our population and only 67.0 months after IUMR. Our results strengthen the finding that mobility decreases from early childhood to the early teen years.³³ Bowman et al showed that the percentage of patients ambulating the majority of time decreased from 76% at 0-5 years to 46% at 20-25 years, with a flattening beyond 10 years.⁵ Assuming a similar progression for children that underwent IUMR, less than 50% might continue to be assisted walkers in their teens.

We are aware of the drawbacks of the conducted study, which might be affected by the inhomogeneity of study designs, study populations, outcome measurements and treatment modality between centers as well as by changes over time. Thus, our retrospectively-collected data might be compared to results assessed in varying populations, suggesting the comparison of 'apples and oranges'. However, we performed a comprehensive review of the literature to identify the best matching study groups for IUMR and historical controls in the outcomes of our interest. Even though studies varied in their study periods and sites, study populations consisted of patients with similar levels of lesions, a factor known to importantly influence the clinical course in MMC. Therefore, we assume that our cohort, as well as the study population of included studies reflects representative cross-sections of the 'true' MMC population.

Conclusions

Considering the limitations of the presented study and the data available today, a clear benefit of IUMR has not yet been proven. The implementation of a close interdisciplinary management following postnatal MMC closure results in satisfactory long-term outcomes of patients suffering from this defect. With regards to the well-known challenges of fetal interventions for both, mother and child, in particular preterm delivery, we actually do not consider the implementation of IUMR at our institution as imperative and the results of the MOMS trial should be awaited before initiating a complex intervention like IUMR.

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Moving Toward the Paradigm of Safe Delivery: Incentivizing Checklist Use

Carol Brass

Introduction

Since 1999, when the Institute of Medicine (IOM) released its seminal report, “To Err is Human,” the growing patient safety movement has encouraged systemic change to ensure that medical interventions are delivered correctly.¹ Subsequent legislative responses enacted to protect patients and reduce medical error include the Patient Safety and Quality Improvement Act (PSQIA), mandatory and voluntary error reporting systems adopted by numerous states, and the Centers for Medicare and Medicaid Services’ (CMS) “never-event” reimbursement rule.^{2,3} However, these policies only indirectly attempt to reduce medical error, and perhaps as a result, they have achieved only limited success and have been subject to criticism by academics and practitioners. Critics observe that these policies simply reinforce existing incentives to avoid medical error and provide no insight into the policies that can be implemented to stem the commission of errors by individual providers. On the other hand, recent research indicates that medical checklists are one of the most promising emerging interventions to address medical error. An evidentiary privilege that bars admissibility of checklists in court would encourage healthcare institutions to experiment with new policies that incentivize providers to develop and use checklists and could have a significant positive impact on patient safety.

The PSQIA

The PSQIA creates an evidentiary privilege that protects information submitted to “patient safety organizations” (PSOs), which are specially defined groups (excluding health insurers) that compile information on medical errors. When providers—broadly defined to include hospitals, physicians, and others—create “patient safety work product” and submit it to a PSO, that work product is protected with an evidentiary privilege. The privilege therefore protects the reports created by a provider in the aftermath of an incident. However, the underlying facts of the incident are still open to discovery. The privilege is meant to encourage the creation of these after-incident analyses and reports.

While well-designed error reporting systems do represent a valuable means of gathering incident data so that policies can

be formulated to combat medical error, the PSQIA fails to adequately address the most basic problem inherent in medical error reporting: that all self-reporting systems entail a degree of voluntarism in that they require the cooperation of the reporters. Removal of legal liability may encourage reporting in some instances, but there are still many other disincentives to reporting that the PSQIA—or, realistically, any legislation—cannot address. Thus, it is not clear that an evidentiary privilege in this context is sufficient to overcome the broad array of disincentives to self-reporting that providers face. They may worry that reporting an error will damage their reputations or job security, or will potentially prompt internal disciplinary actions.⁴

Given the presence of these additional disincentives to reporting, a significant amount of errors will go unreported so long as the expected costs of reporting exceed the expected benefits, which limits the efficacy of the privilege and its potential to substantially reduce medical error. Therefore, while the PSQIA does address providers’ concerns about liability, it is significantly flawed in that it relies on providers to act against their perceived self-interest to ultimately reduce the rate of medical error.

State Error Reporting Systems

State error reporting systems may rely on either voluntary or mandatory error reporting by providers. Mandatory error reporting systems do not necessarily solve the problems that arise under voluntary reporting systems. Even when a system is mandatory, many errors will go unnoticed unless the provider steps forward to report them. In fact, it is not clear that making a system “mandatory” will better ensure that incidents are actually reported.⁵ As the president of the American Hospital Association, Richard Davidson, explained, “[t]he idea that a mandatory reporting system is going to change behavior is naive at best. You need to focus on making a cultural change in hospitals, to promote open discussion of errors.”⁶

Rather than promote a cultural change, error reporting systems require effort, paperwork, and self-implication of a provider in potentially tortious conduct. If the provider does not report the error, especially in situations where little or no injury occurs, it is unlikely that anyone will ever find out about the error. Moreover, even the best-designed reporting systems will by their very nature miss the entire class of medical errors consisting of those errors that providers do not notice.

Many other problems with error reporting systems exist.

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Hospitals often receive severely adverse publicity when a government entity publicly disseminates reports with aggregate medical error information, which may reduce public confidence in the medical system and possibly discourage some individuals from going to the hospital when they are ill.⁶ There are also practical limits on the number of conditions for which a state or organization can feasibly gather and analyze data. Resource constraints in healthcare are notoriously tight, and gathering this data can be quite costly. Finally, publication of these reports may raise privacy concerns under HIPAA. The more detailed a report is, the more useful it is likely to be. However, the more detailed it is, the more likely it is to breach patient confidentiality rules. This paradox, along with the other problems plaguing reporting systems, limits the potential efficacy of these error reporting systems in substantially reducing medical errors.

The CMS Non-Reimbursement Rule

The Deficit Reduction Act of 2005 required the Secretary of Health and Human Services to select diagnosis codes that were either high cost or highly prevalent, and that "could reasonably be prevented through the application of evidence-based guidelines."⁷ The "never-event" rule promulgated by CMS in response to the statutory mandate specifies that care for certain conditions known as "hospital-acquired conditions" is non-reimbursable by the government if the conditions were not present on admission to the hospital. Effective October 1, 2008, the categories of these conditions include: (1) foreign object retained after surgery, (2) air embolism, (3) blood incompatibility, (4) pressure ulcers (stages III and IV), (5) falls, (6) manifestations of poor glycemic control, (7) catheter-associated urinary tract infection, (8) vascular catheter-associated infection, (9) deep vein thrombosis, and (10) surgical site infection associated with certain specified procedures.⁸

The troubling aspect of the CMS non-reimbursement rule is that, although it purports to penalize only HACs that are fully preventable by adequate care, in reality a number of the enumerated conditions for which CMS denies payment are not always preventable by the hospital. For example, CMS itself acknowledges that catheter-associated urinary tract infections are not always preventable when a catheter is in place for more than three days; nevertheless, even though medical necessity sometimes requires long-term use of a catheter, such a condition is non-reimbursable under the rule.^{8,9}

Another major criticism of the rule is that it assumes that hospitals and individual providers are not already motivated, both financially and otherwise, to avoid these conditions. The lack of financial incentives likely does not cause these conditions; rather, they occur because the current system fails to identify and implement successful and effective means of preventing them. One scholar observes, "[h]ospitals already have significant financial incentives to reduce preventable complications. What they lack, and urgently need, is proven models to implement the institutional change needed to consistently apply best treatment practices."⁸ Because hospitals already absorb many of the costs associated with HACs, the CMS rule does not "create a new financial incentive for hospitals to prevent infections, but only [amplifies] an existing one."^{8,10,11}

Rather than aligning incentives, the CMS rule creates an increased administrative workload by requiring hospitals to carefully code any conditions present on admission in order to ensure that they are reimbursed later for preexisting conditions.

The rule increases unnecessary diagnostic testing at admission and discourages hospitals from treating the elderly and other patients who are at high-risk for certain HACs. If these conditions later develop the hospital will not be reimbursed regardless of whether or not it was at fault. Overall, the CMS reimbursement rule has only limited potential to reduce medical error rates because it does not successfully align incentives and may ultimately harm the patients that it seeks to protect by effectively rendering them uninsured for the cost of care stemming from medical errors.

First, Do No Harm: Moving Towards a Paradigm of Safe Delivery

The interventions undertaken in response to the IOM Report have not facilitated effective progress towards the Report's recommendation of the creation of "a 'culture of safety' in which systems are designed to keep patients safe from harm..."⁸ Rather than moving toward a culture of safety, these interventions only address error through attenuated mechanisms and reinforce preexisting (and often misaligned) incentives. A culture of safety requires focusing on error prior to its commission, attempting to align incentives properly toward the common goal of patient safety, and making meaningful changes toward new systems that ensure that care is delivered properly in the first place. This requires direct intervention and a cultural shift in hospitals, instead of continued use of indirect interventions currently employed to reinforce the norms already in place.

In contrast to the uncertain results yielded by indirect mechanisms, direct interventions taken at the point of care can substantially reduce medical error. For example, the medical error rate at the VA Hospital in Topeka, Kansas dropped by 57% after the hospital began using bar-code technology to administer medications.¹² Until effective direct measures like this are identified and adopted as hospital policy, there will not be significant progress in reducing the rate of medical error.¹³

Another approach to error reduction utilizes direct action to prevent medical errors before they occur: the medical checklist. Rather than indirectly addressing medical errors by complex, attenuated, and mismatched incentive structures, checklists give providers a blueprint for preventing the commission of these errors. Unlike error reporting systems, checklists align incentives and deal with unrecognized error by improving recognition of improper care and would-be errors. Furthermore, unlike the CMS non-reimbursement rule, checklists provide an actual mechanism for reducing the number of medical errors at the level of the delivery of care. Checklists increase the likelihood that quality-optimizing precautions and procedures will be considered and followed by intervening in the delivery of care at the moment immediately preceding its improper provision.

Unlike the other policies that have been adopted in response to the IOM Report, the medical checklist bridges the gap between altering systems and altering individual behavior. Checklists are the ideal way to look at medical error on a broad-based, institutional level, to diagnose systematic problems, and to ensure that individual actors are incorporating the solutions into their everyday actions.

An Evidentiary Privilege to Encourage Use and Innovation

A major barrier to continued implementation and experimentation with checklist-use policies is that healthcare

institutions and providers are extremely sensitive to litigation concerns.¹⁴ They shape their policies and actions according to the perceived risks of litigation.¹⁵ They may not want to use checklists because in the event of a lawsuit, an incomplete checklist could be entered as evidence by a plaintiff and viewed as overwhelmingly persuasive by a jury, regardless of the context of the injury.¹⁶ Perhaps as a result of these concerns, they have failed to take full advantage of this opportunity to improve care.^{17,18}

An evidentiary privilege that protects against discovery and admissibility of medical checklists used during patient treatment should be created in order to incentivize healthcare institutions to establish policies that encourage their use. Given the potential patient safety improvements to be gained by more widespread use and development of checklists, failing to encourage their use by quelling liability fears is ultimately a disservice to patients and endangers their safety. An evidentiary privilege similar to that instituted for patient safety work product created after-the-fact of an incident under the PSQIA should be extended to medical checklists as well.

This privilege would prevent a person from entering a checklist into evidence to show whether a particular step was performed or not, or from testifying as to whether the checklist indicated that a particular step was performed or not. It is unlikely that plaintiffs would be seriously disadvantaged by this privilege. While a checklist is very valuable to healthcare providers and patients who receive care, its use in litigation is more attenuated and prejudicial than probative.¹⁹ The reality of checklist use is that they are often used in chaotic, hectic, and stressful circumstances; in an emergency room or any surgical setting, providers are not (and should not be) focused on making tick-marks on a piece of paper. They may forget to make marks even though they have performed each item, or the patient may be in such a precarious condition that providers do not have the time to complete each item on the checklist. For example, one study found that, in a random sample of surgical checklists, a median of 80% of items per checklist were marked as completed.²⁰ Furthermore, due to the nature of many items on the checklist, admitting the checklist would typically be unnecessary to establish the cause of injury. Either the item would not be sufficient to establish causation of injury (ie, introducing each team member by name and role) or the item could be established by looking at the underlying facts of the incident. For example, entering a checklist as evidence would be unnecessary to establish that a patient had a sponge left inside his body after surgery; there would be far more compelling evidence than a checklist to show that the care provided was negligent.²¹

The Administrator-Provider Safety Partnership

Traditionally, hospital administrators have not regulated behavior that is considered to fall within the realm of clinical and safety measures.²² However, hospitals are beginning to recognize that patient safety should be the foremost consideration of all hospital employees, not just those who actively deliver care.¹⁸ Administrators and patient safety committees should work together to implement policies that encourage individual care providers to develop and use checklists tailored to their needs and institutional settings.

Various policies, some encouraging checklist use, and others requiring it, should be explored. In some situations, mandates may ultimately be counterproductive because they create a

backlash from providers who feel that their autonomy is being infringed upon. In instances where third parties have mandated that physicians use checklists, doctors have not embraced the concept with considerable enthusiasm. "The checklist has arrived in our operating rooms mostly from the outside in and from the top down. It has come from finger-wagging health officials, who are regarded by surgeons as more or less the enemy, or from jug-eared hospital safety officers . . .".¹⁸ Since "[j]ust ticking boxes is not the ultimate goal here" but rather "embracing a culture of teamwork and discipline[]," ranking providers by mandating checklist use may sometimes not be the right way to proceed.¹⁸ Individual institutions are best suited for determining whether and when mandating use of the checklist is preferable to encouraging it. That determination depends greatly on the personalities of providers and administrators at an institution. In either instance, however, a commitment by administrators to increasing the use of checklists and encouraging provider input in their development is critical.

Beyond their medical efficacy, checklists should also appeal to the cost sensitivity of hospital administrators.^{22,23} Research demonstrates that checklist-use policies are inexpensive to adopt and save hospitals money.²⁴ Moreover, the existing financial disincentives to commit medical error will likely become even more pronounced once Medicare begins tracking hospital medical error rates as required by the Patient Protection and Affordable Care Act (PPACA).²⁵ Medical error is costly to patients in terms of their health and reduced economic productivity and to providers in terms of financial liability. Furthermore, estimates indicate that half of surgical complications alone are preventable.^{18,26} Identifying and implementing effective methods of reducing preventable medical error can critically affect the assets of healthcare institutions and providers, particularly in the current era of Inpatient Prospective Payment System (IPPS) reductions, schedule-based fee reductions, and high medical malpractice payouts. Therefore, the adoption of policies that encourage the use of checklists achieves financial and administrative objectives in addition to patient safety goals.

The State's Role in Checklist Use

Under an alternative approach, state legislatures could mandate that healthcare providers use certain medical checklists as an element of the providers' standard of care. However, such an action would be inconsistent with the legislature's traditional stance of deference to the medical profession in setting the accepted medical standard of care. It would also impede medical professionals from developing and using checklists that uniquely suit each hospital's peculiar environment.

For example, in 2005 the United Kingdom's National Patient Safety Agency (NPSA) required hospitals to implement a specific set of guidelines in order to reduce the frequency of wrong-site surgeries. In 2010, the NPSA replaced the old guidelines with new ones adopting the WHO Surgical Safety standards.²⁷ In the interim, healthcare institutions were bound to the set of 2005 guidelines, which effectively prevented them from progressing to what is now largely recognized as a superior medical practice. Furthermore, new research indicates that a new surgical checklist, the SURPASS system, may replace the WHO standards at some point in the future. Development of new checklists is a constantly evolving and highly context-specific process. Unfortunately, experimental use of new checklists is stymied where use of one set of guidelines is mandated; under

such regimes, providers lack incentives to develop their own wrong-site checklists that would be more appropriate for the unique patient populations at their own hospitals because they are already bound to using a particular set of guidelines to reduce wrong-site surgeries. Accordingly, although checklists may potentially improve care in many areas, the absence of an evidentiary privilege dissuades hospitals from maintaining policies that encourage innovation with new checklist formulations and applications to determine which will optimally suit a particular hospital environment. If hospitals and healthcare providers are not given the freedom to experiment and innovate with new checklists, we will never realize the full potential that checklists have to offer.

In fact, checklists are most useful when they are developed by local healthcare providers to respond to local circumstances and problems. For example, Dr Atul Gawande describes the story of an emergency response team in a small Austrian town in the Alps. In a widely publicized case, a three-year-old girl was lost beneath the surface of an icy fishpond for thirty minutes. When authorities finally retrieved her, she had no blood pressure or pulse. Her brain appeared to have ceased functioning, and she was ostensibly dead. However, through a series of stunning medical interventions over a period of weeks, doctors slowly brought the girl back to life. Dr Markus Thalmann, a cardiac surgeon who operated on the girl, explained to Dr Gawande his understanding of why they were able to achieve this remarkable outcome:

[Dr. Thalmann] had been working in Klagenfurt for six years when the girl came in. She had not been the first person whom he and his colleagues had tried to revive from cardiac arrest after hypothermia and suffocation. His hospital received between three and five such patients a year, he estimated... For a long time, he said, no matter how hard the hospital's medical staff tried, they had no survivors. Most of the victims had been without a pulse and oxygen for too long when they were found. But some, he was convinced, still had a flicker of viability in them, yet he and his colleagues had always failed to sustain it. He took a close look at the case records. Preparation, he determined, was the chief difficulty. Success required having an array of people and equipment at the ready... Almost routinely, someone or something was missing. He tried the usual surgical approach to remedy this—yelling at everyone to get their act together. But still they had no saves. So he and a couple of colleagues decided to try something new. They made a checklist. They gave the checklist to the people with the least power in the whole process—the rescue squads and the hospital telephone operator—and walked them through the details. In cases like these, the checklist said, rescue teams were to tell the hospital to prepare for possible cardiac bypass and rewarming. They were to call, when possible, even before they arrived on the scene, as the preparation time would be significant. The telephone operator would then work down a list of people to notify them to have everything set up and standing by. With the checklist in place, the team had its first success—the rescue of the three-year old girl.¹⁸

The team has had two other such rescues, even after Dr Thalmann's departure to a different hospital. This story illustrates the adaptability of checklists to a wide array of

situations and the importance of providers' freedom to develop new uses for checklists. No legislator in a state capitol would be able to identify the need for a checklist in this circumstance and create one perfectly suited to it; the innovative role of providers should be preserved and encouraged, not minimized by implementation of rigid, centralized checklist policies. Other instances of checklists developed within institutions to meet particular institutional needs abound. For example, in one hospital, the director of surgical administration (who also happened to be a pilot) decided to utilize the aviation approach to checklists by designing a whiteboard to be placed in each operating room that would provide check boxes for nurses to verbally confirm with the team that they had the correct patient and correct surgery site. He also designed a special tent to be set over the scalpel that could only be removed by the nurse once the checklist was completed. Another institution devised a broader, twenty-one-item list to catch a span of potential errors. This checklist was implemented alongside a mandatory team briefing prior to surgery. A Johns Hopkins surgeon devised an eighteen-item checklist that he and eleven surgeons implemented at their institution. A group of Kaiser hospitals in Southern California adopted a thirty-item checklist also premised on aviation checklist principles. The considerable diversity of institutional checklists indicates the need to ensure institutional autonomy in their development. Further, outside of the operating room, "there are hundreds, perhaps thousands, of things doctors do that are as dangerous and prone to error as surgery. . . All involve risk, uncertainty, and complexity—and therefore steps that are worth committing to a checklist and testing in routine care. Good checklists could become as important for doctors and nurses as good stethoscopes."¹⁸ By incentivizing their production with an evidentiary privilege, the potential for such safety gains is enormous.

Conclusion

Medical error is a serious problem in hospitals and the eighth-leading cause of death in the United States.¹ Checklists may be a significant part of the solution to this problem. One study found that the use of a surgical checklist caused complications from surgery to fall by more than a third and the rates of surgical site infections and post-surgical deaths to roughly halve.^{29,30} In a different hospital setting, researchers found that "simply having the doctors and nurses in the ICU create their own checklists for what they thought should be done each day improved the consistency of care to the point that the average length of patient stay in intensive care dropped by half."¹⁸ An evidentiary privilege that bars admissibility of checklists in court would encourage healthcare institutions to experiment with new policies that incentivize providers to develop and use checklists. Such a privilege would increase the willingness of providers to pool their knowledge to develop and use institutional checklists, thereby increasing the quality of patient care. Given that a similar evidentiary privilege has been instituted to protect the after-error data created in response to incidents that have already occurred, an evidentiary privilege is certainly warranted to protect data tools that are used to prevent those incidents in the first place.

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Views of Junior Doctors about Whether Their Medical School Prepared Them Well for Work

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Abstract

Background: The transition from medical student to junior doctor in postgraduate training is a critical stage in career progression. We report junior doctors' views about the extent to which their medical school prepared them for their work in clinical practice.

Methods: Postal questionnaires were used to survey the medical graduates of 1999, 2000, 2002 and 2005, from all UK medical schools, one year after graduation, and graduates of 2000, 2002 and 2005 three years after graduation. Summary statistics, chi-squared tests, and binary logistic regression were used to analyse the results. The main outcome measure was the level of agreement that medical school had prepared the responder well for work.

Results: Response rate was 63.7% (11,610/18,216) in year one and 60.2% (8,427/13,997) in year three. One year after graduation, 36.3% (95% CI: 34.6, 38.0) of 1999/2000 graduates, 50.3% (48.5, 52.2) of 2002 graduates, and 58.2% (56.5, 59.9) of 2005 graduates agreed their medical school had prepared them well. Conversely, in year three agreement fell from 48.9% (47.1, 50.7) to 38.0% (36.0, 40.0) to 28.0% (26.2, 29.7). Combining cohorts at year one, percentages who agreed that they had been well prepared ranged from 82% (95% CI: 79-87) at the medical school with the highest level of agreement to 30% (25-35) at the lowest. At year three the range was 70% to 27%. Ethnicity and sex were partial predictors of doctors' level of agreement; following adjustment for them, substantial differences between schools remained. In years one and three, 30% and 34% of doctors specified that feeling unprepared had been a serious or medium-sized problem for them (only 3% in each year regarded it as serious).

Conclusions: The vast knowledge base of clinical practice makes full preparation impossible. Our statement about feeling prepared is simple yet discriminating and identified some substantial differences between medical schools. Medical schools need feedback from graduates about elements of training that could be improved.

The authors are with the UK Medical Careers Research Group, Department of Public Health, Oxford University, Oxford, UK. The authors would like to thank Emma Ayres who administered the surveys, Janet Justice and Alison Stockford for their careful data entry, and all the doctors who participated in the surveys. Reprinted from BioMed Central, BMC Medical Education, © 2010 Goldacre et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License.

Background

The broad aims of medical school training are to lay the foundations for a medical career and to provide junior doctors with appropriate knowledge and skills for the first stage of their post-qualification career. Although there is no consensus about how best to train medical students, in the early 1990s it was accepted that medical school training needed to be improved.¹⁻³ The need for improvement was emphasised by the General Medical Council (GMC) in 1993, with the first publication of Tomorrow's Doctors, a directive on undergraduate medical training which stated that 'students must be properly prepared for their first day as a Pre-Registration House Officer'; and revisions in 2003 and 2009 followed.⁴

The curricula and student assessment practices of medical schools in the UK have undergone major reforms in recent years. For example, courses on communication skills have been established; and, at some medical schools, problem based learning (PBL) programs have been introduced⁵ to support the development of self-directed learning skills.

In assessing how well medical schools have prepared graduates for work, in addition to relying on judgments by key professional bodies it is important to seek the views of the graduates themselves. Several studies have done so, using postal questionnaire surveys,^{3,6} interviews² and focus groups.⁷ Improvements over time have been reported, with doctors who have qualified recently feeling better prepared for work than those in the past,⁸⁻¹¹ though some of the studies were limited to a single medical school.

We have reported, nationally across all UK medical schools, on considerable variation between medical schools in how well their graduates felt prepared for the first postgraduate year.^{3,10} In this paper, we update and extend our findings. We report, for the first time, on the doctors' views in their third postgraduate year. We covered the third postgraduate year because we considered that the doctors' view of the role of their medical school may have altered with experience. We also, for the first time, report findings by sex, ethnicity and graduate entrant status; report on whether these are confounders in the comparisons between medical schools; report on the broad areas in which respondents did not feel well prepared; and report, for those who did not feel well prepared, on whether this had been a serious, medium-sized or minor problem for them.

Methods

Design, setting, and participants: We wrote to all doctors who had qualified from all UK medical schools in 1999, 2000, 2002 and 2005. All four cohorts were surveyed one year following qualification, and the 2000, 2002 and 2005 cohorts were also surveyed at three years. Questions about the transition from medical school, reported here, were contained within questionnaires that were used to study a broader range of subjects including doctors' career intentions, career progression, future plans and views on various topics. Questionnaires were posted to the doctors' registered addresses, provided by the GMC, and supplemented, in year three, by addresses provided by the doctors themselves in year one.

Questions asked: The following statement was included in the questionnaires: *Experience at medical school prepared me well for the jobs I have undertaken so far*. Respondents were invited to state their level of agreement with the statement on a five-point scale from strongly agree to strongly disagree. When the 2000 cohort was surveyed one year following qualification, this statement was included in only 25% of the questionnaires (selected at random). In presenting the analysis of the responses to this statement in the surveys at one year, we have combined the responses of the 1999 and 2000 cohorts.

The surveys of the 1999 qualifiers and 2000 qualifiers included just this one question on preparedness. In subsequent surveys we added further questions because we were struck by the low levels of 'feeling well prepared' and by differences in this between graduates of different medical schools. We asked the doctors to indicate in which areas they did not feel well

prepared, selecting from clinical knowledge, clinical procedures, administrative tasks, interpersonal skills, and physical/emotional/mental demands. We also asked whether not feeling well prepared actually mattered: *Was lack of preparation a serious, medium-sized or minor problem for you?*? We invited the doctors to add any free text comments on preparedness, if they wished. These were analyzed by theme-scoring the main issues raised.

Analysis: We used descriptive statistics and χ^2 tests to compare responses according to year following qualification (one or three), cohort (1999/2000 combined, 2002, 2005), medical school, sex, ethnicity (white, non-white), whether the doctor had taken an intercalated degree or not, and graduate status at entry to medical school. The entry of these cohorts to medical school largely pre-dated 'fast track' graduate entry and most graduate entrants will probably have had the same medical school experiences as those of the non-graduate entrants. We used binary logistic regression to take account of possible confounding. Binary dependent variables were constructed by, for example, combining respondents who agreed or strongly agreed that medical school had prepared them well, as one group, and all other responses as the second group. In making multiple similar comparisons, we regarded the attainment of a significance threshold of $p \leq 0.01$ as evidence of significant difference.

Results

Response rates: There were 4,219 qualifiers in 1999, 4,432 in 2000, 4,436 in 2002, and 5,129 in 2005. Survey response rates were, in the first year, 66% for the 1999s and 2000s combined,

Table 1 Percentages, by medical school and graduation year, agreeing after one year that they were well prepared

Medical school	Year of graduation					
	1999/2000		2002		2005	
	% (95% CI)	Rank	% (95% CI)	Rank	% (95% CI)	Rank
5	73 (64, 82)	1	85 (77, 94)	1	89 (83, 96)	1
12	44 (34, 54)	7	64 (53, 75)	5	88 (81, 95)	2
1	56 (46, 65)	5	66 (56, 75)	4	78 (70, 86)	3
9	20 (12, 28)	23	70 (60, 79)	3	76 (68, 84)	4
21	24 (18, 29)	17	70 (63, 77)	2	66 (59, 72)	5
15	38 (28, 47)	9	60 (50, 70)	6	64 (55, 73)	6
18	35 (26, 44)	10	47 (37, 57)	13	64 (55, 73)	7
6	26 (19, 33)	16	43 (35, 50)	15	63 (56, 71)	8
2	41 (32, 49)	8	49 (40, 58)	12	62 (55, 70)	9
11	59 (50, 69)	3	58 (49, 67)	7	60 (52, 69)	10
20	29 (22, 37)	15	44 (36, 52)	14	60 (52, 67)	11
8	30 (22, 38)	13	36 (26, 45)	21	60 (51, 68)	12
7	23 (16, 29)	19	52 (44, 60)	10	57 (49, 65)	13
19	58 (49, 67)	4	39 (29, 48)	18	55 (45, 66)	14
3	21 (29, 48)	21	39 (29, 48)	20	54 (44, 64)	15
22	24 (17, 32)	18	39 (29, 49)	19	52 (43, 61)	16
10	62 (55, 69)	2	56 (48, 63)	8	51 (44, 58)	17
17	56 (47, 65)	6	53 (43, 62)	9	49 (39, 60)	18
23	30 (23, 36)	14	42 (35, 49)	16	47 (40, 54)	19
14	33 (25, 41)	11	50 (41, 60)	11	43 (36, 51)	20
13	32 (24, 40)	12	34 (26, 43)	22	42 (34, 51)	21
4	20 (12, 29)	22	42 (30, 55)	17	38 (28, 48)	22
16	21 (14, 29)	20	33 (24, 41)	23	35 (26, 44)	23
Total	36.3(34.6,38.0)	-	50.3(48.5,52.2)	-	58.2(56.5,59.9)	-

Table 2 Percentages, by medical school and graduation year, agreeing after three years that they were well prepared

Medical school	Year of graduation					
	1999/2000		2002		2005	
	% (95% CI)	Rank	% (95% CI)	Rank	% (95% CI)	Rank
5	76 (67, 85)	1	56 (42, 69)	2	73 (62, 85)	1
12	54 (42, 66)	7	61 (49, 73)	1	55 (43, 66)	2
4	42 (31, 52)	18	38 (25, 51)	10	43 (30, 55)	3
1	54 (44, 63)	8	52 (42, 63)	3	40 (29, 50)	4
2	47 (38, 57)	14	32 (23, 41)	17	40 (32, 49)	5
9	47 (37, 57)	13	52 (41, 63)	4	35 (26, 44)	6
6	45 (37, 53)	15	37 (29, 55)	12	32 (23, 40)	7
11	69 (60, 78)	2	48 (39, 58)	5	29 (20, 38)	8
8	43 (35, 51)	16	29 (18, 39)	20	29 (20, 38)	9
15	51 (40, 61)	9	32 (21, 43)	16	28 (19, 37)	10
13	39 (31, 47)	22	27 (18, 35)	21	28 (20, 37)	11
21	40 (34, 47)	20	45 (37, 53)	7	27 (20, 35)	12
20	50 (43, 58)	11	34 (26, 43)	15	27 (19, 34)	13
3	57 (47, 67)	5	37 (27, 47)	11	24 (15, 34)	14
10	59 (52, 66)	4	35 (27, 43)	13	22 (16, 29)	15
7	35 (26, 44)	23	32 (24, 40)	18	22 (14, 30)	16
19	64 (54, 74)	3	29 (19, 39)	19	22 (12, 31)	17
14	49 (39, 59)	12	44 (34, 54)	9	20 (13, 28)	18
16	42 (32, 52)	19	25 (17, 33)	22	19 (9, 29)	19
22	42 (33, 51)	17	16 (7, 24)	23	19 (11, 26)	20
23	40 (33, 46)	21	35 (27, 43)	14	18 (11, 24)	21
18	51 (40, 61)	10	45 (35, 56)	6	17 (10, 25)	22
17	55 (46, 64)	6	44 (35, 53)	8	11 (4, 18)	23
Total	48.9(47.1,50.7)	-	38.0(36.0,40.0)	-	28.0(26.2,29.7)	-

63% for the 2002s and 61% for the 2005s, and in the third year, 67%, 62% and 53% for the 2000s, 2002s and 2005s.

Feeling prepared for clinical work: At year one, 5.6% of respondents strongly agreed that their medical school had prepared them well for the jobs they had undertaken so far, 42.7% agreed, 20.9% neither agreed nor disagreed, 23.6% disagreed, and 7.2% strongly disagreed. At year three, the corresponding percentages were 5.0% strongly agreed, 33.8% agreed, 31.6% neither agreed nor disagreed, 23.4% disagreed, and 6.1% strongly disagreed.

We analyzed all the data on the five point scale and on a three-point scale combining agree/strongly agree (termed agree in the text and tables that follow) and disagree/strongly disagree (termed disagree). The five-point scale added little. The following descriptions are based on the three-way split.

The percentage of doctors in year one who agreed that they had been well prepared increased from 36.3% (95% CI: 34.6, 38.0) in the cohorts of 1999/2000 to 50.3% (48.5, 52.2) of the 2002s and 58.2% (56.5, 59.9) of the 2005s (Table 1). Those who disagreed fell from 41% to 31% to 21%. Those who strongly disagreed fell from 11.6% to 7.2% to only 2.8%.

The percentage of doctors in year three who agreed that they had been well prepared actually decreased in the successive cohorts: it was 48.9% (95% CI: 47.1, 50.7) for those who qualified in 1999/2000, 38.0% (36.0, 40.0) for the qualifiers of 2002 and 28.0% (26.3, 29.7) for the qualifiers of 2005 (Table 2). Those who disagreed showed no obvious trend with percentages of

respectively, 26%, 33% and 30%.

Differences between subgroups of doctors: Differences in preparedness by sex, ethnicity, intercalated degree status and graduate entrant status were modest compared to cohort differences. In year one, ethnicity was a statistically significant predictor of doctors' feeling prepared (49.3% of white doctors and 45.3% of non-whites agreed that they felt well prepared, $p < 0.001$), and sex, intercalated degree status and graduate status at entry to medical school were not ($p = 0.05, 0.7, 0.6$ respectively). In year three, ethnicity was a statistically significant predictor of doctors' feeling that they had been well prepared (whites 40.4%, non-whites 32.5%, $p < 0.001$), as was sex (males 41.5%, females 37.0%, $p = 0.003$) and graduate status (graduate entrants 41.5%, non-graduates 38.1%, $p = 0.003$). Whether or not the doctor had taken an intercalated degree was not a predictor ($p = 0.1$). Binary logistic regression modeling (including cohort, medical school, sex, ethnicity, degree status and graduate status) did not materially affect the significant and non-significant results.

Medical school differences in preparedness: There were substantial differences between graduates from different medical schools in the percentages who agreed and who disagreed that they felt prepared for their first year of work. The numerical codes in the figures and tables denote medical schools, and the same code is used in each figure and table to denote the same school. In year one (Figure 1), the level of agreement varied from 30% at school 16 to 82% at school 5; in year three (Figure 2) it varied from 27% at school 22 to 70% at school 5. In each figure the schools are sorted in declining order of agreement with the statement. The average level of agreement across all

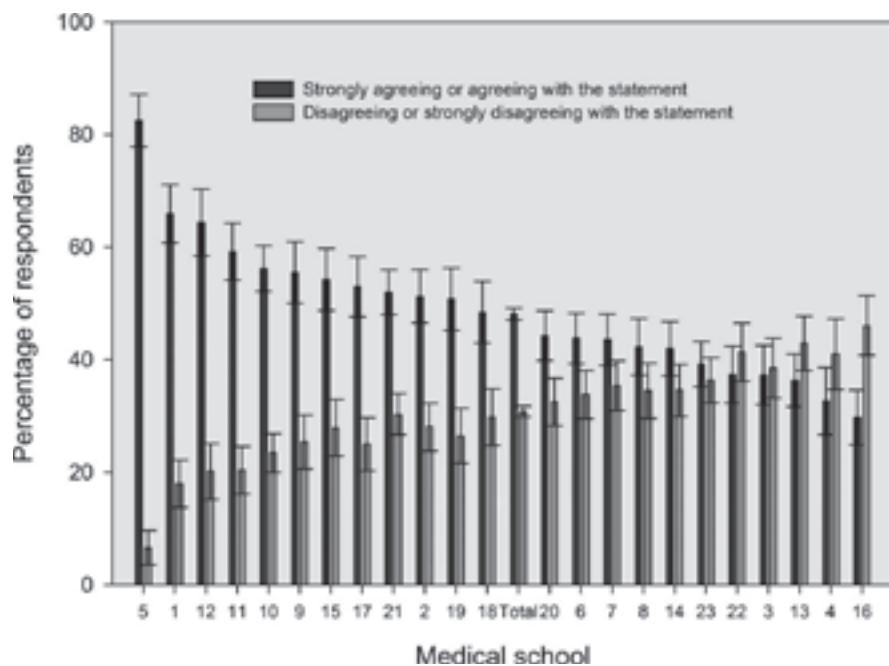


Figure 1 Responses one year after graduation to the statement "Medical school prepared me well for the jobs I have undertaken so far" from graduates of 23 UK medical schools. Footnotes: 1. The data shown are aggregated for the UK medical graduates of 1999/2000, 2002, and 2005 surveyed one year after graduation. 2. Error bars denote 95% confidence intervals for the percentages who "Strongly agreed" or "agreed" and who "strongly disagreed" or "disagreed". For each medical school, the percentage of doctors who stated "neither agree nor disagree" is the difference between 100% and the sum of the two percentages shown.

medical schools is denoted as 'Total' in the figures, and the 95% confidence intervals may be used to judge significant differences. Changes across cohorts in percentage agreement, and in medical school ranking, are shown in Tables 1 and 2. For some schools, the percentage whose graduates agreed that they were well prepared increased substantial, as did their ranking; for others, relatively low ranking did not change much across cohorts or

between years one and three.

Differences between medical schools remained largely unchanged after multivariate adjustment for such factors as sex and ethnicity. In year one, univariate analysis (Figure 1) showed levels of agreement to be significantly high in schools 1, 5, 9, 10, 11 and 12 (based on their confidence intervals not

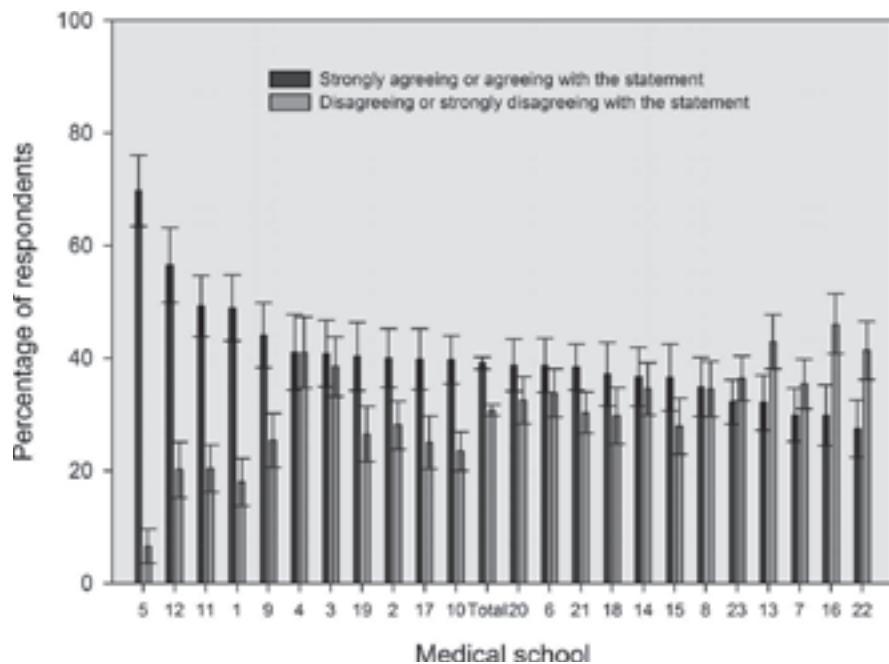


Figure 2 Responses three years after graduation to the statement "Medical school prepared me well for the jobs I have undertaken so far" from graduates of 23 UK medical schools. Footnotes: 1. The data shown are aggregated for the UK medical graduates of 1999/2000, 2002, and 2005 surveyed three years after graduation. 2. Error bars denote 95% confidence intervals for the percentages who "Strongly agreed" or "agreed" and who "strongly disagreed" or "disagreed". For each medical school, the percentage of doctors who stated "neither agree nor disagree" is the difference between 100% and the sum of the two percentages shown.

Table 3 Percentage of respondents* who specified that their medical schools had not prepared them well (and denominator numbers, N)

Year 1/characteristic	N	Clinical knowledge	Clinical procedures	Admin	Interpersonal skills	Demands**
All	5863	17.9	31.5	33.8	2.8	24.2
Cohort	2000	-	-	-	-	-
	2002	2750	18.6	36.7 ¹	34.9	2.4
	2005	3113	17.3	26.9 ¹	32.9	2.1
Sex	Male	2255	18.1	29.6 ¹	37.9 ¹	19.2 ¹
	Female	3608	17.8	32.7 ¹	31.3 ¹	27.3 ¹
Ethnicity	White	4206	17.7	30.9	32.9	1.9 ¹
	Non white	1604	18.5	32.9	36.2	3.2 ¹
Intercalated degree	Yes	2481	16.8	31.5	34.3	2.3
	No	3324	18.9	31.5	33.6	2.2
Graduate entrant	Yes	603	19.1	30.5	30.5	2.2
	No	5222	17.8	31.6	34.2	2.3

Year 3/characteristic	N	Clinical knowledge	Clinical procedures	Admin	Interpersonal skills	Demands*
All	7795	23.7	42.7	32.4 ^{ns}	4.2	30.7
Cohort	2000	2929	22.3 ¹	44.5	33.7 ^{1,ns}	5.0 ¹
	2002	2321	22.1 ¹	40.8	25.9 ¹	3.0 ^{1,ns}
	2005	2545	26.6 ¹	42.3	36.8 ¹	4.2 ¹
Sex	Male	3107	24.1	40.1 ¹	36.5 ^{1,ns}	5.0 ¹
	Female	4688	23.4	44.3 ¹	29.6 ^{1,ns}	3.6 ¹
Ethnicity	White	5371	24.0	43.1	30.9 ^{1,ns}	3.2 ¹
	Non white	1801	22.9	42.4	35.9 ^{1,ns}	6.7 ¹
Intercalated degree	Yes	2993	22.2 ¹	42.2	33.9 ^{1,ns}	4.7
	No	4160	24.9 ¹	43.3	30.8 ^{ns}	3.6
Graduate entrant	Yes	715	21.1 ^{ns}	39.6	26.2 ^{1,ns}	2.5 ^{ns}
	No	6461	24.0	43.3	32.9 ^{1,ns}	4.2

* Percentages of respondents who expressed an opinion about the statement 'Experience at medical school prepared me well for jobs I have undertaken so far.' We received replies to these questions from some respondents who had agreed, overall, with the statement on preparedness. We included these replies in our analysis of the specific aspects of feeling unprepared.

** Physical, emotional and mental demands.

¹ Significant difference (at 0.01 level) within year 1, or within year 3, for each characteristic.

All differences between corresponding cells in year 1 and year 3 were significant, except those marked ^{ns}.

overlapping with that of the overall average). Multivariate binary logistic regression analysis showed the same schools to be significantly high and no others became high (based on analysis of odds ratios, not shown). Schools that were significantly low were 3, 4, 13, 14, 16, 22 and 23; in the multivariate model they all stayed low, and schools 6, 7 and 8 also become significantly low. In year three, Figure 2 shows schools 1, 5, 11 and 12 to be high; the result was the same after multivariate modeling. Schools that were significantly low were 7, 13, 16, 22 and 23; in the multivariate model they all stayed low and 8 also became significantly low.

Extent to which lack of preparation was a problem: Overall, only 2.9% of responders considered feeling unprepared to be a serious problem (2.5% in year one and 3.3% in year three, $p = 0.03$). The only significant findings on 'a serious problem' were that, in year one, doctors who had taken an intercalated degree were less likely to specify this (1.8% did so) than those who had not (3.0%, $p = 0.004$); and in year three, non-whites were more likely to do so (2.8%) than whites 4.1%, $p = 0.01$). All other differences in years one and three were non-significant.

Lack of preparation was regarded as a serious or medium-sized

problem by 31.7% (30.0% in year one and 33.1% in year three, $p < 0.001$). We merged the serious and medium sized response categories and repeated the analysis. In year one, this confirmed that ethnicity (white or non-white) and medical school were statistically significant predictors (both $p < 0.001$), independently of other factors, and graduation cohort, sex, intercalated degree status and graduate entrant status were not ($p = 0.02, 0.4, 0.05$ and 0.5 respectively). In year three, cohort, ethnicity and medical school were statistically significant predictors (all $p < 0.001$), as was sex ($p = 0.02$), but not graduate status ($p = 0.6$) or having an intercalated degree ($p = 0.2$).

Areas where respondents did not feel well prepared:

The broad areas in which the doctors felt unprepared are shown in Table 3. The category with the highest percentage of 'feeling unprepared' was that of clinical procedures (37.9% of all responses overall) whilst interpersonal skills was the area where the lowest percentage indicated that they did not feel well prepared (3.3% overall).

In all areas, except administration, significantly higher percentages of those in year three than in year one did not agree that they had been well prepared. These differences between year one and year three were found, consistently, in all subgroups of doctors except graduate entrants. At both year one and year three, higher percentages of female doctors than male doctors felt unprepared in the areas of clinical procedures and the demands expected of them, and higher percentages of males than females felt unprepared in administration. Higher percentages of non-whites than whites felt unprepared in the areas of interpersonal skills and demands made of them in both year one and year three, and, in year three, in the area of administration. Higher percentages of non-graduate entrants than graduate entrants felt unprepared in the area of administration in year three.

Comments made about preparedness: Additional comments were sent by 1,891 respondents. 20% of these comments (representing 3.5% of respondents) referred to poor levels of exposure to basic clinical skills and lack of clinical experience. Some made general comments about a lack of 'hands-on' experience or a view that medicine should be taught as more of an apprenticeship. Others referred to a need for more training in specific basic clinical skills, tasks and procedures, including prescribing drugs, acute emergency training, administering warfarin, insulin and fluids, carrying out chest drains, central lines and lumbar punctures, dealing with confused, hypertensive or breathless patients, and using a bleep. 18.9% of those who sent comments (3.3% of all respondents) commented that, in their view, their medical school courses had placed too much emphasis on communication skills and other 'soft' skills, at the expense of clinical teaching, and/or that certain subjects had been taught too little (in particular, basic sciences). Comments about problem based-learning were predominantly adverse. By contrast, a similar percentage indicated that they did not feel fully prepared but did not consider it to be a problem.

Discussion

Main findings: Our study shows that, from the doctors' perspective in being prepared for year one, medical school training has improved substantially over time. This supports the findings of others.⁶⁻⁹ The study indicates that, by year three, presumably in the light of experience, the doctors were less likely to agree than in year one that their medical school had

prepared them well. Our findings also show that, in year three, the percentage of doctors who felt that they had been well prepared by their medical school actually declined between the cohorts of 2000 and 2005. Only 3% of respondents regarded being unprepared as being a serious problem for them. About a third regarded it as a serious or medium-sized problem.

There were significant differences between graduates of different medical schools in their views about being well prepared. These differences remained largely unchanged after adjustment for differences between schools in the demographic characteristics of their graduates. Some differences between schools, in whether they ranked high or low, were sustained across cohorts; others changed, improving their score and ranking, substantially. Thus change is eminently possible.

Strengths and limitations: Our study is large and national. Our findings are consistent with other contemporary studies at Liverpool^{7,8} and Manchester⁶ which reported that recent qualifiers feel better prepared than those in the past. Another publication, including some data from our group on the 1999/2000 and 2002 cohorts, reported improvements in preparedness in recent cohorts from UK medical schools.⁹ There is also consistency between our study and other studies in reporting concerns about medical school graduates lacking clinical knowledge.⁶⁻⁸ A recent study shows that the transition from medical school to junior doctor remains stressful in England, with greater levels of clinical experience during the undergraduate years being one of the best mitigators of problems.¹²

A further strength is that our group is independent of organizations that employ, or provide training for, or could influence the careers of, the respondents. We believe that we get honest answers.

It is known that doctors' self assessments of ability do not necessarily correlate well with independent assessments of their ability.¹¹ However, a recent study¹³ has reported the concerns of consultants and specialist registrars about some areas of clinical practice in which year one doctors in the NHS were not well prepared. Its findings are consistent with the subjective impressions of the doctors in our study.

We asked about interpersonal skills and found very small percentages who felt these were a problem. Some studies have used other phrases like 'communication skills'. Responders may interpret these phrases in different ways and may consider they cover anything from taking a medical history to breaking bad news to patients.² Perhaps, therefore, not much emphasis should be put on our findings on this area.

A high percentage of doctors specified that they neither agreed nor disagreed with the statement that their medical school had prepared them well. Some differences between groups of doctors are more evident in the analysis of agree versus other responses than in disagree versus other responses; ie some differences are dependent on how the "neither agree nor disagree" findings are grouped. Where this is so, we are inclined to attach more weight to 'agree versus other responses', on the grounds that doctors who have been well prepared should be able unequivocally to specify that this has been so.

Our study is limited by the possibility of responder bias which

we cannot discount or assess. A further limitation of our study is the bluntness of our measure of the extent to which the lack of preparation was a problem. For example, serious concerns about interpersonal skills might have different implications from serious concerns about carrying out a clinical procedure which can readily be learnt. Our sample sizes are large in this study, and some differences which are shown as statistically significant in the tables are small in percentage terms and hence of limited policy relevance. For example, see the year 3 difference between the 2000 and 2002 cohort in respect of clinical knowledge, or that between whites and non-whites in respect of demands expected of them, both in Table 3.

Unanswered questions: We have no direct insights into the differences between year one and year three views, but two main reasons for differences are possible. First, by year three, some doctors may not think that their medical school training remains relevant to how well prepared they are in their current practice. They might, accordingly, simply be signalling a view that their preparedness owes more to postgraduate than clinical school experience. Second, speculatively, the findings may reflect a greater recognition, by year three, of mismatches between what they were taught and what they have actually done in practice. The facts that there are sustained differences between graduates of different medical schools, and differences between successive cohorts, suggest that many are answering reflectively about their experience at medical school. It is also noteworthy that differences between years 1 and 3 in their overall responses are corroborated by systematic differences in specific areas of their work (Table 3). This, too, suggests that the doctors are making reflective judgments and not simply regarding the general theme of preparedness as redundant by year 3. One possibility, which we cautioned about in our first study,⁹ is that any increase in training medical students to be well equipped for the first year of practice, the PRHO/F1 year, should not be at the expense of clinical knowledge of benefit in the longer term. The views of doctors about their training at medical school, expressed beyond the first year after qualification, deserve further exploration.

Our findings can only be interpreted as broad indications of doctors' views and of broad trends. Investigation is needed in much greater depth. Indeed, this is being done, for example, by the GMC (and formerly Postgraduate Medical Education and Training Board) surveys which evaluate different elements of postgraduate training.¹⁴

Another area for further study, highlighted by others,⁹ is the comparison of subjective feelings of preparedness with independent assessments of doctors' ability. Ethnic minority doctors reported feeling less prepared than white doctors; and in some areas of work, women felt less prepared than men. These differences merit further study: they may reflect differences in learning opportunities, in expectations about how well prepared doctors should be, or in willingness to admit to feeling unprepared. Future research could also investigate the relationship between the medical school curriculum and the graduates' sense of preparedness for practice. A Dutch study suggested that medical school curricula which deliver early clinical experience and foster increasing levels of responsibility appear to produce graduates who feel better prepared.¹⁵

Conclusions

In training students for the first stage of a medical career, medical schools need to strike a balance between preparing

students for their first postgraduate job and for their later years in clinical practice. A balance also needs to be struck between what is taught in medical school, of immediate relevance to the first job, and what is taught as induction at work in the first job. The first year after graduation is the final year of training before doctors become fully registered. It is a period when, under supervision, new doctors put into daily practice the knowledge, skills, behaviors and attitudes that they learned as medical students. It is important to understand more about whether the lack of preparedness is related to the medical school or to the quality of supervision received within the NHS.

The General Medical Council, in the latest edition of Tomorrow's Doctors, is placing emphasis on clinical assistantships and shadowing in the final year of medical school. The medical schools themselves are increasing training in prescribing assessment. With implementation of policies like these, there should be continued improvement. It is also important that the evaluation of changes to medical schools' curricula should not be confined to seeking information from new qualifiers, because medical school training impacts upon the careers of doctors well beyond the first year after qualification.

What should be expected from responses about feeling prepared? Most people starting a new professional job probably will, and probably should, feel unprepared to some extent. The vast knowledge base of clinical practice makes full preparation an impossibility. This is wholly recognized in practice: in the pre-registration year junior doctors work under close supervision from their seniors. Our statement about being prepared, though simple, seems nonetheless to be a discriminating one. For example, it identifies some substantial differences between medical schools and some striking trends in the year one responses. The first year data were collected well into the postgraduate year and therefore represented a reflection on what had been experienced, rather than simply nervous anticipation. We hope that our findings will act as a stimulus to medical teachers to seek feedback from their graduates about what further changes, if any, might be desirable, and practicable, in preparing students for work.

Competing Interests

None. The UK Medical Careers Research Group has no financial relationships with commercial entities that might have an interest in the submitted work; has no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; and has no non-financial interests that may be relevant to the submitted work.

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Use of Rifampin in Persistent Coagulase Negative Staphylococcal Bacteremia in Neonates

N. Margreth van der Lught, Sylke J. Steggerda, Frans J. Walther

Abstract

Background: Coagulase negative staphylococci (CoNS) are the most common cause of neonatal sepsis in the Neonatal Intensive Care Unit (NICU). A minority of neonates does not respond to vancomycin therapy and develops persistent bacteremia, which may be treated with rifampin. We evaluated the use of rifampin in persistent CoNS bacteremia.

Methods: Retrospective study of 137 neonates with CoNS bacteremia during admission to a tertiary NICU between July 2006 and July 2009. Main outcome measures were total duration of bacteremia and the adequacy of vancomycin and rifampin therapy.

Results: 137/1696 (8.0%) neonates developed a CoNS bacteremia. Eighteen were treated with rifampin because of persistent bacteremia (3 positive blood cultures at least 48 hours apart with clinical symptoms) or (a serious suspicion of) an intravascular thrombus. Duration of bacteremia prior to rifampin therapy (8.0 ± 3.6 days) was positively correlated ($p < 0.001$) to the total duration of bacteremia (10.3 ± 3.7 days). After starting rifampin therapy C-reactive protein (CRP) levels of all neonates declined and blood cultures became sterile after 2.3 ± 1.6 days. Vancomycin levels were not consistently measured in all neonates, resulting in late detection of subtherapeutic trough levels.

Conclusion: Rifampin may be effective in the treatment of persistent CoNS infections in neonates. Outcome may be improved by adequate monitoring of vancomycin trough levels.

Background

Sepsis due to coagulase negative staphylococci (CoNS) is common in the neonatal intensive care unit (NICU). The incidence of CoNS sepsis varies between 1.3 and 19.9%, depending on birth weight and gestational age.¹⁻⁵ Most of these infections respond well to vancomycin, the first drug of choice. A minority of neonates develops a persistent staphylococcal bacteremia, which does not respond to vancomycin. For these neonates rifampin may be a safe and effective additive treatment to vancomycin.^{1,6-8} Interaction between vancomycin and rifampin

in treatment of staphylococcal infections is ambiguous, as some studies demonstrate antagonism and others synergism or indifference.⁹⁻¹² High concentrations of rifampin may result in antagonism.^{13,14} Rifampin is only effective as combination therapy, because resistance develops when rifampin is used as monotherapy.¹⁵

Through its highly lipophilic character, rifampin molecules can easily cross biological membranes, resulting in a wide tissue distribution.^{6,16} The efficacy of rifampin in persistent staphylococcal bacteremia is due to its abilities to enhance serum bactericidal activity and to penetrate phagocytic leukocytes for intraleukocytic killing of staphylococci.¹⁷

Pharmacokinetic research has demonstrated a positive correlation between the duration of rifampin therapy and its clearance, the equilibrium clearance is achieved after one to two weeks. The increase in clearance and decrease in half-life are probably due to auto-induction of the metabolism of rifampin and require caution to maintain serum levels within the therapeutic range by adjusting the dose of rifampin, when necessary.^{6,16,18}

Although CoNS bacteremia is common in NICUs and the treatment of persistent CoNS bacteremia with rifampin seems successful, previous studies were only small case reports or studies focusing on pharmacokinetics. The aim of this study was to evaluate the existing local guidelines for the use of rifampin therapy in persistent CoNS infection, checking the current indications to start rifampin therapy and estimating its efficacy.

Methods

Study population: The study population of this retrospective chart review consisted of all neonates admitted to the neonatology department of the Leiden University Medical Center (LUMC) between July 2006 and July 2009. The Medical Ethics Committee of the LUMC did not require approval of this study because it consisted of retrospective chart review, nor did the medical ethics committee require written consent by the parents for their infant's information to be stored in the hospital database and used for research. Approval by the ethics committee and informed consent was not necessary as the patient data were analyzed anonymously.

Inclusion criterion was the presence of a positive blood culture for CoNS. Persistent CoNS bacteremia was defined as 3 positive blood cultures, spaced at least 48 hours apart, in combination

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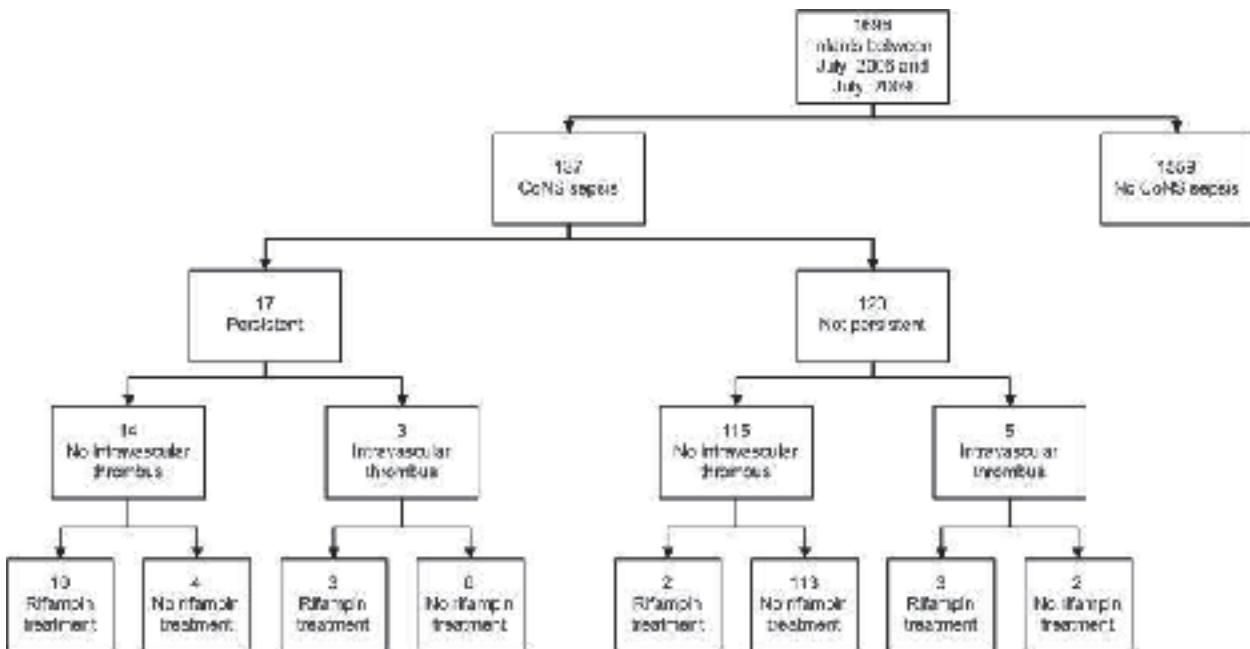


Figure 1 Flow chart of included patients.

with clinical symptoms of sepsis. The indication to start rifampin treatment was persistent CoNS bacteremia despite treatment with vancomycin and removal of indwelling catheters, or a non-persistent CoNS bacteremia in combination with a proven intravascular thrombus. Starting dose of rifampin was 10 mg/kg/day intravenously.

Data collection: Data on demographic, perinatal and postnatal clinical characteristics were collected to provide an overview of baseline characteristics and included birth weight, gestational age, gender, exposure to prenatal and postnatal steroids, presence of chorioamnionitis, hyperglycemia, prolonged rupture of membranes (PROM), asphyxia, respiratory distress syndrome (RDS),¹⁹ bronchopulmonary dysplasia (BPD),²⁰ necrotizing enterocolitis (NEC),²¹ cystic periventricular leukomalacia (PVL)²² and intraventricular hemorrhage (IVH).^{23,24} These data were collected from the neonatal charts and used to compare neonates with non-persistent and persistent CoNS bacteremia.

Primary outcome measures were the total duration of bacteremia and the adequacy of vancomycin treatment, estimated by following trough levels obtained after the initiation of vancomycin therapy until the tenth day of rifampin therapy. The desired range of trough levels of vancomycin was 5–10 mg/L, trough levels <5 mg/L were considered to be subtherapeutic and the desired range for peak levels was 20–30 mg/L. Other variables studied included plasma urea and creatinine levels and duration of vancomycin therapy.

Main outcomes for analysis of the group of rifampin treated neonates were total duration of bacteremia and rapidity of sterilization of blood cultures after the start of rifampin. Age at start of infection, CRP levels from the first day of CoNS positive blood culture until the tenth day of rifampin treatment, and duration and dose of rifampin treatment were additional variables among rifampin treated neonates.

Identification of CoNS isolates was performed by the microbiology department using Bactec Peds Plus bottles (Becton

and Dickinson, Franklin Lakes, NJ USA). Blood cultures, complete blood count and CRP were drawn upon clinical suspicion of sepsis. CRP levels were determined daily during therapy with antibiotics. Vancomycin serum samples were drawn just before the third dose and 1 hour after administration of the third dose. When the dosage of vancomycin was changed, another serum sample was drawn around the second dose after the change. CRP levels were measured using a immunoturbidimetric assay (imCRP, detection limit ≥ 3 mg/L)²⁵ and serum vancomycin levels by a fluorescence polarization assay.²⁶

CoNS bacteremia was an indication for removal of central venous lines and sonography for a remaining vascular thrombus.

Statistical analyses: Data are reported as mean values \pm standard deviation, minimum and maximum, numerical values or categories. Analyses were performed with SPSS Version 16.0 (SPSS Inc., Chicago, IL). Numerical data were analyzed by bivariate Pearson correlation and unpaired T-tests, categorical data were analyzed using a chi-squared test. To correct for potential confounding effects, logistic regression analysis was done.

Results

In the period between July 2006 and July 2009 1696 neonates were admitted to the NICU with a mean birth weight of 1271 ± 663 gram and a gestational age of 29.2 ± 3.2 weeks. The incidence of CoNS bacteremia was 137/1696 (8%), 17 (12%) of these neonates developed a persistent CoNS bacteremia and in 3 of them an intravascular thrombus was identified. One neonate with a CoNS sepsis also had a S. aureus sepsis.

A flowchart of the included patients can be seen in figure 1. Baseline characteristics of the included patients are listed in table 1. Newborn infants with persistent CoNS bacteremia had lower birth weights ($p = 0.008$) and, independent of birth weight, more often hyperglycemia ($p = 0.007$), than infants with non-persistent CoNS bacteremia. Subtherapeutic vancomycin trough

Table 1 Baseline characteristics of all included patients

	Non-persistent CoNS bacteremia N = 120	Persistent CoNS bacteremia N = 17	P-value
Prenatal Steroids			0.668
0 doses	50 (43.1%)	9 (52.9%)	
1 dose	47 (40.5%)	5 (29.4%)	
2 doses	19 (16.4%)	3 (17.6%)	
Chorioamnionitis*	9 (7.8%)	1 (5.9%)	0.784
PROM**	14 (12.0%)	2 (11.8%)	0.981
Asphyxia***	7 (5.8%)	0 (0%)	0.307
Gestational age, weeks	29.4 ± 3.3	28.0 ± 2.3	0.093
Birth weight, g	1,327 ± 686	874 ± 204	0.008
Gender (male)	71 (59.2%)	10 (58.8%)	0.979
			Multivariate P-value (corrected for birth weight)
Hyperglycemia****	8 (6.7%)	8 (47.1%)	0.007
IVH grade 3/4	9 (7.5%)	0 (0.0%)	0.999
Cystic PVL	2 (1.7%)	1 (5.9%)	0.640
NEC grade 2/3	4 (3.3%)	2 (11.8%)	0.766
RDS grade 3/4	23 (19.2%)	7 (41.2%)	0.788
BPD*****	26 (21.7%)	9 (52.9%)	0.771
Postnatal steroids	7 (5.8%)	4 (23.5%)	0.652
Died during admission	3 (2.5%)	1 (5.9%)	0.754

* Smelly amniotic fluid, maternal fever or signs of infection at birth

** Rupture of membranes >24 hours

*** Presence of minimal 3 criteria:

- 1) Decelerative CTG or meconium containing amniotic fluid
- 2) Umbilical cord pH <7.10
- 3) Apgar score <5 after 5 minutes
- 4) Spontaneous respiratory depression >5 minutes after birth
- 5) Multiple organ failure

**** Glucose levels of >10 mmol/L during >12 hours, treated with insulin >12 hours

***** Need for oxygen-therapy at a gestational age of 36 weeks or at discharge

levels were equally divided among the groups with persistent and non-persistent CoNS bacteremia ($p = 0.712$).

Eighteen of the 137 neonates received rifampin treatment, started after 8.0 ± 3.6 (mean \pm SD) days of CoNS bacteremia. 13/18 neonates had persistent CoNS bacteremia (in three of them an intravascular thrombus was found), 3/18 had an intravascular thrombus with a non-persistent CoNS bacteremia, 2/18 received rifampin because of increasing CRP levels during vancomycin therapy in combination with severe thrombocytopenia and a serious suspicion of an intravascular thrombus.

Figure 2 shows the course of the CRP levels before and after the first CoNS positive blood culture, for both infants treated with and without rifampin (start of rifampin is marked, dotted lines represent infants without rifampin therapy).

CRP levels from the first day of a CoNS positive blood culture until the tenth day of rifampin therapy demonstrate a serious decline in CRP levels after starting rifampin therapy (figure 3). Indwelling catheters were removed before the first CoNS positive blood culture (6 times), on the day of the first CoNS positive blood culture (3 times) or after the first CoNS blood culture (6 times, although in all these infants maximum CRP was achieved after removal of the catheter). The most important decline in CRP occurred during the first 3 days after the start of rifampin. In these first 3 days the blood culture of most neonates

became sterile, with a mean duration of 2.3 ± 1.6 days. Values of other infection- and pharmacokinetic parameters of the neonates treated with rifampin are listed in table 2.

Before the start of rifampin all neonates received vancomycin as monotherapy ($n = 1$) or in combination with ceftazidime (until definitive identification and antimicrobial susceptibility testing of gram-positive cocci in clusters) ($n = 17$). The duration of vancomycin therapy was 8.9 ± 4.5 days. Ten neonates had adequate initial vancomycin levels, in 8 infants vancomycin dosage had to be readjusted. Vancomycin trough levels between the first day of CoNS positive blood culture and the tenth day of rifampin treatment are presented in figure 4. In contrast to vancomycin levels, rifampin levels were never obtained. The presence of an intravascular thrombus did not correlate with the total duration of CoNS bacteremia or with the rapidity of sterilization of blood cultures after the start of rifampin treatment.

Discussion

Comparing our incidence of CoNS bacteremia (8%) with other studies is difficult, as the composition of study populations vary. Most studies report a lower incidence, probably due to higher birth weights and gestational ages in these populations.²⁻⁴ One study reported an incidence of 19.9%, but neonates in this study had a lower gestational age.⁵ Effectiveness of rifampin treatment in persistent staphylococcal bacteremia in

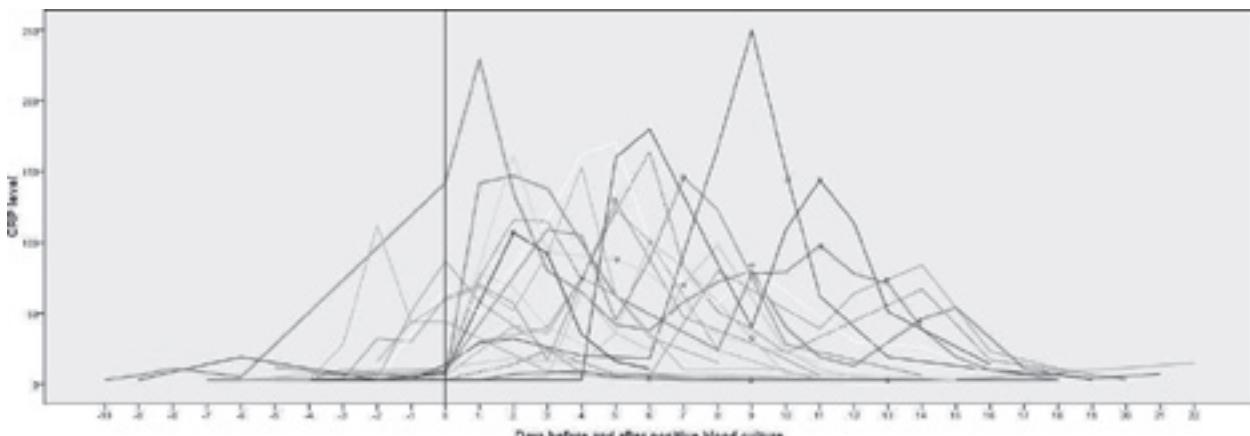


Figure 2 CRP levels (mg/L) from 10 days before positive blood culture until maximum of 10 days after negative blood culture. Each line indicates an individual patient; dotted lines represent infants with persistent CoNS sepsis without rifampin therapy. Start of rifampin therapy is indicated with circles.

neonates has been demonstrated in several case reports and pharmacokinetic studies, in which speed of sterilization of the blood culture was the main outcome.^{1,6-8} Our data also show a substantial decline in CRP during the first days of rifampin treatment. To our knowledge, studies evaluating the treatment of CoNS bacteraemia, focusing on the adequacy of monitoring and responding to vancomycin trough levels and the compliance with starting rifampin after 3 positive blood cultures with an interval of 48 hours, have not been reported earlier.

This retrospective study has several limitations. The most important one is the small size of the study population (18 patients) available for evaluation of rifampin treatment. As most neonates with a CoNS bacteraemia respond well to vancomycin, rifampin is given only incidentally. Another limitation is the absence of an appropriate control group. As 4 patients with a persistent CoNS bacteraemia did not receive rifampin, this group was too small for comparison purposes. Comparison of the occurrence of vancomycin levels below the therapeutic margin between persistent and non persistent bacteraemia appeared

difficult, as vancomycin levels were not regularly assessed in all neonates, especially in neonates with a non-persistent bacteraemia.

Comparing the groups with and without persistent CoNS bacteraemia, significant differences were seen for birth weight and the presence of hyperglycemia. Hyperglycemia is caused by relative insulin deficiency and resistance, due to high levels of circulating cytokines and inflammatory markers during sepsis.²⁷ Persistent bacteraemia may increase the risk for developing comorbidity such as hyperglycemia.

No clear statements can be made about the possible influence of adequate monitoring and the response to vancomycin trough levels on the risk of developing a persistent CoNS bacteraemia. Because vancomycin levels were not consistently obtained in all neonates (especially in those without persistent CoNS-bacteraemia), an accurate comparison of the occurrence of subtherapeutic vancomycin trough levels of infants with and without a persistent CoNS bacteraemia was not possible.

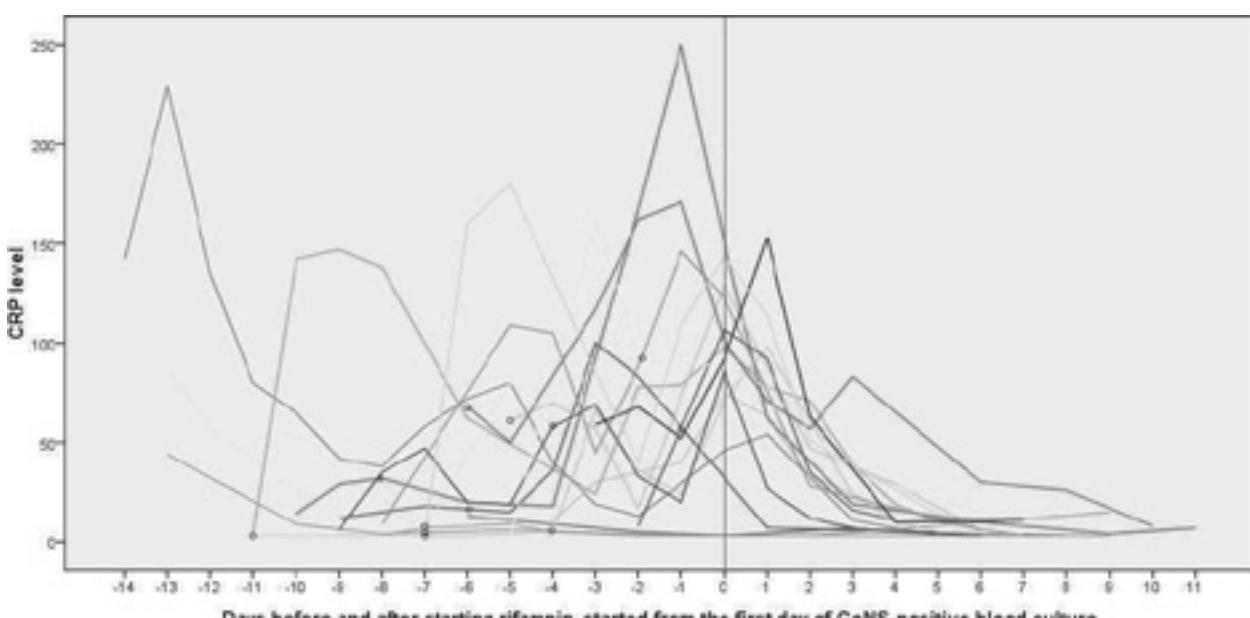


Figure 3 CRP levels (mg/L) from the first day of CoNS-positive blood culture until 10th day after starting rifampin treatment. Each line indicates an individual patient, the time when indwelling catheters were removed is indicated with a circle.

Table 2 Infection and pharmacokinetic parameters of neonates treated with rifampin

N = 18	Mean	SD	Min	Max
Age at start of bacteremia	5.4	2.7	1	11
Days of bacteremia before start of rifampin	8.0	3.6	2	14
Days of vancomycin therapy before start of rifampin	8.9	4.5	2	20
Maximum peak level of vancomycin (mg/L)	26.7	3.5	20.0	32.0
Minimum peak level of vancomycin (mg/L)	20.3	4.7	12.8	28.0
Maximum trough level of vancomycin (mg/L)	10.8	2.6	7.3	15.9
Minimum trough level of vancomycin (mg/L)	7.3	3.6	3.5	15.9
CRP at start of rifampin (mg/L)	77.5	44.8	3	146
Maximum CRP during bacteremia (mg/L)	120.3	64.4	9	250
Duration of rifampin therapy (hours)	147.2	52.5	52	264
Dose of rifampin (mg/kg/day)	10.4	3.0	6.0	17.0
Rapidity of sterilization of blood culture after start of rifampin (days)	2.3	1.6	0	6
Total duration of bacteremia (days)	10.3	3.7	4	15

Conclusion

Our results suggest that the treatment strategy for persistent staphylococcal bacteremia with rifampin may be effective, but can be optimized by improving the monitoring of vancomycin trough levels and minimizing the delay in starting rifampin treatment. If, in spite of adequate vancomycin levels, CoNS bacteremia becomes persistent, rifampin therapy may be started

after 6 days of bacteremia (3 positive blood cultures with a 48 hours interval after each).

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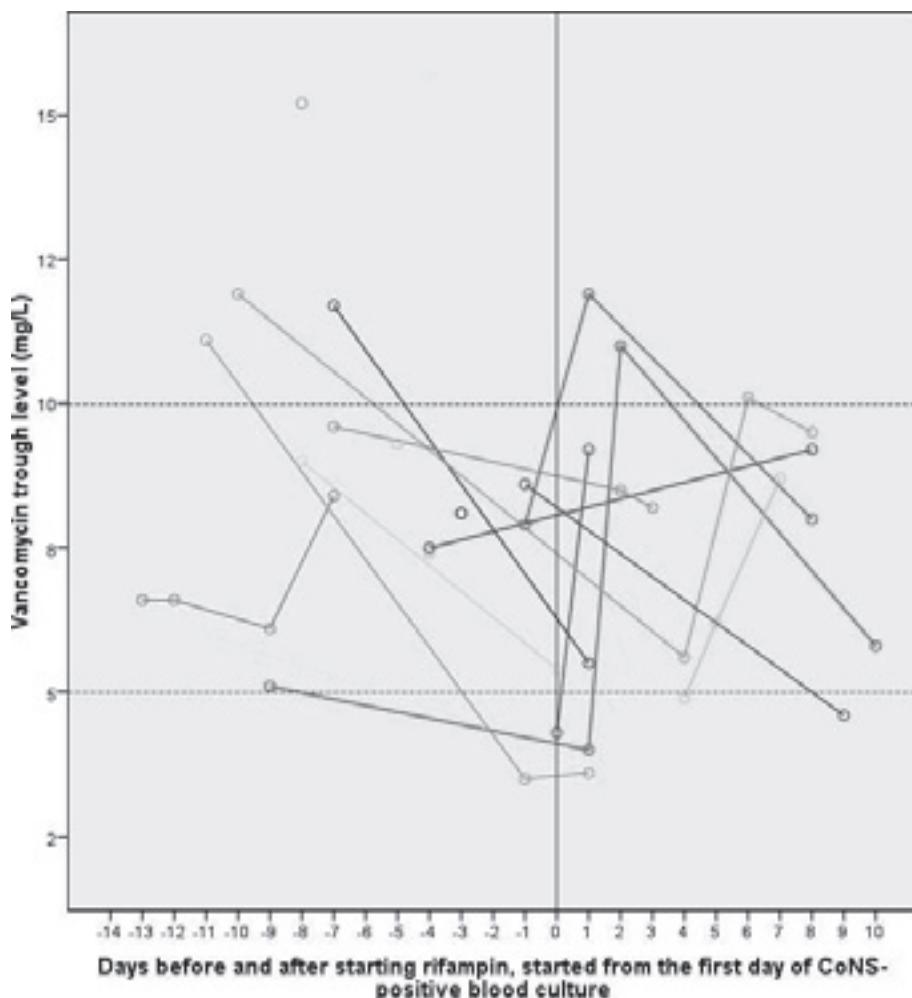


Figure 4 Vancomycin trough levels (mg/L) of rifampin treated infants from the first day of CoNS-positive blood culture until 10th day after starting rifampin treatment. Each line indicates an individual patient.

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