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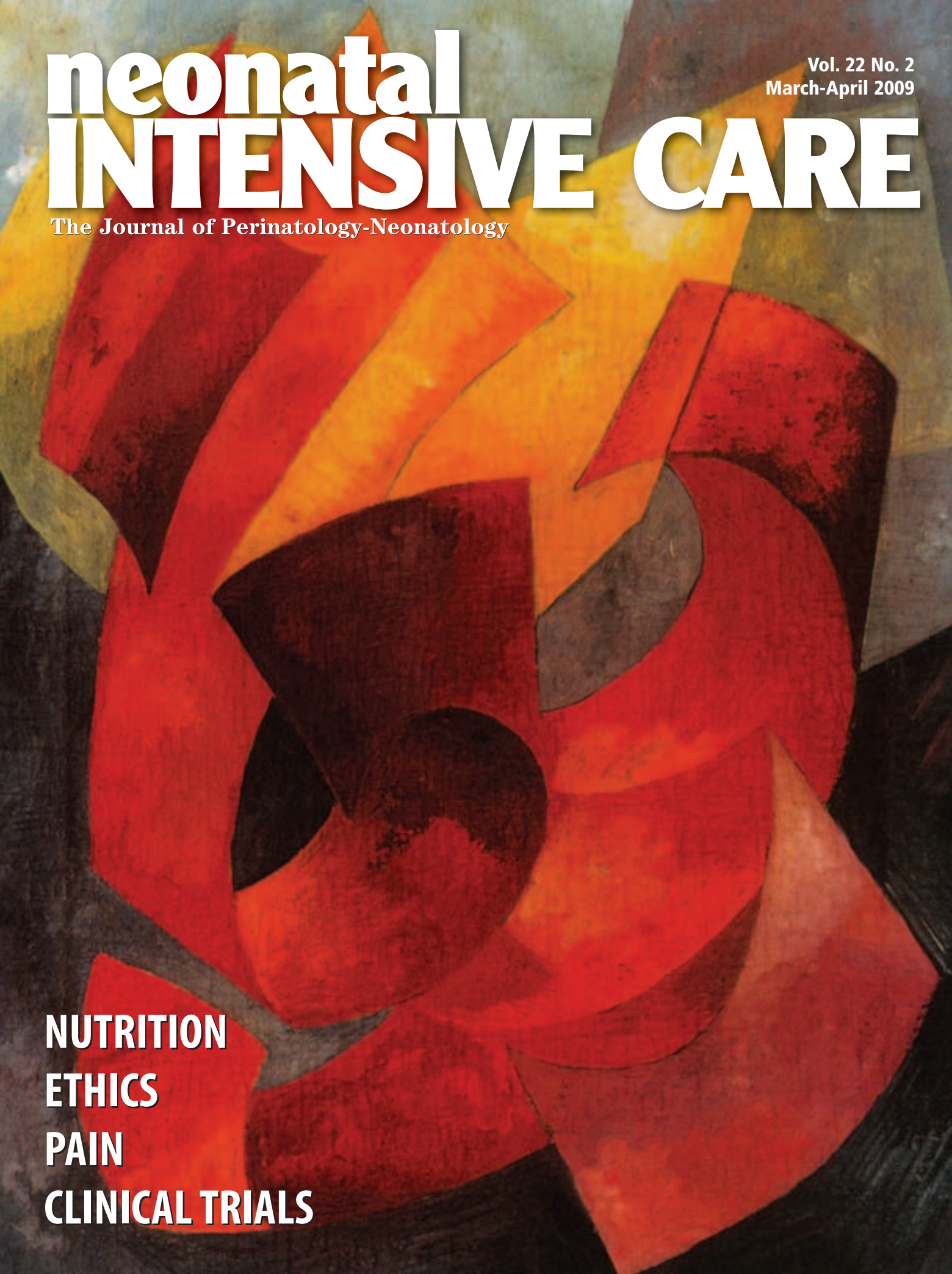
March-April 2009

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology



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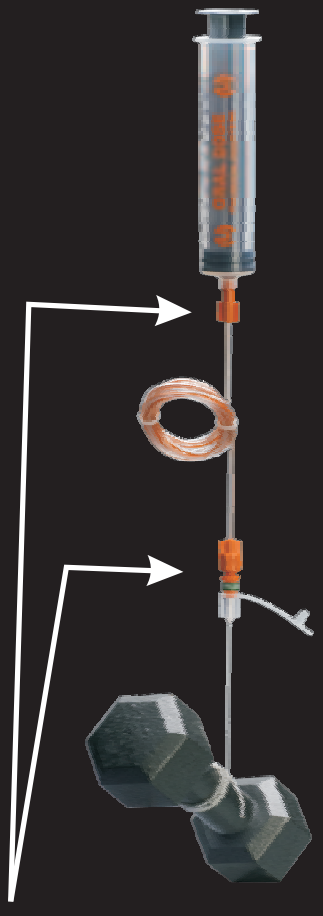

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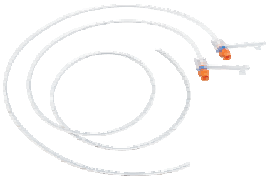

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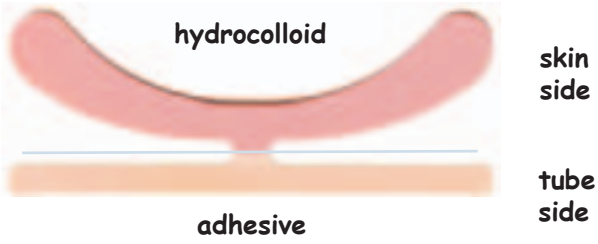

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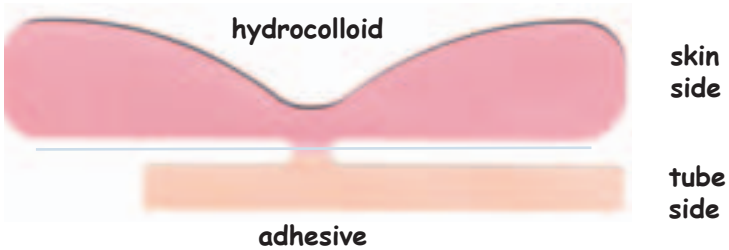

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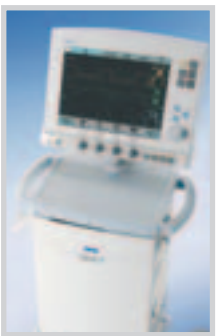

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Editorial

Conflict of Interest

While neonatology-perinatology practitioners don't rely on pharmaceuticals as extensively as other medical care providers, they are at least as dependent on the, shall we say, largesse, of corporate donors in order to carry out clinical studies, make decisions about medication and equipment, and try out new modes of care. Thus I thought you might be interested in an article that appeared in The New York Review of Books, "Drug Companies & Doctors: A Story of Corruption." The story was written by Marcia Angell, Senior Lecturer in Social Medicine at Harvard Medical School and former Editor in Chief of The New England Journal of Medicine.

Angell writes, "No one knows the total amount provided by drug companies to physicians, but I estimate from the annual reports of the top nine US drug companies that it comes to tens of billions of dollars a year. By such means, the pharmaceutical industry has gained enormous control over how doctors evaluate and use its own products. Its extensive ties to physicians, particularly senior faculty at prestigious medical schools, affect the results of research, the way medicine is practiced, and even the definition of what constitutes a disease.

"Consider the clinical trials by which drugs are tested in human subjects. A few decades ago, medical schools did not have extensive financial dealings with industry, and faculty investigators who carried out industry-sponsored research generally did not have other ties to their sponsors. But schools now have their own manifold deals with industry and are hardly in a moral position to object to their faculty behaving in the same way. A recent survey found that about two thirds of academic medical centers hold equity interest in companies that sponsor research within the same institution. A study of medical school department chairs found that two thirds received departmental income from drug companies and three fifths received personal income. In the 1980s medical schools began to issue guidelines governing faculty conflicts of interest but they are highly variable, generally quite permissive, and loosely enforced.

"Because drug companies insist as a condition of providing funding that they be intimately involved in all aspects of the research they sponsor, they can easily introduce bias in order to make their drugs look better and safer than they are. In view of this control and the conflicts of interest that permeate the enterprise, it is not surprising that industry-sponsored trials published in medical journals consistently favor sponsors' drugs—largely because negative results are not published, positive results are repeatedly published in slightly different forms, and a positive spin is put on even negative results. Many drugs that are assumed to be effective are probably little better than placebos.

"Clinical trials are also biased through designs for research that are chosen to yield favorable results for sponsors. For example, the sponsor's drug may be compared with another drug administered at a dose so low that the sponsor's drug looks more powerful. A common form of bias stems from the standard practice of comparing a new drug with a placebo, when the relevant question is how it compares with an existing drug. In short, it is often possible to make clinical trials come out pretty much any way you want, which is why it's so important that investigators be truly disinterested in the outcome of their work.

"Conflicts of interest affect more than research. In a survey of two hundred expert panels that issued practice guidelines, one third of the panel members acknowledged that they had some financial interest in the drugs they considered. Many members of the standing committees of experts that advise the FDA on drug approvals also have financial ties to the pharmaceutical industry. Conflicts of interest and biases exist in virtually every field of medicine, particularly those that rely heavily on drugs or devices. It is simply no longer possible to believe much of the clinical research that

Continued on page 25…

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News

☐ March-April 2009

DO IT QUICK

Rapid drug treatment of babies with HIV cuts their risk of death and debilitating disease, according to research by the Medical Research Council, which found that giving antiretroviral therapy (ART) straight after diagnosis cut the risk of death from Aids by 76%. The study, of 377 HIV-positive South African babies found that babies given treatment immediately after they were diagnosed with HIV cut their risk of dying from the infection to just 4%. The risk of death for those whose treatment was delayed was 16%. Immediate treatment also cut the chance of disease progressing measurably by 75%, from 26% to 6%. The researchers said that CD4 counts do not tell if babies under a year of age are becoming sick and said that treating all infants at the earliest opportunity after diagnosis was the best course of action, despite the side effects of the regimen.

HOT AND COLD

Children who were born very premature can't sense temperature very well, according to a study of 43 eleven-year-old children who were born 14 weeks early. Researchers at the University College of London also said prematurity may affect pain perception. Researchers surmised that the nervous systems of preemies were vulnerable because they were exposed to repeated painful procedures. The study showed that these VLBW kids were less sensitive to hot and cold, especially those who had undergone surgical operations as babies, and suggested that the severity of early trauma influenced the degree of sensory impairment.

BLACK AND WHITE

A mixed-race British couple has had a second set of twins in which one sibling is black and the other white. One kid has dark skin like her dad; her sister is blue-eyed and red haired, like her mom. The couple's previous twins also have different skin tones and eye colors. Both sets of twins are fraternal; that is, from different eggs.

FOOTSIES

A tumor removed from the brain of a baby contained a tiny foot and other partially formed body parts, after an MRI revealed the tumor on the baby's brain. The baby was three days old and otherwise healthy. The growth contained a nearly perfect foot and the formation of another foot, a hand and a thigh. The neurosurgeon who performed the surgery said, "It looked like the breech delivery of a baby, coming out of the brain." The doctor surmised that the growth may have been a type of congenital brain tumor; however, he noted that such tumors usually are less complex than a foot or hand. The growth may also have been a case of fetus in fetu.

OVARY TO GO

A healthy baby girl has been born in London following the world's first transplant of an entire ovary. The 39-year-old mother conceived naturally after receiving the ovary from her twin sister. The nearly eight-pound baby was born to a woman who became infertile at 15 when her own ovaries failed. She hadn't planned to get pregnant, but hoped that the transplanted ovary from her identical twin could relieve the symptoms of her early menopause and restore her periods. The ovary was implanted using microsurgical techniques to reattach it to its blood supply and hold it in place alongside the fallopian tube, so that eggs could be expelled and travel down the tube towards the womb in the normal way. Researchers at the Infertility Center of St Louis said the full transplant was likely to last longer than strips of ovarian tissue, and might allow a woman's ovary to be removed and put back after extended storage. This could allow women who are delaying motherhood to improve their chances of having a baby later in life. The British Fertility Society supports the use of ovary transplantation only in cases in which fertility is threatened by impending radiotherapy or chemotherapy treatment. A UK specialist said the procedure should be used to preserve fertility before cancer treatment, rather than to try to extend it.

CONJOINED TWIN DIES

A month-old conjoined twin who survived a lengthy surgery to separate her from her sister died on the afternoon of Christmas Day at London's Great Ormond Street Hospital. The twin girls were joined from their chests to the lower part of their stomachs. They had separate hearts, but shared a liver and intestines. Recently, the pair underwent an 11-hour surgery to separate them, an operation that doctors hoped could wait until the girls became stronger, but the infants' deteriorating condition made it necessary for the surgical team to separate them twins. The dead twin's lungs were too small to support breathing and circulation, doctors said, and the other twin's lungs were supporting her. The remaining girl's chances of survival were put at 50%. Their mother, 18, is the youngest-ever mom to give birth to conjoined twins. Reported by The Huffington Post.

RARE TREATMENT

A 9-month-old baby girl from Belfast with infantile hypophosphatasia is receiving enzyme replacement treatment with thrice weekly subcutaneous injections of ENB-0040 by Enobia. Typically, up to 50% of patients with the condition die. ENB-0040 is a fusion protein that includes the catalytic domain of human tissue non-specific alkaline phosphatase (TNSALP), and a patented peptide used to target the enzyme to bone. The preclinical studies of ENB-0040 in the knockout mouse model of severe hypophosphatasia were recently published in the Journal of Bone and Mineral Research and showed that subcutaneous administration significantly improved survival and prevented the skeletal and dental manifestations of the disease. In addition to the ongoing trials, pediatric studies are also being planned. Contact enobia.com.

AQUANOT

Boys born to women exposed to hairspray in the workplace may have double the risk of being born with hypospadias, according to a study at the Imperial College London. The incidence of hypospadias has risen sharply in recent decades, and some say the phthalates found in hairspray may be the cause. The latest study looked at phthalate use in higher doses by workers such as hairdressers and beauty therapists. A total of 471 women

whose babies had been born with hypospadias were interviewed, as were a similar number of women with unaffected children. About twice the number of women in the hypospadias group revealed that they had been exposed to hairspray through their job. However, some researchers said it was a big leap of faith to conclude that phthalates were to blame for birth defects. Researchers also noted that taking extra folate can minimize the chance of having a baby with hypospadias. Reported by the BBC.

HEART-STOPPING

In a study just presented at a major medical meeting, researchers have discovered how a unique technology that monitors site-specific blood oxygen levels in the brain after heart surgery can help prevent or reduce these neurodevelopmental deficits in children. Dr George Hoffman, Medical Director and Chief of Pediatric Anesthesiology at the Children's Hospital of Wisconsin's Pediatric Intensive Care Unit, is using an INVOS System brain oxygen monitor to study the connection between low oxygen levels in the brain and poor neurodevelopment. This technology uses noninvasive sensors applied to the forehead to see inside the brain to assess whether it is receiving adequate oxygen. These real-time readings enable doctors to immediately intervene to improve sub-standard oxygen levels that, if left untreated, could cause brain injury. The study led by Hoffman followed children with and without brain oxygen monitoring, and found patients who received brain oxygen monitoring after surgery had improved neurodevelopment outcomes at 4-5 years of age. This was assessed by neurodevelopmental tests including visual motor integration (VMI). Hoffman's study found a significant correlation between inadequate brain oxygen and abnormal VMI. None of the patients monitored by the INVOS System developed abnormal VMI. Conversely, abnormal VMI occurred in 18% of children without brain oxygen monitoring. The study also found that some of today's traditional metrics such as blood pressure, arterial blood measurements and hemoglobin values did not correlate to VMI, suggesting that brain oxygen monitoring provides valuable new data upon which to tailor patient care and improve outcomes. Information provided by Somanetics.

PAY UP AND SHUT UP

The actor Dennis Quaid and his wife have settled their suit with Cedars-Sinai for $750,000 over the heparin overdose their twins received. The Quaid twins were given 10,000 units instead of 10. The hospital didn't admit any wrongdoing but had apologized. Similar labeling for the two dosages was blamed. Because of that, the Quaids also sued Baxter Healthcare Corp for not pulling vials of heparin while it was fixing problems with labeling. That case has been dismissed. The Quaids said other suits for other similarly affected patients have not been ruled out. A new foundation established by the actor said the settlement money would go toward funding the fight about "a conspiracy of silence" about medical errors.

WOMB TO LET

According to an editorial by Thomas Frank on OpinionJournal.com, "At long last, our national love affair with the rich is coming to a close... Some people haven't received the memo, though. Take Alex Kuczynski, author of the New York Times Magazine cover story, which tells how she went about hiring another woman to bear her child. For years Ms Kuczynski worked the plutocracy beat for the New York Times and… went from observer to observed… Ms Kuczynski's trademark concern for the moneyed [became] a memoir as she relates to us, in last week's Times Magazine, her 'adventures with a surrogate mom.' The story starts with Kuczynski's infertility, which is genuinely piteous, but quickly goes wrong, as she and her husband decide to hire a woman to carry their child and review applications from women with available wombs." In his commentary, Frank says, "When money is exchanged for pregnancy, some believe, surrogacy comes close to organ-selling, or even baby-selling. It threatens to commodify not only babies, but women as well, putting their biological functions up for sale like so many Jimmy Choos. If surrogacy ever becomes a widely practiced market transaction, it will probably make pregnancy into just another dirty task for the working class, with wages driven down and wealthy couples hiring the work out because it's such a hassle to be pregnant… It's 'organ rental,' Ms Kuczynski decides; nothing worse. She is taken with the surrogate's reference to herself as an 'Easy-Bake oven,' a toy appliance, and further describes her as 'a vessel, the carrier, the biological baby sitter, for my baby.' And, yes, the surrogate applicants could all use the money, if not desperately; the one who gets the job plans to use it to help pay her kids' way through college. Additionally, one of the surrogate's children, Ms Kuczynski notes, 'had been an egg donor to help pay her college tuition.' … Of the story's nearly 8,000 words, there are only three quotations from the surrogate mother. Ms Kuczynski does not describe this remarkable woman's clothes or, really, tell us her thoughts about much of anything. About Ms Kuczynski's own feelings and fears and cravings we get paragraph after maudlin paragraph. The one who does the labor is almost completely silent."

NEW ATTITUDES

The Down's Syndrome Association surveyed 1,000 parents to find out why they had pressed ahead with a pregnancy despite a positive test result. A fifth said they had known somebody with Down's, a third cited religious or anti-abortion beliefs and 30% felt life had improved for people with Down's. One in five said they simply did not believe the results of the test. Most respondents said they felt supported by their family and friends and considered that the future was far better today for those with Down's syndrome. They pointed to integrated education in particular and a greater acceptance of what it means to be different. The survey was compiled to coincide with the BBC Radio 4 documentary Born With Down's.

THE BIG CHEESE

AWHONN has selected Karen Peddicord, RNC, PhD as its new executive director. A long-time AWHONN member, Dr Peddicord was previously the administrator for the women's and children's service line at Anne Arundel Medical Center in Annapolis, MD. Before that, she was an Associate Professor in Maternal Child Health at the University of Maryland School of Nursing. Peddicord received her PhD in Health Education and her Master's in Maternal Child Nursing from the University of Maryland.

TAKE CARE

In collaboration with the US Centers for Disease Control and Prevention, experts representing a variety of professional organizations including the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN); the American College of Nurse-Midwives; the American Academy of Family Physicians; and the American College of Obstetricians and Gynecologists summarized the evidence supporting preconception health care in a special supplement to the American Journal of Obstetrics and Gynecology. The CDC

defines preconception care as interventions that identify and decrease medical, behavioral and social risks to the health of a woman before conception. The journal supplement reports on fifteen areas, such as infectious disease, immunization, nutrition, environmental exposures and psychosocial stress. The supplement concludes that there is strong evidence to support more screening, health promotion and primary care interventions for women, such as smoking cessation and the intake of folic acid, calcium and other vitamins. Unfortunately, the current status of preconception care in the United States is far from ideal. Only one in six obstetrician/gynecologists or family physicians provide preconception care to the majority of the women for whom they provide prenatal or maternity care.

ANOTHER BIG ONE

Doctors at Saddleback Memorial Medical Center in Laguna Hills, CA delivered a 14-pound, 2 ounce baby by C-section; it took two of them to lift it out. A nurse was quoted as saying, "Oh my God!" The father said, "We thought our first baby was a miracle, and now we have this little guy," dad Richard Sault told the OC Register. "Guess he's not so little." The kid was the largest delivery out of the more than 100,000 in the hospital's 21-year history, with the previous record at 12 pounds. Bigger babies to date were a 16-pounder in Russia and a 17-pounder in Brazil. Reported by Fox News.

DON'T BE A PIG

Eating a high-fat diet in pregnancy may cause changes in the fetal brain that lead to over-eating and obesity early in life, according to researchers at Rockefeller University. Tests on rats showed those born to mothers fed a high-fat diet had many more brain cells specialized to produce appetite-stimulating proteins. Previous studies revealed that when triglycerides circulate in the blood they stimulate the production of orexigenic peptides, which in turn stimulate the appetite. The latest study suggests that exposure to triglycerides from the mother's diet has the same effect on the developing fetal brain, and that the effect lasts throughout the offspring's life. The researchers found that rat pups born to high-fat diet mothers ate more, weighed more throughout life, and began puberty earlier than those born to mothers who ate a normal diet. The pups also had higher levels of triglycerides in the blood at birth, and as adults, and a greater production of orexigenic peptides in their brains. Detailed analysis showed that, even before the birth, the high-fat pups had a much larger number of brain cells that produce orexigenic peptides, and that their mom's high-fat diet stimulated production of the cells and their subsequent migration to parts of the brain linked to obesity. Researchers warned, however, against extrapolating too readily from animal studies, particularly as the rats in the study were fed a very unnatural diet. Reported by the BBC.

DANGEROUS, EH?

A survey by the Society of Obstetricians and Gynaecologists of Canada (SOGC) says there's not enough committed Canadian ob/gyns to provide adequate emergency obstetrical care. The new generation of ob/gyns don't want to put in the long hours and sacrifice their family life to the demands of obstetrical practice. SOGC found that there are currently only 1,370 obstetricians providing prenatal, antenatal and postnatal care, and that this number is expected to drop by a third over the next five years. Currently, these ob/gyns are dealing with caseloads of 300 births a year. The newer ob/gyns want to work fewer hours, limit on-call duty, share jobs with other physicians, and be able to take up to three months of maternity or paternity leave. The report also noted deficiencies in proper education and training for new ob/gyns. At the same time, moms are expecting more and better care.

FORGET IT

Women's memories of the pain of labor decline over time, according to a study of 2,428 Swedish women. But for a small number, the memory of pain is reported to increase. Researchers found that women who reported labor as a positive experience two months after birth had the lowest pain scores. When asked again after a year and then again after five years, their memory of the intensity of pain during childbirth declined. For women who said that their childbirth experience was negative or very negative, on average, their assessment of labor pain did not change after five years. Sixty percent of women reported positive experiences and less than 10% had negative experiences. Women who had epidural analgesia remembered pain as more intense than women who did not have epidurals, perhaps because extreme pain made them request epidurals in the first place. For the small group of women with a negative birth experience, long-term memory of labor pain stayed vivid even five years later.

DRIVE MY CaR

The molecule CaR (calcium receptor) is a crucial factor in the control of lung development in the womb, according to researchers at Cardiff University and Childrens Hospital Los Angeles. This information may help develop new drugs for treating preemies with immature lungs. CaR coordinates messages from the fetus that tell the lungs to develop thousands of channels and tiny air pockets. CaR works by sensing calcium and there are already drugs available that are designed to regulate how calcium is used in the body. Researchers said that the next step is to identify which drugs could modulate the action of CaR.

DRIVE MY CAR II

The New York Times reports that a company is using car parts to build incubators for use in poor countries. According to Madeline Drexler, writing in the Times, "The heat source is a pair of headlights. A car door alarm signals emergencies. An auto air filter and fan provide climate control." These incubators are cheap, too, and easily repaired, because all its working parts come from automobiles. And, you can build one for about a thousand bucks. The instigator of the car parts incubator is Cimit, a Boston nonprofit consortium. The incubator, made for babies born at 32 weeks or more, is also portable. Its inventor is Jonathan Rosen of Boston University. He noted, in discussions with doctors from impoverished countries, that "no matter how remote the locale, there always seemed to be a Toyota 4Runner in working order." He hired Design That Matters, a nonprofit firm in Cambridge, MA, to design the machine. According to Drexler, writing in the Times, "What resulted was a serious-looking gray-blue device that conjures up a cyborg baby buggy, but fits comfortably in hospitals and clinics with few resources… The supply of replacement parts is virtually limitless, because the modular prototype can be adapted to any make or model of car." Robert Malkin of the Engineering World Health program at Duke University is quoted as pointing out that the future medical technologists in the developing world are the current car mechanics, HVAC repairmen, bicycle shop repairmen, a good source of technology-savvy individuals to take up the medical device repair and maintenance. The car parts incubator has received $150,000 in initial financing from Cimit. Because it

doesn't rely on original products or processes, the incubator will most likely not be patented. A doctor at a hospital reinforced the need for this technology by recalling his trip to a hospital in Indonesia. He's quoted as saying, "'When I walked [into an] incubator room, a whole family was sobbing around a crib.'" Their 7-day-old baby boy, who was born slightly underweight and suffering from infection, had just died, after lying for hours on a cold cot. With warmth and proper care, he would have survived. Crowding the room were six donated high-tech incubators from the West. None of them worked." Reported in the New York Times by Madeline Drexler. For pictures and more, see the December 15, 2008 edition by typing "Looking Under the Hood and Seeing an Incubator" in Google Search.

GET WITH IT

Southeast Asian hospitals aren't using antenatal corticosteroid treatment enough, according to researchers at the University of Adelaide. The researchers conducted an audit of medical records of 9,550 women and their infants who were admitted to the labor wards of nine hospitals across Indonesia, Malaysia, the Philippines and Thailand, and found that the the administration of antenatal corticosteroids was the least performed beneficial intervention in the prenatal period.

GET WITH IT II

Economists are predicting a drop in the birth rate as a result of the economic crisis. The Los Angeles Times tracked fertility rates through economic periods for the last 75 years, and said obstetricians expect to see a decline in pregnancies, especially among middle-class families, any time now. However, some economists say the poor economy could lead to more births, since women who are out of work may have more time on their hands, so to speak, to make and raise children. It's predicted that we'll know what happens in about seven months. Reported by the Los Angeles Times, redacted from The Advisory Board Company, © 2008.

ETHICS TEST

The Houston Chronicle recently examined the debate surrounding a new prenatal DNA test that screens fetuses for hundreds of genetic abnormalities, including disorders undetectable with previous tests. According to the Houston Chronicle, a new genetic screening process developed at Baylor College of Medicine uses a computer chip to analyze the fetal cells for defective components. The test can detect more than 200 genetic syndromes, including conditions not detected by standard genetic analysis and conditions that do not appear until after birth. The test also is available commercially. Baylor is participating in a multi-institutional study with Emory and Columbia University that is evaluating the test in 4,000 pregnancies. Researchers said it represents a sea change in prenatal diagnosis that should replace current prenatal screening within five years, becoming the new test of choice for couples seeking the maximum information about their developing fetus. However, the availability of the test has led to an ethical debate over whether its accuracy has been sufficiently established, whether it should be regulated by FDA and whether such screening reflects a trend toward eugenics. Supporters say it can allow parents to prepare for raising a disabled child or give parents peace of mind if the results come back negative. The test also can allow couples to decide to terminate a pregnancy. Some say the genetic test has troublesome implications" because it suggests an attitude that deems the lives of people with disabilities not worth living, and add that it is likely to be used by people with money, since it costs $1,600 and isn't covered by insurance. An editorial in Nature magazine also noted that children may be born with unexpected disease or fetuses may be terminated on the basis of false information. However, researchers said the vast majority of screenings produce clear-cut diagnostic results, with ambiguous test results occurring only about 1% of the time. According to a study published in Prenatal Diagnosis, out of 300 tests, the screening found 15 cases of clear-cut abnormalities and three ambiguous results. Five of the couples who received a diagnosis of abnormalities decided to abort the fetus, but none of the couples receiving the uncertain diagnosis did so. Couples who used the screening service also were also offered genetic counseling. Information is from Medical News Today, copyright 2008 by The Advisory Board Company.

PREECLAMPSIA CLAMPDOWN

A new technology that could help physicians screen pregnant women at risk for preeclampsia has been developed at The University of Western Ontario. The technology employs a panel of biomarkers found to have changed levels in the placenta of women who develop preeclampsia. Researchers said the technology was highly relevant to early-onset severe preeclampsia that presents before 28 weeks gestation. The researchers developed an early warning system for identifying proteins and related biomarkers that, in combination, predicts the likelihood of and risk associated with the disease. The process is currently being patented by Biosite Inc, which plans to market the technology.

SMOKE GETS IN THEIR MOUTHS

Smoking during the first trimester of pregnancy has been linked with an increased risk of cleft lip in newborns, according to researchers from the Norwegian Institute of Public Health and the University of Bergen. Closure of the lip occurs about 5 weeks into pregnancy, followed by closure of the palate at week 9. The researchers wanted to see if smoking or exposure to passive smoking plays a role in these defects and whether genes influence the oral cleft risk through the way toxic chemicals in cigarette smoke are processed. Over a six-year period, 676 babies born with oral clefts were referred for cleft surgery, and of these, 573 took part in the study. Controls were 763 babies born during the same period. Blood samples and PKU test samples were taken, and moms and dads donated cheek swabs and blood samples. DNA was extracted from all the samples. Four weeks after birth, the mothers in both groups completed a questionnaire about medical conditions and environmental exposure and specifically asked about smoking habits and exposure to passive smoking before pregnancy and during the first trimester. Forty two percent of case mothers and 32% of control mothers said that they smoked in the first trimester. There was little evidence of an effect of smoking on the risk of cleft palate alone. However, for cleft lip there was an almost two-fold increased risk when the mother smoked over 10 cigarettes per day and a 1.6-fold risk from passive smoking. The researchers estimated that 19% of cases of cleft lip in Norway may be due to maternal smoking in the first trimester. Using the DNA extracted from the babies and their parents, the researchers looked at the genes related to detoxification of chemicals in cigarette smoke but found that these didn't affect the incidence of cleft lip.

MILKING IT

The NIH has awarded nearly $3 million to support a Rush University Medical Center study analyzing how human breast

milk impacts the health outcomes and healthcare cost savings for very low birth weight infants. The grant enables researchers to conduct a five-year study involving the largest prospective cohort of 600 VLBW infants born to racially and economically diverse mothers. More than 95% of VLBW infants in Rush's NICU receive their mothers' breast milk and will be enrolled into the study. The trial will examine the relationship between the amount, the duration, and the timing of human milk feedings and improved health outcomes for NICU babies. Past research indicates that human milk protects such infants from prematurity-specific complications that predispose these infants to short-and long-term health problems and increase cost of healthcare. Data on the variables of dose and exposure period of human breast milk feeding will be collected throughout the infant's entire NICU stay. Researchers also will collect data on short-term costs of providing breast milk such as breast pump rental, total number of storage containers needed and access to lactation experts.

TARGET DATES

Discovery Laboratories, Inc announced that the FDA has accepted for review its Complete Response for Surfaxin (lucinactant) for the prevention of RDS in premature infants. The FDA has designated the Complete Response as a Class 2 resubmission and has established April 17, 2009 as its target action date under the Prescription Drug User Fee Act to complete its review and potentially grant marketing approval for Surfaxin. The Complete Response addressed all of the remaining requirements contained in the May 2008 Approvable Letter that must be satisfied to gain US marketing approval for Surfaxin. Discovery Labs provided the FDA specific data, information and minor clarifying analyses and believes that its Complete Response supports the approval of Surfaxin. The May Approvable Letter did not require any additional clinical trials. Prior to receiving the Approvable Letter, Discovery Labs made notable progress towards gaining FDA approval of Surfaxin, including agreeing with the FDA on the content of the Surfaxin package insert and successfully concluding a pre-approval inspection of Discovery Labs' manufacturing operations. Surfaxin represents the first peptide-containing, synthetic surfactant potentially available for addressing RDS. Contact discoverylabs.com.

GET SMART

Mosby's Nursing Skills, the online nursing skills and procedures reference and competency management system from Elsevier, announced the launch of its Maternal-Newborn Collection for healthcare institutions seeking to improve the quality of their nurses who work with adult, pediatric, and maternal-newborn populations. The 72 web-based skills in the Collection provide coverage of antepartum, intrapartum, and postpartum care of women and newborns and present step-by-step skills and procedures for all aspects of maternal and newborn care, include patient-family teaching tips, outline important physical changes that occur during labor, and provide step-by-step guidance for assessing and caring for pregnant woman, new mothers, newborns, and families. Mosby's Nursing Skills is built using learning management system (LMS) functionality, allowing nurse managers and educators to assign, track and manage skills and test hospital staff. It also includes supplementary material such as searchable database of patient education handouts. The Nursing Skills system also enhances a healthcare institution's recruitment and retention efforts. It is endorsed by the AACN and is the only online competency development tool with testing functionality that now offers more than 530 adult skills, 321 pediatric-specific skills, and now over 70 maternal-newborn skills. For more information visit mosbynursingskills.com.

COOL!

Validating freezer temperatures for storage of essential materials with critical requirements for ultra-low temperatures can now be assured with use of the Dickson Ultra-Low Recorder. This 24/7 monitoring tool with built-in relays to integrate with alarm systems helps assure 21CFR Part 1271 and other regulatory compliance. Features include temperature recording for -100 to 0° F/C, quick reference digital display, glycol bottles available for temperature stabilization, compact and rugged enclosure suited for laboratory use, and relay contacts to integrate into facility alarm systems. Contact dicksondata.com.

FEEDING TIME

In 2007, Utah Medical Products introduced Nutri-Lok, locking enteral-only feeding extension sets and syringes that eliminate the risk of misconnections with IV lines and unwanted disconnections in use. UTMD is expanding the Nutri-Lok family to include a 500 ml Enteral Feed Bag. The bag is made for compatibility with Kendall Kangaroo Pumps. The Nutri-Lok Enteral Feed Bags have an oral dose locking connection that ensures the bag and catheter will not accidentally slip apart, thus minimizing the potential of wasting precious breast milk. In addition, the bags are DEHP-free and incorporate an anti-free flow valve. This unique safety feature prevents the free flow of formula into the patient that may result if the set is loaded improperly or becomes dislodged from the pump. The Nutri-Lok Enteral Feed Bag shares the clinical benefits that apply to all UTMD enteral-only feeding catheters, extension sets, and oral dose syringes. It will not mate with a female luer IV line connector; ensures a secure connection that will not accidentally slip apart; locks onto Utah Medical's oral dose Nutri-Cath catheters, but is compatible with other oral dose enteral feeding catheters via a slip fit connection; it's DEHP-free. The product is patent-pending. Contact utahmed.com.

LETTER TO THE EDITOR

As a Nurse Scientist well versed in the car seat challenge literature, I was pleased to see the article titled "Car Seat Safety: The Challenge" in your January-February 2009 issue. However, in reading the article I discovered inaccuracies that require clarification. First, in the introduction section, Cowan and Coughlin (2009) state that the American Academy of Pediatrics published car seat challenge guidelines in 1996. To my knowledge no such guidelines exist. The 1996 AAP statement titled Safe Transportation of Premature and Low Birth Weight Infants suggests that preterm infants born at less than 37 weeks gestation have a period of observation in their car safety seat prior to hospital discharge and provides additional recommendations for safe transportation of this high risk population, but does not provide guidelines for performing the car seat challenge. From a recent conversation with an AAP representative, it is my understanding that an updated statement regarding safe transportation of premature infants will be made available this spring. Although I have also been informed that even this updated statement will not provide specific guidance for performing the car seat challenge.

Second, the authors indicate that blankets or rolls may provide sufficient postural support to infants who fail the car seat challenge. However it is my experience that many infants fail the car seat challenge despite the use of blankets and small rolls. Experts in this field emphasize that the car seat should be appropriate in size (meeting weight and height limits), and proper positioning using blankets and small rolls should be in place before the car seat challenge is performed. Blankets and small rolls provide only limited support and do not address airway narrowing that can occur with flexion of the head on the body (S. L. Tonkin, 1998; S. L. Tonkin, et al, 2003). Moreover, blankets and small rolls have no impact on periodic breathing or apnea. During sleep, premature infants are more prone to periodic breathing and apnea and are less likely to respond to their body's biofeedback mechanism that would normally signal infants to readjust their body position (DeGrazia, 2007).

Third, the authors recommend reclining the car seat to 30 degrees to alleviate breathing problems. Car seats undergo significant testing for safety by the government and must meet Federal Motor Vehicle Safety Standard (FMVSS) 213 (American Academy of Pediatrics, 1999). Car seat manufacturers warn that the safety mechanism of the car seat may be adversely affected if not used according to the manufacturer's instructions. Clinicians who recommend increasing the angle of recline may place an infant at increased risk for injury in the event of a crash and the clinician may also place themselves at risk for legal action should injury occur.

Fourth, prescribing a respiratory stimulant has been recommended as a suitable solution for the care of infants who fail the car seat challenge. However, the exact etiology for failing a car seat challenge is not clear and is likely multifactorial (Willett, Leuschen, Nelson, & Nelson, 1989). Prescribing a respiratory stimulant may not solve the problem and may subject the infant to untoward side effects such as tachycardia and GI upset. Infants with breathing problems when positioned in their car seats are recommended for travel in a car bed by the American Academy of Pediatrics (1996, 1999). Infants who demonstrate respiratory stability in a crash-tested car bed that meets FMVSS 213 should use this type of restraint. Best practice is to ensure safe transition from a car bed to a car seat through repeat screening when the infant demonstrates increased maturity. Infants who desaturate in a car bed are recommended to undergo additional diagnostic evaluation for cardiorespiratory issues.

Despite these inaccuracies, authors Cowan and Coughlin note significant voids in the literature pertaining to car seat safety for premature infants. The authors highlight the important role of sleep on respiratory instability/stability. This author agrees that sleep state may play a large role car seat related breathing difficulties and that this phenomenon requires further study. Lastly this author agrees with Cowan and Coughlin that minimizing travel time and never leaving an infant unattended in a car seat are two important messages that should be communicated to parents at the time of hospital discharge.

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NURSES FOR NEONATES

NICU nurses and doctors are often approached by anxious parents wanting to know what to do when they get their preemies home. Helen Vitaris is a postpartum doula with eight years of experience providing specialized cares for twins, triples, preemies, and micro-preemies. She's the consultant for the mom we profiled on page 12 of our September issue, who had her preemies at St Johns Hospital in Santa Monica, CA. Ms Vitaris is certified as a newborn care specialist, lactation educator, infant sign language specialist, infant massage instructor, SIDS educator, and postpartum doula. In addition to the above, she can offer assistant with education about homecare equipment like monitors, and other aspects of homecare such as tube feeding, nutrition monitoring, umbilical care, circumcision care, kangaroo care, care for babies with slow weight gain, and sibling interaction. What's the difference between a postpartum doula and baby nurse/newborn care specialist? Ms Vitaris explains that their duties overlap. While a newborn care specialist focuses solely on the newborn, and concentrates on premature or sick babies, and multiple babies, the postpartum doula also works with the entire family. The length of such services is typically for four months after the baby or babies go home, and sometimes longer for preemies and special needs babies. "It used to be that families got a lot of help when they came home with a new baby," Vitaris explains, "but that has changed for many people and new parents, especially parents of preemies or special-needs babies, who quickly realize how overwhelming it is to care for their newborn. Even if the family has outside help, a postpartum doula is a non-judgmental presence in the home whose impartiality can be a lifesaver." Vitaris recommends that parents register for a doula a couple of months before the due date. (A birth doula should be registered by the fifth month of pregnancy, and a newborn care specialist/baby nurse should be sought out six months before the baby is due.) Insurance may cover some postpartum care costs (V24.2 Postpartum Follow Up and CPT code 59425.) Contact hvitaris@yahoo.com or (818) 808-6868.

TOO DEEP HEATING

Vicks VapoRub may cause airway inflammation that can restrict breathing in infants and toddlers, according to researchers at Wake Forest University. They report that they started their study after treating an 18-month-old girl who had developed severe respiratory distress after the salve had been put directly under her nose to relieve cold symptoms. Vicks says youíre

not supposed to use it like that, ie, under the nose, nor are you supposed to give it to kids under two. Still, the intrigued researchers wanted to find out if there had been other instances of problems with VapoRub. According to the lead researcher, there wasnít much information, because parents donít consider VapoRub to be a ìrealî medicine. He said the product ìcan make some adults feel better without really making them better,î but that in kids it can induce inflammation that could ìtip the child over into having [respiratory] problems.î To test whether VapoRub could cause respiratory distress, the researchers conducted experiments with ferrets, because they have airways similar to human airways. The researchers found that Vicks VapoRub increased mucus production by up to 59%; the ability to clear mucus was reduced by 36%. Vicks said one incidence does not a problem make. A researcher at Rainbow Babies Hospital in Cleveland said VapoRub shouldnít be used because it has no medicinal value anyway.

HAPPY ANNIVERSARY

Instrumentation Laboratory (IL), the worldwide developer, manufacturer and distributor of in vitro diagnostic instruments, related reagents and services, recently celebrated the anniversary date of its founding, fifty years ago. The company launched its "50 and Forward" celebration in 2008 and will continue the program through its anniversary year with events that reflect on IL's 50 years of historic achievements, as well as its plans for continued innovation in the future. The company's first instrument, the IL 113, launched a new era of automation in the industry, and set the stage for IL's constant innovation for half a century. From the IL 113 blood gas analyzer, to the IL 143 flame photometer, to the invention of CO-Oximetry, IL launched products that replaced time-consuming manual techniques, setting new standards in hospitals worldwide. The cornerstone of IL's 50th anniversary celebration is the "Passion and Results" Award for customers. Three laboratorians, respiratory therapists, physicians or nurses who have demonstrated passion and dedication resulting in enhanced patient care will receive an award and an educational grant to their institution. Industry professionals are invited to submit an inspiring story of patient care – about themselves or another person – by completing IL's Passion and Results nomination form available through an IL sales representative or online at ilus.com/50forward. Submissions are being accepted through June 1, and are open to all worldwide customers. Winners will be honored in July, 2009. IL's leadership in the development of diagnostic instruments is largely due to its many renowned thought leaders. Members of the 50 and Forward ILeader Panel of esteemed experts in a variety of diagnostics-related areas are available to contribute to the betterment of diagnostics through forums, webcasts, roundtables, seminars and press comments throughout IL's 50th anniversary celebration year. Persons and publications interested in securing the ILeader Panel's services should contact IL's Sally McCraven at 781-861-4577, smccraven@ilww.com. Instrumentation Laboratory, founded in 1959, is a worldwide developer, manufacturer and distributor of in vitro diagnostic instruments, related reagents and controls for use primarily in hospitals and independent clinical laboratories. The company's product lines include critical care systems, hemostasis systems and information management systems. IL's GEM product offerings, part of the critical care line, include the new GEM Premier 4000 analyzer with Intelligent Quality Management (iQM), GEM Premier 3000 analyzer, GEM OPL, a portable whole blood CO-Oximeter and the GEM PCL Plus, a portable coagulation analyzer. IL's hemostasis portfolio includes the ACL TOP Family of Hemostasis Testing Systems, fully automated, high-productivity analyzers, including the ACL TOP and the new ACL TOP 500 CTS. IL also offers the ACL ELITE and ELITE PRO, other hemostasis analyzers and the HemosIL line of reagents. As the world's leading developer of hemostasis testing systems, IL began 2009 with the launch of another innovative addition to its ACL family of hemostasis testing instruments, that use chemiluminescence technology to automate specialty assays. The AcuStar is the first fully automated random-access chemiluminescence analyzer dedicated to specialty assays in hemostasis.

FDA CLEARANCE

Draeger Medical, Inc announced that it has received 510(k) clearance from the FDA to market Proportional Pressure Support, Draeger's latest feature for the Evita XL ventilator. Proportional Pressure Support generates pressure supported breaths which are directly proportional to patient effort. This technology may minimize the risk of asynchrony between ventilator pressures and the patient's efforts to breathe. By constantly measuring the compliance and resistance of the patient, the support provided remains dynamic and constantly changes to meet patient demand. Proportional Pressure Support for the Evita XL is expected to be commercially available this month [March] in the US. For more information, please visit the website draeger.com or contact your local Draeger sales representative at 1-800-4DRAGER.

DIDN'T WORK

A treatment thought to improve a preemie's chance of fighting infection due to neutropenia doesn't really do any good, according to a study at Guy's and St Thomas' Hospital. Neonatal specialists have been using the GM-CSF protein for increasing white blood cells and preventing infection, a procedure that has worked in cancer patients and those receiving chemotherapy. But research in 280 babies born at 31 weeks or less found it didn't prevent sepsis. Researchers found no significant difference in deaths from blood sepsis - due to infection in those who had GM-CSF or those who had standard management. White blood cell counts went up, yet this didn't affect survival. Reported by the BBC.

SCREEN TEST

Checking blood oxygen levels increased detection of ductus arteriosus. According to a study at Gothenburg University. Researchers screened all 39,800 babies born in the West Gotaland region of Sweden between July 2004 and March 2007 using pulse oximetry before a physical examination was carried out. Sixty babies were found to have the disorder. A combination of pulse oximetry and physical checks detected 92% of duct-dependent heart disease cases, compared with 72% picked up through physical checks alone. No babies died in West Gotaland from undiagnosed heart disease, while there were five deaths in Swedish regions. The researchers concluded that pulse oximetry was a low risk and low cost strategy.

LIKELY TO DIE

The BBC reported that women in poor nations are 300 times more likely to die in childbirth or from pregnancy complications than those in the developed world, according to a report by Unicef. The lifetime risk in the poorest countries was one in 24, compared with one in 8,000 in richer countries. About 99% of the 500,000 maternal deaths in 2005 occurred outside industrialized

Continued on page 35…

Aspiration of Parenteral Nutrition—A Previously Unreported Complication of Central Venous Access in an Infant: A Case Report

Luke A. Jardine, Garry D.T. Inglis,Mark W. Davies

Abstract

Introduction: The insertion of percutaneous central venous catheters is a common procedure in neonatal intensive care nurseries. Placement of the catheter tip in a large central vein is most desirable. Occasionally, due to difficult venous access, catheter tips are left in places that are less than ideal.

Case presentation: A female infant with a complicated gastroschisis developed signs of short bowel syndrome post surgery. She was treated with a combination of parenteral nutrition and enteral feeds. A central venous line was inserted through a scalp vein. The tip was noted to be in a vessel at the level of the mandible. She subsequently became unwell with large milky pharyngeal aspirates and episodes of bradycardia. Chest radiography revealed aspiration. The central venous line was removed because of presumed extravasation. This is the first reported case of parenteral nutrition extravasation into the pharynx causing aspiration in an infant.

Conclusion: This complication may have been prevented by recognizing that the tip of the catheter was not correctly placed. When catheters are in unusual positions it may be useful to obtain a second radiograph from a different angle or an ultrasound scan to confirm the positioning of the catheter tip.

Introduction

The insertion of percutaneous central venous catheters is a common procedure in neonatal intensive care nurseries. Placement of the catheter tip in a large central vein is most desirable. Occasionally, due to difficult venous access, catheter tips are left in places that are less than ideal. Here we present an unusual complication in an infant with a central venous catheter located in a vein of the upper neck.

The authors are with the Grantley Stable Neonatal Unit, Royal Brisbane and Women's Hospital; Davies is also with the Department of Paediatrics & Child Health, The University of Queensland, and is a Visiting Fellow, Medical Engineering, Faculty of Built Environment and Engineering, Queensland, Brisbane, Australia.

A female infant with an antenatal diagnosis of gastroschisis was born by emergency caesarean section for fetal bradycardia at 33+3 weeks post menstrual age. Her 23 year old mother was G2P1, Hepatitis C positive and on Methadone (90 mg daily). Birth weight was 1450 grams.

Initial examination revealed a complicated gastroschisis with a segment of small bowel atresia. The remainder of her clinical examination was otherwise normal. During the first six weeks of life she had three laparotomies with reduction of her abdominal contents, resection of two atretic segments, end to end anastomoses, iatrogenic small bowel perforation, adhesionolysis and the eventual formation of a divided colostomy. Other complications included two episodes of infection in the laparotomy wound requiring intravenous antibiotics. During this period she had two peripherally inserted central venous lines and multiple peripheral intravenous cannulae.

On day 67 of life, because of short bowel syndrome and intolerance of full enteral feeds of a semi-elemental formula, she was recommenced on parenteral nutrition (120 mL/kg/day) with some nasogastric feeds (60 mL/kg/day). Venous access was extremely difficult to obtain and after two different attempts a 24 French peripherally inserted central venous line (Neocath, Vygon, Ecouen) was inserted through a right sided scalp vein. Blood was easily aspirated from the line at the time of insertion. As per our usual practice, the central venous catheter was slowly injected with 0.5 mL of Isovue 300 (Isovue® 300, Regional Health Care Products Group Medi-Consumabales Pty Ltd, Rosebery) and a radiograph was taken while injecting the dye.[1] The tip was noted to be in a vessel at the level of the mandible and was deemed to be satisfactory for the infusion of parenteral nutrition. The Radiologists report stated the catheter tip location as the "internal jugular vein."

On day 80 she became unwell with vomiting and fever. She underwent septic evaluation and was commenced on antibiotics. Enteral feeds were stopped and parenteral nutrition was continued via the central venous line. Over the next 20 hours she became increasingly unwell with worsening vomiting, large milky pharyngeal aspirates and episodes of bradycardia. She required frequent oral suctioning and developed an oxygen requirement. She was intubated and ventilated on day 81.

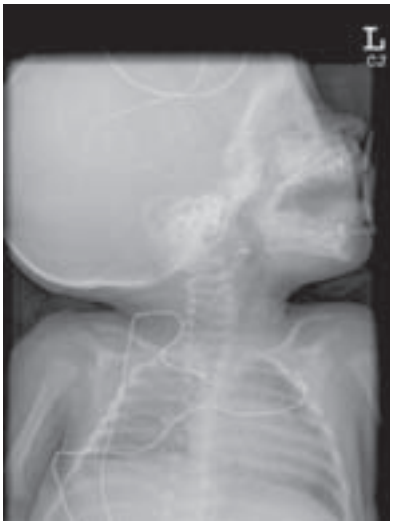

Figure 1. Radiograph post peripherally inserted central venous line insertion.

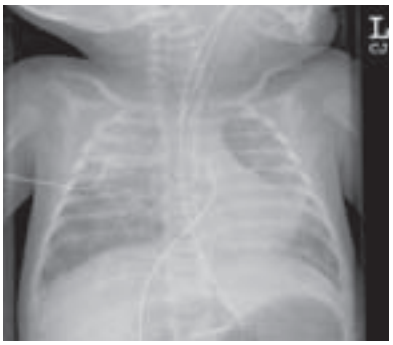

Figure 2. Radiograph taken following episode of aspiration requiring intubation.

Intubation was difficult with copious milky secretions noted. Chest radiograph showed patchy opacification. Secretions from the oropharynx and nares were so copious that her bedding was wet.

It was suspected that the aspirates contained parenteral nutrition and a sample was sent for microscopy and chemistry. The results were consistent with parenteral nutrition.

On stopping the lipids and parenteral nutrition, a dramatic decrease in the oral secretions was noted and they changed from a milky to clear. The central venous line was then removed because of presumed extravasation. Her condition continued to improve and she was extubated on day 84. She has remained well since extubation apart from ongoing problems with short bowel syndrome.

Discussion and Conclusion

While extravasation is a recognized complication of central venous catheters, to our knowledge this is the first reported case of parenteral nutrition extravasation into the pharynx causing aspiration in an infant. Frequently reported sites of extravasation include the pleural and pericardial cavities,[2,3] Rarely reported sites of extravasation include the pulmonary parenchyma,[4,5] renal pelvis,[6] scrotum,[7] retroperitoneal space,[8] spinal epidural space[9] and subdural space.[10]

This complication might have been prevented by recognizing that the tip of the catheter was not in the internal jugular vein. It is difficult to accurately locate the catheter tip with a single view.

When catheters are in unusual positions it may be useful to obtain a second radiograph from a different angle or an ultrasound scan to confirm the positioning of the catheter tip.

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Cerebral Oxygenation Responses During Kangaroo Care in Low Birth Weight Infants

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Abstract

Background: Kangaroo care (KC) has been widely using to improve the care of low birth weight infants. However, very little is known about cerebral hemodynamics responses in low birth weight infants during KC intervention. The objective of this study was to elucidate the response of cerebral hemodynamics during KC in low birth weight infants.

Methods: Near infrared spectroscopy measured regional cerebral oxygenation (rSO_2), heart rate (HR), respiration rate (RR) measured by electrocardiogram, and percentages of oxygen saturation (SpO_2) measured by pulse oxymetry was monitored in 16 preterm infants (< 1600 g) in three sessions: before, during, and after KC. Using power spectral analysis, total power (TP), low-frequency (LF, 0.02–0.20 Hz) and high-frequency (HF, 0.20–0.50 Hz) bands, the ratio of LF/HF were calculated and normalized as %LF or %HF = LF or HF/TP × 100 (%).

Results: Significant differences were not observed in the mean rSO_2, HR, and SpO_2 throughout sessions; however, the TP of these parameters was significantly decreased during KC and increased after KC ($p < 0.001$). The %LF of $LrSO_2$ and $RrSO_2$ was decreased during KC ($p < 0.05$) with decreased %HF in $RrSO_2$ ($p < 0.05$). The %LF of HR was significantly increased during KC while %HF was decreased ($p < 0.05$). Mean and TP of RR was increased during KC ($p < 0.01$ respectively) with the increase of quiet sleep state ($p < 0.05$) and decreased after KC ($p < 0.01$). The %LF of RR was increased after KC ($p < 0.05$) with decreased %HF ($p < 0.05$); however, significant changes were not observed during KC.

Conclusion: KC intervention appears to have influence on cerebral hemodynamics as well as cardiorespiratory parameters. The results of rSO_2 and HR might be associated with quiet sleep states. The results of this study may indicate the contribution of KC intervention to the activation of central nervous system and brain function. Further study is needed to determine the underlying physiology responsible for these differences.

Introduction

Recently, skin-to-skin care, called kangaroo care (KC), has been widely practiced for preterm and low birth weight (LBW) infants in the neonatal intensive care unit (NICU). During kangaroo care, the mother holds a naked infant in a vertical position against the breasts so that the infant can achieve skin-to-skin contact. KC was first introduced in Bogotá, Columbia by Dr. Edgar Rey and Hector Martinez in 1978 as a way of compensation for the overcrowding of incubators in hospitals caring for preterm infants.[1] According to their report on KC, they have found improved outcomes in survival rates and health status. Now, KC is practiced not only in developing countries, but also in developed countries.

Many studies have been performed to evaluate the psychological and physiological responses during KC in preterm infants.[2-4] Positive psychological effects on mothers and mother – infant bonding are well recognized;[5] however, the physiological effects of KC are still inconclusive. Previously, it has been reported that KC improves thermal regulation,[6-8] respiratory pattern and oxygen saturation,[9-10] reduces apnea and bradycardia,[9,11] accelerates weight gain,[12] increases vagal tone responses,[13] reduces activity level, and enhances the duration of quiet sleep[14,15] in preterm infants. On the other hand, increases in body temperature have been found to be associated with an increased frequency of apnea and bradycardia[16] and an increased oxygen requirement during KC was found in intubated infants.[17] Most of these studies were performed on cardiorespiratory parameters rather than cerebral hemodynamics. Preterm infants are highly susceptible to develop various cerebral lesions like intraventricular hemorrhage or periventricular leucomalacia

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Table 1: Characteristics of 16 low birth weight infants participating in Kangaroo care

Subject number	Sex	GA (wks)	BBW (g)	Apgar score 1 min/5 min	Acute phase illness	At the day of Kangaroo care		
						PCA (wks)	BW (g)	Theophylline
1	M	28	1228	8/8	PPHN	34	1531	Yes
2	M	28	1258	8/9	TTN	33	1458	Yes
3	F	31	1282	7/9	RDS	34	1222	No
4	F	30	1538	7/8	RDS	34	1482	No
5	F	30	1228	7/8	RDS	36	1298	No
6	F	28	1140	6/8	TTN	40	1638	No
7	F	27	1152	1/6	RDS	36	1298	No
8	M	33	1586	7/9	TTN	36	1752	No
9	M	24	692	8/8	RDS	40	1064	Yes
10	M	25	756	5/7	RDS	35	1043	Yes
11	M	27	1272	2/3	RDS	37	1581	No
12	M	25	866	5/8	RDS	41	1858	No
13	F	29	1106	9/9	RDS	36	1359	No
14	M	26	982	9/10	RDS	36	946	No
15	M	25	772	6/6	RDS	42	1334	No
16	M	27	1130	7/9	CLD	36	1540	No

GA: gestational age, BBW: birth body weight, PCA: postconceptional age, BW: body weight, PPHN: persistent pulmonary hypertension of the newborn, RDS: respiratory distress syndrome, TTN: transient tachypnea of the newborn

following cerebral hypoperfusion because of their immature brain.[18] Cerebral oxygenation is one of the important parameters in cerebral hemodynamics, has been widely used to monitor cerebral perfusion in infants with birth asphyxia or brain lesions like hypoxic-ischemic encephalopathy.[19-21] The response of cerebral hemodynamics in accordance with sleep states was reported previously;[22] however, no study has yet been performed on the response of cerebral hemodynamics in preterm infants during KC intervention.

Spectral analysis of time series data using Fast Fourier transformation (FFT) has been widely utilized to study the autonomic nervous system.[23-26] In power spectral analysis, low-frequency region from 0.02-0.20 Hz is reflected sympathetic activities and high-frequency region from 0.2-2.0 Hz is reflected parasympathetic activities and total power, a index of total variance (the total area under the curve of power spectral density) and the ratio of LF/HF power reflects the balance between sympathetic and parasympathetic activities. Two studies have been reported on the heart rate variability (HRV) during KC using power spectral analysis;[27,28] however, their results were not conclusive. Further, previous studies on cerebral hemodynamics using power spectral analysis have reported the position dependent responses in adult,[29] however, no study have been performed on the spectral characteristics of cerebral hemodynamics during KC position in preterm infants.

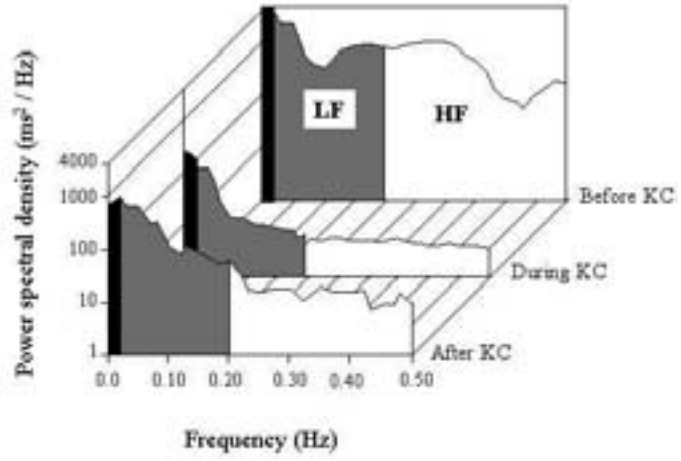

Figure 1. A typical graph of power spectral density (ms^2/Hz) of right rSO_2 displaying the power of the low frequency (LF: 0.02 – 0.2 Hz) and high frequency (HF: 0.2 – 0.5 Hz) bands before, during, and after the KC session.

In this study, we investigated cerebral hemodynamics in addition to cardiorespiratory parameters in preterm infants during KC intervention using power spectral analysis. Therefore, we investigated regional cerebral oxygenation (rSO_2) as a parameter of cerebral hemodynamics, heart rate (HR), respiratory rate (RR), and SpO_2 in stable low birth weight infants during KC using power spectral analysis.

Materials and methods

Subjects: Nineteen preterm infants with birth body weight < 1,600 g and gestational age < 33 weeks (wks) were enrolled in this study. All of the infants were stable and breathed spontaneously without supplemental oxygenation with postconceptional age ≥ 32 wks. Infants who had severe congenital malformations, severe asphyxia, and a potential cause of apnea other than immaturity, such as sepsis or intracranial hemorrhage, were excluded from the study. Three infants were excluded because of interrupted observation. Finally, 16 infants were selected for further analysis (Table 1). The median gestational age was 28 wks (range, 24 - 33 wks) and median birth body weight was 1,228 g (range, 692 - 1,586 g). Postconceptional age on the day of the study was 36 wks (range, 33 - 42 wks) and body weight was 1,458 g (range, 946 - 1,858 g). Eight infants were born via caesarean section. Seven infants had received mechanical ventilation after birth for a median duration of 6 days. Four infants had received theophylline for apnea on the day of KC intervention.

KC and data collection: KC intervention was performed for one hour. The temperature of the room ranged from 27 to 28°C and the humidity ranged from 60 to 70% during KC. Infants were observed carefully and monitored in three conditions: 30 minutes in the incubators (before KC), 1 hour of KC intervention (during KC), and 30 minutes in the incubator again after KC intervention. Mothers were seated on a reclining chair at a 60° angle, wearing a front opening blouse. The infants were placed naked except

Table 2: Central tendencies and coefficient of variances of physiological variables before, during and after KC intervention

Variables	Measures	Before KC	During KC	After KC
Heart rate (bpm)	Mean	149.4 ± 6.3	150.0 ± 10.0	150.4 ± 8.7
	CV	6.8 ± 3.2	4.6 ± 1.3*	7.5 ± 4.7 †
Respiratory rate (bpm)	Mean	39.4 ± 8.9	44.0 ± 5.1**	39.7 ± 7.9 † †
	CV	24.1 ± 5.4	22 ± 6.7	19.7 ± 7.6
SpO_2(%)	Mean	98.0 ± 1.3	97.6 ± 2.5	97.5 ± 1.7
	CV	2.3 ± 1.4	1.5 ± 0.9	2.9 ± 2.4
Left-rSO_2(%)	Mean	46.8 ± 5.6	47.3 ± 6.1	47.5 ± 7.3
	CV	6.6 ± 4.1	5.8 ± 3.3	4.1 ± 1.6
Right-rSO_2(%)	Mean	48.6 ± 6.9	49.1 ± 9.4	47.8 ± 6.9
	CV	7.2 ± 4.6	7.2 ± 5.5	5.6 ± 2.3
Body temperature, (°C)	Mean	37.0 ± 0.2***	37.3 ± 0.3	
	Median (range)	37.1 (36.6 – 37.4)	37.3 (36.8 – 37.4)	

Data were expressed as mean ± SD or median (range). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, before versus during KC and † $p < 0.05$, † † $p < 0.01$, during versus after KC. CV: coefficient of variance, rSO_2: regional cerebral oxygenation.

for a diaper directly onto the skin between the breasts and covered with a light blanket. Infants were fed 1 hour before KC. All infants were continuously monitored with electrocardiogram to determine HR, RR and with pulse oxymetry for percentages of oxygen saturation (SpO_2). Regional cerebral oxygenation was measured with a near infrared spectroscopy, NIRS (INVOS 4100, Somanetics, Troy, MI), with the two probes positioned on the bilateral frontoparietal areas. Physiological data were recorded at 10 second intervals (averaged over 10 second period) through a Wave Archiving System (WAS-J: Agilent Technologies, Inc.) and further analyzed. Data from the first 30 minutes during KC were excluded from the analysis to minimize the effects of changes due to the adaptation process. The data for rSO_2 were recorded from both the left and right hemispheres independently ($LrSO_2$ and $RrSO_2$, respectively).

Behavioral states of infants were recorded throughout the observation period using the Brazelton Neonatal Behavior Assessment Scale.[30] Behavioral states of infant were observed by nurses trained on the observational scale. Five different behavioral states were observed: 1) Quiet sleep; 2) Active sleep; 3) Drowsiness; 4) Alert inactivity; and 5) Active awake. Behavioral states were judged before KC, during KC, at the end of KC, and 30 minutes after KC. Body temperature was measured at the beginning of data recording before the KC session and after the end of KC. Informed consents were obtained from the parents and the study was approved by the ethical committee of the institute.

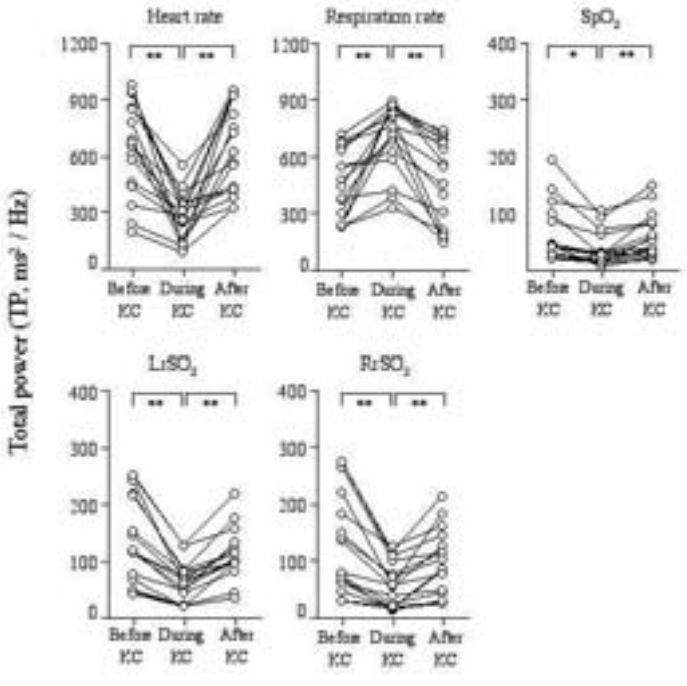

Figure 2. Individual values of total power (TP) of power spectral density before, during, and after KC, displaying visually qualitative changes during KC. A repeated measures ANOVA was performed to determine the statistical differences among the three sessions: before, during, and after KC. * $p < 0.01$, ** $p < 0.001$, before vs during KC or during vs after KC.

Power spetral analysis: Power spectral analysis was performed on rSO_2, HR, RR, and SpO_2 in three sessions as previously reported.[28] The power spectral density was calculated and divided into two frequency bands in each session as shown in Figure 1. The regional power of low – frequency (LF, 0.02 – 0.2 Hz) and high – frequency (HF, 0.20 – 0.5 Hz) bands, and the ratio of LF/HF were calculated. The powers of LF and HF were normalized using the formulas % LF = LF/TP × 100 (%) and % HF = HF/TP × 100 (%).[31] Total power (TP) was obtained by integrating the power spectrum from frequency 0.02 to 0.50 Hz.

Statistical analysis: Data were analyzed with SPSS 13.0 for Windows (SPSS Inc., Chicago, IL). A repeated measures ANOVA was performed to analyze the differences of parameters among three sessions. Conventional statistics: mean, standard deviation, coefficient of variance (CV), range, normal distribution, and median were performed for all parameters. Data are expressed as median (range) or mean ± SD.

Results

Descriptive statistics of HR, RR, SpO_2, $LrSO_2$ and $RrSO_2$ are shown in Table 2. In mean HR, SpO_2, $LrSO_2$, and $RrSO_2$, there were no significant differences among the three sessions; however, RR was significantly increased during KC and decreased after KC ($p < 0.05$, respectively). Body temperature was increased by 0.3°C during KC ($p < 0.01$). The CV of HR was decreased by 2.2% during KC ($p < 0.05$), while it was increased again after KC by 2.9% ($p < 0.05$). There were no significant differences in the CVs of RR, SpO_2, $LrSO_2$, and $RrSO_2$.

Changes in TP during the sessions were shown in Figure 2. The TP of HR was significantly decreased during KC and increased after KC (before: 635 ± 280, during: 268 ± 134, after: 618 ± 240 ms^2/Hz; before vs during and during vs after, $p < 0.01$). The TP of SpO_2 had a similar tendency to that of HR. On the other hand, the TP of RR was significantly increased during KC and decreased after KC (before: 458 ± 186, during: 713 ± 175, after:

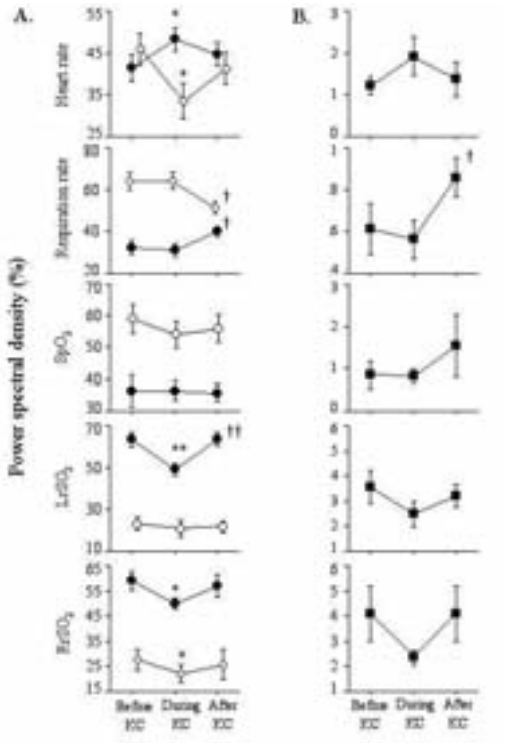

Figure 3. A: Power spectral density in low – frequency (LF: close circle) and high – frequency (HF: open circle) bands before, during, and after KC. LF and HF are expressed as normalized values (%LF = LF/total power × 100 and %HF = HF/total power × 100). B. The ratio of LF/HF before, during, and after KC. Data is presented as means ± SEM. A repeated measures ANOVA was performed to determine the statistical differences among the three sessions: before, during, and after KC. * $p < 0.05$, ** $p < 0.01$, before vs during KC. † $p < 0.05$, † † $p < 0.01$, during vs after KC.

461 ± 231 ms^2/Hz; before vs during and during vs after, $p < 0.01$). In regional cerebral oxygenation, the TP of either $LrSO_2$ or $RrSO_2$ was significantly decreased during KC and increased again after KC ($LrSO_2$: before: 121 ± 91, during: 54 ± 41, after: 90 ± 56 ms^2/Hz; $RrSO_2$: before: 123 ± 69, during: 55 ± 30, after: 98 ± 46 ms^2/Hz; before vs during and during vs after, $p < 0.001$, respectively in each parameter).

The percentages of LF, HF, and the ratio of LF/HF are shown in Figure 3A and 3B. For HR, the %LF was significantly increased during KC (before: 41.4 ± 11.5, during: 48.3 ± 9.8%, $p < 0.05$), while %HF was decreased (before: 45.9 ± 13.9, during: 33.5 ± 15.3%). In contrast, the %LF of rSO_2 was significantly decreased during KC for both $LrSO_2$ (before: 63.5 ± 11.2, during: 49.2 ± 9.2, after: 63.8 ± 10.2%; before vs during and during vs after, $p < 0.01$) and $RrSO_2$ (before: 59.1 ± 11.5 during: 49.9 ± 6.9, after: 57.0 ± 13.6%; before vs during, $p < 0.05$). The %HF was decreased during KC for $RrSO_2$ (before: 28.1 ± 13.8, during: 22.6 ± 10.9, after: 26.2 ± 19.2%; before vs during, $p < 0.01$), although there was no significant change in this parameter for $LrSO_2$ during the sessions. For RR and SpO_2, significant changes were not observed in %LF or HF during KC, although the %LF of RR after KC was significantly increased while the %HF was decreased ($p < 0.05$, respectively) with an increased LF/HF ratio ($p < 0.01$). There were no significant differences in the ratio of HR, SpO_2, $LrSO_2$, and $RrSO_2$ during the sessions (Figure 3B).

At the day of KC, four infants had received theophylline. Infants who received theophylline showed the similar tendency to those without theophylline during KC and after KC.

Behavioral analysis: The behavioral states during the observation period are shown in Figure 4. The percentage of infants with quiet sleep states remarkably increased during KC (61.5%) compared to those before KC (15.4%). This percentage increased further to 76.9% at the end of KC and decreased to 38.5% at 30 minutes after KC. In contrast, the percentage of infants in active sleep was 53.8% before KC, decreased to 23.1% in the middle of KC, and increased to 54.0% at 30 minutes after KC.

Discussion

In this study, regional cerebral oxygenation using NIRS was measured during KC in addition to cardiorespiratory parameters in stable low birth weight infants and analyzed by using power spectral analysis. By conventional analysis, the CV of HR was decreased, and mean RR and body temperature were increased during KC as previously reported;[7,9,14] however, significant changes were not found in mean rSO_2. By power spectral analysis, TP was decreased in rSO_2; HR, and SpO_2 during KC, whereas the TP of RR was increased. Further, the LF of rSO_2 was found to be decreased during KC while the LF of HR was increased with decreased HF. This study has shown that the spectral characteristics of cerebral oxygenation are significantly different between during KC and before KC or after KC as well as HR, RR and SpO_2; however, there were no significance differences in their mean values. The power spectral analysis was found as a more effective analytic approach for revealing the physiological responses compared to the conventional analysis.

In spectral analysis of heart rate variability (HRV), low-frequencies (0.02 - 0.20 Hz) reflect sympathetic activities such as the baroreceptor reflex, high-frequencies (0.2 - 2.0 Hz) reflect parasympathetic activities such as vagal activity, and the ratio of LF/HF power reflects the balance between sympathetic and parasympathetic activities.[23-26,32] Several studies have been published on autonomic function of HRV in preterm infants and only two studies had been previously reported on HRV during KC intervention using power spectral analysis up to now. One of them showed a decrease of LF and HF during KC,[27] while the other showed an increase of LF during KC.[28] In our study, the LF of HR was increased during KC and the LF of rSO_2 was decreased. In general, the increase in sympathetic activities and decrease in cerebral oxygen delivery with the head in an up-tilting position are assumed to be due to gravity causing pooling of blood and thereby activating baroreceptors as previously reported,[29,33] and the decrease of LF of rSO_2 during KC with increased LF of HR described in this study might be supported previous studies. These results could be understood as activation of the central nervous system and brain function during KC position. Besides these, the increase in body temperature and respiration observed in our study may have an effect on the LF of HR as previously reported on HRV.[28,34] Further, TP is the index of total variance in power spectral analysis and changes in TP during KC indicate the changes in total variance. In our study, TP of rSO_2, HR, or SpO_2 have been shown to decrease during KC. A possible explanation for these decreases during KC might be associated with reduced activity and increased quiet sleep state during KC as previously reported.[35,36] These results could be interpreted as physiological stability elicited by KC intervention. Although the dominance of HF has been reported in HR during the quiet sleep state,[37,38] this was not observed during KC in a previous study[28] or in the current study. The position of the head

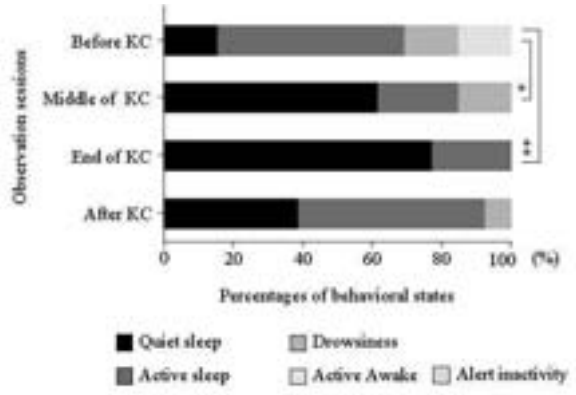

Figure 4. Behavioral states of infants observed before KC, in the middle of KC, at the end of KC, and 30 minutes after KC. The quiet sleep state was remarkably increased in the middle of KC and at the end of KC. A chi square test was performed to determine the significant differences in the four behavioral states.* $p < 0.05$, ** $p < 0.01$, before versus middle of KC or before versus end of KC.

of infants during KC might be responsible for the discrepancy between the left and right rSO_2.

To our knowledge, the present study was the first study to analyze the response of rSO_2 due to KC in LBW preterm infants through spectral characteristics. Therefore, it was difficult to compare the results of this study with other similar studies and apply to the clinical settings. Despite the sampling limitation, this reference data provide new understanding into the response of cerebral hemodynamics in preterm infants and should have significant implications to generalize the rSO_2 responses with different modalities in LBW infants. Further studies are necessary to determine the clinical relevance of the present findings.

Conclusion

The results of this study revealed that changes of cerebral hemodynamics associated with KC position in preterm infants as well as cardiorespiratory parameters. These changes were especially apparent by power spectral analysis. Furthermore, the results of this study indicate that KC may contribute to the activation of central nervous system and brain function. Further study is needed to determine the underlying physiology responsible for these differences.

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is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal of Medicine.

"Physicians, medical schools, and professional organizations have no excuse, since their only fiduciary responsibility is to patients. The mission of medical schools and teaching hospitals—and what justifies their tax-exempt status—is to educate the next generation of physicians, carry out scientifically important research, and care for the sickest members of society. It is not to enter into lucrative commercial alliances with the pharmaceutical industry. As reprehensible as many industry practices are, I believe the behavior of much of the medical profession is even more culpable. Drug companies are not charities; they expect something in return for the money they spend, and they evidently get it or they wouldn't keep paying.

"So many reforms would be necessary to restore integrity to clinical research and medical practice that they cannot be summarized briefly. Many would involve congressional legislation and changes in the FDA, including its drug approval process. But there is clearly also a need for the medical profession to wean itself from industry money almost entirely… There is seldom a legitimate reason for physicians to accept gifts from drug companies, even small ones, and they should pay for their own meetings and continuing education. If the medical profession does not put an end to this corruption voluntarily, it will lose the confidence of the public, and the government will step in and impose regulation. No one in medicine wants that."

Design of a Randomized Controlled Trial on Immune Effects of Acidic and Neutral Oligosaccharides in the Nutrition of Preterm Infants: Carrot Study

Elisabeth A.M. Westerbeek, Ruurd M. van Elburg, Anemone van den Berg, Jolice van den Berg, Jos W.R. Twisk, Willem P.F. Fetter, Harrie N. Lafeber

Abstract

Background: Prevention of serious infections in preterm infants is a challenge, since prematurity and low birth weight often requires many interventions and high utility of devices. Furthermore, the possibility to administer enteral nutrition is limited due to immaturity of the gastrointestinal tract in the presence of a developing immune system. In combination with delayed intestinal bacterial colonization compared with term infants, this may increase the risk for serious infections. Acidic and neutral oligosaccharides play an important role in the development of the immune system, intestinal bacterial colonization and functional integrity of the gut. This trial aims to determine the effect of enteral supplementation of acidic and neutral oligosaccharides on infectious morbidity (primary outcome), immune response to immunizations, feeding tolerance and short-term and long-term outcome in preterm infants. In addition, an attempt is made to elucidate the role of acidic and neutral oligosaccharides in postnatal modulation of the immune response and postnatal adaptation of the gut.

Methods/Design: In a double-blind placebo controlled randomized trial, 120 preterm infants (gestational age <32 weeks and/or birth weight <1500 gram) are randomly allocated to receive enteral acidic and neutral oligosaccharides supplementation (20%/80%) or placebo supplementation (maltodextrin) between day 3 and 30 of life. Primary outcome is infectious morbidity (defined as the incidence of serious infections). The role of acidic and neutral oligosaccharides in modulation of the immune response is investigated by determining the immune response to DTaP-IPV-Hib(-HBV)+PCV7 immunizations, plasma cytokine concentrations, fecal Calprotectin and IL-8. The effect of enteral acidic and neutral oligosaccharides supplementation on postnatal adaptation of the gut is investigated by measuring feeding tolerance, intestinal permeability, intestinal viscosity, and determining intestinal microflora. Furthermore, short-term and long-term outcome are evaluated.

Discussion: Especially preterm infants, who are at increased risk for serious infections, may benefit from supplementation of prebiotics. Most studies with prebiotics only focus on the colonisation of the intestinal microflora. However, the pathways how prebiotics may influence the immune system are not yet fully understood. Studying the immune modulatory effects is complex because of the multicausal risk of infections in preterm infants. The combination of neutral oligosaccharides with acidic oligosaccharides may have an increased beneficial effect on the immune system. Increased insight in the effects of prebiotics on the developing immune system may help to decrease the (infectious) morbidity and mortality in preterm infants.

Background

Preterm infants are at increased risk for the development of serious nosocomial infections, especially very low birth weight infants at a NICU.[1] In a recent review of the literature, we found that the intestinal bacterial colonization in preterm infants is much more diverse than in term infants and that antibiotics cause a significant delay in the intestinal bacterial colonization.[2] Furthermore, the possibility to administer enteral nutrition is limited due to immaturity of the gastrointestinal tract in the presence of a developing immune system.

Human milk has anti-inflammatory effects and bifidogenic effects on the intestinal microflora.[3,4] Term breastfed infants have less infections and develop less atopy compared with formula fed infants,[5,6] Many factors have been implicated in this effect, including human milk oligosaccharides,[7,8] Many attempts have been made to mimic this effect of human milk. Addition of prebiotics, consisting of neutral oligosaccharides, to infant formula has been found to show potential advantageous effects in term and preterm infants.[9,10] Besides neutral oligosaccharides, breast milk also contains acidic oligosaccharides.[8] In the past, research has mainly focused on neutral oligosaccharides such as galacto-oligosaccharides and fructo-oligosaccharides (GOS/FOS). Supplementation of GOS/FOS in term and preterm infants results in: 1. Stimulation of a bifidogenic intestinal flora;[11,12]

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Table 1: Clinical outcome measures

	Remarks
Infectious morbidity	
Serious infections	Primary outcome
Number of infectious episodes	
Cultured micro-organisms	
Feeding tolerance	
Enteral feeding >120 mL/kg/day	
Age at finishing parenteral nutrition	
Necrotising enterocolitis	Bell et al.[35]
Short-term outcome	
Weight z scores at birth, day 30 and at discharge	Usher et al. [24]
Patent ductus arteriosus	
Ventilatory support	
Use of oxygen at postmenstrual age of 36 weeks	Jobe et al. [36]
Intraventricular hemorrhage	Papile et al. [37]
Retinopathy of prematurity	Committee for ROP. [38]
Death	
Age at discharge from NICU and age at discharge home	

ROP = retinopathy of prematurity; NICU = neonatal intensive care unite.

2. Reduction of pathogens in the intestine;[12] 3. Production of beneficial fermentation metabolites such as short chain fatty acids (SCFA);[10] 4. Decrease of stool pH;1[3] 5. Improved intestinal physiology (stool characteristics, motility);[14] 6. Less infections and atopy.[15,16]

In breast milk 80% of the oligosaccharides are neutral (as in GOS/FOS), and 20% are acidic. Acidic oligosaccharides (AOS) can be derived from carrots with their active component pectin. Pectin is a common structural component of all higher plants. Cooking of pectin-containing vegetables induces the cleavage of the long-chain pectin polymers into acidic oligosaccharides. For already nearly 100 years,[17] carrots are known to have health promoting effects. In 1908, carrot soup was used as treatment of diarrhea In 1997, Guggenbichler identified the anti-adhesive effect of acidic oligosaccharides.[ttt]

The combination of acidic and neutral oligosaccharides may have several advantageous effects:[10,19-21] 1. Improvement of the response to immunizations; 2. Stimulation of Th1 cytokine response (eg TNF-α, IFN-gamma) and decreasing the Th2 cytokine release (eg IL-10, IL-4, IL-5); 3. Stimulation of a bifidogenic intestinal flora; 4. Preventing adhesion of pathogens to epithelial tissues.

As a result of these effects, we hypothesize that preterm infants receiving a combination of GOS/FOS with AOS may have: 1. Less infections; 2. Better response to immunizations; 3. Less atopy later in life; 4. Less feeding intolerance.

As infections are still a major cause of morbidity and mortality in preterm infants, reducing the incidence of serious infections is very important. Controversy exists on the definitions for serious infections in neonates. Therefore in a previous study, we adjusted the criteria of the Centers for Disease Control and Prevention for serious infections in children < 1 year for use in neonates,[1] and found in a prospective study these criteria applicable in preterm infants.[22]

In conclusion, this double-blind randomized controlled trial aims to determine the effect of enteral supplementation of acidic and neutral oligosaccharides on infectious morbidity (primary outcome), immune response to immunizations, feeding tolerance and short-term and long-term outcome in preterm infants. In addition, an attempt is made to elucidate the role of acidic and neutral oligosaccharides in postnatal modulation of the immune response and postnatal adaptation of the gut.

Methods

The study is designed as a double-blind placebo controlled randomized clinical trial. Approval of the study protocol by the medical ethical review board of VU University Medical Center Amsterdam is obtained before the start of the study. Infants with a gestational age <32 weeks and/or birth weight <1500 gram admitted to the level III neonatal intensive care unit (NICU) of the VU University Medical Center, Amsterdam, are eligible for participation in the study. Written informed consent is obtained from all parents. Exclusion criteria are: major congenital or chromosomal anomalies, death <48 hours after birth, transfer to another hospital <48 hours after birth and admission from an extra regional hospital.

To balance birth weight distribution into treatment groups, each infant is stratified to one of three birth weight groups (≤ 799 g, 800–1199 g, ≥ 1200 g) and randomly allocated to treatment within 48 hours after birth. An independent researcher uses a computer-generated randomization table (provided by Danone Research, Friedrichsdorf, Germany) to assign infants to treatment N or O. Investigators, parents, medical and nursing staff are unaware of treatment allocation. The randomization code is broken after data analysis is performed.

Acidic and neutral oligosaccharides powder and the placebo powder (maltodextrin) are prepared by Danone Research, Friedrichsdorf, Germany and are packed sterile. During the study period, acidic and neutral oligosaccharides and placebo powder are monitored for stability and microbiological contamination.

Table 2: Study Schedule

	< 48 h	Day 4	day 7	day 14	day 30	5 months	1 year	2 year
Immune response								
Response to immunizations						x	x	
Cytokine response	x		x	x		x	x	
Faecal Calprotectin/IL-8	x		x	x	x	x	x	
Postnatal adaptation of the gut								
Intestinal permeability	x	x	x					
Intestinal microflora	x		x	x	x	x	x	
Intestinal viscosity					x	x	x	
Long-term outcome								
IgE/IgG4	x					x	x	
Allergic and infectious diseases							x	
Side effects immunizations†								
Neurodevelopment							x	x

†Standardized questionnaires (Preparedness and Response Unit, Centre for Infectious disease Control Netherlands, National Institute for Public Health and the Environment, The Netherlands) after the 1st, 2nd, 3rd and 4th immunization.

Between days 3 and 30 of life, acidic and neutral oligosaccharides supplementation (20%/80% mixture) is administered in a dose of maximal 1.5 g/kg/day to breast milk or preterm formula in the intervention group. Two members of the nursing staff daily add supplementation to breast milk or to preterm formula (Nenatal Start, Nutricia Nederland BV, Zoetermeer, The Netherlands), according to the parents' choice. Per 100 mL, Nenatal Start provides 80 kcal, 2.4 g protein (casein-whey protein ratio 40:60), 4.4 g fat, and 7.8 g carbohydrate. When infants are transferred to another hospital before the end of the study, the protocol is continued under supervision of the principal investigator (EW).

Protocol guidelines for the introduction of parenteral and enteral nutrition follow current practice at our NICU. Nutritional support is administered as previously described.[23]

For each infant in the study, a feeding schedule is proposed based on birth weight and the guidelines as mentioned above. However, the medical staff of our NICU has final responsibility for the administration of parenteral nutrition and advancement of enteral nutrition. After discharge all infants receive breast milk or preterm formula Nenatal Start (without GOS/FOS) until term, and Nenatal 1 (without GOS/FOS) until the corrected age of 6 months.

Study outcome measures

Primary outcome of the study is the effect of acidic and neutral oligosaccharides (20%/80% mixture) supplemented to the enteral nutrition on infectious morbidity as previously defined.[1,22] The occurrence of serious infections is determined by two investigators, unaware of treatment allocation, as previously described.

The following perinatal characteristics are registered to assess prognostic similarity: maternal age and race, obstetric diagnosis, administration of antenatal steroids and antibiotics, mode of delivery, sex, gestational age, birth weight, birth weight <10th percentile,[24] Apgar scores, pH of the umbilical artery, clinical risk index for babies,[25] and administration of surfactant.

During the study period, actual intake of enteral and parenteral nutrition, powder supplementation and type of feeding (breast milk or preterm formula) are recorded daily. Feeding tolerance and short-term outcome are evaluated.

The effect of acidic and neutral oligosaccharides supplemented enteral nutrition on the immune response is investigated, in collaboration with the National Institute for Public Health and Environment, by determining the development of the immune response to DTaP-IPV-Hib(-HBV) + PCV7 immunizations (after the first 3 doses), and the development of the memory function of the immune response to these immunizations by measuring the response after the 4th booster dose. In addition, the plasma cytokine concentrations (Il-2, Il-4, IL-5, Il-8, IL-10, TGF, IFN), fecal Calprotectin measured by ELISA (Buhlmann, Switzerland), and IL8 measured by random-access chemiluminescence immunoassay (Siemens, The Netherlands) are determined.

The effect of acidic and neutral oligosaccharides supplemented enteral nutrition on postnatal adaptation of the gut is studied by measuring feeding tolerance, intestinal permeability, intestinal microflora and intestinal viscosity.

Intestinal permeability is measured by the sugar absorption test.[26] After instillation of the test solution, 2 mL/kg by nasogastric tube, urine is collected for 6 hours. After collection, 0.1 mL chlorohexidine digluconate 20% (preservative) is added to the urine and samples are stored at -20°C until analysis. Lactulose and mannitol concentrations (mmol/mol creatinine) are measured by gas chromatography as previously described.[27] The lactulose/mannitol ratio is calculated and used as a measure of intestinal permeability.

Fecal samples are stored at -20°C until analysis by fluorescent in situ hybridisation (FISH) using specific 16S rDNA-targeted.[28] Intestinal viscosity is measured by high-pressure capillary rheometry (viscosimetry) as described by Mihatsch et al.[14]

Long-term outcome: To determine the incidence of allergic and infectious disease in the first year of life standardized questionnaires will be sent to the parents prior to the follow-up visit at the corrected age of 1 year.[29] Fecal samples (FISH, Calprotectin and IL-8) and IgE/IgG4 levels in blood will

be measured at the age of 5 and 12 months. To investigate neurodevelopmental outcome, neurological status, vision, hearing and Mental Development Index (MDI) and Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development II (BSID-II) at the corrected age of 1 and 2 years (as part of the regular follow-up of NICU infants) are assessed.[30,31]

To determine the frequency of side-effects after the first 4 immunizations, standardized questionnaires will be given to the parents at the time of immunizations. (Table 2)

Sample size: Based on the differences in incidences in infectious morbidity (76% and 50% respectively) in the GEEF study,[22] [22], and a two-tailed $\alpha = 0.05$, $\beta = 0.20$, a sample size of $2 \times [2*7.85*0.63(0,37)]/(0,26)2 = 2 \times 54$ infants is calculated. Based on an expected drop-out rate of 10% during the study period 2×60 infants will be included.

Statistical analysis: To determine whether randomization is successful, prognostic similarity (perinatal and nutritional characteristics) between treatment groups is assessed. The Students' t-test, Mann-Whitney U test, and chi-square test or Fisher's exact test are used to compare continuous normally distributed, nonparametric continuous and dichotomous data respectively. Logistic regression is performed to examine whether acidic and neutral oligosaccharide supplemented enteral nutrition decreases the incidence of serious infections. In an additional analysis, adjustments are made for possible confounding factors such as administration of antenatal corticosteroids, birth weight <10th percentile and administration of breast milk. Analyses of secondary outcomes (only crude) is performed by Students' t- test, Mann-Whitney U test, chi-square test or Fisher's exact test for (non)parametric continuous, dichotomous data and time-dependent data respectively.

Generalized estimated equations[32] are used to analyse differences and changes over time in plasma cytokine concentrations, faecal Calprotectin and IL-8, intestinal permeability, intestinal microflora and intestinal viscosity. Differences of optimal and non-optimal neuromotor development and normal and abnormal mental/motor development in oligosaccharides and control groups is examined by logistic regression with adjustments for possible confounding factors as gestational age and birth weight.

All statistical analyses are performed on an intention to treat basis. In addition, alternative per protocol analyses are performed, excluding all patients who are not treated according to protocol, defined as more than 3 consecutive days or a total of 5 days on minimal enteral feeding or without supplementation. For all statistic analyses a p value <0.05 is considered significant (two-tailed). SPSS 15.0 (SPSS Inc., Chicago, IL, USA) is used for data analysis.

Discussion

There is increasing evidence that prebiotics play an important role in the development of the intestinal microflora and the immune system, and may help to decrease the risk of infectious diseases. Especially preterm infants, who are at increased risk for serious infections, may benefit from supplementation of prebiotics. Most studies with prebiotics only focus on the colonisation of the intestinal microflora. The influence on the immune system is not yet fully understood.[33] Studying the immune modulatory effects is complex because of the multicausal risk of infections in preterm infants.[34] The combination of neutral oligosaccharides with acidic oligosaccharides may have an increased beneficial effect on the immune system of preterm infants due to the specific conditions in the luminal part of the developing gut wall. Not only the immune effects, such as morbidity due to infections and response to immunizations will be investigated, but also other signs and symptoms such as feeding tolerance, short-term, long-term and postnatal adaptation of the gut (intestinal microflora, intestinal permeability, intestinal viscosity). Increased insight in the effects of prebiotics on the developing immune system may help to find ways to decrease the (infectious) morbidity and mortality in preterm infants.

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Heel Lance in Newborn During Breastfeeding: an evaluation of analgesic effect of this procedure

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Abstract

Objectives: The reduction of pain due to routine invasive procedures (capillary heel stick blood sampling for neonatal metabolic screening) in the newborn is an important objective for the so-called "Hospital with no pain." Practices such as skin to skin contact, or breastfeeding, in healthy newborn, may represent an alternative to the use of analgesic drugs. The aim of our work is to evaluate the analgesic effect of breastfeeding during heel puncture in full term healthy newborn.

Methods: We studied 200 healthy full term newborns (100 cases and 100 controls), proposing the puncture to mothers during breastfeeding, and explaining to them all the advantages of this practice. Pain assessment was evaluated by DAN scale (Douleur Aigue Nouveau ne scale).

Results: The difference in score of pain according to the DAN scale was significant in the two groups of patients (p = 0.000); the medium score was 5.15 for controls and 2.65 for cases (newborns sampled during breastfeeding).

Conclusion: Our results confirmed the evidence of analgesic effect of breastfeeding during heel puncture. This procedure could easily be adopted routinely in maternity wards.

Introduction

Scientific studies show that even very premature newborns may experience sensation of distress which could unfavorably influence many clinical and behavioural parameters of their present and future.[1] Pain control in newborns is so primary importance, also stressed by the American Academy of Pediatrics.[2] The purpose of our study was comparing the analgesic effects of sucking own mother milk, versus alternative chances like caressing and/or pacifier, during routine invasive procedures in full-term newborns. The most painful routine invasive procedures in full-term newborns include venous blood sample and capillary heel stick blood sampling.[3] The analgesic effect of oral glucose 24% solution,[4] pacifiers[5] and skin-to-skin contact[6] have already been demonstrated. The use of sucrose and/or pacifier for analgesia may interfere with a correct beginning of breastfeeding,[7] so it may be an interesting alternative to test the analgesic effect of breastfeeding during painful procedures. In a recent review by Shah PS et al[8] breastfeeding is associated with changes in heart rate, duration of cry, percentage of crying time and a decrease of measured pain. Breastfeeding instead, does not seem to be favourable, if compared with higher glucose concentrations, with regards for crying duration, PIPP score and DAN score.[9-11] This

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Neonate: Name..... Surname.....
Date of birth:..... Gestational age:..... Apgar Score:.....
Breastfeeding during distressing procedure: □
Care and/or pacifier during distressing procedure: □

	Score
Facial expressions:	
Calm	0
Snivels and alternates gentle eye opening and closing	1
Intensity of eye squeeze, brow bulge, nasolabial furrow:	
Mild, intermittent with return to calm (present during <1/3 of observation periods)	2
Moderate (present during 1/3 to 2/3 of observation periods)	3
Very pronounced, continuous (present during >2/3 of observation periods)	4
Limbs movements	
Calm or gentle movements	0
Intensity of pedalling, toes spread, legs tensed and pulled up, agitation of arms, withdrawal reaction:	
Mild, intermittent with return to calm (present during <1/3 of observation periods)	1
Moderate (present during 1/3 to 2/3 of observation periods)	2
Very pronounced, continuous (present during >2/3 of observation periods)	3
Vocal expression	
No complaints	0
Moans briefly (for intubated child, looks anxious or uneasy)	1
Intermittent crying (for intubated child, expression of intermittent crying)	2
Longlasting crying, continuous howl (for intubated child, expression of continuous crying)	3
Total score	

Figure 1. DAN scale.

Table 1: DAN scale total scores

	Total	0	1	2	3	4	5	6	7	8	9	10
cases	100	20	13	20	21	9	8	1	2	2	3	1
controls	100	0	4	1	16	23	17	13	14	3	6	3

suggests that neonates undergoing painful procedures may be breastfed or given expressed breast milk to obtain analgesic effect. This special power of breast-sucking may be linked to relational factors (skin-to-skin contact, nearness to mother, entertainment)[12,13] and to specific components of human milk like sugar[14] and triptophane[15] a melatonine precursor that enhances in neonates the production of beta endorphins,[16] or the endogenous opioids like galattorphins.[17] This practice may be useful for driving on breastfeeding by frequent sucking and using mother's breast for comfort.

Methods

We enlisted 200 full term healthy neonates (100 cases and 100 controls). We suggested to all mothers of completely or partial breastfed neonates the execution of metabolic screening from heel puncture during breast sucking, explaining to mothers the advantages of this practice. The magnitude of pain in neonates was measured by DAN scale (Douleur Aigue Nouveau-nè scale—Figure 1), reckoning suffering in full-term healthy neonates by observing facial changes, limb movements and vocal expression.[18] This evaluation regarded both newborns undergoing capillary heel stick for screening while breastfed and control ones, i.e. children refusing breast during puncture, or formula fed ones, or babies who's mother had refused the procedure. In control cases, analgesia was provided by caressing and/or pacifier.

Every child was taken to his own mother and the puncture was performed after minimum two minutes of effective sucking. Capillary puncture was made on the postero-lateral area of the heel, using sterile click prick lancet (the kind of lancets we used were Ames Minilet Lancets by Bayer). Every heel puncture was performed by dedicated nurses of Neonatology Division. Every nurse was trained about enlistment of neonates, about information of mothers, and especially about evaluation of pain according the standards of Dan Scale and attended a course of pain evaluation of newborn. For every enroled newborn, was filled a form including his/her name, date of birth, gestational age, Apgar score and way of punture (while breastfeeding or pacifier) (Figure 1).

A score from 0 (no pain) to 10 (highest pain) was attributed to each child, according to the intensity of pain.[3,19] After discharge,

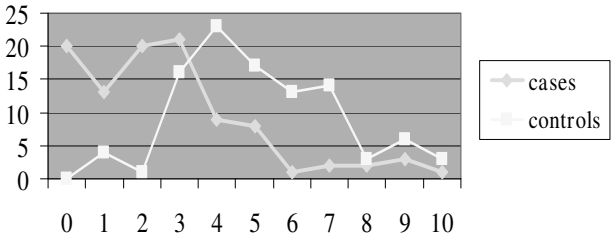

Figure 2. Graph comparing DAN scale total scores for cases and controls.

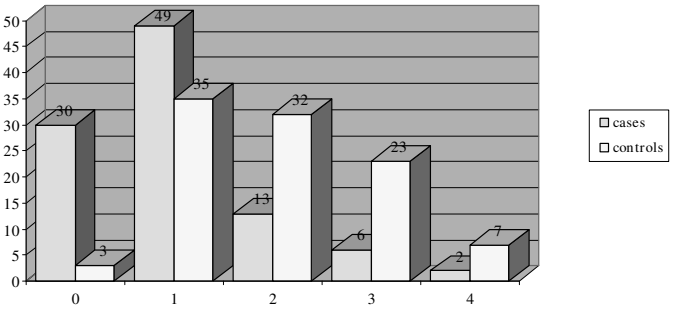

Figure 3. Facial expressions.

mothers were called to verify the outcome in breastfeeding at one month of life in the two groups. Scores obtained in the two groups were statistically analysed by $\chi 2$ test. Dates confirming homogeneity of groups were statistically compared with t-Student test. We used test for relating two proportions in feed evaluation of one month aged children. We did not collect differences between caressing and pacifier in the control group. Statistics data give signs of homogeneity of champions, in fact there are not elements influencing mothers in the choice of way of puncture, except for formula-fed neonates.

Results

The case group included 52 female neonates and 48 males tested with heel puncture while breastfed. The control group included 41 female and 59 male neonates. In the case group, 67 were born by vaginal delivery, 28 by C-section and 5 with use of vacuum extractor. In the control group, 59 were born by vaginal delivery and 41 by caesarean section. The mean gestational age in the case group was 39.42 weeks (DS1.27 and CI95 = 38.16–40.69), in controls one was 39.35 weeks (DS 1.31 and CI95 = 38.04–40.67). The mean first and fifth minute Apgar score in case group was 8.78 (DS 0.69 and CI 95 = 8.09–9.47) and 9.75 (DS 0.52 and CI 95 = 9.23–10); in the control group they were 8.76 (DS 0.85 and CI 95 = 7.90–9.61) and 9.69 (DS 0.71 and CI 95 = 8.98–10). The mean birth weight in the first group was 3335.2 g (DS 434.82 and CI 95 = 2900.38–3770.02), in the second one 3333.45 g (DS 443.89 and CI 95 = 2889.55–3777.34). In the first group, at discharge 93 neonates were being breastfed and 7 were receiving breast milk and formula; at 72 hours after-discharge check-up, only one child receiving mixed feeding began to receive only formula. In the control group at discharge 90 neonates were fed by breast and 4 neonates were fed with human milk and formula. At the age of one month, in the examined group 65 neonates were exclusively breast fed, 14 were mainly breastfed, 13 partially breastfed, 8 were exclusively fed with formula. In controls group instead, at one month 63 neonates were exclusively breastfed, 13 were mainly breastfed, 7 were partially breastfed, 17 were fully formula fed. There is no evident statistical significant difference between the two groups regarding this last specific parameter. Rooming-in during hospital stay was practiced by 47 pairs of mother-child in the first group, and by 37 pairs in the second one. The mother's mean age in the cases group was 32.18 years (DS 5.37 and CI 95 = 26.81–37.55). For half of the women it was their first pregnancy. Eleven percent of women had previous abortions and 5%, voluntary interruption of pregnancy. Between pluriparous mothers, 78% had previously breastfed. In the control group, the mean age of mothers was 31.36 years (DS 4.93 and CI95 = 26.43–36.29); 43% of women were primiparous, 19% had previous abortions and 4% had voluntary pregnancy interruption. In pluriparous women, 78.95% had previously breastfed.

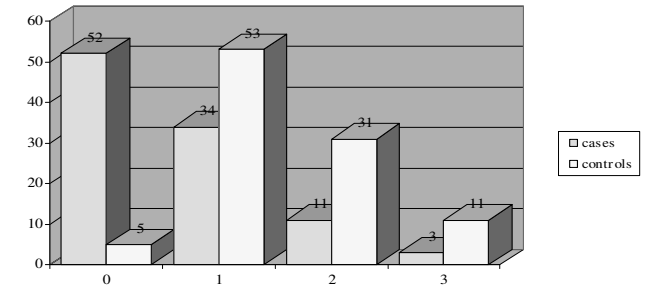

Figure 4
Limb movements.

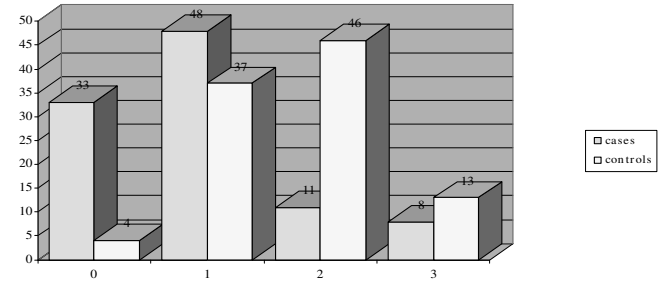

Figure 5
Vocal expression.

The mean DAN score in the case group (neonates with puncture during breastfeeding) was 2.65 (DS 2.31 and CI 95 = 0.34–4.96), for control group 5.15 (DS 2.07 and CI95 = 3.08–7.22). In the case group, 20 neonates obtained score 0, while no neonates in the control group got this score (Table 1 and Figure 2). From statistical analysis a significant difference resulted between the score obtained in the two groups, even when the single parameters of the DAN scale were considered independently: face expression (Figure 3), limb movements (Figure 4), vocal expression (Figure 5).

Discussion

Our results strengthen the already well-known analgesic effect of breastfeeding. This analgesic effect may be successfully exploited for minor distressing procedures in full term healthy neonates. The choice of this easy and effective method is useful in reducing all external interferences with a beginning of breastfeeding, while other analgesic systems such as pacifiers or sucrose might disrupt a good start at breastfeeding. Moreover, stressing the curative effects of human milk may be an important confidence boost for mothers, hopefully rendering breastfeeding easier to pursue. (Regarding this point, we need a longer follow-up). In our study, doing a heel lance without sucking did not seem to influence the kind of feeding at one month of age. In our next collection of data, we would include a further group of newborns—the ones pacified with sucrose.

In our opinion, this analgesic system may easily become a routine way of performing heel lance in maternity wards. This procedure may be suggested to available mothers of newborns who are sucking effectively, and possibly also extended to other painful minor procedures like intramuscular injection or venous puncture. Further studies might consider this method in older children, for instance during vaccination.

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Why Aren't We Practicing Homogenized Medicine?

Mervyn Singer

Abstract
Why is the practice of intensive care so heterogenous? Uncertainty as to "best practice," conservatism, and complacency may all contribute to our divergent management strategies. The need for further generalizable research, anonymized audit, external peer review and open access databases is discussed.

Commentary
Lauralyn McIntyre and colleagues have neatly used a septic shock scenario-based survey to highlight considerable variations within Canadian critical care practice.[1] They acknowledge the potential pitfalls of translating survey results into real life; however, my own experience of the diversities within UK practice suggest this would be representative of at least one other industrialized country, albeit with some variation in the detail (for example, use of gelatin as a plasma expander is much commoner in Europe).

They found decisions regarding treatment strategy (choice of fluid, use of inotropes and transfusion triggers) to be highly variable. However, they did demonstrate consistency in a continuing reliance on basic monitoring (blood pressure, heart rate, central venous pressure, urine output, pulse oximetry). This was to the relative exclusion of other, more sophisticated techniques (cardiac output, central venous saturation) whose use has been linked with outcome improvements in specific situations, such as the scenario on which their survey was based.

Is this heterogeneity a triumph of uncertainty and/or natural conservatism and/or arrogance and/or sloth over heavily promoted, multiple Society-endorsed guidelines [2] based primarily on the important yet limited Rivers study?[2,3] Why aren't we all practicing homogenized medicine? What does it take to standardize our approach to care of the critically ill?

Uncertainty does exert a considerable effect. The Institute of Healthcare Improvement's Surviving Sepsis Campaign website boldly states that a bundle – a group of interventions related to a disease process – "when executed together will result in better outcomes than when implemented individually" and that "the science behind the elements of a bundle is so well-established (my italics) that their implementation should be considered a generally accepted practice."[4] Yet three of the major planks upon which the two sepsis bundles are based, namely the use of corticosteroids, activated protein C and early goal-directed therapy are currently being questioned via, respectively, the CORTICUS study findings, the European Agency for the Evaluation of Medicinal Products (EMEA), and the National Institutes of Health (through their recent $8.4 million funding of the ProCESS study). These new challenges will, I believe, serve to increase uncertainty still further in the short-term and, thus, affect participation in an approach that is worthy but, in my opinion, critically flawed through a lack of prospective validation.[5]

Medics are a naturally conservative bunch – the avid uptake of new technologies by a rapid responder minority is rarely translated into standard practice, often because the initial enthusiasm for a drug, device or strategy fails to pass muster when more rigorously scrutinized or trialed. Too many bandwagons have lost their wheels and this has nurtured an understandable cynicism. It was not that many years ago that we were being exhorted to use high doses of dobutamine to achieve "supranormal" cardiorespiratory goals in the critically ill, as an extrapolation of findings from a high-risk surgical patient cohort.[6] When subsequent randomized trials made it painfully clear that the intensive care unit (ICU) patient outcomes did not match up to expectation,[7,8] the concept was generally discarded, even from the surgical patient population in whom the benefit was repeatedly seen.[9,10]

What about complacency? I've yet to meet a self-confessed mediocre intensivist so we all need to take a critical and regular look at our own individual performance. We do require a healthy degree of self-confidence to support our decision-making ability, but are we ready to accept that our ICU is perhaps offering an inferior level of care to the hospital down the road? Or if we do acknowledge poor performance, is this from someone/everyone/anyone else but me? Anonymized audit should, in a non-threatening manner, facilitate recognition and, hopefully,

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correction of our shortcomings. The Dutch offer external peer review "visitations" that can be initiated either by the ICU or their hospital administration. How widespread is this practice?

Finally, it is also a deficiency of ourselves as a community that we still cannot answer many fundamental questions. For an individual patient, what constitutes optimal targets, for example, for blood pressure and tissue perfusion, or 'best' treatment, such as the optimal duration of a course of antibiotics? Altruistic, multi-centre, generalizable research addressing simple questions is evolving. The Canadians and Australasians have clearly led the way while European and other countries are catching up. Perhaps these studies could (should) be better coordinated to complement each other. Perhaps this spirit of cooperation could (should) also be extended to open access, anonymized patient databases as a means of comparing models of care and for future hypothesis generation.

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News…continued from page 17

nations, more than half of them in Africa, Unicef said. Liberia had the highest rate of neonatal mortality at 66 deaths per 1,000 live births. In Niger, the country with the world's highest maternal mortality, a woman has a one in seven chance of dying, during pregnancy or childbirth. Ireland is the safest place to have a baby; the risk of death is one in 47,600. Unicef also noted that girls who give birth before the age of 15 are five times more likely to die in childbirth than women in their 20s. About four in 10 of all births worldwide are not attended by a doctor or other health professional.

FORCED LABOR

Mothers in Scotland are being unnecessarily induced into labor, according to a study of 17,000 births by Aberdeen University. Concerns have been raised about pregnant women being induced unnecessarily, after a Scottish audit of 17,000 births. In the UK, the commonest method of induction is the use of a gel containing prostaglandins to bring on contractions and start the labor process. Researchers identified 32% of births in Scotland between 1999 and 2003 were induced, and no clear indication why was available for 28% of the cases. Reported by the BBC.

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A Predictive Model for Respiratory Syncytial Virus (RSV) Hospitalization Of Premature Infants Born At 33-35 Weeks Of Gestational Age, based on data from the Spanish FLIP study

Eric A.F. Simoes, Xavier Carbonell-Estrany, John R. Fullarton, Johannes G. Liese, Jose Figueras-Aloy, Gunther Doering, Juana Guzman, and the European RSV Risk Factor Study Group

Abstract

Background: The aim of this study, conducted in Europe, was to develop a validated risk factor based model to predict RSV-related hospitalization in premature infants born 33-35 weeks' gestational age. Methods: The predictive model was developed using risk factors captured in the Spanish FLIP dataset, a case-control study of 183 premature infants born between 33-35 weeks' GA who were hospitalized with RSV, and 371 age-matched controls. The model was validated internally by 100-fold bootstrapping. Discriminant function analysis was used to analyse combinations of risk factors to predict RSV hospitalisation. Successive models were chosen that had the highest probability for discriminating between hospitalised and non-hospitalised infants. Receiver operating characteristic (ROC) curves were plotted.

Results: An initial 15 variable model was produced with a discriminant function of 72% and an area under the ROC curve of 0.795. A step-wise reduction exercise, alongside recalculations of some variables, produced a final model consisting of 7 variables: birth ±10 weeks of start of season, birth weight, breast feeding for ≤2 months, siblings ≥2 years, family members with atopy, family members with wheeze, and gender. The discrimination of this model was 71% and the area under the ROC curve was 0.791. At the 0.75 sensitivity intercept, the false positive fraction was 0.33. The 100-fold bootstrapping resulted in a mean discriminant function of 72% (standard deviation: 2.18) and a median area under the ROC curve of 0.785 (range: 0.768-0.790), indicating a good internal validation. The calculated NNT for intervention to treat all at risk patients with a 75% level of protection was 11.7 (95% confidence interval: 9.5-13.6).

Conclusions: A robust model based on seven risk factors was developed, which is able to predict which premature infants born between 33-35 weeks' GA are at highest risk of hospitalization from RSV. The model could be used to optimize prophylaxis with palivizumab across Europe.

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Background

Respiratory syncytial virus (RSV) causes a severe lower respiratory tract disease that results in substantial morbidity in premature infants.[1,2] Infants born up to 35 weeks' gestational age (wGA) lack the necessary pulmonary and immunologic development and function essential to combating infection.[3,4,5] It is estimated that 1-3% of previously healthy infants are hospitalized because of RSV infection,[6] whereas the RSV-hospitalisation rate ranges between 3.75% and 9.8% for infants born between 33-35 wGA.[1,7,8] Studies suggest that infants born between 33-35 wGA are at risk of developing severe RSV infection that can result in morbidity and health care resource utilization similar to infants born ≤32 wGA.[9,10] Additionally, RSV-related hospitalization in 32-35 wGA infants causes significant morbidity and healthcare utilization in the subsequent years.[11]

Palivizumab, a humanized monoclonal antibody, has been proven a safe and efficacious option to significantly reduce RSV disease in prematurely born infants up to and including 35 wGA.[12,13,14] Based on the findings of the pivotal Phase III trial (IMpact RSV Study),[12] palivizumab received European approval in 1999 for use in infants up to and including 35 wGA.[15] Despite the clinical evidence, only a few countries in Europe make passive immunoprophylaxis available to at-risk 33-35 wGA infants, as reflected in current national guideline and reimbursement policies.[16,17,18] Passive immunoprophylaxis for all infants born at 33-35 wGA is not financially viable. However, based on risk profile and a higher rate of RSV-related hospitalisation, a certain proportion of these infants may be legitimate candidates for prophylaxis.

Table 1. A comparison of the risk factors for RSV hospitalised and non hospitalised infants in the FLIP and Munich studies†

	FLIP [9]				Munich [8]			
	Hospitalised (n=186)	Non-hospitalised (n=367)	Odds Ratio (CI 95%)	P-value*	Hospitalised (n=20)	Non-hospitalised (n=357)	Odds Ratio (CI 95%)	P-value*
Birth ± 10 weeks of start of season	*136 (73.1%)*	*145 (39.5%)*	*4.16 (2.78-6.23)*	***<0.0001***	*12 (60.0%)*	*148 (41.5%)*	*2.12 (0.77-6.12)*	*0.1101*
Birth weight, kg[a]	*2.20 (0.38)*	*2.12 (0.42)*	-	***0.0419***	*2.14 (0.38)*	*2.11 (0.39)*	-	*0.7526*
Breast fed ≤ 2 months or not[§]	*146 (78.5%)*	*206 (56.1%)*	*2.85 (1.87-4.40)*	***<0.0001***	*18 (90.0%)*	*286 (80.1%)*	*2.23 (0.51-20.3)*	*0.3887*
Number of siblings ≥2 years	*1 (0-1)*	*0 (0-1)*	-	***<0.0001***	*1 (0-2)*	*0 (0-1)*	-	***0.0172***
Number of family with atopy[§]	*0 (0-0)*	*0 (0-0)*	-	***0.0117***	*12 (60.0%)*	*175 (49.0%)*	*1.56 (0.57-4.51)*	*0.3671*
Male gender	*117 (62.9%)*	*199 (54.2%)*	*1.43 (0.98-2.09)*	*0.0513*	*18 (90.0%)*	*177 (49.6%)*	*9.15 (2.13-82.14)*	***0.0003***
Number of family with wheeze	*0 (0-1)*	*0 (0-0)*	-	***0.0004***	-	-	-	-
Gestational age								
33 weeks	49 (26.3%)	77 (21.0%)	1.34 (0.87-2.07)	0.1554	4 (20.0%)	119 (33.3%)	0.50 (0.12-1.60)	0.3265
34 weeks	60 (32.3%)	139 (37.9%)	0.78 (0.53-1.15)	0.1935	11 (55.0%)	172 (48.2%)	1.31 (0.48-3.68)	0.648
35 weeks	77 (41.4%)	151 (41.1%)	1.01 (0.69-1.47)	0.9544	5 (25.0%)	66 (18.5%)	1.47 (0.40-4.44)	0.5544
Number of regular carers	2 (1-2)	2 (1-2)	-	**0.0377**	-	-	-	-
Furred pets at home	46 (24.7%)	68 (18.5%)	1.44 (0.92-2.25)	0.0885	-	-	-	-
Educational level of parents								
No school	7 (3.8%)	4 (1.1%)	3.54 (0.89-16.71)	0.0711	-	-	-	-
Primary	53 (28.5%)	84 (22.9%)	1.34 (0.88-2.04)	0.1491	-	-	-	-
High school	78 (41.9%)	156 (42.5%)	0.98 (0.67-1.42)	0.8978	-	-	-	-
University	48 (25.8%)	123 (33.5%)	0.69 (0.45-1.04)	0.0639	-	-	-	-
Number of births in delivery	1 (1-2)	1 (1-2)	-	0.531	1 (1-1)	1 (1-2)	-	0.1675
Smoking during pregnancy[b]	56 (30.3%)	79 (21.5%)	1.58 (1.03-2.40)	**0.0241**	-	-	-	-
Number of smokers around infant[c]	1 (0-2)	1 (0-2)	-	0.062	0 (0-1)	0 (0-1)	-	0.9479
Number of family with asthma	0 (0-0)	0 (0-0)	-	0.1114	-	-	-	-

The 8 variables used in the final model are shown in italics. All variables were used in the initial 15 variable model
† Mean (standard deviation), median (P25-P75), number (%)
* Student's *t* test, Mann-Whitney *U* test, χ^2 test
§ Recorded as breast fed yes/no and atopy yes/no for Munich
a 2 missing values for FLIP, 5 missing values for Munich
b 1 missing value for FLIP
c 2 missing values for Munich

A comprehensive review of the literature revealed environmental and demographic risk factors that predispose infants to developing severe RSV leading to hospitalization.[19] Subsequent prospective studies in Spain,[9] Canada,[7] and Germany[20] examined those risk factors in infants born 33-35 wGA. The risk factors identified include: chronological age, number of siblings/ contacts, history of atopy, absence/duration of breastfeeding, postnatal cigarette smoke exposure, male sex, and day care attendance.[7,9,20] Despite these data, no predictive tool that can identify infants most at risk of RSV-hospitalization has been developed. We have developed an objective, evidence-based model to assist clinicians to predict the likelihood of RSV hospitalisation in European infants born 33-35wGA. Such a model would facilitate the effective and responsible application of passive immunoprophylaxis in this population.

Methods

Population used for modeling: The predictive model was derived from the Spanish FLIP dataset,[9] a prospective, case-control study, which aimed to identify those risk factors most likely to lead to the development of RSV-related hospitalization among premature infants born at 33-35 wGA. The dataset comprises 186 cases and 371 age-matched controls recruited from 50 centres across Spain during the 2002/2003 RSV season (Oct. 2002-Apr. 2003).

Criteria for inclusion as a case included: GA between 33-35 weeks, discharge during the RSV season (or age ≤6 months at the start of the RSV season), and proven RSVrelated hospitalisation. Controls were selected from premature infants born or discharged from the same hospital, during the same time period, and within the same GA limits as cases, but who had not been previously hospitalized for any acute respiratory illness during the RSV season. Additionally, although not a criterion for study exclusion, no infant had chronic lung disease.

Statistical methodology: Discriminant function analysis[21] was used to build the predictive model. Univariate analyses included the Student's t test, the χ^2 test, the Mann-Whitney's U test, and the calculation of odds ratios (with 95% confidence intervals). The model was internally validated using bootstrapping methods.[22] All data were analyzed by SPSS software (version 10).[23] Records with missing values for one or more of the predictor variables were excluded from the analyses.

Development of a model to predict RSV-related hospitalisation of infants 33-35 wGA: All the available risk factors collected in the FLIP study were included in the discriminant analysis. The discriminant analysis established how well the presence or absence of certain risk factors was able to separate infants in the hospitalized group from those in the non-hospitalized group (generating a discriminant function).

Following the development of an initial model, backward selection was used to remove the variables that contributed least to the discriminant function. The elimination of a variable from the analysis was based on a comparison of the discriminant power of the function derived with and without the variable. At each stage, the functions for each reanalysis were compared to identify the most discriminatory.

Table 2. Analyses of the predictive accuracy of the various models.

	True Positive	False Positive	False Negative	True Negative	Sensitivity	Specificity	PPV %	NPV %	LR	Diagnostic Accuracy %
FLIP 15 variable model[§]	130	102	53	265	0.71	0.72	56	83	2.56	72
FLIP Final 7 variable model[¤]	139	113	45	254	0.76	0.69	55	85	2.45	71
Munich 6 variable model[†]	14	106	4	247	0.78	0.70	12	98	2.59	70

[§] Records for 550 infants were included within the analysis. Seven records were dropped from the analysis due to missing data for one or more of the predictor variables

[¤] Records for 549 infants were included within the analysis. 8 records were dropped from the analysis due to missing data for one or more of the predictor variables

[†] Records for 370 infants were included within the analysis. Three records were dropped from the analysis due to missing data for one or more of the predictor variables. Two records for hospitalised cases were removed from the analysis, as they each had one negative RSV test

PPV = positive predictive value

NPV = negative predictive value

LR = likelihood ratio of a positive test; for information about likelihood ratios see reference 25

Standardised canonical discriminant function coefficients for the FLIP final 7 variable model: birth ± 10 weeks of start of season=0.678, birth weight, kg=0.184, breast fed ≤ 2 months or not=0.511, number of siblings ≥2 years=0.489, number of family with atopy=0.151, female sex=-0.113, number of family with wheeze=0.125

Receiver operator characteristic (ROC) curves were constructed by plotting the sensitivity against 1- the specificity. The area under the curve was calculated for each ROC plot, with areas closer to 1 representing better predictive accuracy. To explore diagnostic accuracy, positive predictive values (PPV), negative predictive values (NPV), and likelihood ratios were generated.[24,25] Additionally, example numbers needed to treat (NNT) were calculated.

Validation of the predictive model: The FLIP dataset was subject to 100-fold bootstrapping validation.[22] For each of the 100 samples, coefficients for each predictor variable were calculated. The 100 coefficient sets were then used to derive predictor functions on 100 replicates of the original data. The correct prediction of RSV-related hospitalization was calculated and ROC curves were plotted for each of the 100 outputs. The distribution of correct prediction rates and areas under the ROC curve were then assessed. To test for normality in the distribution of correct prediction rates and areas under the ROC curve, the Kolmogorov-Smirnov test was used.[26] The results were also tested for skewness.

Test of the predictive model against an external dataset: Despite extensive investigation, there were no suitable European datasets available against which the model could be fully externally validated. Therefore, to gain a measure of the applicability of the model to other European populations, the model was tested against data from the Munich RSV study.[8] The Munich RSV study, a population based cohort study, examined the incidence and risk factors for RSVrelated hospitalisation of premature infants born ≤35 wGA. Questionnaires were sent to all parents of infants discharged from primary neonatal care to determine the event of rehospitalization for acute respiratory infections. A total of 717 infants were studied, 375 of whom were born between 33-35 wGA and were used in the validation.

There were 37 RSV-related hospitalisations (5.2%) overall and 20 amongst the 375 preterms of 33-35 wGA (5.3%). Of the 20 RSV-related hospitalisations, six had a confirmed diagnosis of RSV, with the remaining 14 cases being classified as having a clinical suspicion of RSV, although two had a negative RSV test on one occasion. The two infants with a negative RSV test were excluded from the analysis.

The predictive function derived from the FLIP dataset was tested in two ways against data from the Munich RSV study. Firstly, the predictive variables identified from the FLIP dataset were used to generate a discriminant function from the data of the Munich RSV study itself. Secondly, the non-normalised coefficients (derived from unadjusted variable data) generated from the FLIP dataset were applied to the Munich data.

Prior to testing, the final model had to be adjusted to account for differences in the data captured within the FLIP study and that which were captured within the Munich RSV study. The variable, "number of family members with wheeze" had to be removed, as this was not available in the Munich dataset, the variable "breast fed for ≤2 months or not" had to be modified to "breast fed Yes/No," and the variable "number of family members with atopy" had to be changed to a categorical "family member with atopy Yes/No."

Test of the predictive model against the Spanish Guidelines recommendations for prophylaxis of 32-35 wGA infants: To put the clinical usefulness of the model into perspective, its predictive ability was compared to that based on the Spanish Neonatal Society Guidelines[16] recommendations for prophylaxis of infants born 32-35 wGA. The Spanish Guidelines[16] recommend that premature infants born 32-35 wGA who are ≤6 months old when the RSV season starts and have two risk factors (less than 10 weeks when RSV season starts, tobacco smoke at home, daycare assistance, no breastfeeding, family history of wheezing, school age siblings, and crowded homes [≥4 residents and/or visitors at home, excluding school age siblings and the subject him/herself]) receive prophylaxis with palivizumab. Using these criteria, a discriminant function was generated from the FLIP dataset, a ROC curve plotted, and diagnostic accuracy tested. The results from this analysis were then compared to the results for the model.

Results

Development of the predictive model: The 15 variables in the

Table 3. Final seven variable model number needed to treat analyses*

ROC AUC plus confidence limits	True Positive Fraction	True positives treated	False Positive Fraction	False positives treated	NNT	NNT (80% efficacy)
0.791 (mid point)	0.75	75	0.33	627	9.4	11.7
0.751 (lower limit)	0.75	75	0.39	741	10.9	13.6
0.830 (upper limit)	0.75	75	0.26	494	7.6	9.5

*Number needed to treat (NNT) to prevent hospitalisation of 75% of at risk infants, assuming a 5% hospitalisation rate and 80% treatment efficacy (n=2,000)

Table 4 100-fold bootstrap statistics on the FLIP dataset

	Percentages correctly predicted	Areas under ROC curves (AUC)
Mean	72.00	0.784
Median	72.20	0.785
Standard deviation	2.18	0.004
Minimum	66.20	0.768
Maximum	77.40	0.790
Kolmogorov-Smirnov Z	0.56 (P=0.910†)	1.22 (P=0.101†)
Skewness statistic	0.19 (0.48§)	-1.20 (0.48§)

n= valid: 100, missing: 0
† Asymptotic significance (2-tailed)
§ 2 standard error of skewness

FLIP study are compared in the hospitalized and nonhospitalized infants in Table 1. In a univariate analysis of the FLIP data, hospitalized infants were significantly more likely to be born within 10 weeks of the start of the RSV season, be heavier at birth, have more family members with atopy or who wheezed, had more carers at home, had mothers who smoked during pregnancy, had more siblings ≥2 years of age, and were breast fed for ≤2 months or not at all.

The initial analysis of the FLIP dataset produced a function based on 15 risk factors, which could discriminate significantly between hospitalised and nonhospitalised infants. This function could correctly classify whether a child was hospitalized or not in 72% of cases (table 2). Importantly, the correct classification of hospitalised infants was 71%. The area under the ROC curve was 0.795 (Figure 1A).

The variable reduction exercise resulted in a final model of seven variables (table 1), with an area under the ROC curve very similar to that of the 15 variable model (Figure 1B). Discrimination also remained similar at 71%, with 76% of hospitalizations classified correctly (table 2). At the 0.75 sensitivity intercept, the specificity was 0.67, with the false positive fraction (FPF) being 0.33. The NNT to prevent hospitalization of 75% of at risk infants was calculated to be 11.7, assuming a 5% hospitalization rate (consensus of European RSV Risk Factor Study Group based on a review of the available data[1,7,8]) and 80%[12] treatment efficacy (table 3). At the point of maximum sensitivity/specificity the NNT was 10.7, again assuming a 5% hospitalization rate and 80% treatment efficacy (Figure 1). The likelihood ratio for this model was 2.45 and the PPV and NPV were 55% and 85%, respectively.

Contribution of individual variables: A variable reduction exercise on the 7 variable model showed that, although some variables were more important than others, removing any variable produces a decrease in discrimination and/or area under the ROC curve. For example, removing "sex" reduced the area under the ROC curve to 0.789 (Figure 1D). On this basis, no clear case could be made for removing any of the constituent seven variables. Thus, the final seven variable model includes: birth within 10 weeks of the start of season, birthweight, breast-fed for ≤2 months or not, number of siblings ≥2 years, number of family members with atopy, male sex, and number of family members with wheeze.

Validation: The bootstrapping analysis resulted in a tight symmetrical distribution of results for the 100 calculations of percentage correctly predicted and area under the ROC curve (table 4). The mean percentage of cases predicted correctly was 72% (standard deviation [SD]: 2.18) and the median area under the ROC curve was 0.785 (range 0.768-0.790). The Kolmogorov-Smirnov test indicated that the distribution of results for the correct prediction of outcomes (asymptotic significance: P=0.910) and for the ROC curves (asymptotic significance: P=0.101) is assumed to be normal for the purposes of calculation. Calculation of the skewness statistic found no indication of skewness in the distribution of results for the correct prediction of outcomes (0.19, two standard errors of skewness [SES]: 0.48), but did find significant skewness in the area under the ROC curve results (-1.20, 2xSES: 0.48). However, a Q-Q plot for the areas under the ROC curve suggests that the deviation from normality was symmetrical (figure not shown). In summary, this means that two SDs for the correct prediction of hospitalization (2x2.18 = 4.36) can be take as the 95% CI for the results ie 72% ± 4.36.

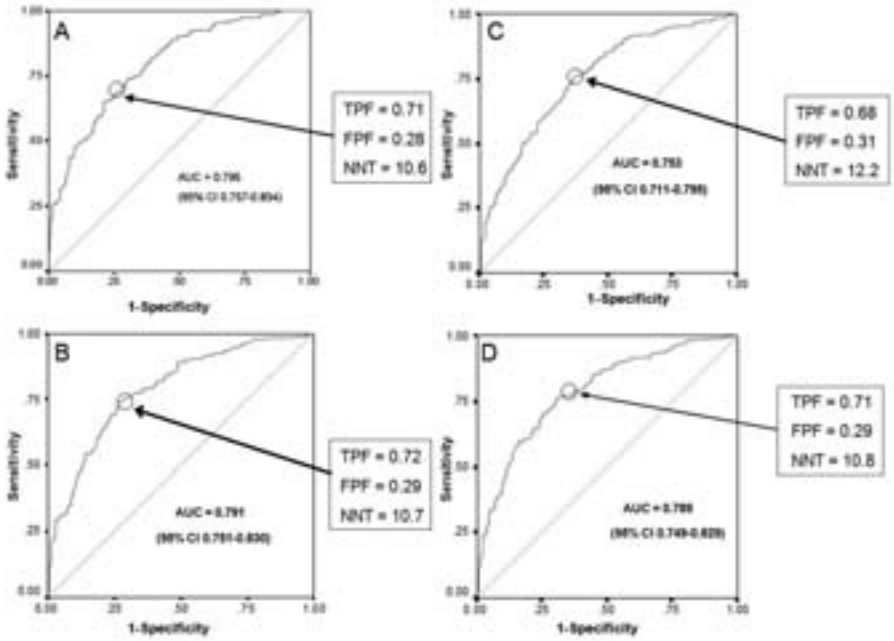

Figure 1. Receiver operating characteristic (ROC) curves for 15 variable model (A), final 7 variable model (B), 6 variable model for Munich test (C), and 6 variable model with sex removed (D).

The number needed to treat (NNT) at the point of maximum sensitivity/specificity is based on a hospitalisation rate of 5% and a treatment efficacy of 80%. Each point on the ROC curve represents a case being either a true positive or a false positive, based on their discriminant score. CI = confidence interval; TPF = true positive fraction; FPF = false positive fraction.

External Test: The Munich dataset did not include numbers of family members with wheeze, so coefficients obtained for the remaining six variables of the seven variable model were used. The recalculated six variable model was somewhat weaker than the seven variable model defined earlier. However, its power, derived by running the model on the FLIP data, was adequate for running the validation tests (correct classification: 68%; area under ROC curve 0.753 (Figure 1C).

When we used the six variables identified in the FLIP study to derive coefficients from the Munich dataset, the function derived solely from the Munich data was comparable to that obtained with the FLIP dataset (correct classification: 70% [table 2]; area under ROC curve 0.812, 95% CI 0.737-0.887). Applying the FLIP derived coefficients (from the seven variable model) to the Munich data produced a function that could correctly classify 64% of cases, with an area under the ROC curve of 0.677 (95% CI 0.551-0.804).

Spanish Guidelines Test: The discriminant function based on the guidelines recommendations could correctly classify 38% of cases, which is no better then chance, and had an area under the ROC curve of 0.520 (95% CI 0.468-0.573). The PPV was 36%, the NPV 100%, and the likelihood ratio 1.04. (It is worth remembering that a completely nondiscriminatory test that selects all patients for treatment except one, would have a NPV of 100% if this patient were truly negative.) Based on a 5% hospitalization rate and 80% efficacy, the NNT to prevent hospitalization of 75% of at risk infants was calculated to be 24.7.

Discussion

We have developed and validated a robust European predictive model to identify the risk of RSV-related hospitalization in infants born between 33-35 wGA. The FLIP 7-variable model correctly classifies over 70% of cases, which, to put into context, compares to a figure of 38% when using the Spanish Guidelines[16] for prophylaxis. The predictive ability of the model was confirmed through validation. The tight symmetrical distributions for both the correct predictions of hospitalization and area under the ROC curve results and the mostly convex nature of the ROC curve demonstrate that the model is not skewed by outliers in the FLIP dataset and is, therefore, highly reproducible however the data may be sampled. This lends a high degree of confidence to the model derived from the FLIP dataset.

The seven variables used in the final model were: birth within 10 weeks of the start of season, birth weight, breastfed for ≤2 months or not, number of siblings ≥2 years, number of family members with atopy, male sex, and number of family members with wheeze. All of these variables have been documented as risk factors for RSV-related hospitalization.[7,19,20,27] Indeed, a critical evaluation of the literature concluded that "male sex" and "crowding/siblings" were significant risk factors for severe RSV lower respiratory tract infection.[19] However, the same review also reported that a lack of breast feeding did not appear to increase the risk of severe RSV lower respiratory tract infection or RSV-related hospitalization.[19] A recently published nested case-control study supports that familial atopy and wheezing are strong determinants of RSV-related hospitalization.[27]

The strength and utility of the FLIP 7-variable model was highlighted by an examination of NNT. Assuming a 5% hospitalization rate and 80% treatment efficacy, the calculated NNT to prevent hospitalization of 75% of at-risk patients was 11 (range 10-14). A NNT of 11 is better than half the result if infants are prophylaxed based on the Spanish Guidelines recommendations[16] (25) and is considerably lower than the 17 obtained from using the raw numbers of the IMpact-RSV trial.[12]

Although various analytical approaches were considered, it

was decided to develop the model using discriminant function analysis. This approach produced similar results to logistic regression, but was arguably more applicable in the manipulation involved in validation, such as handling missing values and continuous data. Further, models derived from discriminant function analysis can benefit from the inclusion of variables that are not independently significant, but which contribute to the overall predictive ability of the model. Indeed, the discriminatory power of such models is always greater than that afforded by the simple sum of its component parts. To exemplify this, one of the seven variables in the final model was not independently significant (male sex), but is a well known risk factor.[19] The model also has good flexibility, as the sensitivity and specificity along the ROC curve can easily be varied such that different cutoff points can be selected and NNTs calculated according to the needs of the individual European country.

As is the case whenever developing such a model, limitations were imposed by what and how data were captured within the base dataset. Although the FLIP study[9] contained a great deal of information on risk factors and hospitalization rates for children born between 33-35 weeks' GA, it was limited by being a case-control study. Since RSV infection had to be proven and these were likely to have been the most severe cases, this might have lead to selection and, therefore, bias in the dataset. Further, allowance had to be made for the variability in admission criteria for the various hospitals across Spain. Finally, since day care attendance is not commonly practiced in Spain, there were limited data on this variable and it was not included in the final analyses.

External validation of the model presented a challenge as there were no suitable databases in Europe that were available for such a purpose. As a surrogate, the model was tested against data from the Munich RSV study. Allowances have to be made for the differences in how the study was conducted and what data were captured compared with FLIP. For example, no data were captured on wheeze in the Munich study. Perhaps most significantly, data were available for only 20 hospitalized infants within the Munich study. Further, only six of the hospitalized infants had a confirmed diagnosis of RSV, as testing is not routine in Germany. Taking these differences into consideration, the test can be considered a worse case scenario, as it would be not be expected for the model to validate particularly well against the Munich data. However, despite these significant limitations, the FLIP model tested very well against the Munich data. Nevertheless, rigorous external validations of the model are planned when suitable prospective data become available within Europe over the next couple of years.

A recently published Dutch model,[28] which estimated the monthly risk of hospitalization, reported that gender, GA, birth weight, presence of bronchopulmonary dysplasia, age, and seasonal monthly RSV pattern were significant predictors and could potentially be used to discriminate between high and low risk children. The Dutch model included only risk factors that were reported as independently significant in the published literature. In comparison, all risk factors available within the FLIP dataset were included within our modelling, regardless of their individual significance. In addition, the Dutch model does not specifically address the group we are trying to predict RSV-related hospitalisation within, namely, those infants born 33-35 wGA without CLD. Finally, the Dutch model imputed missing values, whereas in the development of the FLIP model, patients with incomplete records were excluded from the analyses. Several other studies have proposed using identified risk factors to predict RSV hospitalization in premature infants;[7,20,29] however, as far as the authors are aware, no other models or scoring systems have been formally published.

Importantly, although the significance of the individual risk factors may vary between countries, the validation and testing process indicates that the model may be applicable for widespread use across Europe. Moreover, the model appears flexible yet robust enough that, if necessary, individual variable parameters can be modified to suit the needs and of individual countries. Further, although the model is suitable for adoption as it stands, countries could use their own data, either existing or prospectively collected, to refine a predictive tool. When considering intervention levels within a predictive tool, variation in hospitalization rates for RSV across different countries would not affect the performance of the model in terms of prediction, as this is not factored into the analysis.

The model could be realized as a working tool in a variety of formats to optimize its applicability to an individual country, or, indeed, an individual unit. Formats could potentially include a bespoke software application, a website, a simple spreadsheet, or even a paper-based form or nomogram. The big advantage of a software application or website is that either could prospectively capture risk factors and outcomes data, which could be used to further refine and validate the model and justify its continuing use. The tool itself would be used in daily practice to predict the risk of RSV-related hospitalization for individual infants. Chronic conditions such as CLD, congenital heart disease, and severe neurological diseases may further increase the risk of RSV-related hospitalisation, and, therefore, should always be taken into consideration when using the tool.

Conclusions

By using data from the Spanish FLIP study[9] and carrying out validation, we have produced an evidence-based model which is applicable for adaptation and use in different countries across Europe. The model has the potential to improve standards of care by better identifying high risk infants and, thus, optimizing prophylaxis. It may also be used to inform guidance and to help clarify the justification of funding and reimbursement for palivizumab within health services. Finally, this study has led to a better understanding of the risk factors and their interrelationships for infants born between 33-35 weeks' GA.

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The Fetuses-at-Risk Approach: Clarification of Semantic and Conceptual Misapprehension

K. S. Joseph

Abstract

Background: Although proponents of the fetuses-at-risk approach describe it as a causal model that resolves various conundrums, several areas of semantic and conceptual misapprehension remain. Differences in terminology include use of denominators such as "ongoing pregnancies" and the need for an ad hoc "correction factor" in order to calculate gestational age-specific rates. Further, there is conceptual disagreement regarding the proper candidates for neonatal death and related phenomena. Perhaps the most egregious misconception is the belief that rising rates of gestational age-specific perinatal mortality observed under the fetuses-at-risk model automatically imply the need for indiscriminate increases in iatrogenic preterm delivery.

Discussion: The term "fetuses at risk" addresses the plurality of candidates for stillbirth in a multi-fetal pregnancy, while the use of standard terminology such as "cumulative incidence" and "incidence density" harmonizes the language of perinatal epidemiology with that used in the general epidemiologic literature. On the conceptual side, it is necessary to integrate clinical insights regarding latent periods into models of neonatal morbidity and mortality. The contention that the fetuses-at-risk approach implies the need for indiscriminate iatrogenic preterm delivery is a non-sequitur (just as rising age-specific cancer death rates do not imply the need for routine chemotherapy and radiation for all middle aged people). Finally, the traditional and fetuses-at-risk models are better viewed in terms of function as prognostic (non-causal) and causal models, respectively.

Conclusion: A careful examination of terms and concepts helps situate the traditional perinatal and the fetuses-at-risk approaches within the broader context of non-causal and causal models within general epidemiology.

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Background

A recent Commentary[1] in the Journal addressed methodologic issues related to gestational age and contested several points discussed in my recent paper on obstetric theory.[2] Whereas this debate has served to focus attention on several key issues in perinatology, some areas of semantic confusion and conceptual misapprehension remain [see sidebar for original article info].

The Commentary advocated using "ongoing pregnancies" as the denominator for calculating the antepartum risk of stillbirth. An alternative term is "fetuses at risk" for antepartum stillbirth.[3-5] The difference between the two denominators is minor, though the distinction, which recognizes the plurality of candidates for antepartum stillbirth within multi-fetal pregnancies, is necessary from an epidemiologic perspective.

A second semantic issue relates to the details of risk quantification. The number of fetuses at risk for antepartum stillbirth decreases from the beginning to the end of each gestational week and the pattern of this decrease varies before and after 40 weeks gestation. The Commentary addressed this by highlighting the need for an ad hoc correction factor.[6] We choose to address the same issue by invoking standard epidemiologic terminology,[5] namely, cumulative incidence (the proportion of a fixed population that develops the outcome of interest over a specified time period) and incidence density (the ratio of the number of new cases of the outcome of interest to the person-time at risk).[7]

With these epidemiologic terms defined, it becomes evident that the prospective risk of stillbirth[8] at any gestation is a cumulative incidence, with the duration over which incidence is measured left open ended (similar to the lifetime cumulative incidence of breast cancer). Alternatively, the cumulative incidence of stillbirth at any gestation can be estimated within a specific time window. From an obstetric perspective, a meaningful length for the time interval would encompass the period after a clinical examination during which fetal/maternal status is expected to be stable, with the specific duration dependent on the risk status and gestation of the pregnancy and the clinical assessment in

question. With medically indicated early delivery predicated on the short-term risks of serious events, it becomes evident that quantification of an open ended prospective risk of stillbirth is not central to the practice of obstetrics.

Conceptual issues

The extension of the fetuses-at-risk approach to encompass perinatal death and other phenomena is criticized in the Commentary because many such events, exemplified by death in the neonatal period, do not occur among fetuses. Such criticisms can be countered on clinical and epidemiological grounds. The focus in modern obstetrics extends well beyond fetal outcomes and encompasses concerns regarding neonatal death, serious neonatal morbidity and even neurodevelopmental disability at 2 years of age.[9,10] This extended focus reflects an appreciation of latent periods (ie, the time interval between disease occurrence and detection.[7] For instance, it is well recognized that the neurologic injury that characterizes cerebral palsy is typically sustained in utero, despite becoming clinically evident a year or more after birth.[11,12] The extended fetuses-at-risk model therefore proposes that the gestational age-specific rates of outcomes such as cerebral palsy are more appropriately calculated using fetuses as the candidates for cerebral palsy.[13] The same argument applies to neonatal death – the pathological events that result in neonatal death typically occur during the intrauterine period. From an epidemiologic standpoint as well, it is commonplace to estimate cancer and other cause-specific mortality rates by age, and in the perinatal realm, calculations of cause-specific infant mortality (eg, rate of infant deaths due to congenital anomalies) use all live births in the denominator.[14]

Perhaps the single, most serious misunderstanding regarding the fetuses-at-risk approach in the Commentary relates to the issue of rising gestational age-specific perinatal mortality rates and the consequent implications for iatrogenic preterm delivery. Although perinatal mortality rates do increase with increasing gestation in fetuses-at-risk models, it is a profound misconception to state that such a pattern automatically implies the need for indiscriminate increases in preterm induction or preterm cesarean delivery. This non-sequitur is analogous to suggesting that those who document the age related rise in cancer mortality advocate routine chemotherapy and radiation for the middle aged.

Selective, carefully-timed, early delivery given fetal compromise (or maternal indication) is the cornerstone of modern obstetrics. Whether early delivery at any gestation can save a compromised fetus depends on the gestational age of the fetus, the degree of compromise and the technologic package available for effecting early delivery and caring for the newborn. Iatrogenic early delivery is carried out at preterm gestation only if the overall risks to the fetus of a continuing pregnancy are judged to exceed those of early delivery and supportive neonatal care. This judgement involves an informal or formal balancing of harms versus benefits.[2,5]

The Commentary provides a listing of outcomes whose rates are judged to require particular denominators. Our alternative viewpoint posits that the choice of denominator depends on whether one seeks to build a causal or prognostic (non-causal) model.[5,13,15] Fundamental caveats in this context include whether: 1) gestational age is to be treated as survival time (causal model) or as just another determinant (prognostic model); 2) the entire biologic continuum from fetus to infant needs to be represented (causal model) or whether a truncated period will suffice (prognostic model); 3) a restrictive approach to variable selection, which avoids variables in the causal pathway, is deemed appropriate (causal model) or whether a more liberal approach is considered appropriate (prognostic model).

Thus models that predict neonatal death among live born infants and use determinants such as gestational age can be valid for prognostic purposes and can serve an important social/medical purpose. On the other hand, such models lead to awkward paradoxical phenomena, for example, by consistently showing that preterm infants of smokers have lower mortality rates than preterm infants of non-smokers. These and other conundrums require a causal model for explication.[5]

This debate highlights the dichotomy that prevails in the use of fundamental epidemiologic constructs within perinatal epidemiology versus other epidemiologic domains. A careful examination of terms and concepts helps situate the traditional perinatal and the fetuses-at-risk models within the broader context of causal and non-causal models in general epidemiology.

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Measuring Perinatal Complications: Methodologic Issues Related To Gestational Age

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Perinatal outcomes differ by week of gestational age. However, it appears that how measures to examine these outcomes vary among various studies. This paper explores how perinatal complications are reported and how they might differ when different denominators, numerators, and comparison groups are utilized.

One issue that can clearly affect absolute rates and trends is how groups of women are categorized by their gestational age. Since most perinatal outcomes can only occur in women and neonates who have delivered, using the number of pregnancies delivered as the denominator of outcomes is appropriate. However, for an outcome such as antepartum stillbirth, all women who are pregnant at a particular gestational age are at risk. Thus, the denominator should include all ongoing pregnancies. When gestational age is used by week this means using both deliveries during a particular week plus those women who deliver beyond the particular week of gestation in the denominator. Researchers should be careful to make sure they are utilizing the appropriate measure of perinatal complications so they do not report findings that would be misleading to clinicians, patients, and policy makers.

Traditional perinatal epidemiology utilized metrics such as the neonatal mortality rate (number of neonatal deaths per 1,000 live births) and the perinatal mortality rate (number of neonatal deaths plus stillbirths per 1,000 total births). Prior to the current age of birth certificate and other large electronic databases, expanding computational power, and statistical software packages, it was recognized that these simple metrics had some small problems, but gave reasonable estimates to compare risk factors. While much of the technological advances have led to better statistical techniques for controlling potential confounders and quicker analysis of large data files, there has been little attempt to develop appropriate metrics to examine rates of perinatal morbidity and mortality and to further improve the accuracy of these measures. This is unfortunate, as the thoughtful approach to measuring complications of pregnancy is paramount and different methods can lead to entirely different outcomes and conclusions.

For example, when examining the complications among all patients with term and post-term pregnancies (37 0/7 weeks and beyond), the denominators can simply be either per 1,000 live births or total births. However, when simply dichotomizing these births to examine the effect of post-term pregnancies (42 0/7 weeks and beyond) as compared to term pregnancies (37 0/7 ñ 41 6/7 weeks of gestation), the denominator used can matter, depending on the outcome examined. In the setting of antepartum stillbirth, one cannot simply use total births as the denominator because the pregnancies at risk of an antepartum stillbirth are not only those pregnancies delivered at a particular gestational age, but all pregnancies that reached that gestational age (ie, ongoing pregnancies). Thus, for this simple example, the denominator for the term pregnancies should include all of the term pregnancies as well as the post-term pregnancies, while the denominator for the post-term pregnancies should include just the post-term pregnancies. Most commonly, when describing the risk of complications, the week of gestation is used. Thus, the denominator for an outcome measured with respect to pregnancies delivered, would simply be those pregnancies delivered during that particular week. When the outcome is better examined using ongoing pregnancies, this means using both deliveries during a particular week plus those women who deliver beyond the particular week of gestation in the denominator.

In a recent paper by Joseph, the idea of using the ongoing pregnancy denominator was explored beyond simply stillbirths to include all perinatal deaths as well as small for gestational age. There are fundamental problems with modifying the denominator for neonatal deaths and SGA as they can only be diagnosed in neonates that are delivered. Thus, the following text will review different approaches to analyzing a variety of perinatal complications with a focus on determining the correct denominator and identifying the proper control group when making comparisons. Broadly, the discussion will focus on two clinical/research settings: Measuring perinatal complications by gestational age and examining obstetric interventions such as induction of labor.

The denominator used is paramount when considering complications of term and post-term pregnancies. The effects of utilizing the wrong denominator in the setting of antepartum stillbirth are primarily: 1) the absolute rate of antepartum stillbirth is increased when the smaller, inappropriate, denominator is utilized and 2) the relationship of the relative rates of stillbirth by week of gestation is distorted. One of the

earlier commentaries on this problem noted that if the risk of antepartum stillbirth was considered by week of gestation using the denominator of total live births occurring at that gestational age, the risk seemed highest among preterm patients as they had the smallest denominators. However, when they utilized the denominator of ongoing pregnancies, they found that the rate of antepartum stillbirth decreased until 39 weeks of gestation, then increased through 41ñ42 weeks of gestation. It was demonstrated that since the women who deliver during a particular week are not actually at risk for antepartum stillbirth the entire week, a correction factor can be applied. Without it, there is an obvious difference in the overall trend when examining the antepartum stillbirth rates by PD and OP. However, when using the correction factor, the rise in antepartum stillbirths occurs earlier and appears to be more dramatic.

But even this formula has two flaws that can be rectified with better data. The first is that while the use of the correction term will subtract one half of the births in a particular week in order to get a better estimate of ongoing risk, in any particular week of pregnancy, the number of births per day is unlikely to be a uniform distribution. Rather, like the overall distribution of gestational ages, the number of births will increase prior to 40 weeks of gestation and decrease thereafter. Thus, the exposure to the women delivered at a given week of gestation is likely to be higher prior to 40 weeks of gestation and lower after this threshold. Furthermore, the correction term will lead to a falsely larger denominator for the women prior to 40 weeks of gestation and a smaller denominator for women after 40 weeks of gestation.

The second problem is that while we utilize the day that the patient delivers as the gestational age of the antepartum stillbirth, by definition, the stillbirth may occur prior to the day of delivery. Just how much prior to delivery stillbirth occurs may lead to a lag effect in the difference in the estimated rates. For example, if all of the antepartum stillbirths occurred, on average, a week prior to their delivery, then the rates would necessarily increase a week earlier than currently estimated. Thus, a better approximation of the gestational age of stillbirth would be to generate an estimate of the date at which stillbirth occurs using the date(s) of the last known viable heart rate, last known fetal movement, and the date the stillbirth was documented.

Even among those who are interested in improving the antepartum risk assessment of stillbirth, there is disagreement on how to measure and utilize this risk. A controversial paper on the topic, Cotzias et al, used ongoing pregnancy as the denominator, but changed the numerator to include all current and future stillbirths to generate a prospective stillbirth risk. Using this equation, they found that the prospective stillbirth risk was higher with preterm gestations, decreased in term pregnancies until 40 weeks of gestation, then increased through 42 weeks of gestation. They used these calculations to suggest that induction of labor should be considered with the onset of fetal pulmonary maturity at 38 weeks of gestation. The responses to this article found the use of this calculation objectionable as the rate of stillbirth derived from such estimation does not consider the length of time of exposure, nor does the suggestion of early induction of labor consider the costs or the marginal, incremental benefits that might be incurred or achieved.

While it is clear that ongoing pregnancies should be utilized in the denominator for antepartum stillbirth as these are the women at risk, it is less clear whether other maternal or neonatal complications of pregnancy should be considered in the same way. Consider neonatal and perinatal deaths (stillbirths plus neonatal deaths). In order for a neonatal death to occur, the fetus had to become a neonate by being born. Thus, the fetuses of ongoing pregnancies are not yet at risk. This leads to the rate that has been used historically, that is, the number of neonatal deaths divided by the number of live births. Therefore, this is a problem with the metric proposed by Joseph. In a recent paper which suggests combining stillbirths plus neonatal deaths into one outcome, it is demonstrated that such a metric finds the risk of perinatal death to rise beyond 35 weeks of gestation, supporting possibly earlier induction of labor. Unfortunately, while at term, such decision-making based on the ongoing risk of stillbirth is sensible, causing more preterm births which are themselves associated with higher rates of morbidity and mortality may not be supported by such algebraic manipulation. A better measure of the total ongoing risk to a pregnancy was proposed by Smith as what he describes as the cumulative probability of perinatal death which combined both stillbirth and neonatal deaths.

What about measures of neonatal morbidity? These might include five-minute Apgar scores less than 4 or 7, admission to the neonatal intensive care unit, birth trauma, or intrauterine growth restriction (birthweight < 3rd, 5th, or 10th percentile). For all of these outcomes, the neonate cannot experience the outcome until birth, so the standard measure utilizing pregnancies delivered should apply. The birthweight metric should also be examined using pregnancies delivered, since one does not know the actual birthweight until the infant is delivered. Interestingly, one could use the estimated fetal weight from sonographically predicted birthweight to generate risks of intrauterine growth restriction. If one did perform weekly ultrasounds of an entire population of pregnant women, then, and only then, could ongoing pregnancy be used as the denominator.

Again, Joseph uses "revealed SGA" as the number of SGA fetuses born at a particular gestational age over a denominator of all ongoing pregnancies. This metric, will of course increase over time as the denominator shrinks with further deliveries, so again provides little insight to an optimal time of delivery. The only types of neonatal morbidities that can be measured using ongoing pregnancies as a denominator would be those that can be measured in all pregnancies. For example, if we routinely measured all in utero fetuses by ultrasound and identified the SGA fetuses, then the proper denominator would be ongoing pregnancies. However, since we wouldn't deliver these SGA fetuses before 34ñ36 weeks of GA, the numerator would have to be the SGA fetuses identified by ultrasound, not delivered.

For maternal complications of pregnancy, it is more difficult to identify the group of women at risk for various complications of pregnancy. There are some complications which clearly occur in women who are antepartum. For example, preeclampsia is usually an antepartum diagnosis. Thus, it makes sense to utilize ongoing pregnancies as the denominator when estimating the risk of preeclampsia at a particular week of gestation. For mode of delivery (cesarean, vaginal, or operative vaginal) and outcomes related to the mode of delivery such as wound complications or perineal lacerations, clearly pregnancies delivered should be used as the denominator. However, there

are a number of complications that can occur either prior to the onset of labor or during labor such that determination of the appropriate denominator to be used may be difficult. For example, chorioamnionitis occasionally occurs prior to the onset of labor. In this setting, its risk should be determined based on all women at risk, ie, ongoing pregnancies. However, the majority of chorioamnionitis occurs during labor, and thus would only apply to the pregnancies delivered during a particular week of gestation. The same holds true for placental abruption, which can occur prior to the onset of labor, but its risk is increased during labor. When attempting to describe these risks, it is important to specify what aspect of the complication is being examined.

Of note, in studies that examine perinatal morbidity by gestational age at term, a number of complications appear to increase with increasing week of gestation beyond 38 to 39 weeks. Complications which do increase by week of gestation at term include neonatal outcomes such as acidemia and macrosomia as well as maternal morbidities such as preeclampsia, postpartum hemorrhage, perinatal infection, and cesarean delivery.

For some time, it has been assumed that induction of labor is associated with an increased risk of cesarean delivery. Interestingly, the majority of studies reporting that labor induction is associated with an increased rate of cesarean delivery are not randomized trials. However, when induction of labor and mode of delivery are considered more carefully, some interesting contradictions arise. While large, prospective, randomized, controlled trials of labor induction in low-risk women at term are yet to be conducted, a number of randomized trials which examined induction of labor in several high-risk subgroups, including post-term pregnancy, pregnancies complicated by diabetes, and pregnancies suspicious for large-for-gestational age fetuses. Studies that examined pregnancies at or beyond 41 weeks of gestation have demonstrated a decrease in cesarean delivery among women who have undergone induction of labor. Prospective trials report no statistically significant difference in the rate of cesarean delivery in pregnant women with diabetes and in those who were induced for suspected fetal macrosomia.

Thus, the existing prospective randomized trials directly contradict the retrospective or prospective cohort or case-control studies by demonstrating either a decrease or no difference in cesarean delivery. One possible reason for the discrepancy between these two types of studies is that the majority of the cohort and case-control studies do not control for gestational age. Since induction of labor is likely to occur more often as gestational age increases, and increasing gestational age itself is a risk factor for cesarean delivery, this is an important confounder to consider in the analysis of such data. However, confounding by gestational age does not entirely explain the above discrepancy, since there are recent studies that do control for gestational age and still find that induction of labor is associated with cesarean delivery. Consider the analytic design: by either matching on gestational age or utilizing multivariable techniques to do so, one makes a comparison between women who are induced at a given gestational age as opposed to women who experience spontaneous labor at the same gestational age. However, when caring for a pregnant woman at term, a clinician's options are not between induction of labor and spontaneous labor; rather, the options at hand are induction of labor versus expectant management of the pregnancy, the latter of which results in either spontaneous labor or induction at a greater gestational age.

In order to examine the effect of comparing induction of labor to spontaneous labor by week of gestation, a recent analysis of this question was conducted. In the comparison that is commonly made, namely when women who underwent labor induction were compared to those with spontaneous labor, the cesarean delivery rate was higher for women being induced at each gestational age. However, when women who underwent labor induction were compared to the expectant management group, the differences in the bivariate comparisons were not statistically significantly different. Further, when the potential confounders were controlled for, the cesarean delivery rate was statistically significantly higher for the expectant management group at 38, 39, and 40 weeks.

Thus, it appears that in this setting, choosing the appropriate comparison group is enormously important as it changes the findings from induction of labor leading to higher rates of cesarean delivery to induction of labor leading to either no difference or even lower rates of cesarean, depending on the gestational age.

With the increasing availability of large birth cohorts and datasets, it is incumbent upon researchers to carefully choose their metrics and comparison groups when examining perinatal complications and mode of delivery. Determining the wrong absolute rate, or more seriously, concluding findings in the opposite direction, could lead to misleading information for clinicians, patients, and policy-makers alike. In this light, it is also important for journal editors and reviewers to ensure that appropriate measures are being utilized.

It should be noted that the intent of combining stillbirths plus neonatal deaths as a measure of pregnancy outcome for interventional trial is well-intended. However, how best to do so is a bit unclear. If a trial was investigating a drug utilized throughout pregnancy and the intent was to have mortality play a role as one of the outcomes, one simple way would be to simple compare the proportions of pregnancies which experienced a mortality event, whether fetal or neonatal. However, if the intent was to develop a metric which incorporated weeks of pregnancy at risk, it should be made clear that this would really only apply to stillbirths, not neonatal deaths. In that setting, one could simply control for gestational age at delivery, or use as a denominator, total weeks of pregnancy for the stillbirths, but the neonatal deaths would need to be examined as a separate outcome. Certainly, the metric of revealed SGA would, similarly, be best as proportion of SGA infants out of the total.

When the issue of outcome by week of gestation is the primary outcome to be examined, careful choice of the appropriate denominator is paramount as demonstrated both in the work on stillbirth and induction of labor. However, in the setting of interventional trials, this is less important. Certainly, the most important issue is that for any study, careful attention be paid to choosing the appropriate outcome measures and how best to measure them.

The Need to Reform Our Assessment of Evidence From Clinical Trials

Sean M. Bagshaw, Rinaldo Bellomo

"All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."
—Sir Bradford Austin Hill

Abstract

The ideology of evidence-base medicine (EBM) has dramatically altered the way we think, conceptualize, philosophize and practice medicine. One of its major pillars is the appraisal and classification of evidence. Although important and beneficial, this process currently lacks detail and is in need of reform. In particular, it largely focuses on three key dimensions (design, [type I] alpha error and beta [type II] error) to grade the quality of evidence and often omits other crucial aspects of evidence such as biological plausibility, reproducibility, generalizability, temporality, consistency and coherence. It also over-values the randomized trial and meta-analytical techniques, discounts the biasing effect of single center execution and gives insufficient weight to large and detailed observational studies. Unless these aspects are progressively included into systems for grading, evaluating and classifying evidence and duly empirically assessed (according to the EBM paradigm), the EBM process and movement will remain open to criticism of being more evidence-biased than evidence-based.

Introduction: The widespread acceptance of the principles of Evidence-Based Medicine (EBM) have generated a significant paradigm shift in clinical practice, medical education and in how studies are designed, reported, appraised and classified.

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The general principles of EBM are now considered as the golden standard for appraising the quality and strength of evidence created through clinical research. These principles also allow for evidence to be classified into different levels according to specific characteristics. From these categorical levels of evidence, recommendations are generally issued, each with its own grade. (Table 1) These summary recommendations on evidence are then typically used to influence clinical practice through consensus conferences, clinical practice guidelines and systematic reviews or editorials on specific aspects of patient care.

In this commentary, we will argue that the present system(s) for classifying the quality of evidence and subsequent formulation of graded recommendations would benefit from reform. A reformed method for classifying evidence should integrate additional dimensions of evidence not traditionally considered, as well as incorporate a method of assigning weight to each dimension when determining the overall quality of the evidence. In this context, we will further comment on the newly proposed hierarchal system, the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system, for gauging the quality of evidence and strength of recommendations from research evidence. The objective of our reflections is to generate further dialogue and discussion about how we currently evaluate evidence from research and how we might improve such evaluation.

Prediction, truth, and evidence: Ideally, physicians would be able to predict the biological future and clinical outcome of their patients with unbiased certainty and naturally use this knowledge in their care. As an example, physicians would know that the early administration of tissue plasminogen activator (tPA) to a patient with acute massive pulmonary embolism would lead to survival where other interventions would not. Moreover, the physician would also know with certainty that the patient would not suffer any harm as a consequence of having received tPA.

Regrettably, we cannot predict the biological and clinical future with such certainty. Rather, the physician can only be partly reassured by knowing the operative truth for questions about this intervention: What would result if all such patients

Table 1: Summary of a simplified evidence hierarchy, A) Levels of evidence across clinical research studies, and B) Grading of recommendations based on levels of evidence (Adapted from [2,3])

A)	
Levels of Evidence	
Level I	Well conducted, suitably powered RCT
Level II	Well conducted, but small and under powered RCT
Level III	Non-randomized observational studies
Level IV	Non-randomized study with historical controls
Level V	Case series without controls
B)	
Grades of Recommendations	
Grade A	Level I
Grade B	Level II
Grade C	Level III or lower

with massive pulmonary embolism were randomly allocated to receive either tPA or an alternative treatment? Would one intervention significantly increase survival over the other? By what magnitude would survival increase? How would such an increase in survival weigh against the potential harms? The physician could then apply knowledge of the operative truth about such interventions to guide the course of patient care.

Yet again, such truth in absolute terms is unknown. Rather, physicians are dependent upon estimation and/or measures of probability of the truth for predicting the biological and clinical future of interventions. Naturally, we obtain and apply estimates of the effects of an intervention through the generation of evidence.

Evidence, can be derived from a multitude of sources: from personal experience, teaching by mentors, local practice patterns, anecdotes, case series, retrospective accounts, prospective observations, non-interventional controlled observations, before-and-after studies, single center randomized evaluations, randomized evaluation in multiple centers in one or more countries to blinded randomized multicenter multi-national studies. The evidence generated in each of these forms has both merits and shortcomings. Nonetheless, the focus of this discussion is an examination of how the medical community currently formally appraises, classifies and grades the various forms of evidence.

The process of understanding how new, evolving or "best evidence" is translated into knowledge integrated into patient care remains a great challenge. All physicians would generally agree that the provision of high quality care in medicine would, at a minimum, mandate that clinical practice be consistent with the current best evidence. Naturally, as a consequence of this notion, numerous evidence hierarchies for classifying and generating recommendations have arisen to aid the busy physician in decisions about management of patients. While they may all have a common theme, to promote the use of best evidence in clinical practice, their redundancy may add confusion and threaten to dilute the overall value of EBM.

The evidence hierarchy: The evidence hierarchy should emphasize that evidence exists on a continuum of quality. Simply, the evidence generated from some study designs is logically more prone to bias than other designs and, as a consequence, has traditionally provided a weaker justification for influencing clinical practice. Unfortunately, as the levels of evidence have traditionally been expressed as step-wise increases in strength (levels), they have failed to emphasize such continuity.

The apex of the pyramid of evidence has generally been considered the well-conducted and suitably-powered multicenter multi-national blinded placebo-controlled randomized trial. Such a trial would be characterized by demonstration that intervention X administered to patients with condition A leads to a significant improvement in a clinically-relevant and patient-centerd outcome (ie survival), when compared to placebo, assuming a genuine and plausible treatment effect of intervention X.

By all current evidence hierarchies, this would be considered as level I evidence that intervention X works for condition A. (Table 1) These findings would generally elicit a strong recommendation (ie Grade A) to conclude that intervention X would benefit patients with condition A, assuming no contraindications and that the patients fulfilled all the necessary inclusion/exclusion criteria used to enrol patients in the trial. Yet, there may be circumstances where a strong recommendation may not be appropriate for such a trial. This may occur when an intervention does not lead to or is not correlated with improvements in a clinically-relevant patient-centered outcome, when a trial employs, as a primary outcome, a surrogate measure (ie physiologic or biochemical endpoint) or when the apparent harm related to an intervention outweighs the benefit. Under these conditions, a lower grade of evidence may be assigned (ie Grade B).

In the absence of suitably-powered multicenter multi-national blinded placebo-controlled randomized trials, many would also regard a high-quality systematic review as level I evidence. Yet, systematic reviews require vigilant interpretation and should not necessarily be considered as high level evidence due to issues related to poor quality, incomplete reporting and the inclusion of evidence from trials of poor quality. We contend that systematic reviews/meta-analyses represent an important hypothesis generating activity. However, meta-analyses are not primary evidence, they are statistically assisted interpretations of primary evidence. They have been shown to contradict by confirmatory trials, especially when such meta-analyses are based upon small, low quality studies. We argue that meta-analyses, while perhaps having an important role for the synthesis of previous or current evidence, emphasizing deficiencies and creating a research agenda, they should not be used for devizing recommendations. As such, should likely be deemphasized and/or even removed from any classification of evidence in a reformed classification system.

This archetypal hierarchal system would appear reasonable and not in need of reform. Yet, we also contend that traditional hierarchal systems have broadly focused on only three dimensions for defining, classifying and ranking evidence: study design; probability of an alpha or type-I error; and probability of beta or type-II error. We consider these fundamental aspects of trial design for evidence hierarchies below and further discuss a recent initiative (the GRADE system) to improve and standardize how evidence generated from clinical research is classified and graded. Before embarking upon a detailed discussion of the tools used to assess the quality of evidence, we wish to emphasize that no EBM tool can be possibly expected to answer all questions related to evidence. We further notice that a good randomized

Table 2: Overview of the GRADE system for grading the quality of evidence (Adapted from Reference[7]): A) Criteria for assigning grade of evidence; B) Definitions in grading the quality of evidence.

A)	
Criteria for assigning level of evidence	
Type of Evidence	
Randomized trial	High
Observational study	Low
Any other type of research evidence	Very low
Increase level if:	
Strong association	(+1)
Very strong association	(+2)
Evidence of a dose response gradient	(+1)
Plausible confounders reduced the observed effect	(+1)
Decrease level if:	
Serious or very serious limitations to study quality	(-1) or (-2)
Important inconsistency	(-1)
Some or major uncertainty about directness	(-1) or (-2)
Imprecise or sparse data*	(-1)
High probability of reporting bias	(-1)

B)	
Definitions for levels of evidence	
High	Further research is not likely to change our confidence in the effect estimate
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low	Any estimate of effect is uncertain

*Few outcome events or observations or wide confident limits around an effect estimate

controlled trial is neither necessary nor sufficient to change practice. However, as we argue below, both are perfectible in specific directions.

The Grades of Recommendation Assessment, Development and Evaluation (GRADE) System

An updated scheme for grading the quality of evidence and strength of recommendations has been developed by the GRADE Working Group, GradeWorkingGroup.org. The primary aim of this informal collaboration was to generate broad consensus for a concise, simplified and explicit classification system that addressed many of the shortcomings of prior hierarchal systems. Moreover, the GRADE Working Group proposed to improve the standardization and transparency of grading evidence and formulating recommendations when translating research evidence into clinical practice.

The GRADE system defines the "quality of evidence" as the amount of confidence that a physician may have that an estimate of effect from research evidence is in fact correct for both beneficial and harmful outcomes. A global judgment on quality requires interrogation of the validity of individual studies through assessment of four key aspects: basic study design (ie randomized trial, observational study), quality (ie allocation concealment, blinding, attrition rate), consistency (ie similarity in results across studies) and directness (ie generalizability of evidence). Based on each of these elements and a few other modifying factors, evidence can then be graded as high, moderate, low or very low (Table 2).

The "strength of a recommendation" is then defined as the extent in which a clinician can be confident that adherence to the recommendation will result in greater benefit than harm for a patient. Furthermore, there are additional important factors incorporated into the GRADE system that affect the grading of the strength of a recommendation such as target patient population, baseline risk, individual patients' values and costs.

The GRADE system represents a considerable improvement from the traditional hierarchies of grading the quality of evidence and strength of recommendations and has now been endorsed widely by a spectrum of organizations and societies. Yet, we believe there remain elements of evidence from research that have not been explicitly addressed in the GRADE system and require further consideration and debate.

Traditional measures of the quality

Study Design: The design of a clinical trial is a central determinant of its performance and outcome. The principles of EBM would typically focus on several simple key components of study design, such as measures aimed at reducing the probability of bias (ie randomization, allocation concealment, blinding). This philosophical stance assumes that the randomized controlled trial represents the "gold standard" as the most scientific and rigorous study design available. Accordingly, for a trial to be classified as level I evidence, it essentially requires incorporation of all of these elements into the design. This approach, while meritorious, often fails to consider additional aspects of study design that warrant attention.

First, as an example, in the ARDS Network trial evaluating the impact of low tidal volume ventilation in critically ill patients with acute respiratory distress syndrome (ARDS) on mortality, it now appears that, in the study centers, not all patients allocated to the control group were given a current or near-current accepted therapy or standard of practice. Second, this

Table 3: Aspects of association to consider prior to the provisional inference of causation as proposed by Sir Austin Bradford Hill (Adapted from [1])

Criteria	Description
Strength	Correlation or relative measures of effect (i.e. risk ratio)
Consistency	Across variable studies in design, populations, settings, circumstances, and time
Specificity	Intervention causes the effect
Temporality	Intervention precedes effect
Biologic Gradient	Dose-response curve between intervention and effect
Plausibility	Based on the current biologic knowledge of mechanisms of disease
Coherence	In the context of knowledge of natural history and related treatments
Experiment	Prospective clinical investigations of hypotheses

Table 4: Selected historical examples of interventions widely endorsed and seldom contested that are not based on any evidence from randomized trials. (Adapted from [63])

Intervention
Blood transfusion for severe hemorrhagic shock
Defibrillation for ventricular fibrillation or pulseless ventricular tachycardia
Neostigmine for myasthenia gravis
Suturing for repair of large wounds
Closed reduction/splinting for displaced long-bone fractures
Insulin for diabetes mellitus
Directed pressure/suturing to stop bleeding
Activated charcoal for strychnine poisoning

pivotal trial cannot be easily classified according to the GRADE tool. It is unclear how one can classify trials that assess the implementation of protocols or changes in process of care, which, cannot be blinded. Despite being an unblinded protocol-driven trial, such trials provide the best possible evidence in the field. Assessment of such processes is complex. Clinical trial designs incorporating fixed treatment protocols risk the creation of practice misalignment. This term refers to the disruption of a fundamental concept in clinical medicine: the relationship between illness severity and the allocated intervention in the control group. The unintended consequence of such trials, as also demonstrated in the ARDS Network Trial and the Transfusion Requirement in Critical Care (TRICC) Trial, may be the formation of non-comparable subgroups across both allocated therapies that potentially lead to harm and generate bias. No discussions of these complex interactions between trial design, current practice and adjustment of treatment for illness intensity currently exist or are part of EBM assessment tools.

Second, how can we classify, categorize and compare trials of surgical interventions or devices (ie extracorporeal membrane oxygenation (ECMO), high-frequency oscillatory ventilation (HFOV), continuous renal replacement therapy (CRRT)) where true blinding is impossible? Finally, do the study investigators from all centers have genuine clinical equipoise on whether a treatment effect exists across the intervention and control groups? If not, bias could certainly be introduced.

We contend these questions suggest a need for further refinement of how we classify the quality of evidence according to study design. At minimum, this should include principles on how to classify device and bundle of care trials and how to incorporate a provision that demonstrates that, as a minimum, the control arm received standard therapy (which of itself would require pre-trial evaluation of current practice in the trial centers).

Type I Error (Alpha): A Type I or alpha error describes the probability that a trial would, by chance, find a positive result for an intervention (ie effective) when, in fact, it is not (false-positive) and represent a chance or statistical error. In general, the alpha value for any given trial has traditionally and somewhat arbitrary been set at < 0.05. While recent trends have brought greater recognition for hypothesis testing by use of confidence intervals, the use of an alpha value remains common for statistical purposes and sample size estimation in trial design.

The possibility of a type I error is generally inversely related to study sample size. Thus, a study with a small sample size or relatively small imbalances across allocated groups or in the context of numerous interim analyses might be sufficient, alone or together, to lead to detectable differences in outcome not attributable to the intervention. Likewise, a trial with few observed outcome events, often resulting in wide confidence limits around an effect estimate, will potentially be prone to such an error.

The potential bias due to type I errors can be recognized by evaluation of key aspects of the study design and findings. These include whether the trial employed a patient-centerd or surrogate measure as the primary outcome, evaluation of the strength of association between the intervention and primary outcome (ie relative risk or odds ratio), assessment of the precision around the effect estimate (ie confidence limits), and a determination of the baseline or control group observed event rate. Level I evidence mandates that trials have a low probability of committing a type I error. While desirable, how do we clinically or statistically measure a given trial's probability of type I error? Should we adjust the statistical significance of an intervention found in a clinical trial to the probability of a type I error? These questions suggest a need for both discussion and consensus on the concept of alpha error and its practical application. This discussion has not formally taken place in the literature.

Type II error (Beta): A type II or beta error describes a statistical error where a trial would find that an intervention is negative (i.e. not effective) when, in fact, it is not (false-negative). An

Table 5: Summary of components to consider when evaluating the quality of evidence from research.

Components
Study Design:
Randomized
Allocation concealment
Blinding (if possible)*
Clinically important and objective primary outcome
Beta-error**
Multi-centre
Study Conduct:
Intention-to-treat analysis
Follow-up or attrition rate
Completion to planned numbers
Study Findings:
Biological plausibility
Strength of estimate of effect
Precision of estimate of effect
Observed event rate
Study Applicability:
Complex intervention
Consistency across similar studies
Generalizability
Cost of intervention

*Blinding may not be possible in device or protocol/process trials
**Adequately powered, appropriate estimate of control event rate and relative or absolute reduction in patient-centred and clinically important primary outcome.

increase in sample size and the number of observed outcome events reduce the probability a type II error, on the assumption that a genuine difference in effect exists across the allocated groups. Thus, to minimize the chance of a type II error, clinical trials must be suitably "powered". In general, the probability of type II error is conventionally and arbitrarily set at 0.10–0.20 (ie power 0.80–0.90). The calculation of power is used in study design to determine and justify the overall sample size. Inadequately powered trials risk missing small but potentially important clinically differences in outcome attributable to the intervention under assessment. Naturally, the ideal trial is one in which the power is high. Yet, while maximizing the power of a trial may appear logical, such an increase has both ethical and cost implications. For a given increase in power (i.e. from 0.20 to 0.10), trial recruitment would correspondingly need to increase, potentially exposing a larger cohort of patients to a placebo intervention and certainly leading to an increase in trial costs.

Given these implications, should attaining suitable power for a trial simply be a matter of statistical consideration? Can we standardize what suitable power represents for a given intervention? Should we subject suitable power in trial design to additional public health considerations such as: the size of the population likely to benefit from the intervention if proven effective; the clinical relevance of the outcome being assessed; and the potential downstream cost of integrating the intervention in clinical practice? We also contend that these issues warrant consideration in the context of trials of equivalency or non-superiority and more specifically for trials that are pre-maturely terminated at interim analyses. Finally, we believe that future trial design should address whether estimates of risk reduction used to justify sample size calculations for an intervention are biologically plausible, are supported by previous preliminary evidence and are truly feasible while considering the aforementioned issues.

Additional insights and considerations: In 1965, Sir Austin Bradford Hill described nine issues he considered important, in a Presidential Address to the Section of Occupation Medicine of the Royal Society of Medicine, for potentially inferring causation from statistical associations observed in epidemiology data. (Table 3) These considerations were not simply intended as criteria, as has been widely interpreted, but instead as a pragmatic and philosophical method to assess the potential for affecting our confidence in concluding causality. Hill said, "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non." We have now considered and discussed the limitations of several traditional measures to evaluate the quality of evidence, in particular with a focus on what EBM considers the old standard – randomized trials. We contend that there are additional dimensions to evidence that merit attention, both for randomized trials and epidemiologic studies, when appraising, classifying and grading the quality of evidence. Moreover, many of these dimensions take into account the issues identified by Hill when deciding whether an observed association was a causal relationship.

Evidence from randomized trials does not and cannot stand on its own, independent of previous information or studies. As discussed previously, prior knowledge can be accrued from a variety of sources ranging from personal experience to in vitro studies, experimental data, epidemiologic investigations and additional randomized trials. In fact, there may be circumstances for which randomized trials are unnecessary (ie due to obvious and large treatment effect), or more importantly, unethical. For instance, there is an extensive list of historical examples of widely accepted and uncontested interventions that are based solely on case-series and non-randomized cohort studies. (Table 4) By all reasonable consideration, no human research ethics board would support a randomized trial that compared insulin to placebo for patients with new onset type I diabetes mellitus or a randomized comparison of neostigmine versus placebo for initial therapy of proven myesthenia gravis. Accordingly, the systematic methods for how we evaluate and classify evidence need to consider these circumstances.

More recently, there have been high profile examples of large epidemiologic studies (phase IV studies) of interventions showing previously unknown potential harm. This represents one important aspect of Hill's philosophy that has often been neglected, specifically, the postponing of action or the dismissing altogether of new data due to its limitations of potential harm associated with interventions. Similarly, we need to consider a means for incorporating the evolution of evidence and these additional aspects, such as harm, outside of the usual realm of randomized trials.

Biological plausibility, temporality, and coherence: These issues were central to Hill's viewpoints and, while seemingly obvious, are in fact not always evident. For example, most, perhaps all, reasonable clinicians would reject the findings of a randomized trial of retroactive intercessory prayer compared with usual care showing a statistically significant decrease in the duration of hospital stay in patients with septicemia. Such a study completely lacks biological plausibility, along with rejecting the tenets of temporality and coherence. On the other hand, perhaps fewer physicians would have rejected the findings of the first interim analysis of the AML UK MRC study of 5 courses of chemotherapy compared to 4, where the investigators showed a

53% decrease in the odds of death (odds ratio 0.47; 95% CI, 0.29–0.77, p = 0.003). Yet the data safety and monitoring committee decided to continue the trial because these initial findings were considered too large to be clinically possible, and lacked biological plausibility and coherence. Accordingly, the committee recommended the trial be continued and the final results (no difference between the two therapies) vindicated this apparent chance finding at interim analysis. These examples both afford an opportunity to highlight how the results of randomized trials can be influenced by chance statistical findings, however improbable, and further deviate from the current and recognized knowledge of the day. To date, there has been no formal incorporation of biological plausibility into the grading of the quality of evidence or strength of recommendations. We believe this dimension, along with issues of temporality and coherence, should be more formally acknowledged in a reformed classification system. We similarly believe that careful attention must be paid to robust findings which contradict current beliefs and concepts of what is biologically plausible.

Consistency and applicability: Consistency in evidence refers to finding reproducibility in the effect of an intervention in numerous studies and across diverse populations, settings, and time. For example, the PROWESS trial tested the efficacy of rhAPC in severe sepsis, however, it was limited in scope by the study inclusion criteria (i.e. adults, weight < 135 kg, age > 18 years, number of organ failures etc.) Yet, the evidence for a similar beneficial effect of rhAPC in additional studies enrolling different populations, in different settings and under different circumstances has been remarkably less certain. Accordingly, rhAPC has lacked consistency in the treatment of sepsis. In addition, we also need to consider the extraordinary cost of rhAPC. The expense makes its applicability outside of wealthy industrialized countries unfeasible and more likely near impossible. While the cost of an intervention clearly has no bearing on the quality of such evidence, it has major relevance to its applicability outside of rich countries, where such treatments are nonetheless heavily promoted by drug companies. This population relevance limitation could be similarly applied to numerous innovations in medical interventions and can be usefully incorporated in a grading tool.

Likewise, complex interventions, which involve devices, therapies, protocols or processes (ie high-frequency oscillatory ventilation, continuous renal replacement therapy [CRRT], intensive insulin therapy or medical emergency teams, early-goal direct therapy for severe sepsis) pose major challenges for researchers. The findings of such trials, if negative, often require consideration of whether the intervention was ineffective, whether the intervention was inadequately applied or applied in an inappropriate method, or whether the trial used an unsuitable design, selected an inappropriate patient population or used the wrong outcome measures for determining effect. Conversely, if the "complex intervention" leads to a beneficial effect, further challenges arise for how to apply such data in a broader context. In addition, examples of complex interventions as applied in a given trial often imply or assume equity across an entire infrastructure of medical, surgical and nursing availability, knowledge, expertise and logistics. Yet, such equity is far less common than appreciated. Moreover, such interventions are often not universally available. Thus, the translation of a complex intervention in isolation to a setting outside of its initial development may have both negative health and economic consequences. Similarly, one can present a moral and ethical argument regarding the vast resources utilized for the development and evaluation of interventions that are likely to benefit very few and reach even fewer patients.

We contend that due thought needs to be given to how the results of a trial can be translated into interventions that reliably work, are reproducible, are broadly applicable and can be applied elsewhere. The GRADE system does incorporate a subjective assessment of consistency as criteria for grading the quality of evidence and, in the setting of unexplained heterogeneity across trials, suggests a decrease in grade. We consider that a formal grading of applicability is needed in future classifications of evidence.

Generalizability: The generalizability of findings from a clinical trial represents a fundamental dimension of evidence, that of external validity. Narrow controls designed to optimize the internal validity of a trial (ie inclusion/exclusion criteria, intervention protocol) can compete with and compromise overall generalizability. Whether an individual trial is widely generalizable can also be the result of additional factors. For example, the power of a local investigator-protagonist needs to be taken into account. Such investigators, when involved in single center studies, especially unblinded ones, have the power to profoundly influence outcome and behaviour through their commitment to the cause, expertise, dedication and enthusiasm. Examples of such studies include use of early-goal directed therapy, higher volume CRRT, or tight glycemic control. All these studies were single center evaluation of complex interventions, but importantly, all had a local protagonist. Alternatively, the findings of a multi-center trial of an intervention may not be generalizable if only large tertiary/academic centers were involved, where there may be a natural predilection to selection bias.

How generalizable are the findings of a single center study, however well designed? Should single center trials ever lead to level I evidence or grade A recommendations? Accordingly, how should we classify the evidence from a single center trial showing benefit? For example, would early goal-directed resuscitation really improve the outcome of all patients with septic shock presenting to emergency departments worldwide or do the findings of this trial simply reflect improvements in patient care in a single institution where there existed a very high pre-intervention mortality? These are more than idle questions because numerous single center studies have profoundly influenced and are continuing to influence the practice of critical care medicine worldwide and have been incorporated in international guidelines. Yet, two recent assessments of interventions that in single center studies looked extraordinarily promising (ie steroids for the fibro-proliferative phase of ARDS and introduction of a Medical Emergency Response Team), failed to show a benefit when evaluated in a multi-center setting.

In the end, there needs to be a greater understanding and consensus around the limitations of data from single center studies. We need to consider the meaning of multi-center and how it relates to grading the quality of evidence. Additionally, we need to consider and discuss the implications of multi-center studies sponsored by industry that evaluate new pharmaceutical interventions. We also need to relate the control population studied in any single or multi-center trial to other large populations with respect to the same condition, so that we can consider the generalizability level of a given study.

Importantly, we also need to give a greater consideration to the weight of evidence from observational studies in the context of the known limitations of randomized trials. While randomized trials are certainly the most ideal study design in some circumstances, in other cases observational studies may in fact be more feasible and accurate. Well-conducted observational studies have a pivotal role in the generation of high-quality research evidence and not only serve as an adjuvant to the data generated from randomized trials. Such observational studies may enable better "real world" estimates of the impact of an intervention (including potential harm) compared with that of a randomized trial of the same intervention which enrolled patients within tight inclusion/exclusion criteria. Why do we, by default, rank the randomized trial higher on current classification scales? How do we empirically know it to be more robust evidence? Where are the studies testing how many very large observational studies have been refuted or confirmed by subsequent large randomized controlled trial compared with single center randomized controlled trials? The recent trial-based confirmation of the risks associated with aprotinin during cardiopulmonary bypass and the related FDA alert (For details visit: fda.gov/cder/drug/early_comm/aprotinin.htm) arose from observational data and were missed in single center studies. Even more powerfully, such single center studies had led to widespread prescription of beta-blockers in high-risk patients receiving non cardiac surgery. The recent POISE trial of > 8000 patients demonstrated that such prescription actually increases mortality.

While there are obvious differences in study design, well-performed observational studies may provide a powerful mechanism to improve the generalizability of evidence and may well provide more robust evidence than single center randomized controlled trials. Randomized trials, especially if evaluating complex interventions or with strict inclusion/exclusion criteria, often only provide data in a clinical context that does not exist outside the trial itself and have limited power to detect harm. Importantly, observational studies have the distinct advantage of examining the long-term effects or prognosis of an intervention and, as discussed above, evaluating for adverse or rare outcome events. We contend work needs to be done to evaluate how prior observational studies perform in comparison with small or single center randomized trials in their ability to detect an effect and which was subsequently confirmed in at least one large multi-center randomized trial. It may well be that such studies might show that observational studies with appropriate detailed variable collection and statistical correction are statistically more likely to detect beneficial effects or harm than small or single center studies. If this were the case, objective evidence would exist to reform a classification system, which was not yet considered this issue.

The need for further reform and consensus: An argument can be made that proposed classification schemes, especially the new GRADE system, are best left alone. They are reasonably simple, explicit, have been validated and now are increasingly endorsed. Furthermore, the additional dimensions of evidence we have discussed (i.e. study design, biological plausibility, coherence, consistency, and generalizability) are often difficult to simply measure and their impact on how the findings of an individual trial approximate the truth is hard to quantify. (Table 5) On the other hand, we believe these issues are valid and deserve broader discussion, consideration and debate.

A classification system which is simple is indeed desirable but becomes a problem when, for the sake of simplicity, it fails to take into account important aspects of the growing complexity of the evidence available. Accordingly, summary classifications of the quality of evidence and strength of recommendations, such as the GRADE system, will continue to have an important and expanding role in medicine. We believe that as the GRADE system becomes more widely endorsed, additional refinements to the system will result in appropriate recognition of higher quality evidence and contribute to greater confidence in recommendations for clinical practice. We also believe that this field is very much "work in progress" and needs to evolve more explicit recognition and classification of the dimensions of trial design discussed in this manuscript.

Conclusion

In this commentary, we have argued in favor of the concept that assessing of the quality and strength of evidence from clinical studies requires reform. Such reform should, in particular, reflect those dimensions of evidence, which are currently not routinely or explicitly addressed. The GRADE Working Group has made considerable contributions to improving how the quality of research evidence and recommendations are graded. We believe that additional reform is needed to explicitly address and quantify dimensions of evidence such as biological plausibility, reproducibility, temporality, consistency, ability to detect harm and generalizability. We also believe that observational studies need to be graded and that, under some circumstances, such studies provide either evidence that cannot be detected in single center studies or even better evidence than produced from small, randomised trials. We believe such reform should occur through consensus. We also believe that such reform will have lasting beneficial effects on clinical practice and on the future design, reporting and assessment of clinical studies.

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