

neonatal INTENSIVE CARE

Vol. 20 No. 7
November-December 2007

The Journal of Perinatology-Neonatology



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imagination at work

Blame Game

As we went to press, a father in San Diego was fighting Kaiser over treatment of his seven week old son after two other babies from a set of triplets died. The father wanted the remaining son moved to another hospital because, he said, Kaiser was providing inadequate neonatal intensive care. Kaiser contended that the baby was receiving good care at its hospital and refused the transfer.

The father was quoted in the Los Angeles Times as having written to Kaiser: "Two of my children have already died in your hospital. Please make the transfer and allow Andrew to get good medical care and not kill my son." Kaiser said it "went above and beyond" in the care of the baby.

The dad appealed to the state Department of Managed Health Care, which ruled in his favor and okayed the move. However, no other hospital would take the baby because they were full or because of the baby's severe condition, so it was kept at Kaiser. So that's where things stood until a hospital was found and the baby was transferred.

Those are the facts as we know them. But as always, there are mitigating circumstances. So here's some questions to ponder: what are the limits of responsibility in this case? Who shares responsibility? If the mother was carrying triplets, did she not know it, and was she not apprised of the risks involved in giving birth to triplets? How much care is adequate or "good" care, and how far does a hospital have to go to provide such care? Who is "the decider" about what constitutes good care?

To make the above more ethically challenging, it should be noted that the father is an ob gyn, age 50, his wife is 37. Having triplets is a known risk, as it were, not uncommon with the in vitro fertilization the wife underwent. This is something the parents must have been aware of. Obviously they decided to try for having a kid despite the complications and risks for in-vitro, for going forward with all three fetuses. The surviving baby weighed 660 grams. At the time of the decision refusing the infant's transfer from Kaiser he suffered from bleeding in the brain, underdeveloped lungs and a congenital heart defect. Of the two other triplets, one died the day she was born, the other a week later.

So if there is to be someone at fault – for the preemie triplets, for the quality of care they might have received – just where does the parents' culpability end and Kaiser's begin? Now what would be your considered opinion about this?



Les Plesko, Editor

PS: Call for papers: Now is the time to submit papers for the 2008 issues of Neonatal Intensive Care. All submissions will be considered, including case studies and works in progress. Special themes for 2008 include ethics of intensive care, advances in monitoring, neonatal nursing, and respiratory care, but all papers on subjects relating to neonatology-perinatology are welcome. Our process for publication is simple: just e-mail your manuscript to us in an unformatted, word-compatible file, and we will notify you of its status in about a week after receipt. Neonatal Intensive Care strives to provide an open forum for its readers. As such, all submissions from any segment of the neonatal care community will be considered. Please contact me if you have any questions.



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Published seven times each year by
Goldstein and Associates, Inc.

10940 Wilshire Blvd., Suite 600
Los Angeles CA 90024
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**Design, Typography, Prepress
and Production Management**
<http://accugraphics.net>

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rates, space sizes, and similar
information are available to prospec-
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¹AMERICAN ACADEMY OF PEDIATRICS: Pediatrics, Vol. 106 No. 2 August 2000, pp. 344-345, Use of Inhaled Nitric Oxide, Committee on Fetus and Newborn
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20.9

Isn't it strange how a peculiar number such as 20.9 can make us stop for a moment? And for what? Is it the Olympic record for the 200 meter dash, or the square root of 438? Or maybe it has no meaning at all and you just wasted the last 20.9 seconds of your life?

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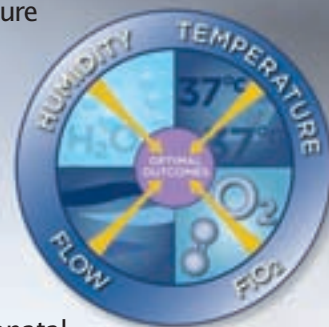
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¹Brian Walsh, Comparison of high flow nasal cannula (HNC) devices. Respiratory Care 2006; Vol 51 No 11.



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News

□ November-December 2007

CORRECTIONS

In this year's Directory of Products and Services (September issue), please disregard the contact name listed for **Children's Medical Ventures**. For information, please contact the company at 1010 Murry Ridge Lane, Murrysville, PA 15668, phone (724) 387-4000, (800) 345-6443, fax (724) 387-5012, info@childmed.com, website: childmed.com. The company makes products for jaundice, respiratory care, monitoring, sleep & positioning, and calming, soothing & feeding.

The correct contact e-mail and website address for **Sylvan Fiberoptics** on page 17 of the Buyers Guide should be: jfedorka@sylvanmed.com, website: sylvanmed.com.

GIGANTIC

After a six-hour struggle and with the help of four midwives, a woman gave birth to a baby boy weighing 14 lb 7oz, twice the birth weight of the average baby. "I couldn't understand why he wasn't coming easily," the mom said. She gave birth naturally with only gas and air to help her. At a week old, the kid was the size of a six-month-old, two-feet long and the equivalent weight of seven bags of sugar. The mom's other two children were normal weight. Because of the boy's size, his shoulders became lodged behind the mother's pelvic bone and it took four midwives to set him free. The mother said the family had bought some baby clothes, but had to go out and buy new ones. The father noted that his mother was 130 lbs. The heaviest baby born, according to the Guinness Book of World Records, was a boy born in Canada weighing 23.12 lbs, who died shortly after birth, and a baby born in Italy weighing 22 lb 8 oz, who lived.

TURNED AWAY

A Japanese woman in labor was turned away by eight and a ninth hospital refused to admit her even after she miscarried in an ambulance and her baby died. The woman, who was in the sixth month of her pregnancy, lived just three minutes away from a hospital, but she was forced to travel 45 miles by ambulance, looking for a facility that would admit her. The woman, who lives in the countryside, called an ambulance in the middle of the night because she was suffering from stomach pains and bleeding. For more than an hour the ambulance crew tried to find a hospital to accept her. On the way to a ninth hospital the ambulance crashed and the woman miscarried. The hospital then changed its mind and refused to admit her. An official told ambulance staff that treatment would be difficult and they were already busy with an emergency operation. Eventually, almost three hours after they first arrived to pick her up, the ambulance crew found a hospital that would take her. Last year a pregnant woman who lived in the same area died after she was refused admission by about 20 hospitals which said their beds were full. Japan doesn't have enough doctors or emergency facilities. The number of obstetricians has declined and medical students are said to be put off by the long hours of training needed to qualify and a rise in the number of malpractice suits. Japanese officials said they would do something about it. The health minister has promised to try to improve the situation, but measures already in place like scholarships for doctors willing to work in rural areas have not made much of a difference.

MORE DEATHS

US women are dying from childbirth at the highest rate in decades. The maternal death rate rose to 12 per 100,000 live births in 2003, the first time the maternal death rate rose above 10 since 1977. The death of infants is much more common; the nation's infant mortality rate was 679 per 100,000 live births in 2004. As recently as 90 years ago, the maternal death rate was one in 100 live births; nonetheless, some researchers find it disturbing that the maternal rate is rising. Some researchers point to the rising C-section rate, now 29% of all births, far higher than what public health



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experts say is appropriate. Like other surgeries, cesareans come with risks related to anesthesia, infections and blood clots. Excessive bleeding is one of the leading causes of pregnancy-related death, and women with several previous C-sections are at especially high risk, according to a review of maternal deaths in New York. Blood vessel blockages and infections are among the other leading causes. Experts also say obesity may be a factor. Heavier women are more prone to diabetes and other complications, and they may have excess tissue and larger babies that make a vaginal delivery more problematic. The age of mothers could be a factor, too. More women are giving birth in their late 30s and 40s, when complications and risks are greater. Studies also found that the maternal death rate in black women is at least three times greater than it is for whites. Black women are more susceptible to complications like high blood pressure and are more likely to get inadequate prenatal care. Three different studies indicate at least 40% of maternal deaths could have been prevented.

NO ROOM FOR 4

A Canadian woman has given birth to extremely rare identical quadruplets, but had to deliver at a US hospital because the Canadian hospital ran out of space in its NICU. The mother taken to a Montana hospital where the girls were delivered was two months early by C-section. A medical team and space for the babies had been organized for the family at the Foothills Medical Centre in Calgary but several other babies were born unexpectedly early, filling the neonatal intensive care unit. Health officials said they checked every other neonatal intensive care unit in Canada but none had space. The parents, a nurse and a respiratory technician were flown 310 miles to the Montana hospital, the closest in the US. The babies' weights at birth ranged from 1.07kg to 1.33kg but they did not need to be put on a respirator. The girls were conceived naturally. The chances of having naturally-conceived identical quadruplets is one in 13 million.

HOW WE LEARN

When do we become capable of revising our mental representations of objects or situations based solely on what someone tells us. To answer this question, Boston University psychologist Patricia Ganea and her colleagues asked 19-month and 22-month-old infants to name a toy that was presented to them in the lab. Then, the toy was taken from the infants. Later, while the toy was out of view, the researchers told the infants that the toy had become soaking wet after someone mistakenly spilled a bucket of water. The question was whether the infants would incorporate this information into their mental representation. When asked to retrieve the animal from the next room, would they reach for the newly wet stuffed toy, or a dry version identical to what they had been previously presented? The researchers found that the 22-month-olds, but not the 19-month-olds, were able to identify the toy based solely on the property that they were told about but had never seen. The study suggests that before the end of their second year, infants have become capable of updating their knowledge using what other people tell them.

NEVER TOO SOON

COPD prevention should start before birth, since poor airway function soon after birth is a known risk factor for airflow obstruction during early adulthood, according to researchers at the Arizona Respiratory Center in Tucson. Investigators carried out a study on 169 babies who were enrolled at birth. Each baby

had its maximum expiratory airflows measured using the chest compression technique at the age of 2.3 months. One hundred twenty three of the babies had further lung function tests carried out when they were 11, 16 and 22 years old. Measurements were taken of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC (FEF25-75), both before and after treatment with a bronchodilator. The scientists found that those in the bottom 25% for maximum expiratory flows when they were babies had inferior values for FEV1, FVC, and FEF25-75 when they were 22 years old. Adjustments were made for age, sex, height and weight. Even after further adjustments were made for wheeze, atopy, parental asthma and/or smoking the differences remained the same. The researchers concluded that those born with inferior lung function tend to continue this trend well into early adulthood. They said further research would show how the lungs develop in the fetus. It is possible that the process is being impaired in utero by either genetic or environmental factors, or both. Previous studies have linked poor lung function in infants and older children to maternal smoking. The research suggested that a better understanding of the mechanisms that control normal lung growth in utero would contribute to development of strategies for the prevention of COPD in adult life.

TWO TIMES THREE

A 39 year old woman has given birth to her second set of triplets. The babies were born after 34 weeks of pregnancy. The chances of having triplets once are 1 in 8,000, but twice are 1 in 64 million. The mom didn't use fertility treatments, and the babies were delivered by C-section. After their first set of triplets the parents decided they would like to have one more child; the first set of triplets was two girls and a boy, born after 28 weeks and weighing under three pounds. Despite initial lung functions, they are now healthy. The new triplets are boys. The last time a woman gave birth to her second set of triplets was in New Brunswick, NJ, in 2006. There have been cases of eight babies, octuplets, all being born alive. In 1997 a woman gave birth to octuplets, in Texas; seven of them survived. There have been cases of nonuplets (nine babies) with some being born alive, however, none of them survived for more than a week.

RIGHT IS WRONG

Mothers who cradle their baby to their right hand side are displaying signs of extreme stress, a new study suggests. Although most moms feel stressed in the early stages of their baby's life, the study by Durham University researchers suggests their baby cradling habits are a key indicator of whether this stress could become overwhelming and lead to depression. Previous research has already shown that the majority of mothers prefer to cradle their baby to their left regardless of whether they are left or right handed. As at least one in ten women develop postnatal depression, studying nonverbal cues such as baby cradling could potentially help doctors and health visitors identify which mothers are depressed. The study looked at 79 new mothers and their babies, who were an average age of seven months. In their own homes, mothers were asked to pick up their babies and cradle them in their arm. The moms also completed a survey which quizzed them on their mental state. The research methodology established there was no link between cradling side and left or right handedness. The study found that of the mothers who expressed no signs of stress or depression in the survey, 86% preferred to hold their babies to the left. However, cradling babies to the right was more

prominent among stressed moms, with 32% showing a right-sided bias.

IT'S IN THE BLOOD

A toxin released by bacteria causes severe bleeding in the lungs by patients with pneumococcal pneumonia, but it's the bleeding, not inflammation, which makes the infections deadly, according to researchers at the University of Rochester, NY. The study also revealed why antibiotics often fail to help prevent early death. The bacteria *Streptococcus pneumoniae* infects the upper respiratory tracts of the elderly and young children mostly. There are 500,000 cases of pneumococcal pneumonia annually in the United States, with about 40,000 of them fatal. These numbers would be worse in children younger than 2 years if not for the introduction of Prevnar, according to one report. The picture remains far more serious outside of the United States, however, where pneumococcal infections take the lives of at least one million children each year. Researchers suggested that the finding provides a better understanding of what makes a major global bacterial infection deadly, and marks the beginning of realistic efforts to save lives worldwide and note that doctors should think twice about whether standard drug treatments are doing more harm than good.

LET IT BLEED

Recognizing molecules as "self," versus foreign invaders to be labeled for destruction, is a central responsibility of the human immune system. Vaccines are mixtures, made of parts of many bacterial strains in this case, designed to help the immune system recognize and remember an invader without causing a full-scale infection. The hope is that when the real disease comes along, the immune system will be primed to combat it. Complicating matters, children under two, the elderly and those with HIV have weaker immune systems than a typical healthy adult. Thus, they cannot mount as strong an immune response to a vaccine that would later protect them against the actual infection. Even worse, bacteria can thwart the protection afforded by vaccines by reproducing and evolving so quickly that they become unrecognizable to both vaccine and immune system. For all these reasons, new, more effective ways to treat these infections are a major thrust of research efforts worldwide. The medical establishment had for years believed that breathing difficulty was brought on by inflammation: the swelling and fluid buildup caused as immune system proteins rushed to the lungs to fight the infection. A medical mystery emerged, however, when studies revealed that such inflammation was actually lower during the early time period when most people died. The newly published study reveals that a toxin released by *S. pneumoniae* causes severe bleeding in the lungs. Normally, regulatory pathways maintain a balance between the competing tendencies of blood to either become thinner or thicker. Blood clots can represent either a dangerous blockage of blood flow, or a protective mechanism that prevents unchecked bleeding, all depending on a careful balance. Specifically, the ability of blood to clot is increased by the activation of plasminogen activator 1 (PAI-1). Balanced against the pro-clotting influence of PAI-1 is cylindromatosis (CYLD), which blocks the clotting pathway just enough to keep blood flowing under normal circumstances. Researchers found that the *S. pneumoniae* bacteria released pneumolysin, which causes an overproduction of CYLD, which increases the permeability of the lung's blood vessels and causes them to leak blood. They also found that pneumolysin directly increases the permeability of the lung's blood vessels, which causes yet more bleeding.

Furthermore, antibiotic drugs kill bacteria by cutting them open, which releases even more pneumolysin. Too much CYLD inhibits a signaling molecule (p38 kinase), which leads to reduced expression of PAI-1 expression in lung. The most immediate implication of the study is that scientists could make purified, recombinant PAI-1 and inject it directly into the lungs of these patients, and it would have a benefit. The next step would be to design a small molecule, a protein fragment, that can mimic PAI-1, which would be easier to deliver in the lungs, more effective, and have fewer side effects. It would be even better if delivery could be in an aerosol form, researchers said, so you could just spray it into the air around these patients and their bleeding would stop.

TOO BRIGHT

Children born in the winter or fall have better long-range eyesight throughout their lifetime and less chance of requiring thick corrective glasses, predicts a Tel Aviv University investigation. The scientists took data on Israeli youth aged 16-23 and retroactively correlated the incidence of myopia with their month of birth. Babies born in June and July had a 24% greater chance of becoming severely myopic than those born in December and January, the group with the least number of severely myopic individuals. The investigators say that this evidence is likely applicable to babies born anywhere in the world. The study interpolated data from a sample size of almost 300,000 young adults, making it one of the largest epidemiological surveys carried out in the world on any subject. Researchers guessed that long-term effect of early-life exposure to natural light increases the chances of a child becoming short-sighted. A laboratory analysis of myopia in young chickens suggested that the body has a mechanism that causes the eyeball to lengthen (short-sighted eyes are longer than normal) when it is exposed to prolonged illumination. This mechanism is associated with melatonin, though scientists are not sure exactly how it operates. In other words, more sun equals less melatonin, equals a longer eye which is short sighted. While short-sightedness used to be a real handicap before people wore glasses, nowadays there's been a strong link between myopia and intelligence. That is, people who wear glasses really are smarter.

BABY TALK

It's a given that infant-directed language uses nonverbal cues such as pitch, speed, and loudness. Researchers at UCLA now say that this relationship between sounds and intentions are universal, and thus, should be understood by anyone regardless of the language they speak. To test their hypothesis, researchers recorded native English-speaking mothers as if they were talking to their own child and then as if they were speaking to an adult. The speech varied across four categories: prohibitive, approval, comfort, and attention. Then, the researchers played the recordings to the inhabitants of Shuar, a South American hunter-horticulturalists village in Ecuador to see if the participants could discriminate between infant-directed and adult-directed speech, and whether they could tell the difference between the categories in both types of speech. The results showed that the Shuar participants were able to distinguish ID speech from AD speech with 73% accuracy. They were also able to tell which category (eg prohibitive, approval, etc) the English-speaking mothers used, but they were better at this when the mothers used baby talk. The results provide support for the notion that vocal emotional communication manifests itself in similar ways across disparate cultures.

CAN THE PAN

Babies exposed to chemicals used in non stick cookware and similar products while in their mother's womb were born at a significantly lower body weight, according to a study at Vanderbilt University and UCLA. Researchers tested blood from 1,400 pregnant women in a Danish birth registry and found that babies of women with high perfluorooctanoate levels were 175 grams lighter than those born to mothers in the lowest exposure level. Animal tests have previously linked both PFOA and perfluorooctane sulfonate to cancer and developmental problems. Researchers noted that PFOA has a long half-life in the human body and it has been found to produce adverse health effects in animal studies but, as to humans, the research was scant, with the only previous major study provided by a manufacturer who used PFOA in its product, and of course that study showed no adverse effects. Another study by Johns Hopkins revealed that exposure to PFOS and PFOA in the womb is statistically associated with lower weight and head circumference at birth, according to an analysis of nearly 300 umbilical cord blood samples. The study found small decreases in head circumference and body weight in association with higher concentrations of PFOS and PFOA among infants born vaginally. The study also reported a negative association with PFOS and PFOA concentrations and the infant's ponderal index. For unknown reasons, the reductions in birth weight and head circumference were not observed among 65 infants born by cesarian section. The researchers also did not find any associations between PFOS and PFOA concentrations and length at birth or gestational age. The health impact from exposure to PFOS and PFOA is not fully known, but previous studies found these compounds could cause tumors and developmental toxicity in laboratory animals at doses much higher than those observed in the Hopkins study. The researchers analyzed cord serum from 293 newborns. The samples were tested for the presence of PFOS and PFOA and eight other polyfluoroalkyl compounds. The samples were then matched to anonymous patient records, which included measurement of height, weight and head circumference of infants and other health information. PFOA was detected in all of the samples and PFOS in all but two of the samples. The concentrations for both compounds, however, were lower than those typically detected in adults and lower than those known to cause tumors and developmental problems in laboratory animals.

SETTLE DOWN

Researchers hoping to better understand the development of the infant brain have long been stymied because babies don't want to sit still for brain scans. There have been some studies that obtained brain scans of infants while they were napping or sedated, but what researchers wanted was to scan baby brains when babies were reacting to their environment. Now researchers at Washington University School of Medicine in St. Louis report that they've improved a recently developed brain imaging technique to the point where it will allow such scans. In addition to aiding basic research, the technology, known as high-density diffuse optical tomography (DOT), should help clinicians treating infant brain injury by making it possible to monitor brain function at infant incubators. The DOT scanner uses harmless light from the near-infrared region of the spectrum and is much smaller and quieter than MRI equipment, noiseless and the size of small refrigerator. To scan a patient with high-density DOT, scientists attach a flexible cap that covers the exterior of the head above the brain region of

interest. Inside the cap are fiber optic cables, some of which shine light on the surface of the head, and some of which detect that light as it diffuses through tissue. Unlike X-rays or ultrasound, near-infrared light passes through bone with relatively little attenuation. Scientists can use the diffusing light to determine blood flow and oxygenation in blood vessels of the brain. When these characteristics increase, researchers assume that the area of the brain they are scanning is contributing to a mental task. When you add tomography, high-density DOT has four times the density of previous scanners. To prove that they achieved sufficient resolution for functional brain imaging, scientists used high-density DOT on human volunteers to link stimulation of parts of the visual field to activation of corresponding areas in the brain's visual cortex. Researchers are currently collaborating with pediatricians to adapt the technology for use in neonatal and pediatric intensive care units. Scientists hope to use the technology to assess the effectiveness of therapies for brain injury in infants.

FISHING FOR DOWNS

A group of physicians from Singapore and the United Kingdom recently developed a new test that can detect within two hours whether a fetus has Down syndrome. The new FlashFISH test is a modified version of the existing test, which provides results in 24 to 48 hours. Both FlashFISH and the other FISH involve inserting a needle through the pregnant woman's abdominal wall to draw amniotic fluid from the womb, but FlashFISH requires two ml of fluid to be drawn, compared with five in standard tests. Doctors then examine fetal cells in the fluid by maneuvering a molecular probe directly into the cells' nucleus. The probe is a tiny portion of DNA that can attach to a matching sequence in the fetal cell and identify whether it is abnormal. The test has proved to be 99% accurate in detecting Down syndrome and carries the same risk of miscarriage, about one in 100. FlashFISH, which has been patented by Singapore-based INEX Innovations Exchange, is expected to be available at Singapore's National University Hospital by the end of the year.

OVERDOSE

The FDA warns that women who are breastfeeding and taking codeine risk a possible overdose of their infants. Codeine frequently is prescribed for pain associated with episiotomies or cesarean sections. However, some people are ultra-rapid metabolizers of codeine, which transforms into morphine in the body, causing higher-than-normal amounts of the drug to enter the bloodstream and breast milk. A medical journal last year reported that a 13-day-old infant died after a morphine overdose. The infant's mother was taking a less-than-usual dose of codeine but was a fast metabolizer of the drug, though it is the only such recorded instance of infant death. The FDA warning was not intended to discourage women from breastfeeding but rather to encourage them to monitor their infants for signs of overdose, which include infants sleeping for long periods of time, difficulty breast-feeding, constipation, breathing problems and limpness in the baby's arms or legs. The FDA did not recommend that all women who are breastfeeding be tested to determine whether they are ultra-rapid metabolizers because there's no evidence to indicate that such a strategy would reduce complications. Between 1% and 10% of whites, 3% of blacks and 1% of people with Hispanic, Chinese or Japanese ancestry are ultra-rapid metabolizers of codeine, the Journal reports. According to FDA, about 16% to 28% of people with North African, Ethiopian and Saudi descent are ultra-rapid metabolizers. Labs usually charge between \$500 and \$1,000 for a

test that can determine how people metabolize several drugs, including codeine.

PRODUCTS/PEOPLE

NEW VP

MAQUET has announced the appointment of Steven Greenfield as Vice President of Critical Care Sales. Greenfield will be responsible for managing the critical care division's U.S. organization of sales representatives. He began his career as a Registered Respiratory Therapist and worked his way up to department director. He brings over 20 years experience in sales and management in which he has distinguished himself in many leadership roles at world-class companies such as Baxter, Stryker and most recently Johnson & Johnson. Contact maquet.com/us.

TO THE BEAT

For more than two decades the Bunnell Life Pulse High Frequency Ventilator has proven to be an effective therapy for early intervention and treatment of pulmonary interstitial emphysema and for rescue of patients failing on conventional or high frequency ventilators. The "WhisperJet," a new inspiratory valve, reduces noise output by 75%. The development of the LifePort ET tube adapter, in 1996, eliminated the need to reintubate with a special ET tube, making implementation of the Life Pulse faster and easier than ever. For a free trial call (800) 800-4358 or visit us online at bunl.com.

REAL TIME MONITORING

Recently, the clinicians treating a 3-month-old girl undergoing open-heart surgery used a new critical care monitoring device for pediatrics and with the information provided by it, they were able to detect a life-threatening problem after the surgery, treat her, and potentially save her life. Edwards Lifesciences Corporation announced today the introduction of its Edwards PediaSat Oximetry Catheter, the first real-time, continuous ScvO₂ monitoring device designed specifically for children. This new central venous catheter uses fiber optics to monitor and identify potentially life-threatening changes in oxygen-saturation of venous blood in critically ill children. This advanced technology, previously only available for adults, is even more important for children since they typically do not demonstrate the same warning signs of potentially fatal issues and can destabilize much faster than adults. The PediaSat Oximetry Catheter offers continuous real-time insight into the balance of oxygen delivery and consumption, and trending of the patient's status over time. With this information, clinicians can more confidently guide therapy and help improve outcomes for critical care pediatrics. Until now, clinicians have had to rely on manual, intermittent blood sampling to monitor a child's oxygenation status in a critical care setting. Contact Edwards.com.

GOT THE BLUES

GE Healthcare recently released the BiliSoft LED Phototherapy System, a revolutionary blue LED and fiber optic based technology for the treatment of indirect hyperbilirubinemia. This innovative product responds to clinical guidelines at the same time it promotes the natural developmental care of newborns. BiliSoft delivers phototherapy anywhere, in the Neonatal ICU, Pediatrics, Well Baby Nursery or at home. BiliSoft can be used in any environment, in a radiant warmer,

incubator, bassinet, crib, or in a caregiver's arms. Designed with the feedback of neonatal nurses around the globe, BiliSoft provides distinct improvements over existing technologies. BiliSoft utilizes six blue LEDs with a soft large light pad, in two sizes, for use with premature infants or full-term babies. BiliSoft meets the guidelines of the American Academy of Pediatrics Guidelines on Jaundice Management. With a larger surface area, and more intensive light, BiliSoft also creates the opportunity for developmental positioning or swaddling of infants during treatment. A new soft, flexible fiber optic light pad allows the swaddling, or wrapping, of full-term babies to further enable feeding and holding during jaundice treatment. BiliSoft operates quietly, contributing to a soothing, comfortable environment for the newborn.

RESOLUTION

Siemens Medical Solutions, Molecular Imaging division, manufacturer of the Inveon preclinical imaging system, continues to lead the preclinical imaging market with its upgradeable Inveon platform. The Inveon is a modular system that allows users to combine positron emission tomography (PET), single photon emission computed tomography (SPECT) and computed tomography (CT) acquisition systems in one unit. The system also delivers the industry's highest PET resolution and sensitivity and it boasts a suite of research tools that improve the workflow of basic research. These tools can help speed the drug development process as they enable researchers to identify specific biological processes, monitor the efficacy of compounds, and measure the effects of disease progression over time. The Methodist Hospital in Houston has recently installed the thirtieth Inveon preclinical imaging system as part of the hospital's major commitment to research as an institutional priority. The goal of the hospital, using Inveon, is to translate its research findings into clinical applications to improve patient care and to conduct clinical trials to validate research hypotheses. Contact siemens for more information.

Ergonomics in Medical Devices

Ergonomics is derived from two Greek words: “ergon” meaning work and “nomoi” meaning natural laws. Ergonomics (or human factors) is the scientific discipline concerned with the understanding of interactions among humans and other elements of a system. The profession applies theory, principles, data and methods to industrial designs in order to optimize human well-being and overall system performance as defined by the International Ergonomics Association (ILE) in August of 2000.¹

Ergonomics can be separated into three categories, physical (how anatomical, physiological and biomechanical characteristics relate to physical activity), cognitive (how mental characteristics such as perception and memory affect interactions among humans and other elements of a system such as human-computer interaction), and organizational (optimization of sociotechnical systems).² Recent literature has been looking at the cognitive aspects in relation to human factors and medical devices.

Many organizations have been focusing on medical errors and patient safety. Medical device interactions are an important and dangerous potential source of medical errors and ergonomics is playing an important role in the design of today’s medical devices. Murff, Gosbee, and Bates discuss human factors engineering (HFE) in an evidence report for the Agency for Healthcare Research and Quality. Murff et al discuss the use of HFE in reducing device-related medical errors. The group also looked at medical device alarms and how HFE can make improvements in medical devices.

Mechanical ventilation is no stranger to ergonomics. Manufacturers are looking at ways of making mechanical ventilation safer. Improving safety is a major concern in the intensive care unit and several publications have reported improvements in patient safety with intuitive graphic representation. Dr. Mark Wysocki discusses the importance of graphic user interfaces (GUI) during mechanical ventilation and improvement in patient safety.³

This article was provided by Hamilton Medical.

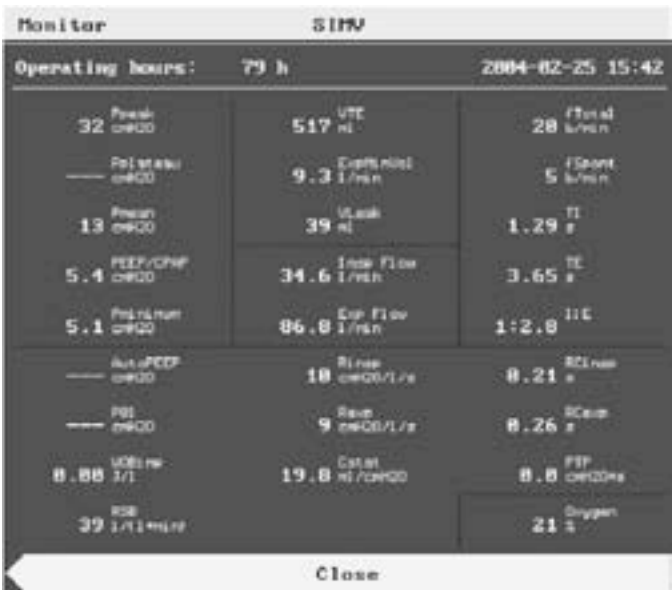


Figure 1. Traditional ventilator monitoring screen.

Other groups have used ergonomics to design simulators. A group from the University of Wyoming described the design of a medical simulator for the Air Force. “The simulator is the precursor to a system that analyzes hemodynamic information in order to act as an intelligent assistant to a Critical Care Air Transport Team (CCATT) monitoring a critically injured casualty.”⁴

Patient safety is a large and growing issue in today’s high technology healthcare. Ergonomics is helping make improvements in the human-computer interface. “Intelligent” systems are helping to increase patient safety by providing valuable patient data in an intuitive and easily understandable way to the clinician. “Intelligent” systems can also be a valuable teaching tool by providing valuable information during a simulation and providing feedback to the clinician in training. It is a very exciting time in medicine as improvements in technology take us to a new understanding of the human body.



Figure 2. Traditional ventilator 'default' screen

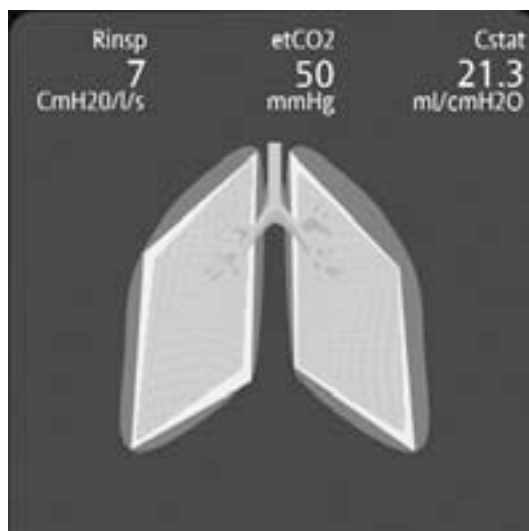


Figure 3. 'Dynamic' Graphical representation of 'stiff' (boxy) lungs and 'open' airways.

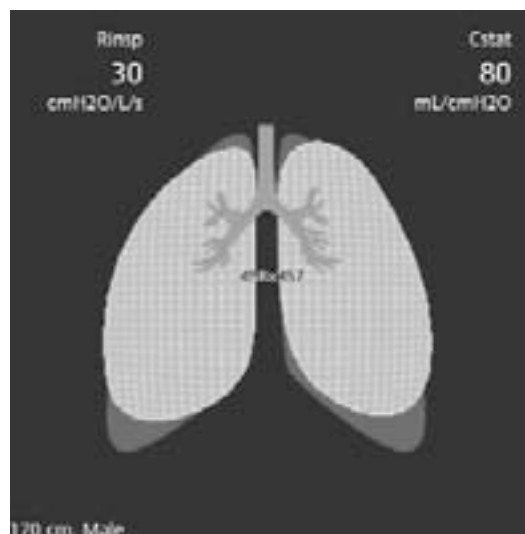


Figure 4. Dynamic representation of 'floppy', highly compliant lungs with airway obstruction (e.g. COPD with bronchospasm).

An example of a GUI's ability to increase situational awareness is Hamilton Medical's G5 Ventilator Cockpit. Figure 1 represents a current typical display of ventilatory parameters. Figure 2 represents a current typical default ventilator display. Figure 3 represents a new Object Oriented Intelligent graphical display of pulmonary mechanics. Which of these, figure 1, 2 or 3, more clearly identifies stiff lungs with normal airways resistance, eg decreased compliance due to a restrictive disease process as a contributing factor to dependence on mechanical ventilation?

- 1 International Ergonomics Association website, iea.cc/index.php.
- 2 Health Services/Technology Assessment Text (HSTAT). AHRQ Evidence Reports. Chapter 41. Human Factors and Medical Devices. ncbi.nlm.nih.gov/books/bv.fcgi?indexed=google&rid=hstat1.section.61782.
- 3 Graphic user interface to improve patient safety during mechanical ventilation. Wysocki, M. International Journal of Intensive Care. Spring 2007, Volume 14, number 4.
- 4 Design of a smart hemodynamic monitoring simulator. Kilty BG, Wright CH, Barrett SF, Calkins JM, Drzewiecki TM. Biomed Sci Instrum. 2007; 43:236-41.

The Economic Burden of Treating Neonates in Intensive Care Units (ICUs) in Greece

Mary Geitona, Magdalini Hatzikou, Zoi Hatzistamatiou, Aggeliki Anastasiadou, Theodora D. Theodoratou

Abstract

Background: In a period when a public-private mix in Greece is under consideration and hospital budgets have become restrained, economic assessment is important for rational decision-making. The study aimed to estimate the hospitalization cost of neonates admitted to the ICUs and demonstrate discrepancies with reimbursement.

Methods: Chosen methodology was based on the selection of medical records of all NICUs and intermediate care admissions within February to April 2004. Neonates (n = 99) were classified according to birthweight and gestational age.

Results: Mean cost per infant was estimated at €5.485 while reimbursement from social funds arises to €3.952. Costs per birthweight or gestational age show an inverse relationship. Personnel costs accounted for 59.9%, followed by enteral/parenteral feeding (16.14%) and pharmaceuticals expenses (11.10%) of all resources consumed. Sensitivity analysis increases the robustness of the results.

Conclusion: Neonatal intensive care in Greece is associated with significant costs that exceed reimbursement from social funds. Reimbursement should be adjusted to make neonatal

intensive care economically viable to private hospitals and thus, increase capacity of the services provided.

Background

The National Health System (ESY) in Greece was established in 1983 providing free access to all public services at the point of use. Given that the private sector had limited space for growth, it embarked on providing services in order to increase market share by setting up diagnostic centres and investing in expensive medical technology. As such, the Greek health care sector was converted in a mixed public-private system. In 2004, the total healthcare expenditure in the country was 7.9% of the GDP of which 52.8% comes from the public sector while the remaining from the private sector.

Intensive care cost is one of the largest components of inpatient care worldwide ranging from 15% to 35% of hospital budgets and accounting for about 0.2% to 1.5% of gross domestic product (GDP). Neonatal intensive care for low birth weight infants is

Table 1: Distribution of NICU beds in public hospitals in Greece

Geographical regions	Number of Births	Beds (NICUs) *	Births per NICU beds
Greater Athens (Attiki)	14,851	85	175
Thessaloniki	6,660	30	222
Macedonia & Thrace	4,064	5	813
Western Macedonia	1,380	-	-
Western Greece	3,664	10	366
Ipiros	2,523	6	421
Ionian Islands	1,033	-	-
Peloponnesus	2,632	-	-
Crete	3,919	15	261
Aegean Islands	2,787	-	-
Thessaly	3,022	8	378
Central Greece & Evia	1,903	-	-
Total	48,438	159	305

Source: National Statistics Service of Greece, 2004

*The number of beds was given on request by the administration of the hospitals; the only official national reporting is the number of NICUS

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Table 2: Characteristics of the Sample (n = 99)

Infants' Characteristics	In absolute numbers (%)	
	ELENA VENIZELOU HOSPITAL	ALEXANDRA HOSPITAL
No. of patients	44 (44.4)	55 (55.5)
Male	28 (63.6)	30 (54.5)
Female	16 (36.4)	25 (45.5)
Place of residence		
Urban Areas	35 (79.5)	35 (63.6)
Rural Area	9 (20.5)	20 (36.4)
Mother's Age*	30.6 ± 5.1	29.44 ± 6.5
Mother's Insurance coverage	41 (93.2)	42 (76.4)
Mean Gestational Age* (wks)	35.1 ± 3.9	32.1 ± 5.06
Mean Weight (grs)*	2327 ± 787.8	1665 ± 846.4
Weight Classification (n)		
< 1000 gr	-	9 (16.4)
1001 – 1500 gr	5 (11.4)	13 (23.6)
1501 – 2000 gr	7 (15.9)	14 (25.4)
2001 – 2500 gr	9 (20.4)	6 (10.9)
≥2500 grs	20 (45.4)	9 (16.4)
Gestational Age (n)		
< 24 weeks	-	-
24 ≤ wks < 28	2 (4.5)	6 (10.9)
28 ≤ wks < 32	3 (6.8)	15 (27.3)
≥32 wks	36 (81.8)	30 (54.5)
Deaths	3 (6.8)	4 (7.3)
Mean LOS in NICU	9.8 ± 15.5	18.4 ± 17.4
Mean LOS in Section II	8.9 ± 8.3	16.1 ± 13.2
Mean Length of Stay (LOS)	18.7	34.5

* Mean ± Standard Deviation

ranked among the most costly hospital admissions and is regarded as one of the most expensive components of pediatric health care accounting for about 10% of total pediatric expenses.

Utilization of NICUs has generated a great deal of concern in several countries due to their continuing increasing demand and resource consumption. Fast technological innovations and improved obstetric practices, in combination with the highly specialized personnel and the intense working conditions, are in large part responsible for the remarkable decline in neonatal and perinatal mortality rates and the aforementioned high share

costs. In the international literature, intensive care has been proved cost-effective since the benefits for saving children's lives are far greater than the relative costs. Hence, in an era of increased financial scrutiny and competing demands for limited healthcare resources, technology assessment constitutes a useful managerial tool since it enables decision-makers or health professionals to make more rational and cost-conscious clinical decisions.

In Greece, during the last decades there has been a significant reduction in neonatal (50%) and perinatal (64%) mortality rates reaching 8% and 4% respectively. However, an increasing rate in the preterm birth and low birth weight newborns has been observed. In addition, the continuing urbanization and depopulation of rural areas, gave a shift in the health services demand to the urban areas resulting in large socio-economic and geographical inequalities in the health services' provision. In Greece there is an inadequate supply and unequal distribution of NICU beds in the various geographical regions. As presented in Table 1, the large urban areas (Athens and Thessaloniki) have the highest share of births as well as the majority of NICU beds since they cover the majority of NICU admissions and consequently, the lowest ratio of births per NICU beds.

Having identified the insufficient coverage of ICU beds of the public sector, the NHS introduced a public-private contract services system, which could allow reimbursement of the provision of intensive care for patients admitted to private hospitals so as to meet population needs. The creation of a public-private mix in the provision of intensive care faces great difficulties in Greece. The vast differentiation between NHS and private sector prices prevents social insurance funds from reimbursing the provision of healthcare of its insured population to the private sector. The maintenance of a per diem hospital reimbursement system by the insurance funds results in deficits in the hospital budgets and prevents the private health providers from accepting any public-private mix arrangements. In addition, the lack of hospital costs assessments either for diagnostic related groups or surgical operations, as well as the overall insufficiency of national costing data, assigned priority to the cost analysis of the intensive care units.

Given the experience outlined above, the objective of the study

Table 3: Total ancillary services cost by weight and gestational age in Athens in 2004 Euros (rounded to the closest integer)

Infants Classification	N	Pharmaceutical Cost (€)	Laboratory Cost (€)	Consumables Cost (€)	Enteral/Parenteral Feeding (€)	Total Ancillary Cost (€)
Weight						
< 1000 gr	9	24,222	5,431	3,566	11,980	45,199
1001 – 1500 gr	18	24,361	14,584	7,057	36,150	82,151
1501 – 2000 gr	21	8,835	7,164	3,470	24,090	43,559
2001 – 2500 gr	15	463	3,181	1,107	7,440	12,191
≥2500 grs	29	2,798	5,588	2,290	12,140	22,816
deaths	7	3,531	2,455	597	1,560	8,143
Gestational Age						
< 24 weeks	0	-	-	-	-	-
24 ≤ weeks < 28	8	11,146	7,730	3,722	17,560	40,158
28 ≤ weeks < 32	18	34,088	11,544	4,934	27,810	78,377
≥32 weeks	66	15,446	16,673	8,833	46,430	87,382
Deaths	7	3,531	2,455	597	1,560	8,143
All Infants	99	64,211	38,402	18,087	93,360	214,060

Table 4: Mean cost per infant in Athens in 2004 Euros (rounded to the closest integer)

Infants Classification	N	Length of Stay (LOS)	Ancillary Cost (€)	Overhead Cost (€)	Cost of Personnel (€)	Total Cost (€)	Cost per Infant (€)	Amount Reimbursed (€)
Birth Weight								
< 1000 gr	9	33.89	45,199	1,651	31,491	78,341	8,705	8,149
1001 – 1500 gr	18	34.50	82,151	3,302	62,981	148,434	8,246	8,441
1501 – 2000 gr	21	12.95	43,559	3,852	73,478	120,889	5,757	4,369
2001 – 2500 gr	15	5.3	12,191	2,751	52,484	67,427	4,495	1,941
≥2500 grs	29	5.0	22,818	5,319	101,470	129,607	4,469	1,380
Deaths	7	3.9	8,143	1,284	24,493	33,919	4,846	724
Gestational Age								
< 24 weeks	0	-	-	-	-	-	-	-
24 ≤ weeks < 28	8	55.9	40,158	1,467	27,992	69,617	8,702	8,757
28 ≤ weeks < 32	18	49.1	78,377	3,302	62,981	144,660	8,037	7,158
≥32 weeks	66	30.6	87,382	12,106	230,931	330,420	5,066	2,837
Deaths	7	3.9	8,143	1,284	24,493	33,919	4,846	724
All Infants	99	27.5	214,060	18,159	346,397	578,616	5,845*	3,952

* including deaths as well

is the cost analysis of resource consumption and the cost estimation for neonates admitted to NICUs in Greece, either per birth weight or per gestational age classification. The identification of cost per infant can facilitate public-private contracts to expand access to neonatal intensive care, once the significant underpayment by the social fund is taken into consideration.

Methods

Alexandra and Helena Venizelou were the selected hospitals of the study. The selection of the specific hospitals was based on the fact that they are acknowledged as the two leading public obstetric and maternity hospitals of Athens, representing almost 45% of the total number of deliveries that took place in Athens in 2004.

Both hospitals have been incorporated into the National Health System (ESY) since 1986, cover 80% of the NICUs admissions of the public obstetric hospitals of Athens and 40% of the total NICU admissions in the public and private obstetric hospitals in the Athens area.

The District Maternity Hospital Helena Venizelou provides tertiary healthcare services with 7,000 deliveries per year and one NICU with 20 mechanical ventilators. It also has a capacity of 384 beds, a prenatal control unit, along with a milk bank and a maternal breastfeeding department. The second University Maternity Hospital, Alexandra, is one of the largest specialist hospitals in Athens, with a capacity of 300 beds, one NICU with

12 mechanical ventilators and 6,500 deliveries per year. According to patient records, although both hospitals are in the center of Athens, they host deliveries from Central Greece, Evia, the islands and neighboring counties of the Peloponnese region.

Data was prospectively collected for all NICU and intermediate care admissions of both hospitals within a three month period (February to April 2004). The sample included neonates who had been admitted to both ICUs as premature and low birth weight, and those who needed intensive care support for various reasons. Both hospitals are maternity hospitals and do not undertake surgeries or any type of operations. In cases of acute events that require the latter, neonates are transferred in pediatric hospitals.

Once the data was collected, infants were categorized into groups according to their birthweight (g <1000, 1001-1500 g, 1501-2000 g, 2001-2500 g and 2501 < gr) and to their gestational age (wk < 24, 24 ≤ wk < 28, 28 ≤ wk < 32, 32 ≤ wk). Neonates that did not survive formed a separate group (deaths) in the analysis to avoid potential underestimation of the cost per infant.

The estimation of cost was performed using a bottom up approach, which identifies all the resources directly employed for an intervention. It is commonly used when considering technologies with a large component of staff input or overheads where healthcare systems do not allocate costs to the intervention level, such as the intensive care unit. In these circumstances and since no national data were available, this microeconomic approach was chosen to increase consistency and transparency of our results. Cost was based on the analytical recording of a) the resource consumption of supplies, medication, laboratory and medical tests and enteral and parenteral feeding on an everyday basis per infant, b) the infrastructure and various overhead costs such as electricity, cleaning, telephone, water, heating, maintenance and repairs and c) personnel cost.

Public sector prices and NHS perspective have been used in the analysis. Depreciation of the capital assets was not included due

Table 5: Cost breakdown per infant hospitalized in NICU (*rounded to the closest integer)

Cost components	Mean Cost per infant* in €	Cost distribution in %
Laboratory-diagnostic tests	388	6.64
Pharmaceutical expenses	649	11.1
Enteral/Parenteral costs	943	16.1
Consumables	183	3.1
Personnel Cost	3,499	59.9
Overhead Cost	183	3.1
Total cost	5,845	100

Table 6: Sensitivity Analysis Results

Infants Classification	N	Length of Stay (LOS)	Ancillary Cost (€)	Cost of Infrastructure (€)	Cost of Personnel (€)	Total Cost (€)	Cost per Infant (€)
Birth Weight							
< 1000 gr	5	31.8	18,909	1,020	19,460	39,390	7,878
1001 – 1500 gr	12	43.7	40,852	2,448	46,705	90,005	7,500
1501 – 2000 gr	21	33.6	43,559	4,285	81,734	129,578	6,170
2001 – 2500 gr	15	15.3	12,191	3,061	58,381	73,633	4,909
≥2500 grs	29	9.8	22,816	5,917	112,871	141,604	4,883
deaths	7	3.9	8,143	1,428	27,245	36,816	5,259
Gestational Age							
< 24 weeks	0	-	-	-	-	-	-
24 ≤ weeks < 28	8	30.5	11,819	816	15,568	28,204	7,051
28 ≤ weeks < 32	18	40.7	49,675	2,857	54,489	107,021	7,644
≥32 weeks	66	18.9	76,833	13,058	249,094	338,985	5,297
deaths	7	3.9	8,143	1,428	27,245	36,816	5,259
All Infants	89	21.7	146,470	18,159	346,397	511,026	5,742

to lack of data. For that reason, the analysis focused only on variable costs.

All personnel cost data were obtained from budgetary control statements provided by both hospitals' finance departments. Personnel cost includes the wages of the medical and nursing staff that was fully employed in the NICU and the intermediate section II of the two hospitals. It also includes the cost of paramedical, administrative and other personnel that were calculated based on the number of patients admitted for each hospital.

The cost of enteral and parenteral feeding was estimated based on the substances used for each infant. Cost of consumables was also reported on a per infant basis and was obtained from each hospital supplies department. Infrastructure and general overhead costs such as electricity, water, heating, telephone and other utilities, were allocated based on the area occupied (square meters) by the NICU and the intermediate section II unit over the total area of the hospital. The cost of diagnostic tests, drug utilization and any other medical exams was reported on a per-case basis.

The estimated cost was compared with the reimbursement from the social security funds based on the per diem payment (Government Gazette 99B/10-2-98). The amount reimbursed per inpatient day for the intensive care unit is at €187, while for the intermediate section II reaches €93.

From the data collected a descriptive statistical analysis was conducted. Mean ± standard deviation values are given when necessary and 95% confidence intervals are estimated. Sensitivity analysis was undertaken to explore the reliability of our estimates. The monetary values used in the paper have been converted to US Dollars in 2004 using an inflation rate of 3% for all studies to allow international comparisons. The conversion rates used depending on the study were: January 1998: 1 US\$: 0.61 GBP; January 2004: 1 US\$: 0.79€.

Results

The study sample consisted of 99 neonates corresponding to approximately 45% of overall NICU admissions annually. Forty-

four were from Helena Venizelou hospital and 55 from Alexandra hospital. Table 2 presents the characteristics of the sample from both hospitals and the classification by birth weight and gestational age separately.

Table 3 provides information on the cost drivers of the ancillary services, including pharmaceutical, laboratory, consumables and enteral/parenteral feeding costs. Pharmaceutical costs include the costs of any drug used during infants' overall stay in the hospital. During the study period, approximately 70 pharmaceutical products were used in the aforementioned NICUs and intermediate section IIs of both hospitals. These included antibiotics, surfactants and others. Laboratory costs included tests such as CBC, blood gas analysis, ultrasounds, MRIs and others.

Table 4 presents analytical costs for infant hospitalization in NICUs in Athens. Mean cost per infant classified by birth weight and gestational age is presented. It is estimated at €5.845 in 2004, with mean length of stay of 27.5 days. It is observed that cost per infant is inversely related to both birth weight and gestational age, which is compatible with the literature. Also, the underpayment by social security funds becomes evident, except in the small for gestational age and very low birth weight infants where it is fully covered.

According to the cost breakdown presented in Table 5, the highest share of resources was allocated in personnel wages (59.9%), in enteral/parenteral feeding (16.1%) and pharmaceuticals (11%).

Sensitivity analysis

From the data presented in table 4, one can observe that length of stay (LOS) is highly skewed. Therefore, a sensitivity analysis was run to correct for the non-normality of the distribution by excluding outliers (n = 10); all came from the lowest gestational and/or birthweight classification (Table 6). The difference in mean cost per infant between the two scenarios shows statistical significance between the groups (p = 0.018). However, in everyday clinical practice the neonatal intensive care unit admits extremely low birth weight infants accounting for 5-8% of all premature infants. Thus it was assumed appropriate not

to treat them as outliers and exclude them from the analysis.

In order to reflect better the cost of the selected neonates, the median cost per infant was also used. It was estimated at €4.927, showing a difference of €918 from the mean.

Discussion

The present cost assessment has arisen from the insufficient coverage of beds in the intensive care units in general and in particular for neonates, at public hospitals in the country. The continuously rising demand for NICUs in the large urban centers, the lack of ICU beds, and the unequal geographical distribution of public NICUs has recently led the government to contract intensive care services from the private sector. Although the adoption of such a policy is thought to bring about positive results, so far its outcomes have not been evaluated.

The current study had as its primary objective to estimate the cost of neonatal intensive care. The estimation of the hospitalization cost of neonates in comparison to the amount reimbursed from the social security funds could lead to a successful synergy between the public and private healthcare sector, to the reduction of public hospital deficits, and to empower coverage of social security funds with funds from private hospitals.

According to the results of the study, the mean cost per infant hospitalized in a NICU in the two major public maternity hospitals in Athens was estimated at €5.845, while the social security funds reimbursed €3.952 for every neonate admitted. This finding is important since it depicts the factors responsible for a potential failure of this public-private mix in the provision of intensive care for neonates. Private hospitals may not be willing to accept reimbursement according to each infant's nominal cost (€3.952). Reimbursement should be adjusted to make neonatal intensive care economically viable to private hospitals and thereby increase capacity of the service overall.

It is believed that the importance of carrying out such a study was threefold: firstly, because it relates to the analytical identification of cost drivers and the assessment of resource consumption per infant in a NICU in Greece. Secondly, it involved the estimation of hospitalization costs according to patient classification. Similar studies in Greece are not often encountered in the literature due to the lack of specialty unit prices based on diagnostic or clinical performance criteria. Thirdly, because it becomes evident that cost analysis allows for the possibility of introducing diagnostic-related patient grouping and abandoning the per diem payment (which results in enormous deficits in public hospital budgets). It is believed that the classification of infants per birth weight or gestational age could easily constitute diagnostic-related patient categories combined with a prospective hospital payment system. If this were the case, it is apparent that private healthcare providers would have some economic motivation in profiting through an expansion of the public-private mix.

In an effort to compare our results to those of the international literature in cost analysis of NICUs, differences and similarities have been observed. Differences can be explained by the availability of economic data, the choice between private or public healthcare sector unit prices and the variability of the accounting methods for measuring economic costs. According to an extensive literature review performed by Petrou, the mean

cost per infant category of 1001-1500 g was \$45,152 for studies conducted in the US and \$19,975 for the non-US studies (in 2004 USD). A study conducted by the Washington Office of Technology Assessment estimated the mean cost per infant weighting 1501-2000 g to be \$10,948 and for those with birthweight over 2,500 g at \$1,531. In the present study the mean cost per infant hospitalized in a public NICU was estimated at \$10,438 for infants weighting 1001-1500 g, while for those exceeding 2500 g, it reached \$5,657.

Furthermore, as reported earlier, it was found that infant hospitalization cost varies inversely with birth weight, since it reflects differences in both the mean length of stay and in the intensity of treatment during each day of stay. In addition, the high share of the personnel, parenteral feeding and pharmaceutical care costs is found in most cost analysis studies both in Greece and abroad.

At this point some methodological limitations should be mentioned. The mean cost per infant is underestimated primarily due to the use of NHS prices, which are far lower than those of the private maternity hospitals. The lack of data and the non-responsiveness of the private sector in providing the necessary information did not allow us to estimate the latter. Secondly, due to the fact that the official registration of public hospital expenses did not include costs for depreciation of capital assets, they were excluded from our microeconomic analysis.

To avoid overestimation of cost per infant in categories with small sample sizes, groups were collapsed to provide more reliable results. Additionally, sensitivity analysis increased the reliability of the results, since it showed that mean cost per infant were similar when excluding outliers (€5.845 vs €5.742), despite the fact that the difference was found statistically significant.

Conclusion

Through the analysis of this study it becomes evident that the identification of cost per infant can facilitate public-private contracts to expand access to neonatal intensive care, once the significant underpayment by the social fund is adjusted. It seems most important at this time when a public-private mix effort is under consideration and hospital budgets become more restrained. For all the above-mentioned reasons, economic assessment is necessary in Greece, since it will facilitate policy makers in their decision-making.

Reducing One Million Child Deaths From Birth Asphyxia – A Survey Of Health Systems Gaps and Priorities

Joy E. Lawn, Ananta Manandhar, Rachel A. Haws, Gary L. Darmstadt

Abstract

Background: Millions of child deaths and stillbirths are attributable to birth asphyxia, yet limited information is available to guide policy and practice, particularly at the community level. We surveyed selected policymakers, programme implementers and researchers to compile insights on policies, programmes, and research to reduce asphyxia-related deaths.

Method: A questionnaire was developed and pretested based on an extensive literature review, then sent by email (or airmail or fax, when necessary) to 453 policymakers, programme implementers, and researchers active in child health, particularly at the community level. The survey was available in

French and English and employed 5-point scales for respondents to rate effectiveness and feasibility of interventions and indicators. Open-ended questions permitted respondents to furnish additional details based on their experience. Significance testing was carried out using chi-square, F-test and Fisher's exact probability tests as appropriate.

Results: 173 individuals from 32 countries responded (44%). National newborn survival policies were reported to exist in 20 of 27 (74%) developing countries represented, but respondents' answers were occasionally contradictory and revealed uncertainty about policy content, which may hinder policy implementation. Respondents emphasized confusing terminology and a lack of valid measurement indicators at community level as barriers to obtaining accurate data for

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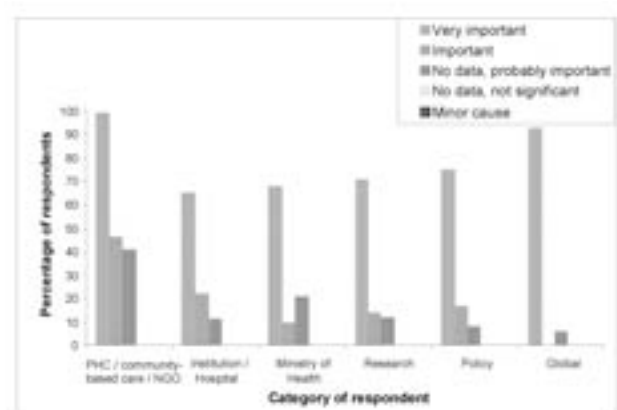


Figure 1
Perceived importance of birth asphyxia by category of respondent (N = 173). PHC: primary health care. There was a significant difference between the perceived importance of asphyxia ("very important" or "important") for those involved in policy or research compared to those in community-level programmes (F-test = 0.05). Those reporting uncertainty about data were significantly less likely to be involved in a programme addressing asphyxia (P = 0.009).

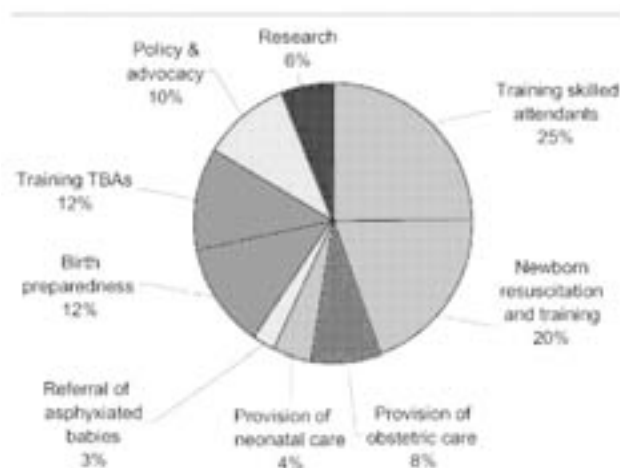


Figure 2
Reported programme activities of relevance to birth asphyxia. 142 of 173 respondents reported involvement in programmes addressing birth asphyxia, yielding 322 replies, as most programmes were implementing several relevant activities.

decision-making. Regarding interventions, birth preparedness and essential newborn care were considered both effective and feasible, while resuscitation at community level was considered less feasible. Respondents emphasized health systems strengthening for both supply and demand factors as program priorities, particularly ensuring wide availability of skilled birth attendants, promotion of birth preparedness, and promotion of essential newborn care. Research priorities included operationalising birth preparedness, effectively evaluating pregnancy risk in the community, ensuring roles for traditional birth attendants (TBAs) that link them with the health system, testing the cost-effectiveness of various community cadres for resuscitation, and developing a clear case definition for case management and population monitoring.

Conclusion: Without more attention to improve care and advance birth asphyxia research, the 2 million deaths related to asphyxia, plus associated maternal deaths, will remain out of reach of effective care, either skilled or community level, for many years to come.

Background

Birth asphyxia is the fifth largest cause of under-five child deaths (8.5%), after pneumonia, diarrhea, neonatal infections and complications of preterm birth. Birth asphyxia accounts for an estimated 0.92 million neonatal deaths annually and is associated with another 1.1 million intrapartum stillbirths, as well as an unknown burden of long-term neurological disability and impairment. If 10 million child deaths are combined with 3.2 million stillbirths, then birth asphyxia plus intrapartum stillbirths constitute the number-one cause of child and late fetal deaths. Yet birth asphyxia is largely invisible in health policy and programmes, and receives limited programmatic or research funding internationally. Here we refer to birth asphyxia in the traditional use of the term by clinicians – the full-term baby who is not breathing and in poor condition at birth with an assumed association to acute intrapartum events. The need for more specific case definitions is apparent, but terminology discussion is not the purpose of this paper.

Recognizing that neonatal deaths (deaths in the first 28 days of life) account for almost 40% of under-five deaths, it is clear that Millennium Development Goal 4 (aiming for a two-thirds reduction of under-five mortality), cannot be met without substantially reducing neonatal deaths. Neonatal and late fetal deaths are closely linked to maternal deaths, requiring common solutions. Over half of neonatal deaths occur at home in the absence of skilled care, and just three major causes account for over three-quarters of these deaths – serious infections, including tetanus (36%), complications of preterm birth (27%) and birth asphyxia (23%). Evidence exists regarding the effectiveness of interventions to reduce deaths due to neonatal infections and improve survival of small babies in the community. However, prevention and management of birth asphyxia are much more complex at the community level and published evidence is scanty. To address this gap, Saving Newborn Lives/Save the Children-US commissioned a review of birth asphyxia to include systematic global estimates, undertaken with the WHO; an expert meeting; and a systematic literature review for impact of interventions. Major limitations were highlighted in the scope and depth of the published literature with respect to high mortality settings with low health system coverage. We therefore undertook a targeted survey of policy makers, program implementers and researchers, specifically selecting those involved in community-based child health programming in resource-poor settings, to identify

Table 1: Home and health system practices identified as contributing to occurrence or severity of birth asphyxia, and number of programmes identifying the problem who were addressing it

Practices amenable to behaviour change	Number (%)	Behaviour change intervention implemented (% of those identifying the problem currently addressing this behaviour)
Home	131 (85%)	35 (27%)
Delay in recognition by families	26 (17%)	10 (38%)
Unsafe practices at home in pregnancy and/or labour	28 (18%)	13 (46%)
Not using skilled attendant at birth/not attending ANC	10 (6%)	0 (0%)
Unsafe practices by TBA	7 (4%)	2 (29%)
Unsafe newborn care traditional practices at home	38 (25%)	0 (0%)
Incorrect use of oxytocin	22 (14%)	10 (45%)
Health care system	23 (15%)	15 (65%)
Unsafe practices by healthcare workers in labour	12 (8%)	7 (58%)
Unsafe newborn care practices by healthcare workers	11 (7%)	8 (73%)
Total respondents	154	50

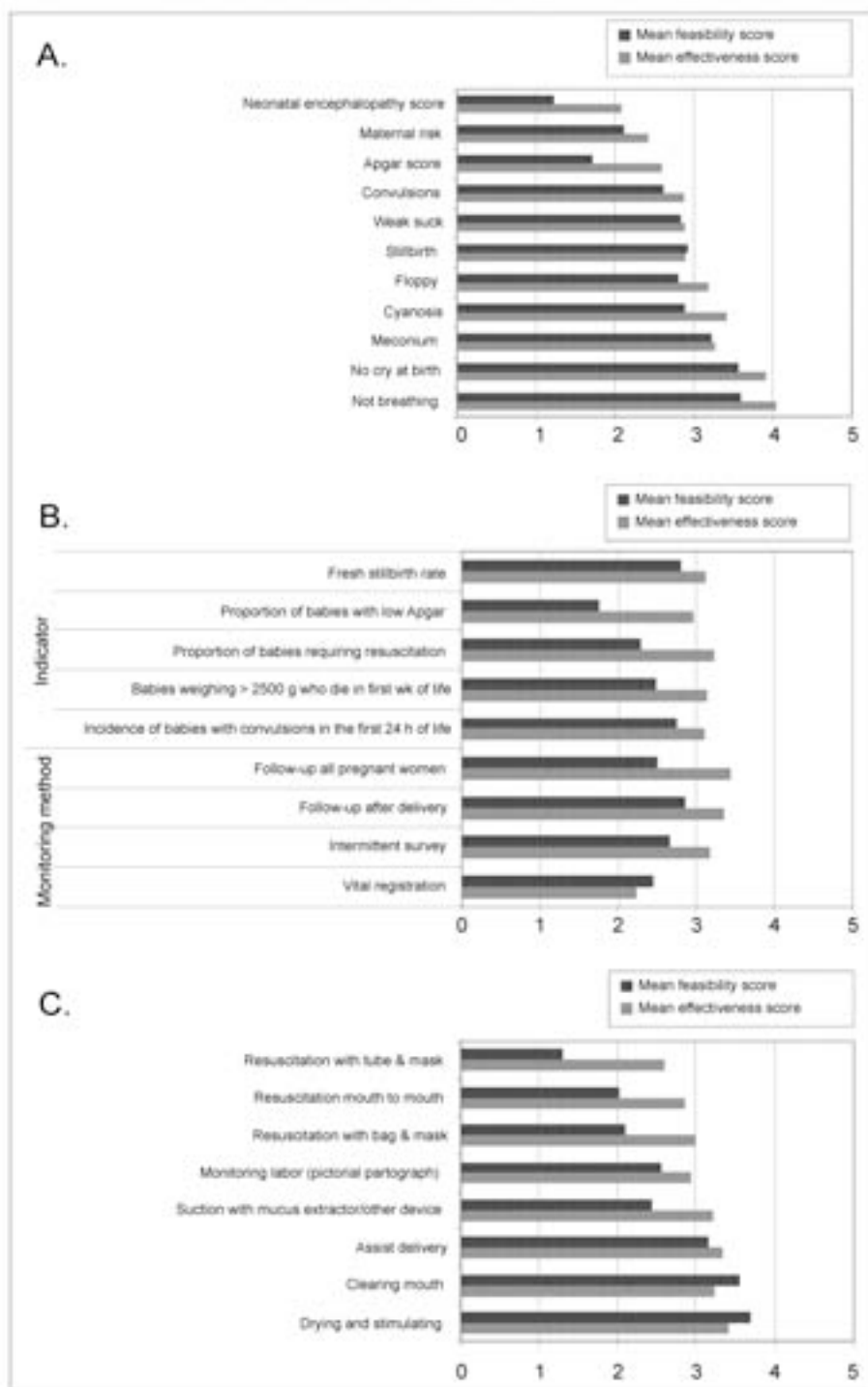


Figure 3. Respondents' views on measurement and interventions for birth asphyxia. A. Perceived effectiveness and feasibility of signs to identify "birth asphyxia" at community level. B. Respondents' assessment of community-based asphyxia programme indicators and monitoring methods. C. Perceived effectiveness and feasibility of various birth asphyxia interventions performed by TBAs/CHWs during labour or delivery.

information on current policies, programmes, practices, and health systems research priorities related to birth asphyxia.

The objectives of the survey were:

1. To identify the presence of national

policies regarding newborn health;

2. To describe current methods to recognise and monitor birth asphyxia in the community;

3. To solicit opinions about the perceived appropriateness and effectiveness of interventions to

address birth asphyxia, particularly at community level and specifically regarding the involvement of traditional birth attendants (TBAs) and community health workers (CHWs) in resuscitation and newborn care;

4. To discover unpublished data, lessons learned and policies relating to birth asphyxia;

5. To compile perceived gaps in programmatic implementation of proven interventions for asphyxia, especially at community level; and

6. To compile perceived knowledge gaps which limit the prevention, recognition and management of asphyxia, especially at community level.

Methods

Survey questions were informed by a systematic literature review of the evidence base for efficacy and effectiveness of interventions to address birth asphyxia, using PubMed, POPLINE, Latin American and Caribbean Health Sciences (LILACS), BioMed Central, African Index Medicus, and WHO Regional Office for the Mediterranean (EMRO) databases. The results of this review will be published separately. The questionnaire was reviewed by an international panel of experts and adapted according to their suggestions, then pilot-tested using a convenience sample of students at the Institute of Child Health, London. A simple scale was developed to allow respondents to rate interventions and indicators for effectiveness and feasibility at community level. Effectiveness was rated from 0 (no evidence) to 5 (several randomized controlled trials). Feasibility was rated from 0 (complete infeasibility) to 5 (extreme ease of application). Additional open-ended questions encouraged respondents to provide further detail. The questionnaire was translated into French to facilitate replies from French-speaking West Africa. Total time to complete the questionnaire was approximately 1 hour.

E-mail surveys usually yield a response rate of approximately 25% or less. To obtain at least 50 respondents, the questionnaire was sent to over 400 recipients active in child health care, particularly at community level in resource poor settings, including individuals from international and local NGOs addressing Safe Motherhood or newborn care; officials from relevant programs within United Nations agencies; members of ministries of health; clinical service providers in relevant settings; academic research units publishing or currently undertaking relevant research;

Table 2: Key research and implementation priorities to address birth asphyxia, according to 173 survey respondents

Programme priorities	% Naming Priority
1. High coverage of skilled attendants at birth	(23%)
2. Promotion of birth preparedness, including emergency transport	(22%)
3. Wide availability of essential newborn care (hygiene, warmth and breastfeeding)	(19%)
4. Competency based training in neonatal resuscitation	(16%)
5. Provision of emergency obstetric care	(11%)
6. Training TBAs and CHWs where appropriate	(5%)
Research priorities	
1. Assess the effectiveness of TBAs/CHWs for neonatal resuscitation	(25%)
2. Evaluate the impact of birth preparedness	(23%)
3. Operations research on successful implementation/scaling-up of known interventions and roles for community cadres	(15%)
4. Accurate identification of women/neonates at risk	(15%)
5. Accurate methods for detection of "asphyxia" in the community	(7%)
6. Appropriate care of asphyxiated newborns in the community	(5%)

and individuals recommended by colleagues. To maximise the information received regarding programmes and policies, 80% of questionnaires were sent to country programme officials and policy makers. The remaining 20% were sent to researchers and global experts. The survey was disseminated by e-mail and, in some cases by airmail, followed up by two e-mail reminders. Recipients who reported difficulties accessing attachments were faxed the form (N = 8). Recipients were encouraged to forward the questionnaire to interested colleagues and/or recommend colleagues with experience addressing birth asphyxia; such individuals were added to the recipient list.

Data from returned questionnaires was entered into a Filemaker Pro version 5.5 database (Filemaker Pro Inc, Santa Clara, CA). Data entry was cross-checked for accuracy. Simple frequencies were calculated using Filemaker Pro; cross-tabulations were calculated using Microsoft Excel (Microsoft Office 1997, Microsoft Corp., Redmond, WA). Significance testing was carried out using chi-square, F-test and Fisher's exact probability tests as appropriate. Individuals' ratings were then compiled across the sample and mean effectiveness and feasibility scores were computed for each intervention/indicator.

Results

The survey response rate was 44% (173/453). Respondents represented 32 countries from all 6 major regions of the world. Half (49%) of all respondents were from South Asia, and 27% and 16% were from sub-Saharan Africa and industrialized nations, respectively. All respondents from industrialized nations were affiliated with global agencies or academic institutions active in policy and/or research in developing countries or with international non-governmental organisations. The developing country respondents included ministries of health, policymakers, programme implementers, clinicians, researchers and public health/primary care workers. A high proportion (39%) reported community-based or primary healthcare experience, reflecting deliberate efforts to target these groups.

Perceived importance of birth asphyxia: Almost all policy makers (93%) identified asphyxia as a major problem, whereas only 52% of community-based program personnel had this perception ($p = 0.05$). An additional 21% of community-based

respondents reported that birth asphyxia was "probably important," but they lacked data (Figure 1). A significantly higher proportion of individuals from industrialized countries perceived asphyxia as very important compared to those from developing countries (82% vs. 64%, respectively; $p = 0.044$). Respondents from sub-Saharan Africa perceived asphyxia as causing more neonatal deaths (>30%) than those from other regions ($p = 0.029$). Respondents who considered asphyxia "very important" were more often involved with programs to address asphyxia than those who were unsure of the scope of the problem ($p = 0.009$). Among respondents not currently involved in birth asphyxia activities, 45% cited other priorities, while 40% cited financial, human resource or knowledge barriers.

National policies: National-level newborn survival policies were reported to exist in 20 of the 27 (74%) developing countries represented, but in 8 countries, answers from different individuals were contradictory. Seventy percent of the 20 countries with policies had a perinatal and/or neonatal mortality reduction target (N = 14), and one-third (N = 7) listed asphyxia as a specific priority. Lack of data on neonatal mortality and effective interventions was the most common explanation for the lack of a national policy (37%), followed by an assumption that newborn survival was included under child survival programs (36%), and higher priority of other issues such as malaria or HIV/AIDS (32%). A significantly higher proportion of respondents in Latin America (71% of 7) and East Asia/Pacific (75% of 4) reported a national policy in their country compared to South Asia (32% of 77), or sub-Saharan Africa (47% of 42). The few replies from North Africa and the Middle East (N = 2) precluded regional comparison.

Programs that address birth asphyxia: Reported program experience ranged from large systems with several integrated levels of care to small, stand-alone community projects. Most respondents (88%) were actively engaged in programmes to address asphyxia. Although some interventions were newborn-specific, for example neonatal resuscitation training (N = 62, 44%), most were maternal health programs, predominantly training of skilled birth attendants, and emergency obstetric care (Figure 2) (N = 80, 56%). South Asian programmes more often reported birth preparedness and training of skilled birth attendants or TBAs; African programmes more often reported

emergency obstetric care. Community-based interventions such as birth preparedness and training of TBAs were reported by less than one-third of programs represented, despite our pre-selected community-orientated audience. Provision of neonatal care and referral of asphyxiated babies were elements of fewer than 10% of programs.

Recognition of birth asphyxia in the community: The most frequently reported methods for identifying the asphyxiated baby by TBAs and CHWs were “baby not crying” (55% and 61%, respectively) and “baby not breathing” (48% and 40%, respectively) at birth (Figure 3). “Not crying” and “not breathing at birth” also received the highest scores for both effectiveness and feasibility, concurring with methods already in use (Figure 2). Presence of meconium was also deemed a moderately effective and feasible sign. Other possible clinical identification methods, such as floppy baby, cyanosis, and convulsions in the first 24 hours after birth, received fairly high scores for effectiveness but lower scores for feasibility at community level (Figure 3). Apgar score, neonatal encephalopathy score, and maternal risk factor assessment received low effectiveness and feasibility scores.

Indicators to track birth asphyxia at population level: None of the possible indicators to measure birth asphyxia at community level received high effectiveness and feasibility scores (Figure 3). Of respondents involved with programmatic activities, 35% reported that their programs did not collect routine data on birth asphyxia. Most mentioned struggles with identifying asphyxia and collecting meaningful data to guide decisions about asphyxia interventions in the community. Among the 36% of respondents who reported that their programme collected asphyxia data, the most common method of obtaining birth asphyxia data was registration records (42%) or routine health information systems (34%). A minority used CHWs to collect data prospectively (18%), or relied on hospital records (14%), and a few (8%) conducted periodic population-based surveys. There was limited consensus about best methods for monitoring birth asphyxia incidence at the population level. While there was moderate agreement that follow-up for all pregnant women would be most effective, respondents doubted its feasibility (Fig 3b). Follow-up of all recently delivered women was considered less effective, but more feasible. Respondents considered vital registration neither effective nor feasible.

Overall, respondents considered fresh stillbirth rate the most promising indicator to track, rated as moderately effective yet feasible with training input. Onset of convulsions in the first 24 h of life and death in the first week of life in a baby weighing > 2500 g were also identified as potentially effective indicators, but difficulty obtaining complete population birthweight data limited the perceived feasibility of the latter approach (Fig 3b).

Perceived effectiveness and feasibility of interventions during pregnancy, labor, and delivery: Essential newborn care, including stimulating, drying and warming the newborn, received the highest scores for both effectiveness and feasibility; however, impact of these interventions on asphyxia-specific deaths is unproven (Figure 3). Also highly rated were antenatal care; birth preparedness; basic obstetric care; and communicating danger signs to the family and/or TBAs/CHWs. Maternity waiting homes and first aid for obstetric emergencies were considered less effective and considerably less feasible, especially by Asian respondents. Neonatal resuscitation,

maternal risk factor assessment and strengthening the referral system were all identified as highly effective, but less feasible.

Training and roles of TBAs and CHWs: One-fourth (24%, N = 42) of respondents had experience in training TBAs and/or CHWs, and some of these provided details of the tasks TBAs and/or CHWs performed and/or the contents of their training program (N = 27). The most commonly mentioned methods for managing asphyxiated babies by community workers were drying and warming (56%), referral (46%), feeding breastmilk (42%), cleaning the mouth with gauze (13%), and ventilation (7%) using bag-and-mask, tube-and-mask or mouth-to-mouth resuscitation. Only one respondent gave results of an assessment of the effect of TBA resuscitation training on perinatal mortality. Several respondents mentioned national policies that discouraged TBAs from practicing or discontinued their training: “...There is no more TBA training program [in] Nepal.” ... “I train the midwives working in the primary health care centers in neonatal resuscitation practices. No evaluation has been made. According to the national health policy, home deliveries not attended by at least a midwife are not advocated and TBAs are not trained within the National Neonatal Resuscitation Training Program” [Turkey].

When asked to rate the utility and feasibility of specific tasks being performed by TBAs and CHWs (Figure 3), most agreed that TBAs/CHWs could monitor labor, assist with delivery, and provide immediate essential newborn care, including drying, warming, and clearing the mouth with a clean cloth. The most effective and feasible postnatal interventions for the asphyxiated baby were considered to be drying and warming, and feeding breast milk (either at the breast or expressed), prior to referral. More advanced interventions, including suction with a mucus extractor or resuscitation with bag-and-mask (mouth-to-mouth if bag-and-mask was unavailable) were considered effective but less feasible. Tube-and-mask resuscitation was rated very low for feasibility, even lower than mouth-to-mouth resuscitation. Responses were mixed regarding the feasibility of TBAs performing resuscitation: “A simplified TBA program, based on the WHO manuals, was used to initiate training for TBAs already in practice. Short courses and refresher courses were modified according to the experience and level of understanding of the TBAs. It gradually focused down to ‘cleanliness’ and ‘reasons for referrals,’ as it took time to build up trust and understanding of basic perinatal care” [Tanzania]. ... “Most of the TBAs are illiterate and they are acceptable in the community not always because of their professional competency but [because] they belong to the community – in the training more emphasis is given to ‘Safe Home Delivery’ rather than management at labor or care of [the] newborn (eg, resuscitation of newborn), although basic antenatal and postnatal care [is] taught” [India]. ... “TBAs are extremely poorly trained and fairly resistant to altering practices. However, they took to bag and mask resuscitation as it was ‘technology’ and gave them prestige” [Pakistan].

Behavior change interventions: Most respondents identified behavior change opportunities as a major gap; 85% identified home practices as contributing to the occurrence/severity of asphyxia, while 15% identified health care system issues (Table 1). However, while 65% of the inappropriate practices in the health system were being addressed by programmes, only 27% of home practices identified as contributing to asphyxia and amenable to change were being addressed. Examples included

delay in recognition of birth asphyxia by families (17%), and unsafe use of oxytocin (14%).

Priority program and research gaps: Universally, respondents prioritized improving coverage with skilled birth attendance, followed closely by birth preparedness (Table 2). Essential newborn care and competency-based training in neonatal resuscitation were considered the next most important interventions for more widespread implementation. Eighty percent of respondents agreed on the top four priority research questions (Table 2). According to the respondents, the single most important question was the effectiveness and safety of TBAs and CHWs in newborn resuscitation.

Discussion

Given the lack of data regarding community-based solutions to address birth asphyxia, respondents revealed remarkable consensus on program and research priorities. Most respondents consistently emphasized preventive Safe Motherhood strategies to reduce neonatal deaths and stillbirths due to intrapartum hypoxia (eg, birth preparedness, presence of a skilled birth attendant, danger sign recognition) while simultaneously saving maternal lives. Most felt that newborn health programs should initiate neonatal resuscitation activities only after establishing basic elements of essential newborn care, including drying/stimulating. Respondents also agreed that skilled birth attendants should be trained in neonatal resuscitation; however, specific roles of TBAs and/or CHWs were disputed.

Need for better data, especially at national and sub-national level: The survey results demonstrated that birth asphyxia is perceived by those active in community level programs as an important newborn health problem and a major public health issue, despite a dearth of data. The significant difference in perception of importance of birth asphyxia between respondents in industrialised versus developing countries, and between policy makers and community/NGO workers appears to be partially accounted for by the relatively large proportion of respondents (particularly community-based/NGO workers in developing country settings) who answered “no data but probably still important.” Policy makers may have had greater access to global data on birth asphyxia, while those in-country may be unaware of or unable to access this data. This perception gap is important, particularly given the significant association found between perceived importance of asphyxia and the probability of action to address it. Those who were uninformed or unsure were significantly less likely to be involved in programs addressing asphyxia. Local data for decision-making is clearly needed, since a large problem at global level may not be perceived as relevant locally in the absence of local data, particularly as most babies dying of asphyxia in poor communities die at home.

Current policies and programs: Reasons why programs did not systematically address birth asphyxia reflect cross-cutting programmatic, financial, knowledge, and human resource constraints in settings where birth asphyxia is most common. That nearly two-thirds of the countries surveyed have a national policy for newborn health is encouraging. But given that 14% of respondents did not know if their country had a national newborn policy, many more were unsure whether the policy addressed birth asphyxia; and answers from respondents in the same country sometimes conflicted, it is clear that policies

require better dissemination and ownership. The success of national policies requires dedication of key implementers, such as the targeted respondents for this survey. Confusion regarding the existence of a national policy and the specifics of its content will limit the translation of policy into programmes. More specific national goals to reduce neonatal mortality are necessary to meet Millennium Development Goal 4, and should focus attention and resources on principal causes of mortality such as birth asphyxia. More detailed national examination of policy content and wider dissemination would empower healthcare professionals, academics, NGOs and other partners to work with policy makers to support national governments in implementing these policies.

Measuring birth asphyxia in communities: A major barrier to collecting quality information is the confusion and inconsistencies of asphyxia case definitions. The survey results highlight this problem, as none of the possible indicators received a high score for both effectiveness (as per the evidence base) and feasibility. Fresh stillbirth rate and incidence of convulsions in the first 24 hours were considered the most favored indicators of birth asphyxia. Despite the Western focus on neonatal encephalopathy and the fact that convulsions and/or a weak suck are among the most valid signs used in verbal autopsy algorithms to assign birth asphyxia as a cause of death, no TBAs and CHWs in the community used these signs to identify cases. Respondents agreed that more precise definitions of and indicators for intrapartum hypoxia and birth asphyxia are needed for programme use. Almost half the programmes implementing birth asphyxia activities made no attempt to collect birth asphyxia data. The lack of effective and feasible methods to recognize and monitor relevant outcomes for mothers and newborns in the community suggests an important need for operational program research.

Overall, follow-up of women after delivery was considered the most effective and feasible method to collect data on asphyxia in the community, a strategy that can also increase coverage of essential interventions during the postnatal period, when most maternal and newborn deaths occur, while also providing an opportunity to collect outcome and coverage data. Such community-based tracking may also promote community accountability for deaths.

Community-based interventions to address asphyxia: Overall, respondents favored preventative measures and basic pregnancy and delivery care over emergency care in the community. Basic obstetric care, an improved referral system, and neonatal resuscitation all have some evidence of effectiveness, yet they received lower effectiveness and feasibility scores than essential newborn care. The challenges with these interventions, especially in isolated rural areas, are the competencies and supportive environment required. Birth preparedness received high ratings, but high quality evidence of mortality impact is lacking. Essential newborn care was also perceived as highly effective and feasible, but its effectiveness in reducing asphyxia deaths is unproven; benefits may be attributable primarily to skilled delivery and immediate newborn care, including drying and neonatal resuscitation.

TBAs and CHWs: controversy and consensus: Appropriate roles of TBAs in maternal and neonatal health are hotly debated. Although 24% of survey respondents had experience in training TBAs and/or CHWs and provided details about the training

program and TBA/CHW roles, little data demonstrates the impact of TBA resuscitation training on perinatal mortality because programs have either not collected or not reported this data. While a meta-analysis has shown a significant reduction (11%) in birth-asphyxia-attributable deaths with trained versus untrained TBAs, this effect was likely largely attributable to antenatal preventative measures and improved intrapartum care, as most of the TBA training schemes provided neither equipment nor specific training for neonatal resuscitation.

As intended, the survey solicited opinions from a wide-ranging audience regarding how TBAs and CHWs might address birth asphyxia. Almost all respondents felt TBAs/CHWs should be involved in newborn care, but most favoured simpler tasks. Respondents rated neonatal resuscitation by TBAs as low on effectiveness and feasibility scales. A variety of technical concerns were noted regarding proper use of resuscitation equipment by CHWs or TBAs, but virtually all respondents considered drying and stimulating the baby and clearing the mouth appropriate tasks, despite the WHO recommendation against clearing the mouth. The virtually unanimous indictment of the mouth-to-tube device, which cannot be used at more than 20 breaths per minute, compared to the recommended 40–60 breaths per minute, suggests that use of this technology should be reviewed. Regarding care of the baby with complications of birth asphyxia, most respondents believed referral, keeping the baby dry and warm, and feeding expressed breastmilk were appropriate, emphasizing referral.

International policy changes regarding TBAs have affected the number of programs training TBAs and it was notable in this survey that while we targeted community-based programs, few were currently training TBAs (12%, Figure 2); however, many were training skilled attendants (25%). Ideally, all women could choose access to a skilled birth attendant, but investments of time and funds to train and sustain the vast numbers of midwives required are steep, and in some areas, infeasible. Considering these limitations, while women and babies continue to face risks in childbirth without skilled care, what interventions are possible? Can the TBAs' roles be adapted to promote birth preparedness, help women to access skilled care once they are in labour and serve as a birth companion, and provide essential immediate newborn care?

Behavior change interventions: Ninety percent of respondents specified at least one practice amenable to behavior change, but only about one fourth of identified behaviors (27%) were being systematically addressed. Most undesirable behaviours (85%) occurred at home, particularly unsafe traditional newborn care practices. However, efforts to address these behaviors took place predominantly within health facilities, most likely reflecting a lack of community-based workers with behaviour change training and logistical and strategic confusion about appropriate behavior change interventions in the home. This is a major, yet potentially feasible and low-cost, implementation gap, and opportunities exist to integrate birth preparedness approaches into other existing community behaviour change messages, benefiting mothers and babies.

Strengths and limitations of the survey: The global geographical representation of respondents is a strength of this survey. Selection to include those active in addressing birth asphyxia was deliberate, and further self-selection, with those most interested being most likely to reply, is apparent, since 88% of

respondents were already involved in asphyxia-related programs, and the response rate (44.2%) was high. This does not compromise the ability of this survey to provide insight into elements of successful programmes already addressing birth asphyxia, but should be considered in interpreting the findings, since they are not representative of all maternal and child health programmes. Using e-mail for survey distribution may have limited responses, especially where e-mail access was unavailable or expensive. Translation into French clearly facilitated replies from West Africa; translation into Spanish might have increased responses from Latin America. Internal consistency checks suggested that respondents answered consistently.

While responses regarding policies and programs were objective, the information requested on interventions and research gaps was subjective. Nevertheless, while objective evidence for effectiveness at community level is important, perceived effectiveness and feasibility are crucial determinants of whether existing evidence will be implemented.

Conclusion

This survey highlights the importance of birth asphyxia as an important problem in developing country communities, accounting for more deaths than measles or malaria, yet receiving much less policy and programmatic attention. If Millennium Development Goal 4 for child survival is to be achieved, a concerted, coordinated effort is required to reduce birth asphyxia deaths by all involved along the pathway to survival, including women, families, the community, community health workers, health professionals and policy makers – this would also benefit Millennium Development Goal 5 and maternal health as well as stillbirths.

Although the survey respondents represent some of the best-developed programs currently addressing newborn health in resource-poor settings, major gaps in current implementation are revealed. There is consensus on the need to escalate training of skilled attendants and include newborn resuscitation, and our data suggests programs are actively doing this. However, cutting all support for TBAs risks leaving a vacuum at community level where most deliveries and most neonatal deaths still occur, areas that will wait longest to have access to skilled midwives. This survey reveals strong agreement regarding more supportive and simple tasks feasible for TBAs and CHWs, as well as key home behaviours that remain unaddressed even where programmes exist. This raises a research agenda to test the ability of TBAs and CHWs to undertake less technically complex tasks than resuscitation, and to serve as links with health systems through referral and facilitating the transition to skilled care.

Respondents showed clear consensus in program and research priorities. The international community must now act on these priorities to reduce the estimated 0.92 million neonatal deaths and 1.1 million stillbirths related to intrapartum hypoxia each year, many of which occur in the world's poorer homes. With business as usual, these deaths will remain out of reach of effective care, either skilled or community level, for many years to come.

Antiviral Therapy In Neonatal Cholestatic Cytomegalovirus Hepatitis

Tanju Basarir Ozkan, Resit Mistik, Banyamin Dikici, Hülya Ozturk Nazlioglu

Abstract

Background: Neonatal hepatitis refers to a heterogeneous group of disorders, caused by many factors including cytomegalovirus infection, revealing similar morphologic changes in the liver of an infant less than 3 months of age. Approximately 40% of cholestasis in infants is due to neonatal hepatitis. It may cause latent or acute cholestatic or chronic hepatitis, including cirrhosis in immunocompetent infant.

Methods: Twelve infants diagnosed with neonatal cytomegalovirus hepatitis in the last one year were included in the study. Group 1 consisted of seven babies treated with ganciclovir for 21 days. Group 2 included five cases who did not receive antiviral treatment. Physical examination, biochemical, serologic and virologic tests were done for both groups at the time of diagnosis and in the third month.

Results: Initial levels of total bilirubin, aminotransferases, gamma glutamyl transpeptidase, and alkaline phosphatase revealed a significant decrease after the treatment in Group 1 ($p < 0.05$) when compared with Group 2. This study revealed that ganciclovir treatment is safe and effective in cases with cholestatic hepatitis. Similarly, all the patients in the treatment group had evidence of improvement serologically and virologically, while the comparison group did not reveal any significant change ($p < 0.01$).

Conclusion: The clinical spectrum of perinatal infection varies from an asymptomatic infection or a mild disease to a severe

systemic involvement, including central nervous system. The treatment in the early period of infection improved serologic markers and cholestatic parameters significantly. Further studies will lead us to clarify the efficacy of ganciclovir treatment in the early period of cytomegalovirus hepatitis, and the preventive role of anti-viral therapy on progressive liver disease due to cholestasis and hepatitis in neonatal cytomegalovirus infection.

Background

Neonatal hepatitis is a specific type of hepatitis seen in the first months of life. Hepatitis A-E viruses and other hepatotropic viruses (Epstein-Barr virus (EBV), herpes viruses, adenoviruses and parvovirus) are known to be the main causes of the disease. It is obvious that A-E hepatotropic viruses are the main causes of etiology in 10% of acute viral hepatitis cases without immunosuppression. Cytomegalovirus (CMV) is a member of herpes virus family, and although it is known that CMV and other herpes viruses can cause significant pathologies (particularly in immunodeficient patients), they can also affect individuals with normal immune system. Typical acute unicteric hepatitis, as a part of systemic infection, is one of these pathologies.¹

Approximately 20% of children less than 15 years of age and 50-60% of individuals younger than 25-30 years of age are infected with CMV. It is known that virus replicates in both hepatocytes and cholangiocytes during the infection. However, controversy exists about the pathogenesis of hepatic disease whether related to the direct cytopathic effect of the virus or the immune response of the host. In addition, the hepatocyte damage in latent infections has not yet been well explained. Besides this, it is obvious that patients with chronic viral hepatitis and cirrhosis may have more sensitivity to acute CMV infections resulting in additional hepatic damage.²⁻⁴

In severe cases, ganciclovir or foscarnet treatment may be effective. Although ganciclovir treatment reported to be effective in CMV retinitis, esophagitis, hepatitis and pneumonia in adults, there is insufficient research in children. It is

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Table 1: The Demographic Characteristics of the Groups

Groups (n = number of cases)	Age (months) Mean \pm SD Median	Sex		Weight (kg) Mean \pm SD Median
		M	F	
Group 1 (n = 7)	3.7 ± 2.4 3	^{**} 3	4	Δ 5.05 ± 1.6 4.7
Group 2 (n = 5)	6.6 ± 2.2 7	^{**} 4	1	Δ 5.97 ± 2 5.9

*, **, Δ NS

mentioned that ganciclovir may be used effectively in symptomatic congenital or neonatal CMV infections but its side effects are of concern.³

In the current study, the objective was to evaluate efficacy of ganciclovir in cholestasis of neonatal CMV hepatitis, which is an important step for prevention of chronic CMV hepatitis.

Methods

Twelve infants diagnosed with neonatal cytomegalovirus hepatitis in the last one year were included in the study. Local ethics committee (Abant İzzet Baysal University, Düzce Medical Faculty Ethics Committee) approved the study and the written informed consent obtained from the parents of the patients. The babies (n:7) whose parents accepted ganciclovir therapy formed the treatment group (Group1), while the other five babies without ganciclovir therapy formed the comparison group (Group2) (Table 1). One baby with ileal atresia (because he may have additional enterohepatic circulation disorder) and another one with myoclonic convulsions receiving anticonvulsant therapy (because he may have additional toxic hepatitis) were excluded before the study groups were chosen. Liver biopsy was performed in babies with unexplained hypertransaminasemia, icterus and/or hepatomegaly, in order to reveal idiopathic neonatal hepatitis, extrahepatic biliary atresia, immune insufficiency and metabolic hepatic disorders (such as α_1 -antitrypsin deficiency, storage disorders) which were also among exclusion criteria. Convulsions, petechia, purpura, chorioretinitis, microcephaly, neuromuscular dysfunction, cerebral calcifications, and/or severe disease that may be seen in congenital CMV infections were not observed in any patient.

Children in Group 1 were treated with ganciclovir (10 mg/kg/day, in two doses) for 21 days. Antipruritic treatment for cholestasis, calcium, vitamin D, and other lipophilic vitamin supplementation were given to both groups.

All the patients' clinical and laboratory parameters (age, icterus, organomegaly, ALT, AST, ALP, GGT, T. Bil., D. Bil., CMV Ig G and CMV Ig M antibody, CMV avidity and CMV-DNA) were evaluated initially and at the third month of the study. Anti-CMV IgG and IgM ab titers were measured with ELISA method and CMV-DNA was detected with PCR. CMV-DNA was purified with QIAmp DNA Blood Mini Kit (QIAGEN, Hamburg). Quantitative PCR analyses was performed by RealArt CMV RG PCR Kit used with Rotor-Gene 2000/3000. The quantitation standards were defined as copies/ μ l. An equation was used to convert the values determined using the standard curve into copies/ml of sample material:

$$\text{Result (copies/ml): } \frac{\text{Result (copies/\mu l)} \times (\text{Elution volume (\mu l)})}{\text{Sample volume (ml)}}$$

For preparation of PCR assay, a standard volume (20 μ l), of sample DNA was mixed with 30 μ l of CMV RG Master. Data analyses was performed with Rotor-Gene software according to the manufacturer's manual.

Statistical analysis was performed using Mann-Whitney U Test for comparison of the initial and the third month changes of weight and CMV-DNA PCR, Fisher's Chi square exact test for the variants such as sex, organomegaly, jaundice and CMV antibody titers, and Wilcoxon Test was used for the comparison of individuals among each group (SPSS 13.0 version).

Results

The mean age of seven babies (four female, three male) in Group 1 and five babies (one female, four male) in Group 2 was 3.7 ± 2.4 months and 6.6 ± 2.2 months, respectively. One baby in Group 1 and two babies in Group 2 had low weight percentile at the initial evaluation. There were no significant statistical differences between groups regarding to age, sex and weight (NS, NS, NS respectively).

In the physical examination, five babies in Group 1 and two in Group 2 had hepatomegaly (liver was palpated >2 cm below the last rib) at the first evaluation (NS). One baby in each group had palpable spleen evaluated as a normal variation.

Liver biopsy was performed for 7/7 babies in Group 1 and for 4/5 babies in Group 2. Although hepatic inclusion bodies are rarely found in the histopathologic examination of pediatric cases, it was detected in one baby in Group 1. Granulomatous changes and findings related to cholestasis were determined in four babies in the treatment group and two babies in the comparison group. Nonspecific histopathological findings of CMV hepatitis as lymphomonocytic cell infiltration, hydropic degeneration, mild steatosis, perisinusoidal fibrosis, and Kupffer cell hyperplasia were found in all babies.

At the initial evaluation, three babies in Group 1 and one baby in Group 2 had icterus. They were still icteric at the third month (NS) (Table 2,3). In comparison with Group 2, initial levels of total bilirubin, AST, ALT, GGT, and ALP revealed a significant decrease in Group 1 after the treatment ($p < 0.05$) The differences of initial and third month values were statistically significant among the babies in Group 1 (Table 3). No significant change was observed in the comparison group at the third month regarding to initial values (NS) (Table 3). The serological evaluation for CMV revealed that all the babies were CMV IgG

Table 2: The Comparison of the Physical Examination Findings of the Groups

Groups		Jaundice (n)	Hepatomegaly (n)
Group 1 (n = 7)	Initial	*3	**5
	Posttreatment	2	2
Group 2 (n = 5)	Initial	*1	**2
	Control	2	2

*, ** NS

(+) and CMV IgM antibody was found in five and three babies in the treatment and comparison groups, respectively. CMV avidity test was not available for the whole group. The avidity value indicating infection longer than 3 months (avidity index >0.8) was determined in 60% and 33% of the evaluated babies in the treatment and the comparison group, respectively (Table 4). The confirmative serological changes were defined as the decrease in CMV IgG antibody or avidity titers, or loss of CMV-IgM antibody at the third month's evaluation. While all the patients in the treatment group had evidence of serologic improvement ($p < 0.01$), the comparison group did not reveal any significant change (NS). Similarly, CMV-DNA PCR values decreased to desirable levels following the treatment in Group 1 ($p = 0.05$). However, the changes in the comparison group were inconsiderable (Table 4).

Discussion

Neonatal hepatitis refers to a group of pathologies causing similar morphologic changes in the liver of the babies less than three months of age. It is blamed for 40% of cholestatic situations in the neonates after exclusion of extrahepatic biliary atresia. It affects males more frequently than females, and similar results were found in the present study. As the term "idiopathic neonatal hepatitis" refers to the neonatal hepatitis of unknown (but probably multifactorial) etiology, "neonatal hepatitis" is caused by a group of well defined etiologic factors, so treatment should be considered.^{1,3,5}

Neonatal cytomegalovirus infection may occur due to either intrauterine or perinatal exposure to CMV infected cervicovaginal secretion and breast milk. The clinical spectrum of perinatal infection varies from an asymptomatic infection or

a mild disease to severe systemic involvement, including central nervous system.⁶

The clinical presentation of acute neonatal CMV infection resembles the mononucleosis of the Epstein-Barr virus seen in neonates and immunodeficient individuals with fever, malaise, and cervical lymphadenopathy. Severe jaundice and granulomatous hepatitis also have been established due to neonatal CMV infection.^{1,3} Physical examination may reveal minimal hepatomegaly and mild jaundice, in addition to slightly increased serum aminotransferases (less than threefold of normal values).⁴

CMV infection is unlikely to be a cause of massive hepatocellular necrosis in a normal host. Previous studies reported that transaminases reached the highest levels (<200 U) in the second or third week of infection, decreasing to normal values by the fifth week.⁴ In our study, transaminases increased moderately in both groups, but a significant decrease at the third month was observed only in the treatment group.

The laboratory tests used for serologic diagnosis of CMV hepatitis are CMV-IgM ab, CMV early antigen (in tissue or blood), CMV-DNA PCR and virus cultures.^{8,12} We could not obtain viral cultures or early antigen titers of the babies in our study, but the liver biopsy evaluations suggested CMV hepatitis. In the histopathologic examination of liver, the presence of cytomegalic cells and inclusion bodies refers to the intensive immune activation against viral attack. The liver damage in an immunocompetent individual is mostly due to the primary immune response of the host, whereas cytopathic damage of the virus has priority in patients suffering from immune deficiency.¹

Table 3: The Comparison of the Biochemical Values of the Groups

Groups		T. bilirubin mean \pm sd median	D. Bilirubin mean \pm sd median	ALT mean \pm sd median	AST mean \pm sd median	ALP mean \pm sd median	GGT mean \pm sd median
Group 1 n = 7	Initial	*4.6 \pm 3.2 4.6	*3.9 \pm 2.5 4	*119.4 \pm 56.4 80	*167 \pm 68.4 197	*1148 \pm 300 750	◆ 441.4 \pm 186.3 110
	Posttreatment	1.29 \pm 0.82 2.5	0.53 \pm 0.27 0.3	53 \pm 18.5 54	75 \pm 28.1 58	556 \pm 196.5 324	150.7 \pm 61.5 71
Group 2 n = 5	Initial	**2.52 \pm 1.07 1.45	**1.42 \pm 0.45 0.25	**172.7 \pm 57.6 92	**155.2 \pm 68 93	**393.5 \pm 44.7 381	◆◆ 67.7 \pm 25 49
	Control	4.37 \pm 2.21 0.3	2.97 \pm 1.75 0.1	123.2 \pm 18.5 98	152.7 \pm 47 116.5	435.7 \pm 37.5 311	73.2 \pm 24.6 51

Comparison of initial and post treatment values among Group 1

◆ $p < 0.01$ * $p < 0.05$

Comparison of initial and control values among Group 2

**, ◆◆ NS

Table 4: The Comparison of serological CMV markers in Groups

Groups		◊ CMV IgM (+) patient no/total	CMV IgG avidity >0,8 patient n	* † CMV DNA copy/ml
Group 1 (n = 7)	Initial	7/7	5	2230(166–9240)
	Posttreatment	0/7	3	14 (8–1930)
Group 2 (n = 5)	Initial	3/5	3	2178(158–2917)
	Control	3/5	1	1915(656–2900)

◊ The ratio of patients, in each group, having affirmative results in the second evaluation (p < 0.01)

* Median (minimum-maximum)

† The comparison of value changes between first and second evaluation (p < 0.05)

Chang et al. recently evaluated the existence of CMV-DNA in liver biopsy samples of healthy neonates in comparison to the neonates with neonatal hepatitis. He reported that CMV DNA was detected in 46% of babies with neonatal hepatitis (n: 50) whereas none of the healthy group had viral DNA (n: 30). Thus, he suggested that CMV could play a major role in the pathogenesis of neonatal hepatitis.⁹ Although it has been reported that hepatomegaly might regress spontaneously in the first year of life in babies with congenital CMV infection, portal hypertension may occur without the evidence of cirrhosis.^{10,11} In the current study, one patient in the comparison group died of abundant upper gastrointestinal haemorrhage at the age of 18 months as a result of portal hypertension without cirrhosis. Two patients in the same group also progressed to chronic hepatitis.

The necessity of treatment is controversial in neonatal CMV infection, as spontaneous recovery is expected in most cases unless severe systemic disease occurs.^{3,12} However, as in the present study, an increasing number of studies indicate the necessity of treatment, especially in cases with symptoms of acute or chronic cholestatic hepatitis or proven histopathological findings.^{3,13-17} A new study from Lanari et al. demonstrated the importance of high CMV-DNA titer on development of sequelae. Furthermore, they suggested that the CMV-DNA quantity could be useful for identifying the patients who will benefit highly from antiviral therapy.¹⁸

Ganciclovir is recommended as a first step antiviral agent for the management of congenital CMV infection. Most common adverse effects of ganciclovir treatment include dose-dependent neutropenia and blood counts including absolute neutrophil count. Therefore, leukocyte counts should be monitored closely during treatment. In our treatment group, we have not seen any severe adverse effects requiring the cessation of the treatment.^{3,6}

Conclusion

We suggest that ganciclovir therapy significantly improves the clinical course of neonatal cholestatic CMV hepatitis. Currently the number of studies of neonatal cholestatic CMV hepatitis is insufficient. New and extensive research will lead us to clarify the efficacy of ganciclovir treatment in the early period of CMV hepatitis, and the preventive role of anti-viral therapy on progressive liver disease due to cholestasis and hepatitis in neonatal CMV infection.

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Exchange Transfusion in Neonatal Hyperbilirubinemia: Experience in Isfahan, Iran

Z. Bandiee, MD

Abstract

Introduction: This study aims to determine the aetiology and complications of exchange transfusion (ET) performed for neonatal hyperbilirubinemia in Isfahan, Iran.

Methods: A retrospective chart review of 68 term and near-term newborns who underwent ET at two perinatal centers in Isfahan, Iran between January 2001 and January 2004, was performed.

Results: Of the 68 patients who underwent ET, nine (13.2 percent) required more than one ET. The most common causes of ET overall were ABO incompatibility (22.1 percent) and glucose-6-phosphate dehydrogenase deficiency (19.1 percent). The maximum total serum bilirubin concentration was 25.9 \pm 7.5 mg/dL. ET complications occurred in 14 neonates (20.9 percent), the most common being thrombocytopenia (6 percent). One (1.5 percent) of the 68 patients died of complications, probably attributable to ET.

Conclusion: ET causes high morbidity, even in term and near-term newborns. Therefore, it should be initiated only when the benefit of preventing kernicterus outweighs the complications associated with the procedure.

Introduction

Jaundice is a common neonatal problem. This may be due to the limited ability of a neonate to metabolise indirect bilirubin, which leads to hyperbilirubinemia and predisposes to the risk of encephalopathy and longterm sequela if not managed promptly.¹ Administration of anti-D immunoglobulin to prevent

erythroblastosis foetalis, and the use of phototherapy to treat neonatal jaundice, have resulted in a decline in the rates of significant neonatal hyperbilirubinemia.^{2,3} The bilirubin level at which exchange transfusion (ET) is indicated remains controversial; the recommendations attempt to balance the benefits of preventing bilirubin toxicity with the risks of ET.⁴⁻⁶ Mortality rates attributable to ET ranged from 0.7% to 3.2% in studies performed in the 1960s, and from 0.4% to 3.2% during the 1970s and 1980s.⁷⁻¹³ In the study of Keenan et al, among 190 infants who underwent 331 ET, adverse clinical problems were observed in 6.7%, and the observed rate of serious morbidity was 5.2%.¹⁴ Information concerning the risk of adverse events from neonatal ET in the past decade is sparse,^{6,15} and we did not find any report of ET aetiology and complication in Iran. This study was undertaken to determine the aetiology and complications of ET at two perinatal referral centers in Isfahan, Iran.

Methods

The study included all infants below 30 days of age who were admitted to the neonatal intensive care units of Alzahra and Shahid Beheshti Hospitals, Isfahan, Iran. During the three-year period from January 2001 to January 2004, infants were selected if they had discharge diagnosis of ET in their medical record. After excluding records for patients who underwent only partial ET for polycythaemia and severe anaemia, the medical records of the 68 remaining patients were reviewed in detail. The cause of jaundice reported in the records was classified in the following way: Rh disease was defined as jaundice in Rh-positive newborns from Rh-negative mothers and evidence of haemolysis, and ABO disease was defined as jaundice in newborns with positive Coombs test against the A or B antigens from type O mothers. Either whole blood ABO compatible with both the baby and mother, or group O red cells resuspended in compatible plasma (usually AB), was used. ET was performed by a paediatric resident. The double volume exchange procedure was generally completed in about 60–90 minutes by repeatedly removing and replacing small aliquots of blood (5 ml/kg) according to standard published guidelines.⁶ The following investigations were performed on all neonates as a

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baseline: complete blood count, total and direct serum bilirubin, erythrocyte glucose-6-phosphate dehydrogenase (G6PD) level, direct Coombs test, blood culture and pre- and post exchange haemoglobin, bilirubin, calcium and blood glucose. Double volume ET was performed in every case using a single line (umbilical vein). 1 ml of calcium gluconate 10% was given after exchange of every 100 ml of blood. An adverse event was defined as any complication that occurred within three days of an ET. The following definitions were used: hypoglycaemia: serum glucose < 40 mg/dL; hypocalcaemia: total serum calcium < 8 mg/dL; thrombocytopenia: platelet count < 100,000/mm³; bradycardia: heart rate dropping to < 80 beats per minute; apnoea: cessation of respirations for > 20 seconds; seizure: any tonic and/or clonic movement; necrotizing enterocolitis: defined according to Bell et al's criteria.¹⁶

Results

During the three-year study period, 68 patients underwent ET. The infants had a mean birth weight of 2,812.6 ± 531.1 g and a mean gestational age of 38.6 ± 1.8 weeks. Overall, eight infants had two ET and one had four ET. The most common cause of jaundice was ABO incompatibility (22.1%), G6PD deficiency (19.1%), and Rh incompatibility (11.7%). The mean maximum total serum bilirubin level was 25.9 ± 7.5 mg/dL. The mean age at presentation was 4.4 ± 2.1 days. Table π shows the causes of jaundice, maximum total serum bilirubin level before ET and the age of presentation. 19 infants had total serum bilirubin of more than 30 mg/dL at admission. The most common causes of extreme hyperbilirubinemia (bilirubin > 30 mg/dL) were ABO incompatibility (11.7%), and G6PD deficiency (8.8%). Of the 68 infants, five (7.3%) had abnormal neurological examination at the time of ET. This included hypotonia in two infants (2.9%), hypertonia in two (2.9%), and a high pitch cry in one (1.4%) infant. All five infants who developed kernicterus had a serum bilirubin greater than 30 mg/dL. Complications occurred in 14 (20.9%) infants (Table ππ). The most common adverse event was related to thrombocytopenia. Only one infant had suspected disseminated intravascular coagulation (DIC) after ET. Four infants experienced severe complications attributable to ET. These complications included cardiorespiratory arrest (1.5%), apnoea with cyanosis requiring resuscitation during or immediately after ET (1.5%), limb colour change (1.5%), and necrotising enterocolitis (1.5%). One infant expired within 24 hours after ET.

Discussion

This study shows a high rate of adverse events associated with ET for neonatal hyperbilirubinemia. However, most of these complications were asymptomatic and transient, such as thrombocytopenia. Exchange blood transfusion remains the gold standard for effective treatment of neonatal hyperbilirubinemia. Although reports show a progressive decline over the years in the number of neonates needing ET, it is still required in up to 7% of neonates admitted to nurseries.¹⁷ This reduction in the number of ET may be due to the development of anti-Rh globin for Rh-negative mothers and the widespread use of phototherapy for neonatal jaundice.^{18,19} In this study, the most common cause of ET was ABO immunisation, which is similar to the finding in some other series. Dikshit and Gupta, and Sanpavat reported that ABO haemolytic disease of newborns is the most common cause of ET in term neonates (35.9% and 21.3%, respectively).^{12, 20} G6PD deficiency accounted for 19% of all causes of ET in our study. This figure is higher than the estimated 10% prevalence of G6PD

Table I. Causes of jaundice, maximal total serum bilirubin level before exchange transfusion and age of presentation.

Causes of jaundice	Value
Rh disease, n(%)	8 (11.7)
ABO incompatibility, n(%)	15 (22.05)
G6PD deficiency, n(%)	13 (19.1)
Maximum mean bilirubin (mg/dL ± SD)	25.9 ± 7.5
Presenting age (mean days ± SD)	4.4 ± 2.1

Table II. Complications of exchange transfusion.

Complication	n (%)
Death	1 (1.5)
Seizure	1 (1.5)
Platelet < 100,000/mm ³	4 (6)
Calcium < 8 mg/dL	2 (2.9)
Blood glucose < 50 mg/dL	0
Bradycardia < 100	1 (1.5)
Suspected DIC	1 (1.5)
Cardiorespiratory arrest	1 (1.5)
Hypoxia	1 (1.5)
Limb colour change	1 (1.5)
Necrotising enterocolitis	1 (1.5)

deficiency in the Jordanian population.²¹ Abu-Ekteish et al showed that G6PD deficiency, alone and concomitant with ABO haemolysis, accounted for 38% of all causes of ET.¹ A possible explanation for these differences may be the racial differences in the prevalence of G6PD deficiency. Multiple ET was required in 12.3% of our neonates. This is similar to findings of Abu-Ekteish et al, but is lower than some other studies.^{1,12,22} The most common morbidities included seizure (1.5%), cardiorespiratory arrest (1.5%), bradycardia (1.5%), hypoxia (1.5%), limb colour change (1.5%) and necrotising enterocolitis (1.5%). In Jackson's study, permanent serious sequela was observed in 1% of healthy newborns who underwent ET.⁶ Serious transient complications occurred in 17% and asymptomatic complications in 27% of infants. Patra et al showed that the most common adverse events following ET were thrombocytopenia (44%) and hypocalcaemia (29%), none of which were symptomatic.²³ In our study, the mortality rate was 1.5%. Panagopoulos et al in Greece examined 606 exchanges performed on 502 neonates between 1962 to 1966 and reported a mortality rate of 0.66 % per patient and 0.79% per procedure; Keenan et al reported a mortality rate of 0.5%; but Chima et al reported no serious adverse event or death in 22 term infants who underwent 26 ET between 1990 and 1998.^{9,14-15} However, complications are common enough that ET, even in healthy newborns, should be performed only in nurseries prepared to respond to these adverse events. Although apnoea, bradycardia and cyanosis rarely occur during ET of healthy infants, cardiorespiratory and oxygen saturation monitoring should be considered during ET.

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A Randomized Controlled Trial of Early Insulin Therapy in Very Low Birth Weight Infants; NIRTURE (Neonatal Insulin Replacement Therapy in Europe)

Kathryn Beardsall, Sophie Vanhaesebrouck, Amanada L. Ogilvy-Stuart, Jagit Ahluwalia, Christine VanHole, Chris Palmer, Paula Midgley, Michael Thompson, Luc Cornette, Mirjam VanWeissenbruch, Marta Thio, Francis de Zegher, David Dunger

Abstract

Background: Studies in adult intensive care have highlighted the importance of insulin and improved glucose control on survival, with 32% reduction in mortality, 22% reduction in intensive care stay and halving of the incidence of bacteraemia. Very low birth weight infants requiring intensive care also have relative insulin deficiency often leading to hyperglycaemia during the first week of life. The physiological influences on insulin secretion and sensitivity, and the potential importance of glucose control at this time are not well established. However there is increasing evidence that the early postnatal period is critical for pancreatic development. At this time a complex set of signals appears to influence pancreatic development and β cell survival. This has implications both in terms of acute glucose control but also relative insulin deficiency is likely to play a role in poor postnatal growth, which has been associated with later motor and cognitive impairment, and fewer β cells are linked to risk of type 2 diabetes later in life.

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Methods: A multicenter, randomized controlled trial of early insulin replacement in very low birth weight babies (VLBW, birth weight <1500g). Five hundred infants will be recruited from 10 centers in the UK and Europe. Babies will be randomized to receive a continuous insulin infusion (0.05 units/kg/h) or to receive standard neonatal care from the first day of life and for the next 7 days. If blood glucose (BG) levels fall infants will receive 20% dextrose titrated to maintain normoglycemia (4-8 mmol/l). If BG is consistently above 10 mmol/l babies will receive standard treatment with additional insulin infusion. The primary end point will be mortality on or before expected date of delivery, secondary end points will be markers of morbidity and include episodes of sepsis, severity of retinopathy, chronic lung disease and growth.

Background

Perinatal survival in very low birth weight infants (less than 1.5kg) has increased markedly over the last twenty years with improvements in neonatal intensive care. However mortality rates are as high as 20% in those born less than 1kg, and death may be related to either infection or necrotising enterocolitis. Reducing mortality is an important goal of therapy but it is essential that this be achieved without increasing long term morbidity. Postnatal growth may be sub-optimal particularly with regard to head circumference and this can be associated with neuro-psychological problems particularly in the very low birth weight infant, and retinopathy of prematurity is still a major problem.

Studies of adult intensive care patients have highlighted the importance of blood glucose control on rates of sepsis and survival. In the study reported by Van den Berg, where insulin was used to tightly control blood glucose a reduction in intensive care mortality of 32% ($p < 0.04$), a reduction in mean ICU stay by 22% ($p = 0.005$) and a halving of the incidence of bacteraemia ($p = 0.003$) was observed. Studies in both diabetic and non diabetic patients post myocardial infarction indicate that the use of insulin has not only immediate effects with respect of glucose control but also improves long term outcome. In adults receiving parenteral nutrition insulin has



Fixed Dose Insulin and Variable Rate 20% Dextrose Infusion

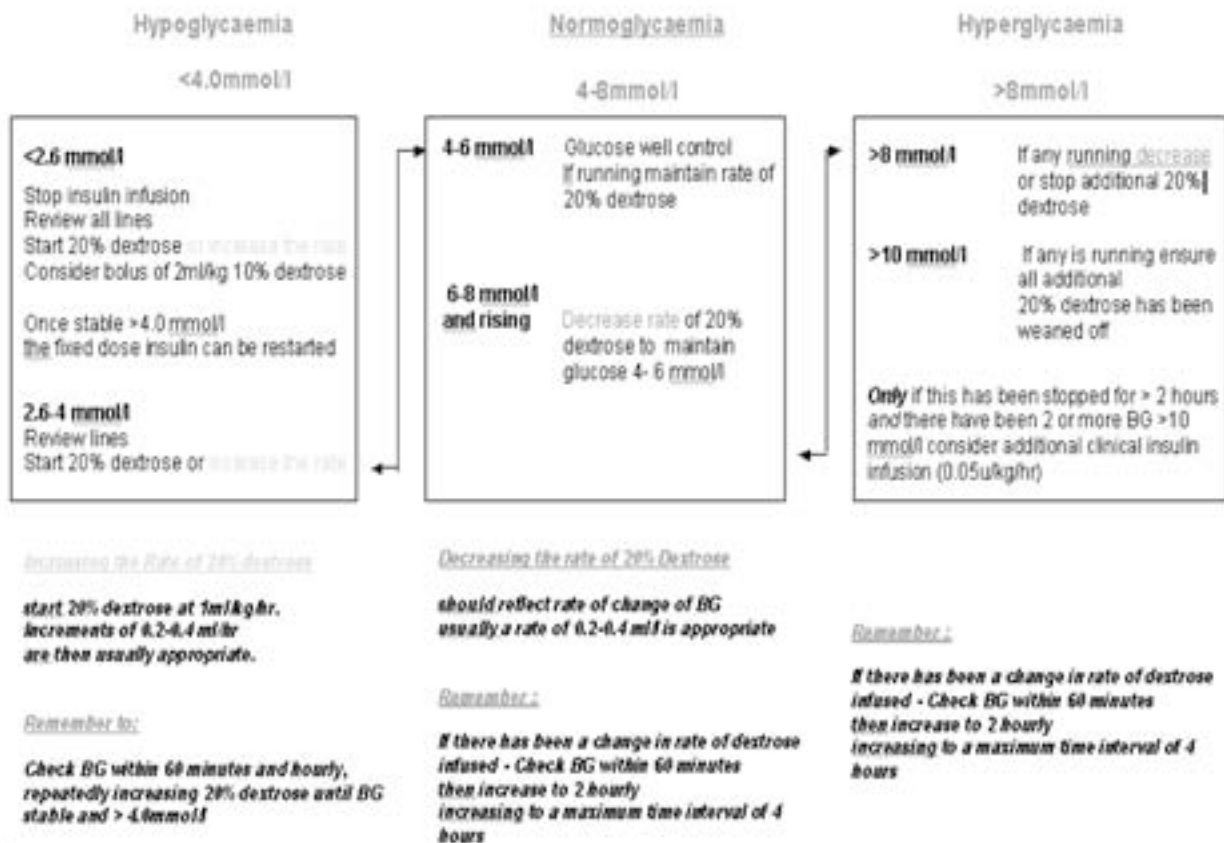


Figure 1

been shown to improve net leucine balance. It is not always clear from these studies whether it is the reductions in blood glucose per se or the anabolic effects of insulin that are important. Furthermore the medical conditions encountered in adult intensive care are not the same as those seen in neonatal units, but nevertheless there are some parallels that suggest that insulin could also have a role in newborn care.

The incidence of hyperglycemia in premature neonates admitted to intensive care has been reported to be between 20% and 86%; those who are small for gestational age having the greater risk. We have assessed blood glucose control over the first week of life in 8 very low birth weight babies using the MiniMed subcutaneous sensor. In these infants receiving standard neonatal care 38% of the readings were more than 10 mmol/l and only 0.5% of the time were readings under 2.6 mmol/l. The hyperglycemia was particularly common on day 2 and 3 after birth. Many of these babies were given insulin treatment by intravenous infusion, as is standard neonatal practice, when blood glucose levels were higher than 10 mmol/l. Hyperglycemia can lead to significant osmotic diuresis and hence electrolyte imbalance and has been associated with increased risk of intraventricular hemorrhage. Uncontrolled hyperglycemia has also been associated with increased episodes of sepsis in post surgical and burns patients. The premature neonate is relatively immunocompromised and with immature skin and renal function is at increased risk of infection and problems with fluid

and electrolyte balance. There is increasing data documenting the association of hyperglycemia in the neonatal population with increased morbidity and mortality. Current neonatal practice of intermittent insulin treatment is only partially effective at controlling hyperglycemia in the infants who require intensive care.

The reason for these prolonged periods of hyperglycemia is not clear. During fetal life, insulin secretion is largely determined by glucose flux across the placenta and blood samples taken from fetuses at cordocentesis demonstrated an exponential increase in fetal plasma insulin with increasing gestation. Lower plasma glucose and insulin as well as higher glucose insulin ratios have been shown in growth retarded fetuses compared to those who are appropriately grown. At birth, the disruption of placental supply of nutrients leads to a period of catabolism with weight loss being maximal two to three days after birth, birth weight not being recovered often until the age of 7 days. Insulin levels are low during this period only increasing with the establishment of oral feeds and the coupling of insulin secretion to meal-related nutrient and hormonal signals. Blood glucose levels during this period of catabolism are maintained by gluconeogenesis and glycolysis driven by catecholamines, growth hormone and cortisol. In a setting of continuing limited substrate availability, these hormones may also play a role by reducing insulin sensitivity, increasing lipolysis, and hence diverting glucose utilisation from muscles to the brain,

protecting the fetal brain from the risk of hypoglycemia.

In the very low birth weight infant, the period of neonatal catabolism may be much more prolonged, as it may not be possible to initiate oral feeding and thus induce normal insulin secretion. As a consequence, birth weight is often not regained for several weeks. The very high blood glucose levels seen on day 3 or 4 may reflect insulin resistance secondary to high levels of growth hormone and the stress related hormones catecholamines and cortisol. They could also reflect relative insulin deficiency and a failure to compensate for any increasing insulin resistance. Fetal growth restriction may be associated with impaired pancreatic development and a reduced β cell mass although intravenous alimentation is often started soon after birth in these infants, enteral feeding and normal β cell function may not be achieved for several weeks. Although insulin therapy is used intermittently on the neonatal unit, there are few studies which have formally assessed its benefits. These studies have been small and some have compared the use of insulin with reduction in glucose infusion. One study in premature infants using continuous insulin infusions to control hyperglycemia showed better glucose tolerance with improved weight gain combined with a reduced incidence of sepsis. The use of stable isotopes has demonstrated a role for insulin infusions in reducing proteolysis in the low birth weight infants. Thus potentially, insulin could limit proteolysis and improve weight gain and growth.

In a recent pilot study, we demonstrated that early continuous insulin infusion effectively controlled blood glucose levels over the first week of life and prevented the high blood sugars seen on day 2 or 3 in infants given standard intermittent insulin therapy. These data indicate that insulin replacement early from birth may prevent some of the catabolism and insulin resistance normally observed in the preterm infant. Thus insulin replacement in the newborn could reverse the risk associated with high blood sugar: it could improve anabolism and weight gain, and theoretically by reducing hyperglycemia, reduce risk of sepsis. Insulin therapy in the newborn could also have more far reaching benefits. Levels of insulin like growth factor 1 (IGF-1) and the inhibitory IGF binding protein IGFBP-1 are regulated by insulin in the newborn. IGF-I has an important role in fetal and postnatal brain growth. Furthermore, low IGF-1 levels and hyperglycemia have been implicated in the pathogenesis of retinopathy of prematurity. Thus theoretically, improved insulin delivery and restoration of IGF-I levels could have important implications for the long term outcome as well as the short term survival of very low birth weight babies.

We propose that relative insulin deficiency in the very low birth weight baby leads to catabolism, insulin resistance and hyperglycaemia during the first week of life. High blood glucose levels may lead to osmotic diuresis and increase the risk of sepsis. Insulin deficiency may contribute to slow weight gain and impaired IGF-I generation which could have implications for risk of retinopathy, brain growth and later neurodevelopmental outcomes. We hypothesize that early intervention with continuous insulin replacement will prevent catabolism and improve glucose control, and could reduce neonatal morbidity and mortality.

Aims of the Study: To carry out a multicenter, randomized controlled study of early insulin replacement in very low birth weight infants (VLBW <1500g). 500 children will be randomized

to receive either a continuous infusion of insulin (0.05 u/kg/hr) from within 24 hours of birth and for the first 7 days of life, or to act as controls and receive standard neonatal care.

Objectives: The primary objective is to investigate whether an early fixed dose insulin infusion, combined with variable dextrose support to maintain normoglycaemia, will reduce mortality on or before expected date of delivery in the very low birth weight neonate. The secondary objective is to note: (i) incidence of sepsis in the first 2 weeks of life; (ii) growth at 28 days; (iii) incidence of necrotizing enterocolitis (iv) severity of retinopathy of prematurity; (v) incidence of intracranial hemorrhage (vi) incidence of chronic lung disease (vii) mortality before 28 days of age (viii) total number of days in neonatal intensive care prior to discharge home.

Efficacy outcomes: (i) Blood glucose control over the first week of life as assessed by the MiniMed subcutaneous continuous glucose monitor (CGMS); (ii) Effects of treatment on circulating IGF-I, IGFBP-1, cytokines.

Methods/Design

The study is a multicenter randomized controlled trial. It is based in 10 neonatal intensive care units and 500 babies will be recruited over 2 years. Very low birth weight babies (VLBW <1500g) will be recruited within 24 hours of delivery and followed until expected date of delivery (40 weeks). They will be randomized to either treatment with early fixed dose insulin (0.05unit/kg/hr) with 20% dextrose to maintain normoglycemia, or to receive standard neonatal care. Those randomized to treatment will receive a fixed dose of insulin combined with variable 20% dextrose support throughout the first week. Additional insulin will be infused if blood glucose levels are consistently above 10 mmol/l; and an infusion of 20% dextrose will be started if blood glucose falls to <4 mmol/l to prevent hypoglycemia (blood glucose <2.6 mmol/l). Controls will receive standard neonatal care. All babies will be monitored using a MiniMed continuous glucose monitor for 7 completed days and have a blood sample taken on Study days 1,3, 7 and 28. A urine sample will be collected from all babies on Study day 7 and all babies will have details of their clinical care recorded daily in the first week then weekly until 4 weeks, at 36 weeks corrected age, at expected date of delivery (40 weeks) and at discharge home.

Study population

Infants must fulfill all inclusion criteria: birth weight <1500g, requiring intensive care and in whom it is considered appropriate to continue intensive care, less than 24 hours of age, and written informed parental consent. Infants must not have any of the following exclusion criteria: maternal diabetes including gestational diabetes, babies where the appropriateness of continuing intensive care is being discussed, or major congenital anomalies.

If all the inclusion and exclusion criteria are met the patient will be included in the study and allocated a sequential patient number. The randomization will be stratified by center, by birth weight (<1000g, 1000-1500g), and by gestational age (<25 weeks and \geq 25 weeks). A 24 hour internet based randomization program will be used which requires user name and is password secure. Treatment with insulin will begin as soon after birth as is possible following randomization. Patient data will be analysed on the basis of intention to treat. Consent will be taken

by a health care professional who has a good working knowledge of the aims and practicalities of the study. Parents will be given a written information leaflet and given the opportunity to read and discuss the information they have been given alone. As patients need to be recruited within 24 hours of delivery, a system of continuing consent will be used over the first 3 days to ensure that parents are happy with the decision to consent to their baby's participation in the study.

Study Medication

The study product is Insulin aspart (NovoNordisk) (pyr) for intravenous injection. Insulin will be given intravenously at a fixed rate of 0.05 u/kg/hour. It will be prepared as a standard strength solution of 25 units/kg insulin aspart in 50 mls of 0.9% sodium chloride to run at 0.1 ml/hr, equivalent to 0.05 u/kg/hour. This will be combined with a variable rate 20% dextrose infusion when required to maintain normoglycaemia. Infusion dose will be based on the infants birth weight and adjusted only if there is concern that the recorded birth weight was inaccurate.

The study device are MiniMed CGMS (continuous glucose monitoring sensors). These comprise a disposable glucose oxidase-based platinum electrode sensor that catalyzes interstitial glucose generating an electrical current every 10 seconds, which is recorded via a cable by a pager sized monitor (6x9x2cm). The monitor records average values every 5 minutes, giving a total of 288 readings per day. Glucose values outside the range 2.2-24 mmol/l (40-430 mg/dl) are reported as <2.2 mmol/l (<40 mg/dl) or >24 mmol/l (>430 mg/dl) respectively. Nursing and medical staff will be instructed in the use of the monitor and asked to enter all blood glucose (BG) measurements taken for clinical reasons using near patient monitoring devices into the monitor for calibration. The data cannot be viewed in real time and therefore cannot impact on clinical care.

Babies will be randomized to insulin treatment. As is usual practice initial management will involve obtaining intravenous access, measuring blood glucose and initiating a dextrose infusion.

Study babies will in addition require: i) Insertion of a MiniMed sensor (subcutaneous insertion in the thigh).ii) Preparation of fixed dose insulin infusion iii) Preparation of a separate 20% dextrose infusion, for use if the BG should fall to <4.0 mmol/l to prevent hypoglycaemia.

The MiniMed sensor will be inserted subcutaneously in the thigh. It will be secured in place with a clear occlusive dressing. The sensor will be sited in the lateral aspect of the thigh by a member of the study team who has been appropriately trained. The sensor will be sited using aseptic technique. The legs will be examined to ensure an area of unbroken skin over the lateral aspect of the thigh. The skin will be gently cleaned with damp sterile gauze and allowed to dry. If the skin is very friable then a fine spray of cavilon will be applied to form a barrier. Any adhesive will be trimmed to ensure minimal contact with the skin but allowing for secure attachment. The individual inserting the sensor will document clearly the time and site of sensor insertion and condition of the site. All BG levels will be entered into the MiniMed Sensor to allow for calibration. These will be taken as frequently as clinically indicated but a minimum of 4 readings (approximately 6 hourly) must be entered every day. These will be entered within 5 minutes, as the monitor will

record subcutaneous readings every 5 minutes. If there are problems with dislodgement of the sensor it can be replaced on up to two occasions. The sensor should be left in situ for 12 hours after completion of the insulin infusion and should therefore be removed at midday on Day 8.

Fixed Dose Insulin Infusion Treatment will be with 25 units/kg insulin (aspart) in 50 mls of 0.9% (or 0.45%) sodium chloride to run at 0.1 ml/hr equivalent to 0.05u/kg/hour. The insulin solution should be prepared in a 50 ml volume to allow a minimum of 20 mls of the solution to be flushed through the connection tubing. This is to reduce the adsorption of further insulin to the plastic tubing during infusion.

All babies receiving insulin will have a 20% dextrose infusion prepared for infusion if the blood glucose levels fall <4.0 mmol/l to prevent hypoglycaemia. Calculation of the dose of insulin will be based on the baby's birth weight and only changed if this is felt in retrospect to be inaccurate.

Initiating treatment

If the blood glucose level is >4.0 mmol/l and the baby is receiving a minimum glucose infusion of 4 mg/kg/min (60 ml/kg/d of 10% dextrose) then the fixed dose insulin infusion regimen will be started. If the blood glucose is <4.0 mmol/l then 20% dextrose will be infused and blood glucose rechecked within one hour, repeatedly increasing 20% dextrose and checking BG hourly until BG is >4.0 mmol/l. Only when the BG is >4.0 mmol/l will the fixed dose insulin infusion be started. Once the insulin infusion has started the BG will be checked hourly until stable and then 2 hourly increasing to a time interval of 4 hours. If a baby is stable the time interval may be increased to a maximum of 6 hours under the guidance of the Principal Investigator. The fixed dose insulin infusion will start within 24 hours of delivery and will run for seven completed days. The fixed dose insulin infusion will be infused via the same line that the baby is receiving its main source of dextrose/parenteral nutrition. This will ensure that if there is a break in the delivery of the main source of dextrose to a baby that there will also be a simultaneous break in the infusion of insulin. The fixed dose insulin infusion will be maintained but any decisions regarding a baby's maintenance glucose infusions and fluid requirements will be taken by the medical team caring for the baby. If there are any clinical changes in the rate of glucose being infused or a clinical insulin infusion is started then a blood glucose will be rechecked hourly until stable.

The aim is to maintain blood glucose 4-8 mmol/l using the infusion algorithm shown in Figure1. If blood glucose levels rise (>10.0 mmol/l on two occasions) and there is no additional 20% dextrose being infused treatment with insulin should be started to maintain normoglycaemia (BG 4-8 mmol/l). If the blood glucose level falls <4.0 mmol/l, intravenous lines should be reviewed and additional 20% dextrose infused to avoid hypoglycaemia—starting at 1 ml/kg/hour extra. A review should be made of the amount of dextrose being received and the additional 20% dextrose infusion that has been prepared should be titrated to prevent hypoglycaemia. Repeated BG measurements should be taken hourly repeatedly increasing the 20% dextrose until the value is stable and >4.0 mmol/l. This should prevent BG levels falling to <2.6 mmol/l. However if BG <2.6 mmol/l then the insulin infusion should be stopped, all lines checked to ensure the baby is receiving the dextrose prescribed and additional 20% dextrose infused. A repeat BG should be

taken after 60 minutes, and hourly with the 20% dextrose repeatedly increased to maintain the BG 4.0-8 mmol/l. Close liaison with the medical and nursing staff is critical to make sure they understand the treatment algorithm and that the study is aiming to control the BG between 4-8 mmol/l. They must be aware of the importance of taking regular and frequent BG measurements to ensure euglycaemia and that 20% dextrose should be started if a BG level is recorded that is <4.0 mmol/l.

After the baby has received 7 days of insulin the infusion should be stopped at midnight on Study Day 7. If the baby has additional 20% dextrose running as well as the insulin then the insulin should be stopped first and the 20% dextrose weaned off over a period of several hours. In all cases the blood glucose should be monitored closely after stopping the insulin to ensure the baby does not become hypoglycaemic or hyperglycaemic. The Minimed sensor should be left in situ for 12 hours after stopping the insulin and be removed at midday on Study Day 8. Appropriate clinical management should be taken by the clinicians responsible for the baby's care.

For babies randomized to control arm, as is usual practice initial management will involve obtaining intravenous access, measuring blood glucose and initiating a dextrose infusion. Study control babies will in addition require insertion of a MiniMed sensor, and blood glucose control as per standard clinical protocol. Therefore if BG, <2.6 mmol/l standard unit management of hypoglycemia, >10 mmol/l if 2 or more readings are >10 mmol/l consider addition of insulin infusion. Once BG has fallen to <10 mmol/l then any insulin infusions should be stopped.

Measurement of outcomes

Primary outcomes: Death on or before expected date of delivery (taken as date considered the most accurate estimate of delivery date).

Secondary outcomes

- i) Episodes of sepsis in the first 2 weeks: a) Culture positive systemic infection will be defined as microbiologically positive cultures of blood, cerebrospinal fluid or suprapubic aspirate of urine plus clinical signs of sepsis. b) Culture negative infection will be defined as clinical signs suggestive of sepsis and considered to warrant >48 hours of antibiotics but with negative cultures.
- ii) Growth: All babies will have measurements of weight, length and head circumference at birth and every seven completed days after recruitment until EDD. Growth will be assessed as change in weight, length and head circumference standard deviation score (SDS) from birth to 28 days using conditional charts.
- iii) Incidence of necrotizing enterocolitis: defined as radiological evidence of necrotizing enterocolitis assessed by consultant radiologist.
- iv) Retinopathy of prematurity: All these babies will be routinely screened, for retinopathy of prematurity and will be graded using the internationally recognized grading system. Infants will be classified by the most severe degree of retinopathy.
- v) Incidence of intracranial haemorrhage: defined as cranial ultrasound evidence as assessed by Consultant Neonatologist.
- vi) Chronic lung disease: defined as respiratory support or oxygen dependency at 36 weeks corrected gestational age.

- vii) Death within and including the first 28 days after delivery
- viii) Days of neonatal intensive care: As defined by BAPM 2002.

Efficacy

- i) Percent of time normoglycaemic: All babies will have a continuous glucose sensor in situ for the 7 completed days. Sensors will be inserted within 24 hours of birth and left in situ for 7 days from the time of insertion. The sensors will be removed 12 hours after the insulin infusion has stopped. This will take a measure of interstitial glucose every 5 minutes and will give an assessment of glucose control throughout the first week. The percent of time spent with blood glucose <2.6 mmol/l, 2.6-10.0 mmol/l, >10 mmol/l and <4.0, 4.0-8.0 mmol/l, >8.0 mmol/l will be measured.
- ii) IGF-I and IGFBP-1: measured in blood taken on Study Days 1, 3, 7 and 28.
- iii) cytokines: measured in blood taken on Study Days 1, 3, 7 and 28.
- iv) protein catabolism: measured by urinary 3-methylhistidine/creatinine ratio on Study day 7.

Continuation of insulin treatment after 7 days

If a baby becomes hyperglycaemic after the study dose of insulin has been stopped it will be a decision of the doctors responsible for the patients medical care whether insulin should be restarted, what preparation will be used and what dose administered.

Concomitant therapy: All other therapy considered necessary for the patients welfare may be given at the discretion of the medical staff in charge of the infant's medical care.

Withdrawal from treatment: A patient will be withdrawn from the study if in the opinion of the Investigator it is medically necessary or if it is the parents wish for a child to be withdrawn. The reason for withdrawal should be clearly documented in the Case Report Form and reported to the co-ordinating centre within 24 hours.

Follow up: Contact details and hospital identifiers for all patients in all centers will also be collected so that future follow up will be possible. If there are effects on short term growth it will be important to review growth, body composition and insulin resistance in later childhood, as well as neurodevelopmental outcome. As is current practice in early neonatal deaths, in any baby who dies during the study period, the parents would be approached for consent to a post mortem being performed.

Statistics: Intention to treat analyses will be performed comparing the outcome of all infants allocated to early insulin treatment compared to those allocated placebo, regardless of how complete treatment was. Statistical analyses will use standard methods to calculate the event rates, time-to-event rates, relative risks, and numbers needed to treat for each outcome in the treatment compared with placebo group, along with 95% confidence intervals. Where appropriate χ^2 , Fisher's exact or log rank tests of significance will be performed and presented with p-values.

The primary outcome will be modeled with logistic regression in order to evaluate a 95% confidence interval for odds ratio according to treatment group adjusted for key prognostic variables, including if significant, geographic centre. No formal

interim analyses are intended although the trial's Data Monitoring Committee (DMC) will meet regularly, have access to unblinded data and would recommend early termination to the Trial Steering Committee if judged appropriate based on ethical, safety or efficacy considerations. Time to event analyses stratified by category of birthweight, using Kaplan-Meier survival analyses and stratified logrank tests will be used to assist DMC decision-making. For the secondary outcomes, modeling with either multiple regression (for continuous variables) or logistic regression (for binary variables) will be employed, adjusting for the same baseline covariates as the primary analysis. If individual terms in models are non-significant at level 0.05, then simpler models may be presented instead. A secondary analysis will be on an "as treated" basis, defining treatment exposure as at least 4 days without interruptions of more than 1 hour.

Power calculation: Sample size is based on the primary outcome variable of mortality. This is based on statistical power analyses for mortality of 20% by EDD. To predict an absolute difference of 10% with 80% power at the 5% level of significance we would need 428 patients. Non-compliance is not likely to be a problem, although withdrawal from treatment may be 5-10%. Thus we aim to recruit 500 patients. Each unit has an admission rate of approximately 100 very low birth weight babies per year. Due to the confined period of recruitment being within 24 hours of delivery we predict 50% availability for recruitment (some babies will be transferred in after delivery). Coupled with an estimated 60% rate of consent we predict we would recruit 500 infants over a 2 year period with a realistic safety margin. For the primary outcome measure of mortality by EDD loss to follow up should be negligible.

Ethical and regulatory issues: Patient information and consent: Parents will be given full verbal and written information regarding the objective and procedures of the study and the possible risks involved. If possible parents will be approached prior to delivery to allow time for considering study details prior to giving assent. However all parents would be asked to confirm informed consent in writing after a baby's birth. As patients need to be recruited within 24 hours of delivery, a system of continuing consent will be used over the first 3 days to ensure that parents are happy with the decision to consent to their baby's participation in the study.

Discussion

This study is based on the hypothesis that early intervention with insulin replacement prevents catabolism and the hyperglycemia seen during the first week of life, in the VLBW preterm infant. The strategy is not simply that used in adult intensive care to actively titrate insulin in subjects with hyperglycemia, although the adult outcome data particularly with respect to reductions in sepsis, with tight glycaemic control, may have interesting parallels. Our approach, to administer continuous insulin with glucose cover also provides additional safety compared to sliding scales of insulin generally used in this population, and also highlights the differences with adult ICU protocols. Although mortality and morbidity rates are much lower in infants 1-1.5kg compared to those <1 Kg it was felt that these infants may well benefit from any long term effect on growth and/or reduction in the incidence of retinopathy and therefore they have been included in the protocol.

Summary

Very low birth weight infants requiring intensive care have relative insulin deficiency often leading to hyperglycemia during the first week of life which has been associated with increased mortality and morbidity. The physiological influences on insulin secretion and sensitivity, and the potential importance of interventions to improve glucose control at this time are not well established. However theoretically, improved insulin delivery and restoration of IGF-I levels could have important implications for short term survival as well as the long term outcomes of these VLBW babies. This is a multicenter, randomized controlled trial of early insulin replacement in VLBW babies. Babies will be randomized to receive a continuous insulin infusion (0.05 units/kg/h) with 20% dextrose support or to receive standard neonatal care for the first 7 days of life. The primary end point will be mortality on or before expected date of delivery, secondary end points will be markers of morbidity and include episodes of sepsis, severity of retinopathy, chronic lung disease and growth.

IL-10, IL-6 and CD14 Polymorphisms and Sepsis Outcome in Ventilated Very Low Birth Weight Infants

R. John Baier, John Loggins, Krishna Yanamandra

Abstract

Background: Genetic variation in the innate immune system of the host may play a role in determining the risk of developing infection, as well as outcome from infection.

Methods: Infectious complications were retrospectively determined in 293 (233 African-American (AA), 57 Caucasian and 3 Hispanic) mechanically ventilated very low birth weight (VLBW) infants (<1500 grams at birth) who were genotyped for the IL-6 -174 G/C, IL-10 -1082 G/A and CD14 -260 C/T single nucleotide polymorphisms (SNPs).

Results: The IL-6 -174C allele was associated with an increased incidence of late blood stream infection (BSI) in AA but not Caucasian infants. In AA infants with the C allele the incidence of late BSI was 20/29 (69%) compared to 94/204 (46%) in homozygous GG infants (RR 2.6, 95% CI: 1.1–6.0, $p = 0.021$). The IL-10 -1082A allele was associated with an increased incidence of late BSI. One or more episodes of late BSI developed in 14 (35%) of 40 infants with the GG genotype, 71 (49%) of 145 infants with the GA genotype and 63 (58%) of 108 infants with the AA genotype ($p = 0.036$). Infants with the A allele (AA or GA genotypes) had an incidence of late BSI that was 134/253 (53%) compared to 14/40 (35%) in homozygous GG infants (RR 2.1, 95% CI: 1.04–4.19, $p = 0.035$). The CD14 -260 C/T SNP did not alter the overall risk for BSI in ventilated VLBW infants. Multiple BSI episodes were more common in the TT genotype group (CC: 17%, CT: 11%, TT: 30%, $p = 0.022$). This effect was due to the strong effect of the TT genotype on the incidence of

multiple BSI in AA infants (CC: 15%, CT: 11%, TT: 39%, $p = 0.003$).

Conclusion: The IL-6 -174 G/C, IL-10 -1082 G/A and CD14 -260 C/T SNPs may alter risk for BSI in ventilated VLBW infants.

Background

Sepsis is a persistent and vexing problem in very low birth weight (VLBW) infants. The development of sepsis in this population has several adverse implications including; prolongation of hospitalization, development of chronic lung disease, adverse neurodevelopmental outcome and excess mortality. The incidence of one or more episodes of late onset blood stream infection (BSI) in this population ranges from 25–30% with higher rates for infants with birth weights less than 1000 grams.

Genetic variation in the innate immune system of the host may play a role in determining the risk of developing and outcome from infection. Variation in the ability to recognize pathogens may influence the risk of infection. One of the primary molecules that function in recognition of pathogens is CD14. CD14 is expressed on phagocytic cells, and along with LPS-binding protein, it acts to transfer lipopolysaccharide (LPS) and other bacterial ligands to the Toll-like receptor 4 (TLR4)/MD-2 signaling complex. The engagement of CD14 and LPS-binding protein during recognition of Gram-negative bacteria results in activation of a complex of innate host defense mechanisms. CD14 expression is influenced by a single nucleotide polymorphism (SNP) found in the proximal CD14 promoter. A C to T substitution 260 base pairs (bp) prior to the start codon diminishes binding of the inhibitory factor sp3 resulting in increased expression of the CD14 gene. Homozygous carriers of the T allele have significant increases in both soluble and membrane-bound CD14. The CD14 -260 T allele may increase or modify the risk for septic shock.

Variation in the magnitude of inflammatory response may also influence the risk of sepsis. Outcome from sepsis depends to a considerable degree on the host response. While an absent or

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Table 1: Organisms causing Nosocomial Blood Stream Infection, Pneumonia and Endotracheal tube colonization in ventilated VLBW infants

	CONS	Fungi	Gram negative bacilli	Enterococci sp.	Staphylococcus aureus	Other
Episodes of Nosocomial BSI	113 (56) ^a	33 (16)	26 (13)	9 (4)	6 (3)	14 (7)
ETT Colonization (patients)	136 (46)	27 (9)	39 (13)	27 (9)	14 (5)	30 (10)
Episodes of Nosocomial Pneumonia	1 (5)	7 (32)	10 (45)	0	3 (14)	1 (5)
Sepsis Related Deaths	0	6	5	2	0	2

^a Numbers represent the number of episodes of infections (blood stream and pneumonia) or the number of patients with ETT colonization by a particular organism. Numbers in parentheses represent the percentages of total infections (bacteremia and pneumonia) or percentage of all patients (ETT colonization rates). Infants may have been simultaneously or serially colonized with more than one organism, thus the sum of the organism-specific rates is greater than the overall rate of ETT colonization (49%).
CONS coagulase negative staphylococci
ETT endotracheal tube
BSI blood stream infections

diminished host response leads to overwhelming infection, an excessive response can lead to systemic inflammation and multiple organ failure.

Interleukin-6 (IL-6) is a proinflammatory cytokine that plays an important role in the host response to infection. The C allele of IL-6 -174 G/C promoter polymorphism is associated with increased IL-6 production in newborn infants. The IL-6 -174 G/C SNP has been inconsistently associated with altered risk for and outcome from sepsis in several studies.

Interleukin-10 (IL-10) is an anti-inflammatory cytokine produced by macrophages and T-helper-type II (TH2) lymphocytes that downregulates inflammatory mediator production by stimulated immune and epithelial cells. Thus, IL-10 can potentially counterbalance the detrimental effects of excessive cytokine production in sepsis. The SNP at -1082 (G to A) modifies IL-10 secretion and may influence outcome in several disease states. The IL-10 -1082 G/A SNP lies within a putative Ets transcription site and is associated (A allele) with lower IL-10 production in vitro. The IL-10 -1082 SNP may modify the response to sepsis from a variety of organisms.

Variation in the IL-10, IL-6 and CD14 genes may be genetic factors influencing the development and outcome of sepsis in the premature newborn. The purpose of this study was to determine if there is a relationship between the IL-10 -1082 G/A, IL-6 -174 G/C and CD14 -260 C/T SNPs and risk for or outcome from sepsis in mechanically ventilated very low birth weight (VLBW) infants.

Methods

The genomic DNA used for this case controlled study was extracted from archival tracheal aspirate (TA) pellets (259) or blood (34 patients) collected prospectively as part of an ongoing study of genetic factors in the development of complications of prematurity. The TAs that were used as a source of genomic DNA were originally collected as part of long term longitudinal studies examining cytokine concentrations and the development of CLD. Infants were included in the study if they fulfilled the following inclusion criteria: birth weight less than 1500 grams, mechanical ventilation (MV) during the first week of life, complete clinical data on infectious outcome and genomic DNA sample that could be used for genotyping. Infants were excluded if complete data on outcome were not available or suitable DNA was not available. In order to compare the frequency of the various polymorphisms with normal term infants, control DNA was extracted from cord blood spots from a random sample of 168 African-American and 96 Caucasian term infants (performed independently as part of another study examining genotype and asthma). Consent was obtained from the parents of study infants to use the TAs and blood samples. The study was approved by the Institutional Review Board for Human Research at Louisiana State University Health Sciences Center in Shreveport.

Cultures for genital mycoplasmas were performed on TA samples collected in the first few days of life. Clinical and outcome data were abstracted from the clinical record and included information on respiratory outcome, survival and development of complications of prematurity. The results of all

Table 2: Effect of the IL-6 -174 GC Polymorphism on Nosocomial Blood Stream Infections in African- American and Caucasian Infants

Organism	African American				Caucasian			
	GG (n = 204)	GC (n = 27)	CC (n = 2)	P value	GG (n = 19)	GC (n = 32)	CC (n = 6)	P value
CONS	72 (35)	12 (44)	2 (100)	0.116	11 (58)	11 (34)	3 (50)	0.249
Non CONS	48 (24)	12 (44)	0	0.185	6 (21)	9 (28)	2 (33)	0.827
Fungal	22 (11)	7 (26)	0	0.071	1 (5)	1 (3)	2 (33)	0.027
Gram negative bacilli	16 (8)	1 (4)	0	0.683	3 (16)	5 (16)	0	0.578
Enterococcus sp.	5 (2)	2 (1)	0	0.354	1 (5)	1 (3)	0	0.817
Other	15 (7)	2 (1)	0	0.924	1 (5)	2 (6)	0	0.820

Numbers in parentheses represent percentages of patients with nosocomial blood stream infections

Table 3: Effect of the IL-10 -1082 GA Polymorphism on Nosocomial Blood Stream Infections in African- American and Caucasian Infants

Organism	African American				Caucasian			
	GG (n = 27)	GA (n = 118)	AA (n = 88)	P value	GG (n = 13)	GA (n = 25)	AA (n = 19)	P value
CONS	8 (30)	45 (38)	33 (38)	0.703	4 (31)	10 (40)	11 (58)	0.276
Non CONS	3 (11)	26 (22)	27 (31)	0.088	2 (15)	10 (40)	5 (26)	0.676
Fungal	2 (7)	13 (11)	14 (16)	0.403	0	2 (8)	2 (11)	0.502
Gram negative bacilli	1 (4)	10 (9)	6 (7)	0.675	1 (8)	4 (16)	3 (16)	0.755
Enterococcus sp.	0	3 (3)	4 (5)	0.440	0	2 (8)	0	0.265
Other	1 (4)	7 (6)	9 (10)	0.376	1 (8)	2 (8)	0	0.242

Numbers in parentheses represent percentages of patients with nosocomial blood stream infections

cultures of blood, tracheal aspirates and cerebrospinal fluid were recorded from the patients' charts. Tracheal aspirates were obtained twice a week in all intubated patients according to unit policy. Infants were evaluated for sepsis at the discretion of the clinical staff when signs and symptoms compatible with sepsis developed. Generally, 2 blood cultures from separate sites were obtained when assessing infants for blood stream infection. For the purposes of this study any positive blood culture was considered a blood stream infection (bacteremia or fungemia). Blood stream infections (BSI) were divided into early if the culture was obtained during the first 3 days of life, and late (nosocomial) if it was obtained thereafter. Nosocomial pneumonia was diagnosed when there was radiological evidence of a new pulmonary infiltrate and the blood and endotracheal aspirate culture grew the same organism. Isolation of an organism from a TA culture in an infant greater than 3 days of age without a positive blood culture or a change in chest radiograph was considered colonization. Sepsis mortality was defined as mortality during an acute episode of sepsis.

Laboratory methods: Isolation of total DNA from blood or TA pellets was performed using the QIAmp DNA Mini kits (Qiagen Incorporated, Chatsworth, CA). Briefly, TA pellets were suspended in 200 µl of sterile phosphate buffered saline by vigorous vortexing, then digested with proteinase K and applied to silica gel spin columns. Columns were washed with the manufacturer's supplied buffers and the total DNA was eluted in 200 µl elution buffer. Blood (200 µl) was extracted similarly to the TA pellets.

The IL-10 -1082 G/A and IL-6 -174 G/C SNPs were genotyped using published allele specific PCR methods. The CD14 -260 CT SNP was genotyped using a published restriction fragment length polymorphism method.

Data analysis: Data analysis consisted of comparing the incidence of infections and their complications between the various genotypes. All statistical analysis was performed using SPSS for Windows version 6.0 (SPSS Inc, Chicago, IL). Differences in frequencies of complications were assessed by Chi square. ANOVA or the Student t-test was used to assess normally distributed variables where appropriate. The Wilcoxon Rank Sum test was used for analysis of factors that were not normally distributed. A probability value of less than 0.05 was considered statistically significant. The data are presented as mean ± standard error of the mean (SEM).

Results: Two hundred and ninety-three (293) patients had complete culture and clinical information. Two hundred and thirty-three (79%) were African-American, 57 (20%) were Caucasian and 3 (1%) were Hispanic. Mean gestational age and mean birth weight of the study population were 26.7 ± 0.1 weeks and 906 ± 13 grams, respectively. Male: female ratio was 176:117. All patients required MV at birth and 264 (90%) infants were treated with exogenous surfactant therapy (Survanta®, Ross Products Division, Abbott Laboratories, Columbus, OH). One hundred and fifty eight (54%) infants were oxygen dependent at 28 days and 64 (22%) were oxygen dependent at 36 weeks PCA. There were 40 (14%) patients who died during their

Table 4: Effect of the CD14 -260 CT Polymorphism on Nosocomial Blood Stream Infections in African- American and Caucasian Infants

Organism	African American				Caucasian			
	CC (n = 109)	CT (n = 101)	TT (n = 23)	P value	CC (n = 23)	CT (n = 24)	TT (n = 10)	P value
CONS	34 (31)	39 (39)	13 (57)	0.065	12 (52)	24 (46)	2 (20)	0.224
Non CONS	26 (24)	21 (21)	9 (39)	0.178	6 (26)	4 (17)	4 (40)	0.346
Fungal	14 (13)	11 (11)	4 (17)	0.685	2 (9)	1 (4)	1 (10)	0.765
Gram negative bacilli	13 (12)	2 (2)	2 (9)	0.021	3 (13)	2 (8)	3 (30)	0.250
Enterococcus sp.	3 (3)	2 (2)	2 (9)	0.229	0	2 (8)	0	0.241
Other	5 (5)	8 (8)	4 (17)	0.095	1 (4)	2 (8)	0	0.592

Numbers in parentheses represent percentages of patients with nosocomial blood stream infections

Table 5: IL-10 -1082 A and IL-6 174C Allele Carriage on Nosocomial Blood Stream Infections

	Carriage of IL-10 -1082 A and IL-6 174C Alleles				P value
	IL-10 A allele – IL-6 C allele – (n = 31)	IL-10 A allele – IL-6 C allele + (n = 9)	IL-10 A allele + IL-6 C allele – (n = 195)	IL-10 A allele + IL-6 C allele + (n = 58)	
Late BSI (all organisms)	11 (36)	3 (33)	98 (50)	36 (62)	0.073
CONS	10 (32)	2 (22)	41 (36)	12 (44)	0.476
Non Cons	3 (10)	2 (22)	23 (20)	10 (37)	0.166
Multiple BSI	3 (10)	1 (11)	17 (15)	6 (22)	0.760
Mortality from sepsis	1 (3)	0	6 (5)	2 (7)	Na

Numbers in parentheses represent percentages na Not able to calculate

initial hospitalization (25 before 28 days of age and 15 after 28 days). Late onset BSI was the major cause of late mortality in ventilated VLBW infants with 14/15 deaths occurring after 28 days of age directly attributable to BSI (RR 15.3, 95% CI 2.0–117.9; $p < 0.001$).

One patient had positive blood cultures (Group B streptococci) during the first 3 days of life (early BSI) and 147 (50%) had one or more episodes of late (nosocomial) BSI. Coagulase negative staphylococci (CONS) were the organisms most commonly isolated from blood cultures. Seventy-one (24%) infants had one or more episodes of bacteremia/fungemia other than from CONS and 46 (15.7%) had multiple episodes of bacteremia or fungemia. Organisms causing nosocomial BSI (bacteremia/fungemia) for the study population are shown in Table 1. There were 15 (5%) deaths directly attributable to sepsis. Fourteen of 15 sepsis related deaths were associated with a non-CONS BSI ($p < 0.001$, RR = 59; 95% CI 7–421).

Endotracheal (ET) cultures obtained during the first 3 days of life grew *Ureaplasma urealyticum* in 86 (29%), *Mycoplasma hominis* in 35 (12%) and other bacteria in 12 (4%) infants. Subsequent bacterial colonization of the endotracheal tube (ETT) was detected in 145 (49%) patients. After birth, ETTs were most commonly colonized with CONS, less frequently with other organisms (Table 1). Nosocomial pneumonia was diagnosed in 22 (7%) infants (Table 1).

IL-6 -174 G/C polymorphism and infectious complications

The frequency of the IL-6 -174 C allele in the study population was 0.128. The frequency of the C allele was significantly less in African-American (0.07) than in Caucasian infants (0.385) ($p < 0.001$). Two hundred and four (87.6%) African-American infants were homozygous GG, 27 (11.6%) were heterozygous GC and 2 (0.8%) were homozygous CC. In Caucasian infants the distribution of genotypes was: 19 (33.3%) GG, 32 (56.1%) GC and 6 (10.5%) CC. The 3 Hispanic infants were all GG. There were no differences in the frequency of the IL-6 -174C allele between study infants and ethnically matched control (term) infants.

Birth weight, gestational age, gender, TA isolation of Uu or Mh and need for surfactant replacement did not differ among genotype groups in either Caucasian or African American infants. Because the frequency of the IL-6 -174C allele was significantly different between ethnic groups, the effects of this SNP on infectious complications were analyzed separately for Caucasian and African-American infants.

The IL-6 -174C allele was associated with an increased incidence

of late BSI in African-American infants. One or more episodes of late BSI developed in 94 (46%) of 204 infants with the GG genotype, 18 (67%) of 27 infants with the GC genotype and 2 (100%) of 2 infants with the CC genotype ($p = 0.046$). In infants who had the C allele (CC or GC genotypes) the incidence of late BSI was 20/29 (69%) compared to 94/204 (46%) in infant who were homozygous GG (RR 2.6, 95% CI: 1.1–6.0, $p = 0.021$). There were no significant differences in organism-specific BSI rates among genotype groups (Table 2). Neither the rates of non-CONS BSI (GG: 24%, GC: 44%, CC: 0%; $p = 0.116$) or multiple BSI episodes (GG: 15%, GC: 19%, CC: 0%, $p = 0.752$) were different among genotype groups.

The IL-6 -174 G/C polymorphism had no effect on sepsis-related mortality in African-American infants. Overall sepsis mortality was (GG: 5%, GC: 4%, CC: 0%; $p = 0.916$). The rate of sepsis mortality for African-American infants with late BSI was (GG: 11%, GC: 6%, CC: 0%; $p = 0.717$).

The rate of colonization of ETT tubes and incidence of nosocomial pneumonia were not affected by the IL-6 -174 G/C SNP. Nosocomial pneumonia rates were: (GG: 8%, GC: 7%, CC: 0%; $p = 0.909$). ETT colonization rates were 25/54 (46%) for infants with the GG genotype, 68/128 (53%) GC genotype, and 52/113 (46%) CC genotype ($p = 0.489$). CONS were the most common bacteria colonizing the ET tube in both groups. Organism-specific colonization rates were not different among genotype groups.

In contrast to that observed in African-American infants, the IL-6 -174 G/C SNP had no effect on the incidence of late BSI in Caucasian infants. One or more episodes of late BSI developed in 12 (63%) of 19 infants with the GG genotype, 16 (50%) of 32 infants with the GC genotype and 3 (50%) of 6 infants with the CC genotype ($p = 0.643$). The incidence of fungal BSI was increased in Caucasian infants with CC genotype (2/6 (33%)) compared to infants with the GG (5%) and GC (3%) ($p = 0.027$) ($p = 0.008$ comparing CC vs. GC and GG). There were no other significant differences in organism specific BSI rates among genotype groups (Table 2). Neither the rates of non-CONS BSI (GG: 21%, GC: 28%, CC: 33%; $p = 0.827$) nor multiple BSI episodes (GG: 21%, GC: 13%, CC: 33%, $p = 0.415$) were different among genotype groups.

The IL-6 -174 G/C SNP had no effect on sepsis related-mortality in Caucasian infants. Overall sepsis mortality was (GG: 5%, GC: 6%, CC: 17%; $p = 0.614$). The rate of sepsis mortality for Caucasian infants with late BSI was (GG: 8%, GC: 7%, CC: 33%; $p = 0.383$).

The rate of colonization of ETT tubes and incidence of nosocomial pneumonia in Caucasian infants were not affected by the IL-6 -174 G/C polymorphism. Nosocomial pneumonia rates were: (GG: 5%, GC: 7%, CC: 0%; $p = 0.813$). ETT colonization rates were: 11/19 (58%) for infants with the GG genotype, 14/32 (44%) GC genotype and 3/6 (50%) CC genotype ($p = 0.620$). Organism-specific colonization rates were not different among genotype groups.

The incidences of necrotizing enterocolitis (NEC), CSF infection and infections in other sites were not different among genotype groups in either African-American or Caucasian infants.

IL-10 -1082 G/A polymorphism and infectious complications

The frequency of the IL-10 -1082A allele in the study population was 0.62. The frequency of the A allele was similar between African-American (0.63) and Caucasian infants (0.55) ($p = 0.191$). Forty (13.7%) infants were homozygous GG, 145 (47.3%) were heterozygous GA and 108 (36.9%) were homozygous AA. Distributions of genotypes were not significantly different between African-American and Caucasian infants ($p = 0.088$). There were no differences in the frequency of the IL-10 -1082 A allele between study infants and ethnically matched control (term) infants. However, the frequency of the A allele was significantly different between Caucasian and African-American controls.

Birth weight, gestational age, gender, TA isolation of Uu or Mh and need for surfactant replacement were not different among genotype groups in either Caucasian or African American infants.

The IL-10 -1082A allele was associated with an increased incidence of late BSI in our study infants. One or more episodes of late BSI developed in 14 (35%) of 40 infants with the GG genotype, 71 (49%) of 145 infants with the GA genotype and 63 (58%) of 108 infants with the AA genotype ($p = 0.036$). In infants who had the A allele (AA or GA genotypes) the incidence of late BSI was 134/253 (53%) compared to 14/40 (35%) in infant who were homozygous GG (RR 2.1, 95% CI: 1.04–4.19, $p = 0.035$). Although they were not statistically significant, similar trends were observed when African-American and Caucasian infants were analyzed separately. There were no significant differences in organism-specific BSI rates among genotype groups (Table 3). The rates of non-CONS BSI (GG: 15%, GA: 40%, AA: 26%; $p = 0.676$) or multiple BSI episodes (GG: 10%, GA: 16%, AA: 18%, $p = 0.528$) were not different among genotype groups. There was a trend towards increased incidence of non-CONS BSI in infants with the IL-10 -1082A allele (5/40 infants with GG compared to 66/253 infants GA/AA; $p = 0.062$).

The IL-10 -1082 G/A SNP had no effect on sepsis-related mortality. Overall sepsis mortality was: GG: 3%, GA: 6%, AA: 6% ($p = 0.721$). Sepsis mortality in infants with late BSI was: GG: 7%, GA: 11%, AA: 10% ($p = 0.877$).

The IL-10 -10814 G/A SNP did not affect ETT colonization or incidence of nosocomial pneumonia. Nosocomial pneumonia rates were: (GG: 11%, GA: 6%, A: 9%; $p = 0.620$). ETT colonization rates were: 18/40 (45%) for infants with the GG genotype, 74/145 (51%) GA genotype, and 53/108 (49%) AA genotype ($p = 0.791$). Organism-specific colonization rates were not different among genotype groups.

The incidences of necrotizing enterocolitis (NEC), CSF infection and infections in other sites were also not different among genotype groups in either African-American or Caucasian infants.

CD14 -260 C/T polymorphism and infectious complications: The frequency of the CD14-260T allele in the study population was 0.33. The frequency of the T allele was similar between African-American (0.32) and Caucasian infants (0.39) ($p = 0.151$). One hundred and thirty-two (45%) infants were homozygous CC, 128 (44.2%) were heterozygous CT and 33 (11.3%) were homozygous TT. The frequency of the CD24 -260T allele was significantly greater in Caucasian term infants than in Caucasian VLBW and African-American term infants. Birth weight, gestational age, gender, TA isolation of Uu or Mh and need for surfactant replacement were not different among genotype groups in either Caucasian or African American infants.

The CD14 -260CT SNP had no effect on the overall incidence of late BSI. One or more episodes of late BSI developed in 63 (48%) of 132 infants with the CC genotype, 66 (52%) of 128 infants with the CT genotype and 19 (58%) of 33 infants with the CC genotype ($p = 0.570$). However, there were significant differences in organism-specific rates of BSI between African-American and Caucasian infants (Table 4). In particular, in African-American infants, Gram-negative BSI was associated with the CC genotype (Incidence of infection CC: 12%, CT: 2% and TT: 9%, $p = 0.020$). There was a trend for non-CONS BSI to be more frequent in infants with the TT genotype (CC: 24%, CT: 20%, TT: 39%; $p = 0.074$). Multiple BSI episodes were more common in the TT genotype group (CC: 17%, CT: 11%, TT: 30%, $p = 0.022$). This effect was due to the strong effect of the TT genotype on the incidence of multiple BSI in African-American infants (CC: 15%, CT: 11%, TT: 39%, $p = 0.003$).

The CD14 -260 CT SNP had no effect on sepsis-related mortality. Overall sepsis mortality was (CC: 6%, CT: 4%, TT: 6%; $p = 0.709$). Sepsis mortality in infants with late BSI was (CC: 10%, CT: 8%, TT: 20% ($p = 0.741$)). The rate of colonization of ETT tubes and incidence of nosocomial pneumonia were not affected by the CD14 -260 CT SNP. Nosocomial pneumonia rates were: (CC: 11%, CT: 5%, CC: 7%; $p = 0.190$). ETT colonization rates were: 66/132 (50%) for infants with the CC genotype, 58/128 (45%) CT genotype, and 21/33 (64%) TT genotype ($p = 0.170$). Organism-specific colonization rates were not different among genotype groups.

The incidences of necrotizing enterocolitis (NEC), CSF infection and infections in other sites were not different among genotype groups in either African-American or Caucasian infants.

Interactions between IL-10 -1082 G/A and IL-6 -174 G/C and incidence of sepsis: Since the IL-10 -1082A and the IL-6 -174C alleles were associated with an increased incidence of late BSI, the interaction of these two polymorphisms were examined on this and other outcomes. The effect of carriage of neither, either or both of the IL-10 -1082A and the IL-6 -174C alleles and IL-10 -1082:IL-6 -174 haplotypes was examined. Eight of the 9 possible haplotypes were present in our patient population. The IL-10 -1082 GG: IL-6 -174CC haplotype was not observed. Carriage of both the IL-10 -1082A and the IL-6 -174C alleles was associated with the greatest risk of late BSI in the overall population ($p = 0.073$) (Table 5). The incidences of CONS BSI, non-CONS BSI, multiple BSI and sepsis-related mortality paralleled that of the

overall late BSI rate but were not significant (Table 5). This increase in risk was seen primarily in African-American infants ($p = 0.031$). No significant trend between haplotype and risk for sepsis was observed, although the highest incidence of late BSI was in infants with the IL-10 -1082AA: IL-6 -174 CC haplotype. In multivariate analysis (logistic regression), carriage of the IL-10 -1082 A allele ($p = 0.035$) but not the IL-6 -174 C allele ($p = 0.152$) was a significant predictor of late BSI.

Discussion

Genetically determined variation in the magnitude of inflammatory response may play a role in determining outcome from serious infections. IL-6 is a pro-inflammatory cytokine associated with the development of shock and mortality from sepsis. Therefore genetic variants that influence production of this cytokine may have important implications in the development of and outcome from sepsis in the preterm neonate. The frequency of the IL-6 -174 C allele in both Caucasian and African-American VLBW infants was similar to control term infants and as described in other populations. This suggests that this polymorphism has no effect on the incidence of prematurity or on the need for ventilation at birth. We found that the IL-6 C allele was associated with an increased risk for late BSI (all organisms) in African-American but not Caucasian infants. However, the incidence of fungal BSI was greatly increased in Caucasian infants with CC genotype compared to infants with GG or GC. This suggests that the IL-6 -174CC genotype may be a risk factor for fungal sepsis in specific ethnic groups. However, because there were relatively few Caucasian patients with the IL-6 -174 CC genotype, caution must be exercised in interpreting this finding. Further studies are needed to confirm this association.

Earlier studies had suggested that the IL-6 -174 G/C polymorphism was either not associated with increased risk of sepsis, or that VLBW infants who were homozygous GG were at increased risk of Gram positive sepsis. However, the infants in these studies were all or predominately Caucasian. Ethnic differences and small numbers of Caucasian infants in our study may account for some of the discrepancies. In addition, our infants were significantly smaller, less mature and required mechanical ventilation, factors that significantly increase risk of infection and may overwhelm any effect of this polymorphism. There was no effect of the IL-6 -174 G/C polymorphism on mortality-related sepsis. The Ahrens study did not address the effect of polymorphisms on sepsis mortality. In adults, the GG genotype was associated with increased survival in sepsis, but had no effect on the incidence of sepsis (intensive care setting).

The role of the IL-6 -174 G/C polymorphism on IL-6 production is unclear. The IL-6 -174 C allele has been associated with decreased transcriptional activity in response to LPS and IL-1. The effects of this polymorphism, however, are more complex and may be stimulus dependent, cell line dependent and different in vivo from in vitro. In vitro IL-6 production in LPS-stimulated mononuclear cells is higher in the CC genotype in newborn infants. Following coronary artery bypass surgery the C allele is associated with increased plasma IL-6, whereas following vaccination the G allele is associated with increased plasma IL-6. This complexity is further compounded by additional functional polymorphisms that are in linkage disequilibrium with the -174 SNP.

IL-10 downregulates inflammatory mediator production by

stimulated immune and epithelial cells. Production of IL-10 can have a potentially beneficial effect by dampening excess inflammatory mediator production in sepsis. Excessive IL-10 production can, however, lead to the phenomenon of immunoparalysis by inhibiting the response of macrophages to pathogenic bacteria. The frequency of the IL-10 -1082 A allele in our ventilated VLBW infants is similar to that in control term infants and to that described in the literature. This suggests little effect of this allele on either the incidence of preterm birth or the need for mechanical ventilation at birth. Our results are consistent with those of Kalish et al., in which the IL-10 -1082 SNP was not associated with risk of preterm birth.

The IL-10 -1082A allele (lower IL-10 production) was associated with a two-fold increase in the incidence of late BSI in ventilated VLBW infants. Although not statistically significant, there was a trend towards increased non-CONS BSI (associated with higher mortality and morbidity) in infants with the A allele. This suggests that a more robust inflammatory response may protect the host from invasive disease. There was, however, no effect on sepsis-related mortality. The effect of the IL-10 -1082 G/A polymorphism on the incidence and outcome from infectious disease has been contradictory and may be organism-specific or vary according to ethnicity. There was no effect of the IL-10 -1082 G/A polymorphism on the incidence of invasive meningococcal disease, but disease severity and mortality were associated with the AA genotype. In contrast, the G allele was associated with the development of septic shock in pneumococcal sepsis and severity of the systemic inflammatory response in community acquired pneumonia, whereas there was no association between genotype and risk of infection. In the VLBW infant, an earlier smaller study showed no effect of the IL-10 -1082 G/A polymorphism on development of sepsis.

The role of polymorphic variation in the IL-10 gene and IL-10 production is unclear. Variation in IL-10 production in relation to the IL-10 -1082 SNP is affected by the nature of inducing stimulus and association of other polymorphisms. The IL-10 -1082 SNP is in linkage disequilibrium with two other SNPs (-819 C/T and -592 C/A) and appears in three haplotypes. The GCC haplotype (G at position -1082, C at position -819, C at -592) is associated with high IL-10 secretion, while the ACC and ATA haplotypes are associated with intermediate and low IL-10 secretion respectively. The -2849 A/G SNP also affects IL-10 production functionally and should be studied.

Genetic variation in the ability to recognize and respond to invading organisms may also significantly influence the development of and outcome from infection. CD14 is an important component of innate immunity and plays a role in recognizing both Gram negative and positive organisms. We found that the CD14 -260 C/T SNP did not alter the overall risk for BSI in ventilated VLBW infants. However, the CC genotype was associated with an increased incidence of Gram negative BSI in African-American infants, suggesting a potential role for this polymorphism in determining risk for certain types of infection or in specific ethnic groups. In addition, multiple BSI episodes were more common in infants with the TT genotype owing to the strong effect of the TT genotype on the incidence of multiple BSI in African-American infants. Ahrens et al. demonstrated no association between this SNP and sepsis or sepsis mortality in VLBW Caucasian infants. The current study extends those findings by examining a higher risk group (ventilated) of infants with different ethnic backgrounds. In

other studies involving primarily Caucasian adults, the CD14 -260 C/T polymorphism does not seem to have a major influence on the risk for or outcome from sepsis. Only a single study suggested that the TT genotype (increased CD14) was associated with the development of septic shock and mortality. Increased soluble CD14 concentrations were associated with mortality from Gram-negative septic shock in earlier studies.

In Caucasians the CD14 -260 T allele was significantly less frequent in VLBW infants than in term infants, suggesting a potential role for this polymorphism in premature birth. The role of CD14 polymorphisms in prematurity has not been studied but a larger prior study reported by Hartel et al. does not support a role for the CD14 -260CT SNP. The frequency of the CD14 -260 T allele in our control population is similar to that reported in other control Caucasian populations (both adult and term infants), which varied between 0.352 and 0.548. The CD14 -260T allele was significantly more frequent in Caucasian control infants than in African-American controls, consistent with other reports. The CD14 -260T allele frequency in African-American infants (both VLBW and term) was similar to that reported in the literature. In contrast to that seen in Caucasians, no effect of the CD14 -260CT polymorphism on prematurity was seen in among African-American infants.

An individual's risk for developing sepsis (and its outcome) probably depends on interactions of several genetic factors. Polymorphisms of both pro-inflammatory (IL-6) and anti-inflammatory cytokines (IL-10) may interact either to increase or to decrease risk. In our study, co-carriage of both IL-6 -174 C and IL-10-1082 alleles was associated with a slightly increased risk of late BSI. Multivariate analysis, however, suggests that the IL-10 -1082 A allele is the dominant risk factor.

Other genetic differences may influence risk for and outcome from sepsis in VLBW infants. We recently reported that the TNF- α -308A allele did not affect the risk for sepsis but increased mortality in septic infants. The 3020insC mutation of the NOD2 gene is also associated with increased risk of sepsis in VLBW infants. Polymorphisms in other cytokines, their receptors and other bacterial pattern recognition molecules have been suggested to alter the course of sepsis and are logical candidates for further study in this population.

The observations of this retrospective case-controlled study are limited by selection bias. Our population of mechanically ventilated infants, most of whom were less than 1000 grams at birth, is at high risk for infection. As a result, the incidence of bacteremia/fungemia in our studied population (47%) is higher than generally reported for a VLBW population and also higher than for the population of VLBW infants in our NICU (approximately 30%). Mechanical ventilation and lower birth weight are known risk factors for late onset sepsis. Because only infants who were mechanically ventilated were included, the true impact of the polymorphisms studied on the incidence of infectious complications of prematurity may be underestimated.

Exchange Transfusion, continued from page 37...

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Midwives Among the Machines: Re-Creating Midwifery in the Late Twentieth Century

Raymond G. DeVries and Rebeca Barroso

It was a strange sight, even by the standards of a large American hospital. Here, among the world's most advanced obstetric technology—electronic monitors, infusers, ultrasound devices and well-appointed surgical suites—a woman was giving birth on the floor.

The laboring woman was Hmong, a recent immigrant from Laos. She arrived at the hospital by ambulance, sent by her relatives who claimed she was not in labor, just 'overdue'. Neither she nor her partner spoke English. While the nurse-midwife was reviewing her scant prenatal records, she quietly left her bed and began squatting on the floor. As she squatted, her waters broke. The attending nurse-midwife hurriedly placed some 'sterile' linen under the woman and joined her in a squatting position. Within minutes, a healthy baby boy slipped into the hands of the midwife.

The odd image of a squatting woman giving birth surrounded by the gleaming, modern equipment of an American maternity ward is an apt metaphor for midwifery's problematic relationship with technology. Can midwifery, with its low-technology, non-interventive tradition, find a place in an environment where competence is equated with the use of the latest, high-technology devices? In deciding how to respond to the new technologies of birth, midwives face a troublesome dilemma: if they adopt the instruments of modern medicine, they risk sacrificing their distinctive tradition; if they cling to their tradition, they are marginalized as anachronistic, quaint, or perhaps, dangerous practitioners.

The importance of machines to modern obstetrics is illustrated in the conclusion of this story, as told by the nurse-midwife: I handed the baby to the nurses as soon as I clamped and cut the cord. I had no safe place to put him while I helped the mother move from the slippery floor. For the next five to ten minutes I was busy finishing the birth of the placenta and checking on

blood loss. It seemed just a few minutes before the nurse brought the baby back, dried and wrapped in a warm blanket. When it was all over, I felt good that I attended this birth in a way that respected the culture of the mother. A few hours later when I was doing the required paperwork, I was shocked to see a note in the baby's records: "10 cc clear gastric fluid per aspiration." They had taken this perfectly healthy, vigorous baby and [using suction] emptied his stomach!

Because there was no medical indication for this procedure, the midwife concluded that the nurses felt an overwhelming, but irrational, need "to use the equipment." Low-technology midwifery had to be baptized by high-technology medicine.

The Re-Creation of Healthcare Professions

The dilemma of "midwives among the machines" is, in fact, a special case of a problem faced by all healthcare professions. As the world around them changes, healthcare professions must adapt, they must re-create themselves.

The sources of change in healthcare practice are varied. The need for professional re-creation is often the result of change coming from within the profession itself. As a profession develops new technology and new techniques, practitioners must adjust, changing routines and discarding old theories, making room for the latest professional knowledge. Who now, for example, purges and bleeds their patients?

But change in technique is not the only source of change originating within the profession. Decisions regarding the organization of a profession also bring about change. Professions consciously re-create themselves when they develop new educational programs, create new areas of specialization, or reallocate tasks among occupational groups. These same decisions can also set in motion processes with unintended, sometimes negative, consequences for that self-same profession. Starr offers an eloquent description of this, showing how the professional autonomy secured by American physicians early in this century eventually (and ironically) lead to the corporatization of healthcare, forcing doctors to adjust to a new, corporately controlled environment.

Reprinted from *Routledge Studies in the Social History of Medicine, Midwives, Society and Childbirth, Debates and Controversies in the Modern Period*, edited by Hilary Marland and Anne Marie Rafferty. © Routledge, 2005. This article has been slightly edited.

Less obvious, but no less important sources of professional recreation are changes in society and culture. Included among the many influences exerted on medicine by society are changes in the economy and in the political environment, the reorganization of healthcare financing, and demographic shifts such as baby booms, ageing populations, and increased urbanization. Healthcare systems must also adjust to shifts in cultural ideas about gender, family, work, science, and religion. Notice, for example, the way healthcare changed in response to new cultural conceptions of gender: the gender balance in medical occupations has been altered, there is a new concern with the treatment of women as patients, and medical research has been re-focused to include women.

A new, or re-created, medical practice is best seen as the result of a combination of factors. The increasing popularity of walk-in medical clinics in the United States offers a case in point. Immediate-care centers are franchised and intended for quick-stop care for minor problems, earning them the name “doc-in-the-boxes” (a pun on the name of a well-known, drive-through restaurant, Jack-in-the-Box). Their appearance and rapid proliferation can be attributed to: the corporatization of healthcare (a corporate strategy to increase profit), changing residential patterns (large suburban tracts offer an ideal market for these clinics), and the desire of physicians for more reasonable work hours deriving from new attitudes about work and family.

All healthcare professions are influenced by these changes, but not all are equally free to re-create themselves. Some, more than others, must labor in an environment where their social capital is limited. A profession's history and consequent cultural authority determine the freedom it has to shape its place in the medical marketplace. Professions with great prestige, greater income, and greater power are more free to influence political, organizational, and cultural processes. Professions like nursing, established as an adjunct to the profession of physicians, find their position controlled by those with more social capital. Professions closely connected to a tradition, like midwifery and homeopathy, find their ability to adjust and re-create themselves limited by that tradition.

In the following pages, we examine the ways in which midwifery has chosen, and is choosing, to re-create itself. We begin by recasting the history of midwifery as a continuing effort of midwives to re-create the profession in light of its tradition, its position vis-a-vis physicians, and developments in society. Next we look at the strategies of re-creation used by midwives on both organizational and individual levels. In order to highlight the socially situated nature of professional re-creation, we use data from both the United States and the Netherlands. We conclude by reviewing the factors that impede the midwives' task of re-creating themselves, focusing on the idea of risk and its place in the medical division of labor.

Re-Creating Midwifery

The history of midwifery in the United States and the Netherlands has been told by many. These histories, like the earlier chapters in this anthology, are a rich source of information about the evolving relationships among health occupations. The details of midwifery's history vary by location and time period, but in each chronicle we find midwives re-creating themselves, or being re-created by others, as the conditions around them, and in their profession, changed.

Reviewing these histories, we find certain events common to the re-creation of midwifery in all industrializing societies: the development of the machinery of obstetrics—from forceps to the most recent techniques of prenatal testing—the rise of hospitals, an increasing faith in science, and changing demographic patterns.

Nearly all histories of midwives assert that midwifery forceps gave a technological edge to male birth attendants. The initial response of midwives was to denounce the new technology, to assert the superiority of the “hands-off” tradition of midwifery. Elizabeth Nihell, an eighteenth-century English midwife, equated the tools used to assist at birth with military weapons: “those instruments, those weapons of death, would one not imagine that the art of midwifery was an art militaire?” Those sympathetic to midwifery's tradition of a patient and natural approach to birth, point out that forceps ushered in a new, “meddlesome midwifery.”

But not all midwives were content to re-create themselves as an alternative to interventionist obstetrics. Marland points out that a significant number of midwives in the Netherlands sought the right to use forceps. She cites an address delivered in 1910, signed by over three hundred Dutch midwives, that claimed the use of forceps and the right to suture were “vital to the well-being of their occupation and their clients.”

Although midwives failed to gain access to tools of modern obstetrics, their attempts to bring the technology of medicine to the tradition of midwifery must be seen as a prudent strategy to preserve and extend their profession. The centralization of care (and scientific technology) in hospitals and increasing public faith in science threatened to eliminate independent midwifery. Physicians, competitors of midwives, easily capitalized on new public attitudes to paint midwives as old-fashioned, unscientific, and dangerous.

In the United States, midwifery suffered further as a result of two important demographic changes: declining immigration and decreasing family size. Reduced numbers of new immigrants diminished the social contexts that supported the traditions and customs brought from the old country. Immigrants wanted to become “American” and the American thing to do was to use a hospital for birth with a physician in attendance. For immigrant families with many children the desire for a hospital birth was often limited by the ability to pay, but as families became smaller, hospital confinement became a luxury most could afford. Lacking an effective organization, American midwives could not respond to changing preferences of clients.

During the latter half of the twentieth century, midwifery has faced increasing pressure to change, to accommodate to the new obstetrics. The social and political position of midwives offered little room to re-create their profession in a way that would extend, or even preserve, their independence. They did not have the resources—in terms of political influence, public confidence in their scientific competence, or support from hospitals and other medical organizations—to compete with obstetrics. Given these limited resources, midwives in most industrializing nations were forced to re-create themselves as assistants to obstetric specialists. In the United States this meant creating an alliance with the established (though subordinate) profession of nursing and seeking work in medically under-served areas. In many European nations

midwives became extensions of doctors, the so-called 'lengthened arm' of obstetricians. As the term implies, midwives found legitimacy by working under the direct supervision of another profession, subordinating their tradition to the ever new, promising, modern approach of medicine. Even in the Netherlands, where an autonomous profession of midwifery survived, the political and cultural power of midwives was no match for that of doctors. Elements of Dutch culture and the Dutch medical system supported the tradition of midwifery, but without the protection of influential gynecologists/obstetricians, it is likely that Dutch midwifery would look much like midwifery in other industrialized nations.

The assimilationist strategy of re-creation chosen by midwives threatened to extinguish the separate tradition of midwifery. In effect, midwives were exchanging their own tradition for the tradition of medicine or nursing. But the 1960s created a detour on the path to extinction. Societal and cultural change in the form of the feminist movement and a new and vigorous questioning of technology gave midwives the opportunity to emphasize their distinct tradition, to re-create themselves as separate from medicine.

In the light of this new cultural atmosphere midwives could renew their identity as a low-tech, high-touch, women-centered occupation. The very image that had weakened the profession earlier in the century now gave them a niche in the medical marketplace. Midwives found further support for their profession during the 1980s and 1990s as governments and healthcare organizations sought to control the costs of medical care. In this environment midwives asserted themselves as more cost-effective, extending their appeal beyond new cultural ideas about women and technology to economic concerns of policy-makers and healthcare administrators.

Strategies of Re-Creation

The changed cultural attitudes of the 1960s and the economic realities of the 1980s and 1990s allowed midwives to maintain a foothold in modern medical systems. But the future of the profession remains unclear. To the extent that it promises to manage risk and to reduce pain, the machinery of modern obstetrics has wide appeal. Midwives face the difficult task of finding a way of re-creating midwifery that preserves the distinctiveness of the profession while remaining up-to-date in obstetric techniques.

The strategies used by midwives to respond to this unmanageable situation fall into two categories: first, organizational strategies, efforts taken by, or on behalf of, midwife organizations, efforts to preserve a place for the profession in the medical marketplace, and, second, individual strategies, efforts by individual midwives to establish and protect the distinct practice of midwifery. These strategies of re-creation, be they organizational or individual, are influenced by social context, a fact that becomes clear in the contrast between the situations of midwives in the Netherlands and the United States.

Organizational Strategies: Re-Creating the Profession of Midwifery

The United States

Midwives in the United States, quite commonly used at the turn of the century, were pressed nearly to extinction in the years

between the two World Wars. Factors mentioned above—increasing faith in science and medicine, changed patterns of immigration and decreasing family size—reduced the popularity of midwifery, as did the midwife debates that took place in the second and third decades of the century. These “debates” were not, in fact, debates at all. They are better described as diatribes by physicians against midwives. Capitalizing on new attitudes, midwives were portrayed as untrained, incompetent and dangerous, the cause of high infant and maternal mortality. If, in the face of these conditions, the practice of midwifery was to survive in the United States, an organizational strategy was needed. It was not enough for individual midwives to practice the tradition of midwifery, as many ‘granny-midwives’ in the southern part of the country were doing, the profession needed to find a way to secure a place for that practice in the changing medical system. The strategy chosen was to ally with the established profession of nursing, adding midwifery training (often secured in England) to certification in nursing. Through the work of Mary Breckenridge and the Frontier Nursing Service in Kentucky, and later the Maternity Center Association in New York City (with its own training program), midwifery claimed a legitimate place in American medicine. In 1955, nurse-midwives took a further step to defend the interests of their profession by establishing the American College of Nurse-Midwifery (ACNM, now the American College of Nurse-Midwives).

Two of the most important tasks of the ACNM were the creation of a nationally recognized program of certification and obtaining licensure in all states and jurisdictions. The recognized place of midwifery remained limited, however, with the newly (recreated) profession serving poor women on the rural and urban fringes of society. Up through the 1970s midwifery played an increasingly limited role in maternity care. The flame of midwifery was not completely extinguished in the United States, but by 1970 midwives were attending less than one-half of one per cent of births there, and the percentage of births outside of medical settings fell to less than one.

How did American midwifery respond to the social and cultural changes of the 1960s? This opportunity to re-create and reaffirm midwifery as separate from the tradition of medicine led to a curious bifurcation of midwifery in the United States. The tenor of the times was a natural source of support for midwifery, but many would-be clients and supporters of midwifery saw nurse-midwifery as a sell-out, too much a part of the system. Thus was born an American version of the direct-entry midwife: variously called the lay midwife, the empirical midwife, or, most recently, the traditional midwife.

The rhetoric of traditional midwifery, as suggested by the name itself, stressed the need to re-create midwifery in its true image, forswearing any connection with “medicine.” Traditional midwives saw themselves as being a genuine response to a new generation of clients with a healthy distrust of technology and believed that hospital-based nurse-midwives co-opted women, promising a midwife birth but doing regular obstetrics. To avoid being co-opted themselves, traditional midwives rejected formal training in favour of apprenticeship and self-education. Textbooks written by physicians were acceptable, but the medical socialization that attended training programs for nurses, midwives, and physicians was to be avoided. Traditional midwives continue to favour home birth, herbal remedies, and simple, non-medical solutions to problem of labor. As might be

expected, the training and competence of these women was (and remains) uneven.

Traditional midwifery flourished among the 1960s and 1970s counterculture. In keeping with the countercultural spirit of “do your own thing,” hierarchical organization, legal regulations, and alliances with existing medical organizations were avoided. Lacking any formal organization, it is difficult to speak of an organizational strategy of traditional midwives of the 1960s and early 1970s. In resisting the medical establishment, some traditional midwives did ally themselves with an odd collection of marginal health practices from reflexology, to aromatherapy and iridology, thus keeping them at the margins of mainstream healthcare. On the other hand, it is possible to see these midwives as part of a larger consumer-based alternative birth movement in the United States that is often given credit for the creation of alternative birth settings inside and outside of hospitals.

Increasing resistance from physicians, in the form of legal actions and unwillingness to provide medical back-up, caused traditional midwives to begin organizing in the hope of gaining legal recognition. In the late 1970s, several state associations of traditional midwives were created, many of which approached state legislatures with licensing legislation. These attempts to gain legitimacy through licensing were largely unsuccessful and today the laws governing the practices of traditional midwives remain a hodgepodge of difficult-to-interpret rules and regulations. In most states traditional midwives remain outside the existing medical system, with no access to hospitals and strained relationships with physicians and nurse-midwives.

Repeated failures of state organizations to gain licensure and increased prosecution of non-nurse-midwives for violation of medical practice acts, led to the creation, in 1982, of a new, national organization, the Midwives' Alliance of North America (MANA). The founders of MANA saw it not just as an organization of traditional midwives, but as an opportunity to promote the profession by connecting with other, more established midwives. Membership was open to all midwives, be they nurse-midwives or traditional midwives, and efforts were made to connect with midwife organizations in other countries and with the International Confederation of Midwives (ICM). Seeing the need for a publicly recognized ‘standard of care’, and in keeping with the non-medical approach of traditional midwifery, MANA created, in 1989, a certification program for non-nurses, the North American Registry of Midwives (NARM). According to MANA, “the test serves as a tool to determine whether entry level knowledge has been achieved, and it assists in fostering reciprocity between local jurisdictions.”

Because they had re-created midwifery in two different ways, it proved difficult for MANA and ACNM to work together. Each claimed to represent the true tradition of midwifery in the United States. But by the early 1990s, the organizations saw the need to join forces and formed the Interorganizational Workgroup (IWG). The IWG produced, in 1993, a statement on Midwifery Certification in the United States that allows for the certification of two types of midwives: the Certified Midwife and the Certified Nurse-Midwife.

The dialogue between nurse and traditional midwives has also increased as a result of the movement of many traditional midwives into nurse-midwifery in the 1980s and 1990s. One of

the more important reasons for a traditional midwife to become a nurse-midwife is the desire for a steady and reasonable income. In the early 1990s, the average annual income of a nurse-midwife was \$55,000, while for most traditional midwives it was nearly impossible to earn a living. In the words of one traditional midwife, “my work is an expensive hobby.”

For their part, nurse-midwives used the favorable cultural climate of the 1960s and 1970s to expand their position, locating themselves between the extremes of obstetrician-controlled, high-technology birth and do-it-yourself, no-technology home birth. Seeking to claim this middle ground, they simultaneously emphasized the tradition of midwifery “with women” and their connection with the latest and best hospital technology. Note the language used by one nurse-midwife to describe her profession: “a certified nurse-midwife...is a specialist with obstetrical nursing experience and graduate training in midwifery...she [also] has the attitudes and approaches of the age-old profession...that...women today are seeking.” During the 1970s, nurse-midwives expanded their training programs, seeking cultural credibility by locating them in university settings, associating with schools of medicine or schools of nursing.

In an effort to increase the supply, and hence the visibility, of nurse-midwifery, the profession is experimenting with new methods of education. The best known of these programmes is the Community-Based Nurse-Midwifery Education Program (CNEP) run by the organization that pioneered nurse-midwifery, the Frontier Nursing Service. CNEP students spend a short period at the facility in Kentucky, finishing their training via self-directed study, regular communication with professors via a computer network, and a residency with a nurse-midwife service in their home community.

A different sort of organizational strategy for the re-creation of midwifery is the establishment of new institutions for the management of birth. The free-standing birth center (FSBC) is particularly suited to the autonomous practice of midwifery. Such centres are structurally and administratively separate from hospitals, equipped for management of low-risk births. Staffed, in most cases, by nurse-midwives, FSBCs have arrangements for backup with local hospitals. By separating their sphere from the sphere of specialist physicians, midwives are given more latitude for practice. As explained by one nurse-midwife:

“The birth center nurse-midwife is constantly reminded that, while the birth center is a place for the practice of midwifery, the hospital is the place for the practice of medicine. In the birth center the whole system is designed to nurture the practice of midwifery. In the hospital, medical practice is the norm, midwifery is different and thus much more of a struggle...It is simply easier to practice midwifery in a birth center.”

Physicians are not especially supportive of FSBCs, but, because they reduce costs, they are increasingly popular with health insurance companies. Faced with the extinction of their profession, the organizational strategies of re-creation used by American midwives have included: (1) alliance with an existing profession; (2) the creation of programs to train and certify the competency of midwives; (3) the establishment of organizations to represent the interest of midwives; and (4) the creation of new forms of delivering maternity care. At this point we can note modest gains for American midwives at the organizational

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level. The changes that began in the 1960s, on a cultural and social level and among midwives, resulted in a small but steady increase in their share of maternity care after 1970.

The Netherlands

The situation of midwives in the Netherlands is unique in the world. Dutch midwives and the maternity care system of which they are a fundamental part are often held up as a model for other countries. The two features of the Dutch system that attract most attention are the high percentage of home births and the autonomous status of midwives. Midwives are part of the primary care system of the Netherlands, the so-called 'first line'. As such, they have the authority to decide which women can remain in the first line—giving birth at home or having a polyclinic, short-stay hospital birth—and which must see a specialist. This is quite the opposite of the situation typical in other countries, where specialists make the decision about the appropriate level of care.

The historical conditions that produced the existing system in the Netherlands suggest that there are four pillars on which the Dutch maternity care system rests:

- 1 The protected position of the midwife, whose profession was defined and protected in the 1865 Act on the Practice of Medicine, and who was given primacy in the health insurance law.
- 2 A generally accepted screening system for high-risk pregnancies, standardized criteria that define as clearly as possible the conditions requiring referral to a specialist.
- 3 A well-organized maternity homecare system, that allows continuity of care in home births.
- 4 The socio-cultural environment in the Netherlands that regards pregnancy and childbirth as normal physiological processes.

In comparison to midwives in the United States it would seem that Dutch midwives have no pressing need to re-create their profession. While there has been a substantial decline in home birth, midwives are providing for a stable and large proportion of the nation's births. Nonetheless, in the face of shifting social and cultural conditions midwives in the Netherlands are concerned to preserve their position. The organizational strategies used by Dutch midwives include efforts to become more scientific, actively supporting features of the culture and the healthcare system favorable to midwifery, seeking reforms that will protect the profession, and finding new ways of delivering care.

Although home birth remains popular in the Netherlands, more clients are choosing to give birth in the polyclinic. Polyclinic births are short-stay hospital births attended by midwives or general practitioners. They are favored by parents who wish to have "alles bij de hand" (everything, that is, medical equipment, on hand). Midwives supervise the majority of these births, but the trend is troubling because it reflects a growing faith in obstetric technology, and because in the polyclinic not only do midwives feel less free to exercise their profession, but there is a higher rate of transfer to specialist care. On an organizational level, midwives have responded to this trend in two ways: first, to become more scientific, that is, to pattern themselves after scientific medical professions, and, second, to reinvigorate public confidence in home birth.

Recognizing the power of science in modern society, midwives face the challenge of becoming more scientific without necessarily becoming more technological. One strategy to accomplish this is to distinguish physiological (normal) birth from pathological birth. Thus separated, midwives can use scientific methods to study normal pregnancy and birth and claim jurisdiction as experts in physiological birth. Science is used to assess technology itself, examining its appropriate and inappropriate uses. In an effort to expand the scientific competence of midwives, a fourth year was added to the education of midwives entering their training schools in 1993, a significant portion of which is dedicated to training in scientific research methods.

Carefully conducted, scientific studies not only enhance the image of a profession, but yield information useful to the promotion of the profession. Recognizing this, the Dutch Organization of Midwives (Nederlandse Organisatie van Verloskundigen, NOV) encourages its members to co-operate in studies of the quality of care. This co-operation was rewarded by favorable results in a recent comparative study of polyclinic and home birth. The study concluded that home birth was at least as safe as polyclinic birth for first-time mothers, and safer for women who already had one child.²⁹ This study became the centerpiece of a public campaign to encourage home birth, entitled "een goede keuze bevalt beter"—a play on words, meaning both "a good choice births better" and "a good choice brings a more pleasing result." The campaign, sponsored by the NOV with the support of the Dutch government, was intended to encourage more women to choose home birth by showing the rationality of this cultural ideal. According to the NOV, the goal of the campaign was to reach pregnant women, their partners, and other influential relatives, as well as midwives and other caregivers; information about the safety and desirability of home birth was given by means of brochures, press releases, a nationwide telephone information line, and visits to groups of midwives, nurses, and physicians.

Because Dutch healthcare is organized differently from that in the United States, midwives, through their national organization, have a voice in the creation of policy affecting their profession. This voice has been used to protect the 'indications list' that defines the work terrain of midwives, to secure a reduction in the average number of births expected of each midwife—in the hope of reducing burnout and attrition of midwives—and to generate support for research projects promoting the practice of midwifery. The government, concerned with the costs of healthcare, is inclined to support midwives and home birth because research consistently demonstrates that they reduce costs while providing compatible, or better, outcomes than clinical births attended by physicians.

But even Dutch midwives, with their favored position and new orientation towards science, are handicapped by their tradition. This is most visible, of course, in questions related to the use of technology. The tradition of midwifery suggests the practice should avoid technology and promote the confidence of women in their ability to give birth without assistance from machines. But Dutch midwives are also a medical profession, with the freedom to use certain medical procedures. Questions naturally arise: why not promote more polyclinic births? After all, centralizing care means less travel, greater ease in attending births, more assistance from nurses and support staff. Why not use ultrasonography routinely? Sending women elsewhere for a

sonogram increases the chance that they will stay under the care of specialists and makes the profession appear old-fashioned. The consequent debates over whether new technology should or should not be employed weaken the image of the profession in the eyes of a public convinced of the value of technology. By way of contrast, the more eclectic and experimental tradition of physicians allows them to “own” new technology. They may discuss its appropriate and inappropriate uses, but they never suggest that technology itself is undesirable.

Like their American counterparts, midwives in the Netherlands are also experimenting with new methods of delivering care. The best-known effort in this regard is the Geboortecentrum (birth center) in Amsterdam. It is not a centre where birth occurs—midwives already have a great deal of autonomy in home births and polyclinic births—it is rather a centre that collects all the various services related to pregnancy and birth under one roof: a prenatal clinic, pregnancy and postpartum courses, a bureau to arrange postpartum care, once-a-week consultations with an obstetrician, a shop with articles for pregnancy and birth, and a clinic for care of the newborn. The idea is to strengthen the position of the midwife, putting her in control of various services associated with birth. Here, too, the tradition of midwifery becomes an obstacle, with some midwives complaining that this type of centre results in the improper commercialization of the profession.

What Works, What Does Not

We can now review the organizational strategies used by midwives to adapt their profession to changing circumstances. Do these strategies re-create the profession in a way that insures its existence and preserves its identity?

The comparison of Dutch and American midwifery reveals a striking difference in the strength of the voice midwives have in policy-making. Like midwives in the United States, Dutch midwives must compete against the prestige and power of physicians, but in the Netherlands midwives have a legitimate place in the government bureaucracy that controls healthcare, allowing them to influence decisions about the place of midwifery in the healthcare system. The structure of Dutch healthcare—with direct government control of healthcare costs by the Ziekenfondsraad (Sick funds council) and the Centraal Orgaan Tarieven Gezondheidszorg (Central committee for healthcare tariffs)—protects and promotes midwifery. Midwives have a seat on the Ziekenfondsraad and are regarded by the government as safe and economical. The American healthcare system allows midwives little influence in the creation of policy. Health policy in the United States is shaped through lobbying efforts of professional groups and medical organizations. Compared to physicians, American midwives have a very small,

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poorly funded lobby, and hence little ability to protect their position.

Some strategies work to guarantee a place for the profession, but threaten to alter the profession so radically that it remains distinct in name only. The affiliation with nursing in the United States is an example of this. The uncritical acceptance of medical technology will bring similar results. A number of Dutch midwives are resisting the trend towards polyclinic births for this reason. They claim that polyclinic births are not merely transplanted home births, but are the first step in a technological transformation of the profession.

Some strategies are essential for the profession but their ability to transform and extend midwifery is constrained by context. Included here are decisions to create midwife organizations. These organizations are necessary to give midwifery a voice, but the strength of that voice is dependent on social and cultural situation. In the United States, the presence of two (more or less) competing organizations hindered the effective re-creation of midwifery.

The decision of traditional midwives in the United States to avoid official organization and to identify with a variety of marginal health practices dissipated professional strength. This radical strategy was seen as a corrective to the medicalization of nurse-midwifery, but it allowed established medical professions to discredit both traditional and nurse-midwifery as dangerous and strange.

Most promising are strategies that strengthen the structural

position of midwives and work to create supporting cultural ideas. The birth center idea, in its manifestation in the United States and in the Netherlands, is a strategy of this sort. It gives the profession more autonomy while making it attractive to policy-makers and clients. As more clients use these services, cultural ideas are transformed in a way that favors the profession. In both countries midwives have created national organizations to promote birth centers, the National Association of Childbirth Centers in the United States, and the Vereniging Geboortecentrum Nederland (Association of Dutch birth centers) in the Netherlands.

As important as these organizational strategies are, they form only a part of the re-creation of midwifery. It is the everyday practices of midwives where the tradition is given life. Midwife organizations might preserve the profession, but the profession loses its meaning if the practices of midwives become indistinguishable from physicians. Thus we turn to strategies employed by midwives as individuals to find a way to practice midwifery among the machines of obstetrics.

The United States

In the United States it is nurse-midwives who are called upon to find individual strategies for re-creating the profession. Traditional midwives, existing outside the mainstream medical system, are free to practice as they please. The organizational strategies of nurse-midwives have earned them a place in a medical environment where they must find ways to remain midwives and not become physician extenders. This is especially difficult when working in a hospital surrounded by medical technology, much of which appears to simplify the work of midwifery. For example, when a labor is proceeding slowly, the tradition of midwifery might suggest that a woman walk around or lie in a warm bath. But in a hospital this is difficult to arrange. It is much more efficient to administer a drug to speed labor.

Given this situation, midwives who wish to remain faithful to the tradition of midwifery must find ways to overcome the limitations of their surroundings including: a lack of knowledge, lack of access to proper equipment or facilities, and limits created by hospital policy.

As the machinery of obstetrics becomes more prevalent, new knowledge replaces old knowledge. For example, knowledge of how to deliver a breech birth vaginally is all but lost in the United States where a breech presentation is almost always an indication for caesarean section. The gradual obsolescence of the fetoscope is another example of lost knowledge. The doptone which uses sonar technology to amplify sounds from the uterus, is a much easier way to find fetal heart tones and to allow them to be heard by the expectant parent(s). But some midwives argue that the fetoscope (or wooden tooter), the traditional tool of the profession, is the better instrument. Without electronic amplification it is possible to find the point where the heart tones are the clearest and loudest, allowing the precise position of the child to be identified. Furthermore, the fetoscope brings the midwife much closer to the woman, allowing the caregiver to assess level of relaxation, skin tone, and overall condition. Midwives in training who wish to learn the proper use of the fetoscope find that their teachers have lost the ability to use one. The response is self-education or association with an old-fashioned midwife, but midwives who gain this knowledge encounter a second problem: difficulty

finding fetoscopes on hospital obstetric wards.

Lack of equipment and facilities is a serious constraint on the continued practice of midwifery. A warm bath is a preferred way to promote relaxation and thus stimulate labor, but in many hospitals there are no bathtubs. A midwife reports similar problems with items needed to use traditional techniques for supporting and relaxing the perineum. In her hospital, all women having an epidural must give birth in a delivery room under sterile conditions, making it impossible to use poultices and oils to minimize perineal pain and prevent lacerations. The midwife's response is to improvise: using available sterile pads, doing a 'clean catch' of a lubricant into a sterile cup in order to allow it to be used in the sterile environment, looking for hot water in labor rooms.

Hospital policy is another constraint on the practice of midwifery. Many hospitals in the United States have a policy, set by their department of anesthesia, prohibiting obstetric patients from receiving anything by mouth after admission. The rationale for the policy is the rare danger of aspiration with the use of general anesthesia. Midwives, believing in the necessity of adequate hydration and nourishment, are forced to find a way around such policies. A simple solution used by some midwives is to deny admission to a laboring woman until she has had something to eat and drink.

These individual strategies are, in fact, strategies of subversion. As such, they show the power of medical technology. Because the task of reforming the structure of medicine and the culture that supports it is so overwhelming, the best midwives can do is to find ways to work within medical settings without compromising the ideas and values of their profession. In fact, many midwives find subversion too difficult or too costly (in terms of their relationships with colleagues) and hence they simply follow the medical protocols.³⁹ In the Netherlands, where the context is different, midwives are able to devise different strategies.

The Netherlands

Given their legitimate place in the first line of Dutch healthcare, midwives have less need to subvert the system. Their position as 'gatekeepers' in the first line gives individual midwives the power to defend the practice of midwifery. When a woman first suspects or knows she is pregnant, her first visit is to the midwife or the general practitioner. A specialist cannot be seen except by referral from the first line. This gives midwives a great deal of power over the behavior of specialists. Midwives tell of situations where a local gynecologist is treating women poorly, or discouraging women, sent for consultations, from having a home birth. The response is to simply cease sending women to this specialist. Eventually, the specialist will call and ask what might be done to once again receive referrals. This strategy works best in areas where several hospitals exist and compete for clients; but even midwives in rural areas report traveling extra distances to avoid unwanted practices in a local hospital.

Dutch midwives do, however, feel an increasing need to subvert culture. As more women choose polyclinic births, seeking the safety of medical technology, midwives are becoming more active in promoting home birth. Not just organizationally, as discussed above, but also in individual practices midwives seek to encourage women to remain at home for birth. Many

midwives will ask women choosing a polyclinic birth to explain their choice. In so doing midwives are protecting (and promoting) a cultural value that says home birth is the preferred choice, and all other choices must be explained. Women who persist in their desire for a polyclinic birth are advised that when contractions start they can choose to remain at home; when labor begins some midwives will visit the home, reminding the woman and her partner that it is possible to simply stay at home.

But why encourage home birth? Is it not possible to practice midwifery in a Dutch hospital? It is true that Dutch midwives exercise a great deal of autonomy in the hospital, but many midwives believe that the peaceful, familiar setting of the home is one of the tools of traditional midwifery. In the hospital you cannot tell an overwrought partner to go and make some coffee, in the hospital the laboring woman feels less at ease, less in control, she is not free to walk about. And, as in the American situation, as simple a thing as a bathtub is often unavailable.

Conclusion: Midwives, Machines, and the "Risks" of Birth

Not all efforts to re-create midwifery are equally successful. Our review of the situation of midwives in the Netherlands and in the United States makes it clear that the structural position of midwifery affects the possibilities for re-creation. Individual strategies of re-creation can be little more than subversive or marginal if the profession has not secured a legitimate and autonomous place in the healthcare system. Midwives interested in preserving a place for a distinctive profession, one that is not simply the lengthened arm of physicians, must work towards gaining structural legitimacy. And in order to gain this legitimate place, there must be an effort to re-create and reinforce cultural ideas that support midwives. Thus, free-standing birth centers will not gain great success in the United States unless women (re)gain trust in their ability to give birth without the assistance of the technology of obstetrics.

Thus we are brought back to the image of midwives among the machines. The response of midwives to the machines of obstetrics, from forceps to ultrasonography, has been uncertain. For good reason. If midwives shun obstetric technology they seem out of date. In an expose of nurse-midwives in public hospitals in New York City, midwives at one hospital were faulted for having a cesarean section rate of 12.9%, far below the city average of 23%. In a technological culture it is unthinkable not to use the latest technology; this is one reason many midwives in the Netherlands were anxious to bring ultrasonography into their practices. But if midwives adopt obstetric technology, they set in motion a process that changes their profession so drastically that it becomes subsumed by, or indistinguishable from, obstetrics.

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1. AHA Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Part 6, p. 1-87.

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Why do the machines of obstetrics have this effect on midwifery? It is because these machines expand the notion of risk and increase uncertainty. Ultrasonography and other means of prenatal diagnosis turn every pregnancy into a risky pregnancy, supporting the idea of many American obstetricians that a pregnancy is low risk only in hindsight. Because the technology is available, women are forced to make a choice: should it be used or not? Their choice is often influenced by their placement in a risk group; thus, normal pregnancy ceases to exist and uncertainty over the outcome of pregnancy grows. The wealth of information produced by the technology of obstetrics also increases uncertainty. Electronic fetal monitors, for example, produce an unending stream of data, all of which is subject to different interpretations, each leading to a different clinical decision. Increasing risk and uncertainty mean one of two things for a midwife: either she, as an expert in normal birth, is no longer needed, or she must become more technological.

What is to be done with the midwife? The question itself suggests the subordinate, passive position of her profession, a position controlled by cultural and social factors. It is true that midwives have little control over societal and cultural forces: support and resistance often come unbidden. But a profession that understands the way these forces work is better equipped to work with them, to influence them, to turn the question around: what should the midwife do?

Ten Most Common Skin Eruptions in the Neonatal Period

Arie L. Alkalay, MD; Charles F. Simmons, MD

Background

Papulo-vesiculo-pustular (PVP) skin eruptions are common findings in the newborn period. Most of these eruption dermatoses are transient, and self limited but must be differentiated from more serious and sometimes life threatening conditions. Prenatal history, race, hygiene, climate and nutrition may be important factors in the diagnosis and management of these eruptions. These eruptions can cause parental anxiety. However, as the majority of these skin lesions are benign, after a simple diagnostic work-up, the physician can reassure the parents.

Eruption Dermatoses

1. Milia: Multiple yellow or pearly white 1-2 mm papules, which are scattered over cheeks, forehead, nose, nasolabial folds and rarely on the genitalia. Milia are inclusion cysts which contain trapped, keratinized stratum corneum. When they appear on the hard palate, they are referred as Epstein's pearls; when on alveolar ridges, they are referred to as alveolar cysts or Bohn's nodules. No racial or sexual predilection is recognized.

Incidence: Incidence is between 44-95%.^{1,2} The larger and more mature the infant, the higher the incidence of milia is. The

The authors are with the Division of Neonatology, Department of Pediatrics, Ahmanson Pediatric Center, Cedars-Sinai Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA. The authors wish to thank the following people, institutes and Web sites for granting us permission to use their pictures for this article: American Academy of Pediatrics (Pediatrics in Review - Neonatal Dermatologic Challenges by Johr R.H. and Schachner L.A.) for the pictures of miliaria rubra, acropustulosis of infancy, congenital candida, neonatal scabies and neonatal herpes; "Dermis" web site for the pictures of neonatal milia, neonatal scabies and neonatal impetigo; "Dermatlas" web site for the pictures of acne neonatorum, miliaria crystallina, acropustulosis of infancy, neonatal scabies, neonatal herpes and neonatal impetigo; Auckland District Health Care and Crown company for the pictures of erythema toxicum, miliaria crystallina, and Transient Neonatal Pustular Melanosis; Dr. Jeffrey L. Melton, MD, and Loyola University Medical Education Network for the picture of "diaper rash."



Milia

condition is very common in USA, but no known figures on prevalence.

Diagnosis: No investigations are necessary. The clinical appearance is diagnostic.

Management and prognosis: No therapy required, milia resolve spontaneously within a few months.

2. Erythema Toxicum Neonatorum (ETN): Small 1-2 mm erythematous papules, vesicles, and occasionally pustules, surrounded by irregular erythema, occur 24 hours to two weeks after birth. Involve trunk, arms and legs, spare the palms or soles. The rash usually resolves in 5-7 days. Approximately 90% of the cases occur after 48 hours. The lesions can appear and disappear within minutes to hours. Lately it was suggested that ETN is caused by coagulase - negative staphylococci which enter the hair follicles and cause local inflammation. In this study,³ 84% of the infants were colonized with the bacteria, and electron microscopy of skin biopsies identified coagulase negative staphylococci.



ETN

Incidence: Incidence in the USA is between 31-72%.⁴ The incidence differs in different countries and is lower, for

example, in Spain, Taiwan and India. The incidence is higher in males, term infants, first pregnancy birth, in summer and autumn, vaginal delivery and formula fed infants.⁵

Diagnosis: Wright stain or Tzanck preparation reveals a lesion populated primarily by eosinophils.

Management and prognosis: No treatment is required. ETN is a benign, asymptomatic, self-limited condition with excellent prognosis and typically resolves within two weeks.

3. Acne Neonatorum: Small papules, pustules or comedones (blocked hair follicles), 1-3 mm white or skin-colored lesions with symmetrical distribution usually on the face but also on the neck and chest. It is suggested that neonatal acne is actually a condition that is associated with *Malassezia sympodialis*.⁶ In one study, 61% of the patients with neonatal acne grew *Malassezia* and showed good response to ketoconazole cream. These patients are diagnosed by some as having cephalic pustulosis.⁷ Another possible etiology is stimulation of sebaceous glands by maternal androgenic hormones. The resolution of this condition occurs when maternal hormones wane after three months.⁸



Acne Neonatorum

Incidence: Incidence is between 5-20%.^{9,10}

Diagnosis: Resembles teenage acne. Wright stain and Tzanck preparation shows many neutrophils. Gram stain negative for bacteria.

Management and prognosis: The lesions appear mainly at 2-4 weeks of life, healing spontaneously without scarring after four weeks to 3-6 months. In more resistant cases, can use low pH acne soaps, or benzyl peroxide wash (5%) or gel (2.5%). For comedones, use retinoid preparations such as tretinoin cream (0.025-0.05%), or azelaic acid cream (20%) daily or in alternating days. For resistant inflammatory lesions, use topical antibiotics such as erythromycin 4% pads.⁸

4. Miliaria: In miliaria crystallina there are 1-2 mm fragile, clear vesicles which appear as crops, and are a result of an obstruction of the most superficial sweat ducts in the stratum corneum with subsequent leak of sweat into the upper epidermis. The mean age of eruption is one week. In miliaria rubra, there are 1-3 mm discrete, very pruritic erythematous papules or papulovesicular lesions as a result of a deeper obstruction of the sweat ducts of the epidermis. If pustules develop in these lesions, they are called miliaria pustulosa. The mean age of eruption is 11-14 days. In miliaria profunda, the ductal obstruction is even deeper at the dermis-epidermis

junction, causing sweat leak into the dermis and producing asymptomatic flesh-colored papules. Miliaria crystallina and miliaria rubra (prickly heat) are most common and miliaria profunda is rare. Although the distribution of miliaria lesions is mainly on the face, neck and trunk, it also can be generalized. The lesions favor skin covered by clothing and intertriginous areas. The primary stimuli for developing of this condition are high heat and humidity which lead to excessive sweating. The incidence of miliaria is greatest in the first few weeks of life because of the relative immaturity of the eccrine (sweat) ducts which tend to become obstructed.

Normal skin flora such as *Staphylococcus epidermidis* and *aureus* are thought to play a role in the pathogenesis of miliaria. Patients with miliaria have 3 times more bacteria per skin area in comparison to controls. Also, intraductal plugs in patients with miliaria showed similarity to the extracellular polysaccharide substance of staphylococci.

Incidence: Between 7-15%.^{11,12} In humid countries the incidence can be as high as 30%. Miliaria is most common in tropical environments.

Diagnosis: History of high environmental temperature and humidity. Improved with cooling. In miliaria crystallina, cytological examination of vesicular contents does not reveal inflammatory cells. In miliaria pustulosa, cytological examination reveals neutrophils and Gram stain may reveal gram positive cocci (*Staphylococci*). Histological examination of miliaria crystallina lesions may reveal obstruction of eccrine sweat ducts in the stratum corneum without surrounding inflammatory cells. In miliaria rubra the vesicles are observed in the stratum Malpighian and there is a periductal inflammatory process.

Management and prognosis: Prevention of heat and humidity and frequent showering is the best management. Topical application of calamine, boric acid, menthol, and cool wet-to-dry compresses may also be helpful. Anhydrous lanolin can prevent ductal blockage, allowing sweat to flow. Occasionally, topical steroids and antibiotics are necessary. Miliaria crystallina is an asymptomatic and self limited condition that resolves without complications over a period of days. If hot and humid conditions persist, it may recur. Miliaria rubra is symptomatic and can cause itching. In affected sites extensive anhidrosis may develop, which may lead to hyperpyrexia and heat exhaustion. Secondary infection can occur as either impetigo or multiple discrete abscesses.



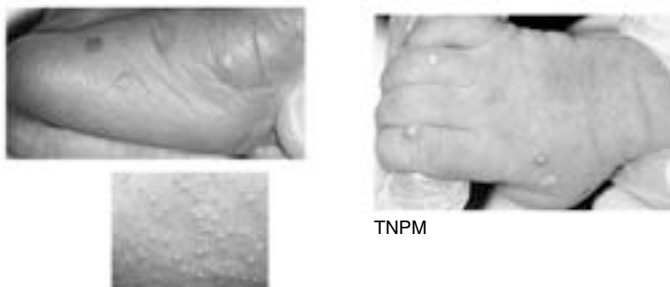
Miliaria Crystallina



Miliaria Rubra

5. Transient Neonatal Pustular Melanosis (TNPM): Well demarcated 2-3 mm pustular lesions and hyperpigmented macules. This benign skin condition is twice as common in black infants as in white infants. Lesions are present at birth as vesicles, macules or both. The eruptions consist of non-erythematous vesicles filled with a milk-like fluid. These vesicles rupture and leave a central pigmented macule. These pigmented spots may persist for a few months. Near-term infants may have only vesicles and term infants may have only pigmented macules. Males and females are equally affected. The lesions can be profuse or sparse, and are found under the chin, neck, back and buttocks. Occasionally the lesions occur on the palms and soles. The cause of this condition is unknown.

Incidence: Varies between 0.16-15%.^{13,14} In term African American newborns the incidence is 2-5%, and in Caucasian term infants incidence is approximately 1%.¹⁵



Diagnosis: Tzanck stain shows predominantly neutrophils. Gram stain does not show bacteria. Both pustules and pigmented macules present at birth.

Management and prognosis: This is a benign condition, no management needed. The hyperpigmented spots may clear after a few months.

6. Acropustulosis of Infancy (AI): Red papules of 1-3 mm that change within 24 hours to pruritic papulovesicular and/or vesiculopustular lesions. Lesions are predominantly on the hands (palms, or dorsal hands) and feet (soles, or dorsal feet), but can be found in other parts of the body. The lesions begin after birth through the first year of life, occur in crops lasting 1-2 weeks and recur every 2-4 weeks. The infants are very irritable due to the pruritus, and eosinophilia in the blood is common. This condition is more common in African American males. A prior history of scabies is common in patients with AI.¹⁶

Incidence: Approximately 1% of the population.¹⁵



Diagnosis: Tzanck smear and Gram stain of pustular content reveals neutrophils, occasionally eosinophils, but no bacteria. Histology shows intra-epidermal or subcorneal neutrophilic pustules.

Management and prognosis: Antihistamines and topical steroids

are helpful. This is a self-limited condition. The number of lesions is greatest in the early phase episodes and decline in number during subsequent episodes until permanent resolution occurs at 6-48 months.

7. Neonatal Candida Infection: Congenital candida infection (in utero acquired infection) is manifested at birth by pustular or vesicupustular lesions. The lesions can occur everywhere including palms and soles. Neonatal candidiasis is an acquired infection, usually acquired through an infected birth canal, and less commonly from handling or care givers. The disease can present as diaper rash that looks like red, glazed dermatitis in the genital area. The lesions have clear borders, and in the periphery, there may be a papules or vesicupustular satellite lesions, or as an oral thrush. Infants infected at birth harbor candida for several days before developing cutaneous or oral candidiasis.

Incidence: Is 0.6% for cutaneous candidiasis.¹⁷ The incidence of oral thrush is between 0.14-19%.¹⁸

Diagnosis: KOH preparation shows budding yeasts and pseudohyphae, and cultures identify *Candida albicans*.



Management and prognosis: Topical skin treatment with nystatin, or other anticandidal creams, for oral thrush, nystatin liquid preparation. Often congenital infection clears spontaneously within a few weeks, however, the severity can vary from mild to widespread severe disease.

8. Neonatal Scabies: The lesions are papulovesicular and nodular with secondary infection and eczema. Incubation period is 3-6 weeks, and therefore there is no congenital scabies. A history of itchy rash in hospital personnel or family members is common. The lesions are spread in the scalp, neck, palms and soles. There may be signs of excoriation, and the newborn can be irritable and a poor feeder. Scabies is caused by the mite *Sarcoptes scabiei*, whose size is 0.3-0.5 mm, at the limit of visibility. The disease is associated with poverty and overcrowding, and all family members and close contacts need to be assessed and treated. Scabies can also infect domestic animals. The mites burrow in the epidermis and are resistant to soap and water. Fertilized female mites penetrate the epidermis and burrow parallel to the corneal layers at a rate of 0.5-5 mm per day which creates a tunnel seen as a wavy line as a result of host reaction around the tunnel. Papules that change to vesicles and even bullae occur. Fertilized female produce 2-4 eggs per day in the tunnel, larvae hatch in 2-4 days and adult mite develop in 10-14 days. Female mites live for 4-6 weeks.^{19,20}

Incidence: In industrial countries varies from 0.05-0.2%²¹ during non-epidemic periods to 2.6%²² in epidemic periods. In poor countries the incidence is much higher, and in certain parts of the world scabies is endemic. For example, in Bangladesh

overwhelming majority of the population is infected.²³



Diagnosis: Mineral oil preparation that detects the mite, ova or fecal pellets in microscope. This skin scraping test has a low sensitivity and diagnostic usefulness. Therefore, even with a negative scabies scraping test, but with suggestive clinical picture, therapy should start.

Management and prognosis: Permethrin cream (5%) is the standard treatment. It is highly effective after a single application and has low toxicity. Lindane (1%) was the first-line medication for scabies, however, due to neurotoxic effects this medication is considered now as second line drug only. Scratching can lead to denudation of the lesion and secondary infection. In conditions where there is a use of topical steroids or in immunosuppressed individuals, a crusted scabies may occur. Clinically, scabies is a parasitic disease that causes major public health problems in many resource-poor regions. Secondary infection with group A streptococci in older children can cause post-streptococcal glomerulonephritis.

9. Neonatal Herpes Simplex Virus Disease (HSV): Vesicles and vesicubolous lesions spread over the skin. The clusters of lesions can occur anytime between birth to approximately 4 weeks of age. Usually, the virus is transmitted during birth from infected vaginal canal. Infection from vaginal canal of mothers with primary herpes is 33-50%, and of mothers with recurrent herpes is less than 5%.²⁴ Intrauterine infection causing congenital herpes is rare. Postnatal infection by caregivers is also possible. Localized disease to the skin, eye and mouth is in 30% of the cases, in 30% of the cases the disease is localized to the central nervous system, and in 30% it is a disseminated disease involving multiple organs, especially, liver and lungs. There may be an overlap between the clinical presentations.

Incidence: Between 0.005-0.03%.²⁴

Diagnosis: Tzanck preparation reveals multinucleated giant cells. Swabs from the mouth, nasopharynx, conjunctiva and rectum are positive for herpes if taken 48 hours after birth, to differentiate between colonization and active infection. Direct fluorescent antibody staining of vesicle scrapings are diagnostic, as well as PCR assays to detect HSV DNA.



Management and prognosis: Intravenous acyclovir is the treatment of choice for neonatal HSV. The best outcome is of newborns that have HSV limited to the skin, eyes and mouth. Infants with ocular involvement should receive topical ophthalmic medication. Most neonates treated for HSV encephalitis survive, but most of them have significant

neurological sequelae. Approximately 25% of the newborns with disseminated disease die.²⁴ If Cesarean section is done, less than 4 hours prior to rupture of membranes, the incidence of neonatal infection is diminished significantly.

10. Neonatal Impetigo: Discrete fragile vesicles with an erythematous border that become pustular and rupture to discharge a yellow seropurulent fluid that form a crust similar in color of honey. The lesions are usually seen on the face, near the nose and mouth, perineum, peri-umbilical and extremities. This infection is caused by direct invasion of *Staphylococcus aureus*, and to a lesser extent by group A *Streptococci*, into



superficial cutaneous abrasions or compromised skin. At birth the skin is sterile, and organisms are acquired from the birth canal, secretions and personnel. Up to 40% of newborns are colonized with *Staphylococcus aureus* in the anterior nares and genitalia. This condition may occur in the second or third day of life, and is very contagious. The spectrum of disease in the presence of exfoliative exotoxins includes more severe forms such as bullous impetigo and scalded skin syndrome (SSS=Ritter Disease).²⁵

Incidence: This is the most common bacterial skin infection in newborns. However, there are no available statistics of this condition. In a 12 years study of neonatal infections (1987-1998), it was found that impetigo neonatorum comprise only 1.4% of all bacterial neonatal infections.²⁶

Diagnosis: Gram stain of the lesions shows Gram positive cocci in clusters and a predominance of neutrophils. In systemic disease, peripheral white blood cell count shows a shift to the left and in SSS there is a positive Nikolsky sign (skin sloughing when rubbed).

Management and prognosis: In localized disease, antibiotic ointment can be used. Since newborns are susceptible to widespread disease, systemic therapy with the appropriate antibiotics is indicated. Scalded skin syndrome in the newborn lacks long term sequelae such as scarring, and the prognosis with appropriate therapy is excellent, however, mortality may occur, and may reach 3% in children.²⁵ Strict isolation is mandated to prevent outbreaks in the nurseries.

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⁽¹⁾ A new device for administration of nasal continuous positive airway pressure in the newborn: An experimental study. Authors: Gunnar Moa, MD; Kjell Nilsson, MD; Henrik Setterstrom, MD, PhD; Lars O. Jonsson MD, PhD. Critical Care Medicine Vol. 16, No. 12 1988

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