Vol. 23 No. 4
July/August 2010

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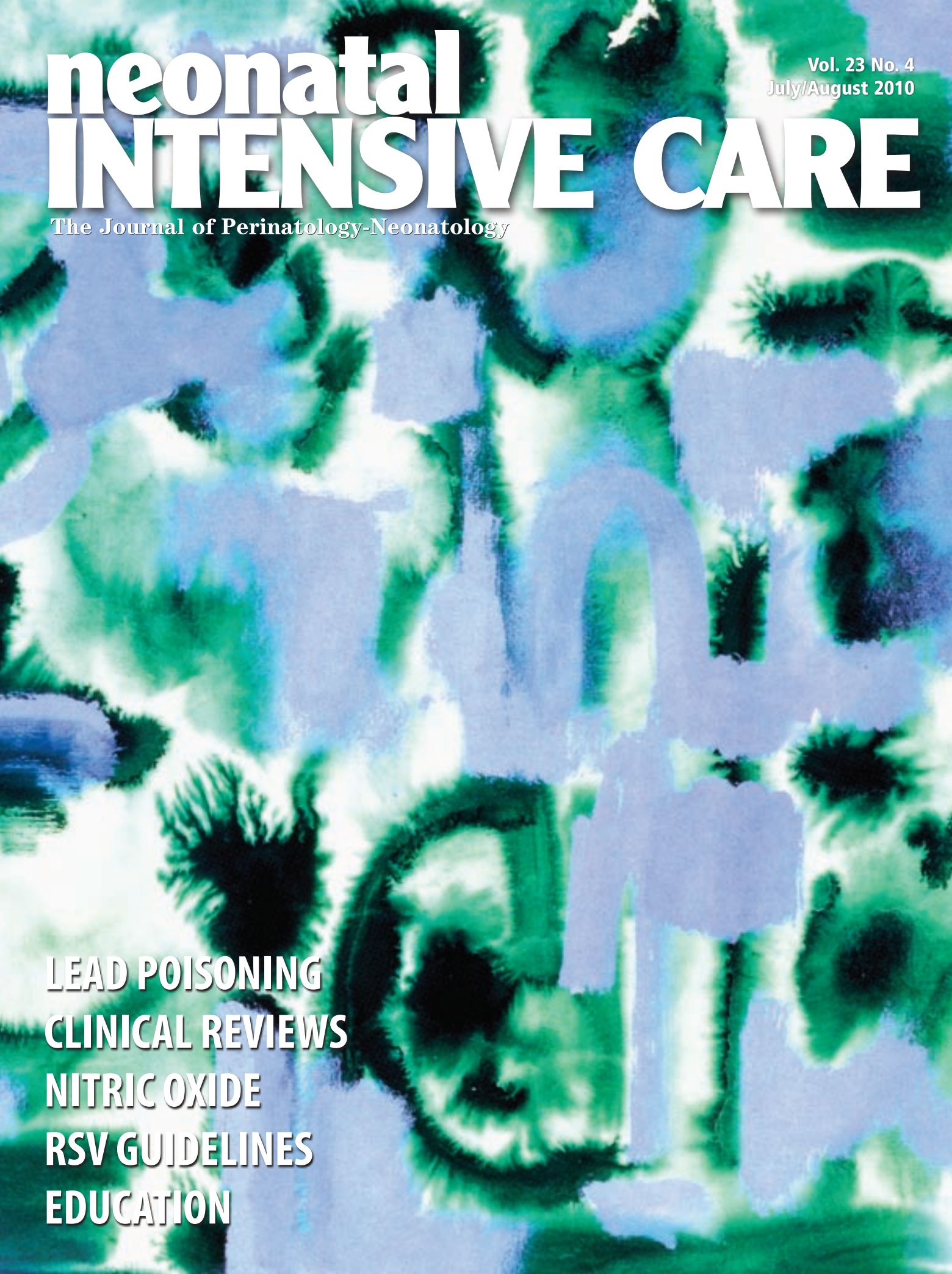
The Journal of Perinatology-Neonatology



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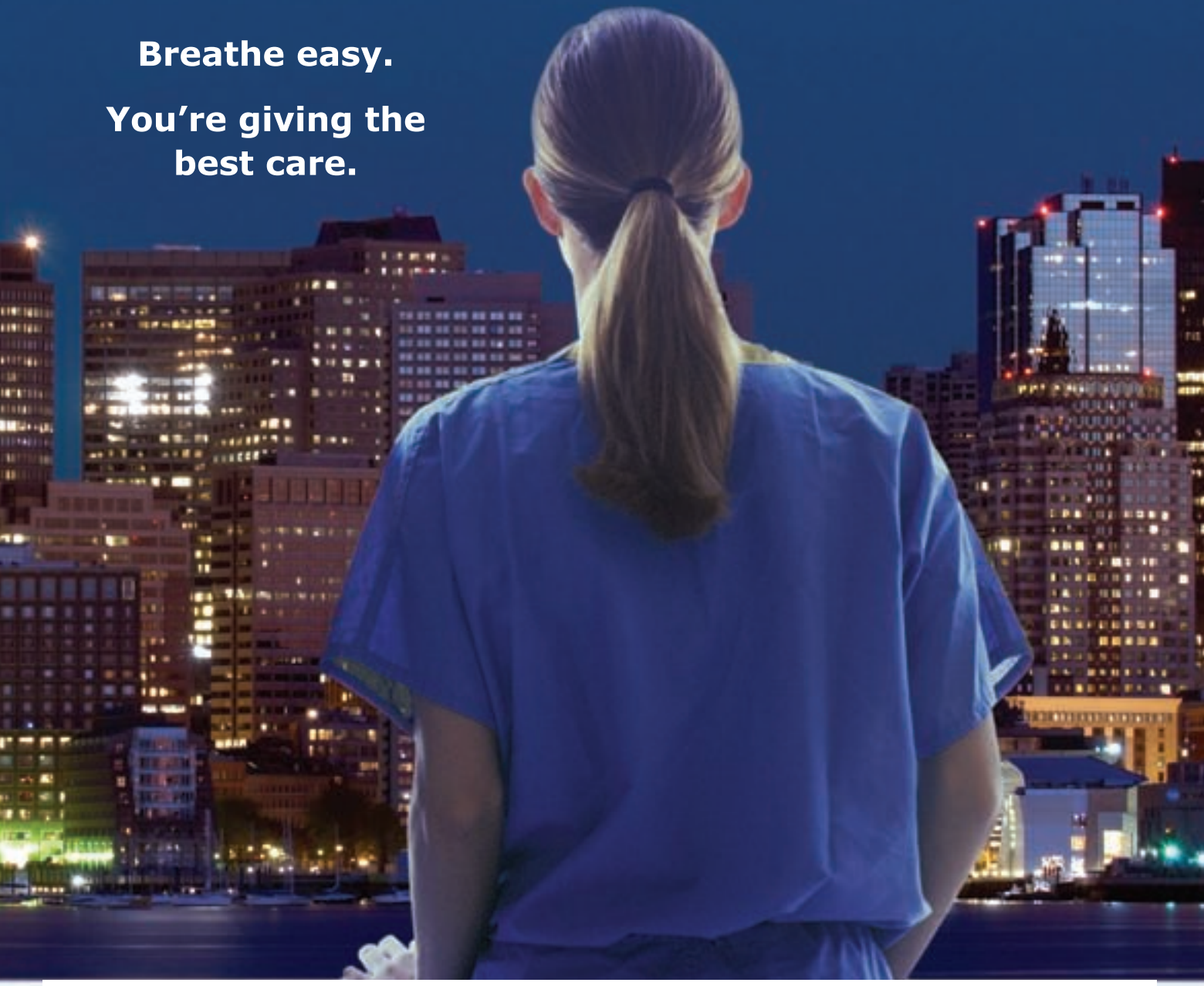

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Vol. 23 No. 4
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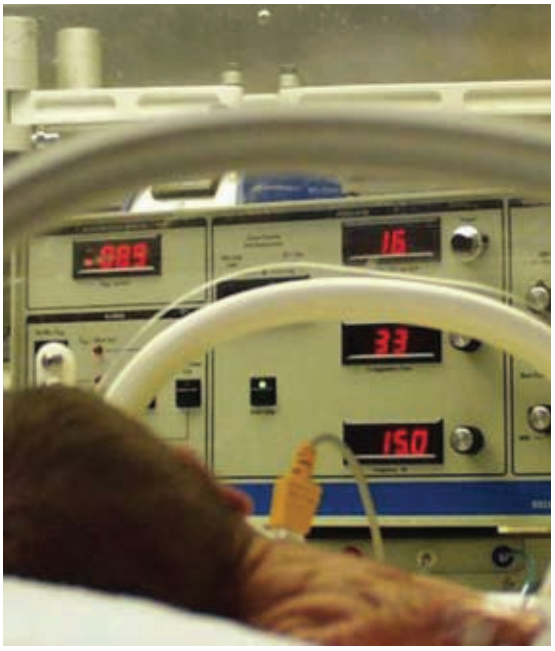
Editorial

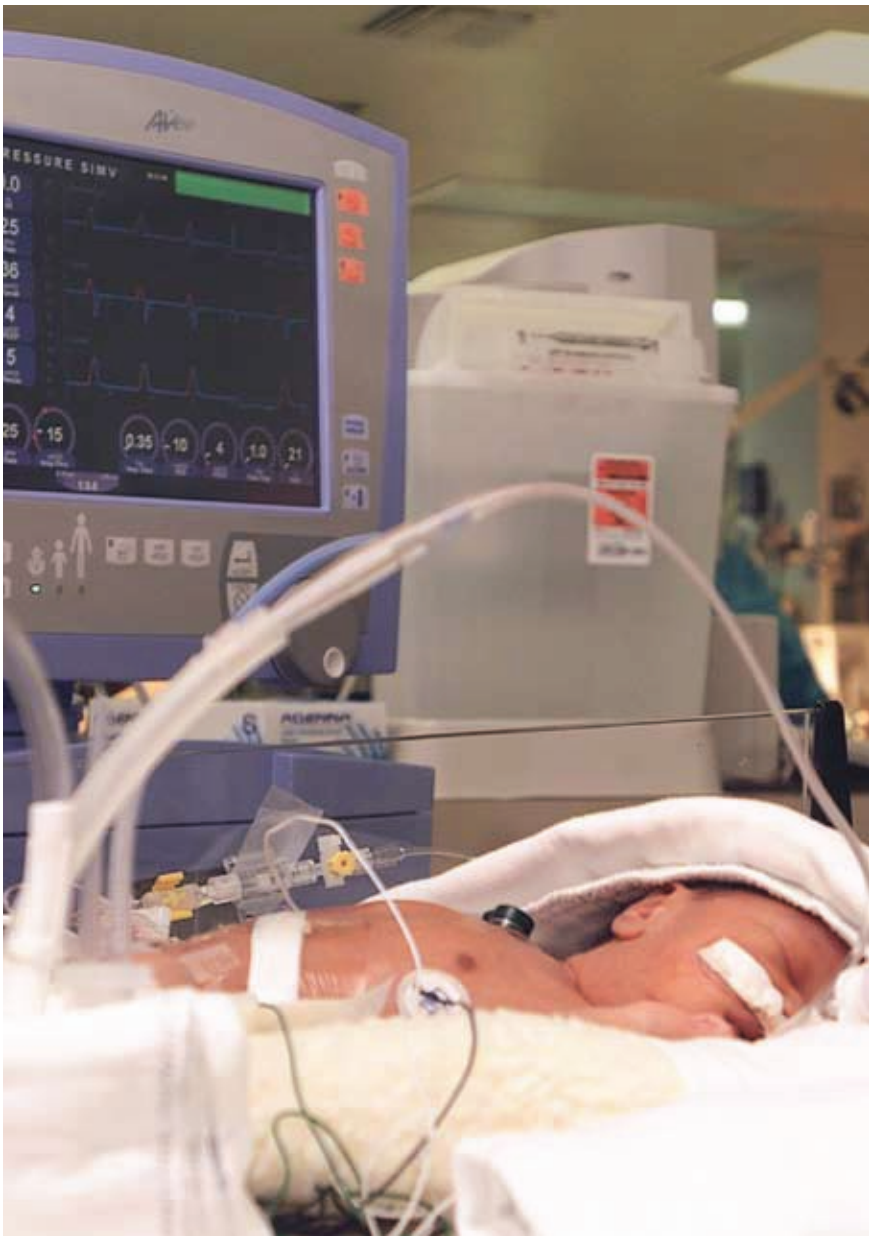
Think About It

The New York Times reported recently that an Indian tribe collected damages from Arizona State University, which had allowed its researchers to use DNA for multipurpose research. The Indians claimed the university had not received informed consent for more than one test. What's this got to do with you, you may ask? Are any of your NICU patients enrolled in clinical trials? A recent paper on BioMed Central addressed some of the latent concerns with the extent of permissible research and consent. [See: Handling ethical, legal and social issues in birth cohort studies involving genetic research: responses from studies in six countries, by Riesl, et al.] According to the paper, "The growing number of longitudinal, pediatric studies that involve genetic research present even more complex challenges to ensure appropriate protection of children and families as research participants. Long-term studies with a genetic component involve collection, retention and use of biological samples and personal information over many years. Cohort studies may be established to study specific conditions (eg autism, asthma) or may have a broad aim to research a range of factors that influence the health and development of children. Studies are increasingly intended to serve as research platforms by providing access to data and biological samples to researchers over many years."

The study examined how six birth cohort studies in North America and Europe that involve genetic research handled key ethical, legal and social issues, including recruitment, parental authority to include a child in research, initial parental consent and subsequent assent and/or consent from the maturing child, and withdrawal, confidentiality and sample/data protection, as well as handling sensitive information and disclosure of results. The studies varied in breadth of initial consent, but none adopted a blanket consent for future use of samples/data. The researchers found that the clearest differences among studies emerged in handling of sensitive information and return of results. Not all the studies informed potential participants of disclosure duties in consent materials. Likewise, not all cohort studies advised participants of procedures for handling serious risks. The paper noted that such aspects should be explained to ensure that potential participants are aware of how sensitive issues concerning the health and welfare of their families will be handled. In regard to reporting of results, none of the studies intended to report findings of unknown clinical significance but varied in whether results of more routine tests and measures would be returned. The authors noted, "Having regard to participants' informational autonomy, it is useful to offer choices about return of clinically meaningful results and to explain at the study outset how other types of results, such as incidental findings, will be handled… Some studies had established ethical and other advisory committees to provide expert guidance throughout the duration of the cohort… Such committees will help ensure impartial and specialized advice, particularly in areas where studies do not yet have policies or where existing policies require amendment to reflect new circumstances. For instance, policies on return of results may need to be changed as clinical significance becomes apparent." The authors concluded, "Birth cohort studies are complex undertakings, especially if they involve collection and storage of biological samples for genetic analyses… Profound ethical, legal and social issue exist… Consideration of [the foregoing] and further scholarly exploration of [such] issues provides insight on how best to address these aspects in ways that respect the well-being of participants, especially children who become research subjects at the start of their lives."

Les Plesko





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

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http://accugraphics.net

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Responsible for up to 125,000 infant hospitalizations in the US annually[3]

- From 1997 to 2000, RSV bronchiolitis was the leading cause of hospitalizations for infants <12 months of age[1]

A threat in all outpatient settings

- 22% of infants <1 year of age infected with RSV will develop bronchiolitis[4]
- 28% of children <2 years of age infected with RSV will develop bronchiolitis[4]

Adapted from Paramore LC et al. *Pharmacoeconomics*. 2004;22:275-284.[2]

Potentially serious long-term consequences

- RSV-related lower respiratory tract illnesses (LRTIs) in infancy may be associated with an increased risk of asthma in the first decade of life[5-7]

Age	Asthma RR† (95% CI‡)
3 years	**21.8** (2.90–163.57)[5]
7 years	**9.23** (2.79–30.55)[6]
13 years	**6.8** (2.7–17.3)[7]

Based on a prospective cohort of 47 (93 control) Scandinavian children <1 year of age in 1989 hospitalized with RSV and followed for 13 years.

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*RSV = respiratory syncytial virus.
†RR = relative risk.
‡CI = confidence interval.

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News

☐ July-August 2010

PHOTOTHERAPY UPDATE

With the advent of the internet, there are many informative sources of information available for neonatal caregivers to stay abreast of developments in phototherapy. Simply googling "phototherapy for infants" brings up about a dozen fairly informative articles, though because of the way the Google search engine works, the latest materials may not pop up first. Another excellent source to stay updated is BioMed Central. Interestingly, a solid source of information is Wikipedia, at least in terms of cross-referenced sources. Some of the material is scattershot, however. The article appearing most frequently on Google is Aggressive vs Conservative Phototherapy for Infants with Extremely Low Birth Weight, by Brenda H. Morris, MD, et al, from the October 2008 issue of the New England Journal of Medicine. The authors posit: it is unclear whether aggressive phototherapy to prevent neurotoxic effects of bilirubin benefits or harms infants with extremely low birth weight. They assigned 1,974 infants with ELBW to aggressive or conservative phototherapy. Aggressive phototherapy, as compared with conservative phototherapy, was found to significantly reduce the mean peak serum bilirubin level (7.0 vs 9.8 mg per deciliter) but not the rate of the primary outcome (52% vs 55%). The rate of neurodevelopmental impairment alone (but not death) was significantly reduced with aggressive phototherapy. Another useful article that turned up in our search was in Arch Dis Child's Fetal Neonatal Edition 94: F314-F316, published last year. Also worth noting are the articles Unbound (Free) Bilirubin: Improving the Paradigm for Evaluating Neonatal Jaundice, Clin Chem 55: 1288-1299, and Phototherapy for Infants: Not All Sweetness and Light, JWatch Pediatrics 2008, 4-4. Neonatologists and nurses counseling parents on phototherapy might want to check out Home Phototherapy for Infants on Google Video. This brief module takes parents through the most effective way of providing home phototherapy. For a collection of home videos on phototherapy in action, as it were, go to YouTube, type "phototherapy," then open up the first picture with an infant on it. This will allow access in the right-hand column of your screen to about nine additional home movies of babies receiving phototherapy.

ROP PIONEER DIES

The Wall Street Journal reported on the death of Dr Arnall Patz, who helped solve the riddle of how 10,000 babies went blind. Patz was the Johns Hopkins ophthalmologist who in 1954 showed that treating premature babies with pure oxygen had the unexpected result of destroying eyesight in some. By the simple expedient of regulating oxygen levels inside incubators, the epidemic was quelled. According to the Wall Street Journal, "An epidemic of retrolental fibroplasia (RLF) seemed to have grown up just as treatments for preemies had improved. By the time of Dr Patz's investigations in the early 1950s, an estimated 10,000 children had been blinded in the US and abroad. Patz nearly didn't manage to bring his study off, because it involved experimenting on babies, and because the idea that oxygen could cause harm was so counterintuitive. The gas provided obvious benefits for preemies, often turning them to a healthy pink from blue in the incubator. Patz borrowed funds from his family and demonstrated that oxygen could cause blindness in opossums, rats and kittens, by causing blood vessels in the eye to became overdeveloped, damaging the retina. By turning down the oxygen on half the infants in his study, Dr Patz was able to demonstrate that oxygen therapy had caused the epidemic [of ROP]." Reported in the Wall Street Journal.

EYE TEST

Researchers at various New York hospitals showed that early treatment for high-risk premature babies can improve their vision. This research promises to transform the way babies with ROP are treated, according to the researchers, who noted that there wasn't a single treatment strategy that worked for all infants with ROP, but rather, doctors need to determine whether the baby has a mild or severe form of the disease before proceeding with retinal surgery. Previously, doctors treated infants with ROP when they estimated their risk for retinal detachment to be 50%, but many infants went on to develop severe eye disease. Therefore, the first phase of the ETROP study aimed to discover if doctors could identify infants at a higher risk for progression of the disease and intervene early to improve their vision. In 2003, the ETROP study found that early treatment improved the vision and retinal health of certain infants after nine months for infants with Type 1 ROP. Eyes with Type 2 ROP, or a more moderate amount of new blood vessel growth, did not benefit from early treatment. The current study followed the same 370 children through six years of age, when researchers checked their vision and examined the development of their eyes. The nine-month study recommendations were confirmed through six years. Type 1 eyes benefited from early treatment, and Type 2 eyes had similar results with either early treatment or treatment at the standard time. Seventy-five percent of the early-treated Type 1 eyes were spared legal blindness, compared with 67% of Type 1 eyes that received treatment at the standard time. Of the Type 2 eyes that were monitored for disease progression through the standard protocol, more than half improved without treatment.

SCREENING SURPRISE

A recent study suggested that heel-stick tests routinely performed on newborns are not very good at identifying cytomegalovirus infection. Researchers at UT Southwestern said that if neonatologists rely exclusively on the standard heel-stick test to detect CMV, more than half of the babies who are infected will be missed. The research is part of a multicenter investigation seeking to find the most effective screening test for CMV infections in newborns and study the natural history of hearing loss among these babies. Currently, the only way to identify accurately a CMV infection is to culture a urine or saliva sample collected from the patient, a process unlikely to be widely adopted because it is labor-intensive and requires a tissue culture facility. The researchers used polymerase chain reaction (PCR) testing to analyze dried blood samples obtained using the heel-stick procedure from more than 20,000 infants. Of

the babies screened, 92 were confirmed to have congenital CMV infection. The CMV rapid culture method identified all but one of those children. In contrast, of the 11,422 children screened with a basic version of the diagnostic test of dried blood spots, only 17 out of 60 infected children were identified. Eleven out of 32 infected babies were identified in a group screened with a slightly more sensitive test.

PRO-BING

ELBW infants who received feedings supplemented with probiotics had better weight gain than infants who were not given the supplements, according to a study presented at the recent PAS conference. Probiotics are healthy, live organism supplements that provide benefit to the host. In the study, researchers from three medical centers and the Vermont Oxford Network evaluated the effect of supplementing enteral feedings with probiotics in extremely premature infants who weighed 2 pounds, 2 ounces or less. Fifty infants received 500 million colony-forming units (CFU) of Lactobacillus rhamnosus GG and 500 million CFU of Bifidobacterium infantis in enteral feedings once a day until discharge or 34 weeks postmenstrual age. Fifty-one infants received feedings with no probiotics. Results showed superior weight gain in infants who received the probiotics even though the average daily volume of their feedings was less than infants in the control group. There were no statistically significant differences in other complications of prematurity such as sepsis or necrotizing enterocolitis. In addition, no side effects were seen as a result of probiotic supplementation. According to the researchers, the findings strongly suggested that probiotic supplementation to enteral feedings plays a major role in feeding tolerance and nutrient absorption, which leads to better weight gain in ELBW infants.

BMC NEWS

The CONSORT 2010 statement has been co-published by eight journals, including Trials and BMC Medicine. Building on new evidence and experience, the revised guidelines are intended to improve the reporting of randomized controlled trials by providing a checklist of essential items for use by authors, reviewers and editors… A new thematic series in Biology Direct brings together cancer researchers and mathematicians to provide insight into the various roles of evolution in cancer… Research by Valerie Hu and colleagues, recently published in Genome Medicine, suggests that microRNAs have a role in the gene expression changes which can underlie autistic spectrum disorders… The journal Herpesviridae is now accepting submissions. It's a new open access journal dedicated to distributing knowledge of the role of herpes viruses in health and disease… Critical Care has co-published 10 free review articles as part of a joint effort with the Springer Yearbook of Intensive Care and Emergency Medicine, with each article selected for relevance to healthcare professionals working in intensive care medicine… The Journal of Biomedical Semantics has now launched and publishes articles on all aspects of semantic resources used for data integration, modeling, interpretation and exploitation in biomedical research. BMC Biology and Journal of Biology are joining forces as a single journal committed to the publication of high-quality commissioned content and research articles of exceptional importance. The combined journal will operate

under the name BMC Biology, reflecting the strong relationship with the subject-specific BMC-series journals, and will be edited by Miranda Robertson, who explains in an inaugural editorial how she sees the fusion combining the strengths of both journals, with continuation of the re-review opt-out experiment initiated by Journal of Biology.

DON'T DRINK UP

Researchers from France and the UK found that drinking alcohol during pregnancy was linked to a significantly higher risk of children developing acute myeloid leukemia. The researchers conducted a systematic review and meta-analysis of published studies to find all the already established links between maternal alcohol consumption during pregnancy and childhood leukemia. They found 21 case-control studies where they could analyze links between diagnosis of leukemia in children born to mothers who answered yes or no to a question about alcohol consumption during pregnancy. The results showed a statistically significant link between maternal alcohol drinking during pregnancy and diagnosis of AML in the children and no statistically significant link with acute lymphoblastic leukemia. For AML, drinking an extra drink a week was linked to a 24% per cent increase in risk. The researchers concluded that maternal alcohol consumption during pregnancy is associated with a significantly increased risk of AML in young children. Alcohol consumption during pregnancy is 12% in the US, 30% in Sweden, 52% in France, 59% in Australia and 60% in Russia.

BIG BAD TWIN

Among twin pairs in which there is a 20% or greater difference in birth weight, the twin who weighs more appears more likely to have conduct problems at age 3 to 4 years. Researchers at Hadassah Hebrew University Hospital identified 112 Israeli families with twins born at unequal weights in 2004 and 2005. According to mothers' reports, the twin with the higher birth weight had more conduct problems in 41% of twin pairs, whereas the twin with lower birth weight had more conduct problems in 21% of twin pairs. This association tended to be stronger in dizygotic vs monozygotic twins.

FAT AS MOM AND DAD

A new study has found that as Americans are gaining more body fat, so are their babies. The research, by Children's Mercy Hospitals and Clinics, reviewed data from more than 74,000 births and found that a key measure of body fat composition in newborns increased significantly over a 15-year period, mirroring similar increases among pregnant mothers. As the body mass index of pregnant mothers increased from the years 1990 to 2005, so did the ponderol index measure of body fat composition in newborns. Researchers noted that adult diseases like obesity may have their foundation during the fetal period, so efforts to safeguard the health of the fetus could translate to future adult health for newborns.

GASP!

Long-term lung function needs to be monitored for all preemies, not just those born severely early or underweight, as was previously thought. According to the research by Children's Mercy Hospitals and Clinics, older children born only mildly preterm and not severely underweight had lung function measures comparable to their peers born extremely preterm and with severely low birth weight. Previous studies have demonstrated that extremely preterm and low birth weight babies grow into children and adults with decreased lung function and oxygen consumption measurements, suggesting a poor level of fitness compared to full-term babies. Researchers noted that they expected there would be more lung function abnormalities in the most extreme preterm infants, since they had more opportunity for lung injury immediately after birth, but their findings indicate that long-term lung function outcomes needed to be assessed for all preterm infants, not just those with extreme low birth weight or severe neonatal lung disease.

TAKE YOUR VITAMINS

Taking vitamin D supplements during pregnancy is safe and can prevent preterm labor and infections, according to results of a randomized controlled study at Medical University of South Carolina. Recent studies have shown that vitamin D deficiency during pregnancy is a serious public health issue. Researchers randomized 494 pregnant women at 12-16 weeks' gestation into three treatment groups. Group one received 400 IU of vitamin D a day until delivery; group two received 2,000 IU and group three received 4,000 IU. The women were evaluated monthly to ensure safety. Investigators also looked at the effects of vitamin D supplementation on complications during pregnancy, including preeclampsia, gestational diabetes, infections, and preterm labor and birth. The studies showed that women replete in vitamin D had lower rates of preterm labor and preterm birth, and lower rates of infection. The greatest effects were seen among women taking 4,000 IU per day.

JUST ONE NANOSECOND

Researchers exploring the medical uses of nanotechnology believe that the use of molecular-level nanomedicine techniques in children (and by implication, babies), will require its own specialty. The editors of Pediatric Research recently presented some of the research that will form the basis of the emerging field of nanopediatrics. It was noted that nanotechnology and nanomedicine were anticipated to be major drivers of personalized medicine. The papers in Pediatric Research highlighted the potential uses of molecular-level nanotechnology to promote children's health in a variety of areas, including disease diagnosis. Nanotechnology could detect subtle DNA abnormalities for rapid, point-of-care diagnosis of genetic-related conditions. Molecular thermometry techniques could detect very small changes in temperature down to the subcellular level, aiding in early detection of tumors or infections. The development of combined diagnostic and treatment techniques, called "theranostics," it was noted, may one day enable diagnosis and treatment of cancers in a single procedure. Nanoinformatics and DNA-based computing could revolutionize processing of medical information, promoting the clinical uses of nanomedicine. Papers in the journal describe possible uses of nanomedicine techniques for the treatment of diseases in children: Nano-modified coatings could help to prevent infection of ventilator tubes; designer molecules called "protacs" could be used to disrupt the growth of cancer cells, providing new approaches to cancer treatment. Tissue engineering techniques could be used to grow new organs, including bladders for children with congenital bladder dysfunction; and anticancer drugs encapsulated in liposomes could provide highly targeted new approaches to cancer treatment.

GUMMED UP

Successful treatment for gum disease cuts the risk of pregnant women giving birth early, US research suggests. Moms whose gum disease wasn't treated were three times as likely to give birth before 35 weeks. Doctors have established that severe gum

infections cause an increase in the production of prostaglandin and tumor necrosis factor. Researchers at the University of Pennsylvania studied 160 women with gum disease, who were given treatment, which was successful in one third of the cases. The researchers found a strong and significant association between successful treatment and full-term births. Those whose treatment did not work were "significantly more likely" to give birth before 35 weeks. The researchers noted, however, that previous studies hadn't established such a link, and that other general lifestyle factors may play a part. Nonetheless, it was noted that this was another piece of evidence that pregnant women should take care of their periodontal health and receive appropriate treatment during their pregnancy to reduce as far as possible their chance of a pre-term birth.

HELPING

International Medical Corps and partners announced the launch of a new medical facility in Kalonge, Democratic Republic of the Congo, the first remote rural reproductive health center in eastern Congo devoted to serving women and survivors of gender-based violence. The facility, the Kalonge Reproductive Health Complex, has completed its 18th operation on local women to repair fistula. This debilitating and painful condition, often caused by obstetric emergencies, as well as sexual violence, leaves a woman incontinent and causes severe reproductive damage. Previously, women seeking medical care for fistula had to make an arduous trip, mostly on foot and through rebel-held territory to receive care. The Kalonge Reproductive Health Complex also provides reproductive and maternal health care for 20,000 women of child-bearing age. International Medical Corps has worked in the DRC since 1999 to provide healthcare, nutrition, food, security, sexual and gender-based violence prevention and treatment, and water and sanitation services. In many areas, International Medical Corps is the only international NGO that has maintained a permanent presence. Today, International Medical Corps supports 85 health facilities in DRC, and has served more than a million people in the Congo, 80% of them displaced by war.

CASH FOR KIDS

The city government of Taipei, Taiwan said it would give 20,000 Taiwan dollars ($429) for every newborn born in 2011, plus monthly subsidies to lower-income families with children under five. Birth rates in Taipei were at an all-time low in 2009 with fewer than 20,000 babies. The drop of 40% from a decade ago is attributed to financial concerns, especially the rising cost of childcare. This incentive is the latest in a series of proposals to encourage births and the program is expected to cost three billion Taiwan dollars annually. The city government is concerned that a decrease in population will lead to serious social and economic problems in the future. The island's birth rate stood at 8.29 per 1,000 people last year, compared to a global average of more than 20 births per 1,000 people. Reported by Sky News, via The Huffington Post.

DEATH BY INSURANCE CO?

The following was reported in the Star-Telegram, by Jan Jarvis, via The Huffington Post: "At birth, Houston Tracy let out a single loud cry before his father cut the cord and handed him to a nurse. But the baby wasn't turning pink fast enough." The problem was a d-transposition of the great arteries, which surgery could correct, but the father learned that his application for health insurance for his son had been denied, due to a pre-existing condition. Of course, as the father noted, "How [could] he have a pre-existing condition if the baby didn't exist until now?" New federal legislation that will prevent insurance companies from denying children coverage based on a pre-existing condition came too late for the Tracys. The legislation, passed by Congress and signed by President Barack Obama, won't go into effect until September. The couple carry health insurance for their other two children, but as a result can't afford any for themselves, and they paid out of pocket for the mom's care and the baby's delivery. Their carrier, Blue Cross Blue Shield of Texas declined to comment, but noted that the kid would have no coverage if the parents didn't. While the insurance company's decision was being appealed, the baby received the surgery and was doing fine.

JOBS JOBS JOBS

AOL's website Daily Finance reports that healthcare is the fastest growing job market, especially with the passage of The Healthcare Reform Act. Seventeen of the next decade's 30 fastest-growing occupations are healthcare-related. During the recession, healthcare added 600,000 jobs. In March, for instance, healthcare accounted for 27,000 new jobs: 16,000 in ambulatory services and 9,000 in nursing and residential care facilities. Growth is happening at all levels, from physicians to home health aides. The Labor Department projects 22% growth in the number of physicians; however, nursing will create the largest number of new healthcare jobs. Already, RNs constitute the largest occupation in the health industry, at 2.6 million. Another 581,500 new nurses will be needed over the next 10 years. The next fastest-growing area in terms of the most number of new jobs, at 461,000, is home health aides, an area predicted to grow by 50%. Healthcare technology is another growth area, what with government-mandated electronic medical record-keeping and new medical coding standards.

APPROVED

Somanetics that it has received 510(k) clearance from the FDA to expand features on its Vital Sync bedside monitor and research data aggregation system. The clearance allows for interface with a broader range of bedside devices, display of derived parameters of calculated clinical indices, and an automated events trigger to alert clinicians when patient parameters fall outside desired thresholds. The Vital Sync system provides the clinician with a view of patient data at the point of care to help medical professionals detect deteriorating patient condition early. It allows the clinician to select specific patient data from an array of bedside devices and view the data on a single, time-synced display at the bedside. Contact somanetics.com.

NEWS FEATURE

ASV Mode Using the Hamilton G5 Ventilator in the NICU

Heloisa Georgiev, RRT-NPS

The author is Children's Education Coordinator, Disney Children's Hospital, Orlando, FL. This article was provided by Hamilton Medical and appears in the company's newsletter.

Our NICU, at Florida Hospital for Children in Orlando, trialed the Hamilton G5 ventilator in May 2009. Infants who weighed between 760 grams and 6.8 kg were placed on different modes such as APV/CMV, APV/SIMV and ASV. Out of all the patients who were placed on the G5, the one that definitely stood out the most was baby "A" who had been in our NICU for six months and weighed 6.8 kg.

At that time baby "A" was being ventilated on a Draeger Babylog 8,000+ infant ventilator in the Assist/Control mode with peak inspiratory pressures as high as 42 cmH_2O. Baby "A" was having multiple desaturation and bradycardia episodes and was asynchronous with the Babylog. This asynchrony was delaying the weaning process.

Taking into consideration that the patient weighed over 3 kg, and his increased work of breathing in the assist/control mode, the decision was made to place him on the ASV mode (Adaptive Support Ventilation) on the Hamilton G5. The staff had utilized this mode in the pediatric unit and felt very comfortable managing the patient.

"Adaptive Support Ventilation (ASV) is a construct of closed loop ventilation. ASV designates programmed ventilator setpoints based on assessments of patient lung mechanics and breathing effort. Adaptive Support Ventilation provides for an optimal adaptation of ventilator settings in concert with the patient's passive and active respiratory mechanics."[1]

Prior to making the switch, the patient's minute volume on the assist/control mode was carefully noted and recorded. The goal was to set a target minute volume that was similar to what the patient was requiring before. Initial settings were: 1.7 L target minute volume, 7cm PEEP and 21% O_2.

Due to an initial increase in respiratory rate and patient actual minute volume, the minute volume setting was increased from 100% to 130% in order to match his actual minute volume need and provide the support required.

His respiratory rate decreased rapidly after this change and he appeared to be a lot more comfortable. Peak inspiratory pressures continued to be in the high 30's cmH_2O range and tidal volume mid 30's to mid 40's mls.

A capillary blood gas was obtained an hour after placing him on the ASV mode. Results were: pH 7.56, PCO_2 35, PO_2 67, HCO_3 31 and base excess +8. At that point the percent VE was weaned back to 100%.

Baby "A" dictated how he wanted to be ventilated switching back and forth between breathing spontaneously with the aid of pressure support or receiving full controlled breaths from the ventilator. His respiratory rate remained stable in the mid 30's to 40's whenever breathing spontaneously. There was a remarkable decrease in his work of breathing due to improved patient synchrony in the ASV mode.

Another capillary blood gas was drawn 3 hours after being on the ASV mode at 100% VE setting which revealed pH 7.44, PCO_2 44, PO_2 48, HCO_3 30 and base excess +5, the best capillary blood gas result the patient had in days.

PIPs had decreased significantly to the mid 20's without compromising delivery of volumes.

Baby "A" continued on the ASV mode for over 36 hours. Every capillary blood gas obtained during that time was within normal limits. He appeared very comfortable on the ASV mode. No desaturation or bradycardic episodes were noted on ASV. When the trial time was over, it was a difficult task to take him off the ASV mode and place him back on his previous ventilator/ settings.

The NICU staff was very pleased with the result they witnessed. Ventilating large infants in our NICU can be challenging at times.

In utilizing the ASV mode, the infant was able to dictate how he wanted to be ventilated and it made weaning completely up to the patient. Pressure support was automatically adjusted as the patient's lung compliance and resistance improved. Synchrony is a big issue in the neonatal population. ASV improved baby "A's" clinical status by automatically tailoring settings to the needs of the patient.

ASV has several distinct advantages that aided in improving synchrony. The ability of the ventilator to adjust to the constantly changing status of our patients is critical. ASV has these desired effects:

The ability to automatically transition from full to partial to minimal support as the patient's lung mechanics and respiratory drive/strength recover. Passive breaths are time cycled, however active breaths are flow-cycled to promote synchrony.

ASV automatically sets the optimal tidal volume and rate targets based on the patients pulmonary mechanics to minimize work of breathing.

ASV additionally employs a set of protective rules to prevent volutrauma, hypoventilation and autopeep.

These benefits translate into decreased ventilator days, decreased sedation, and decreased total hospital stay. [Reference: 1. David Wheeler RRT, NPS. Ratiocinative Ventilator Control Algorithms. Focus Journal May/June 07 Page 24, 27.]

CLINICAL REVIEWS

NONINVASIVE ACCURACY

Masimo, the inventor of Pulse CO-Oximetry and Measure-Through Motion and Low Perfusion pulse oximetry, announced that a clinical study demonstrates that noninvasive and continuous hemoglobin (SpHb) from Masimo Rainbow SET Pulse CO-Oximetry provides comparable accuracy as point-of-care invasive measurements of total hemoglobin versus standard laboratory invasive measurements of total hemoglobin. The study confirms that SpHb is accurate, reliable, and a clinically-acceptable alternative for monitoring hemoglobin, and is the first SpHb study presented in pediatric patients. Dr Fay Jou and colleagues at the Cincinnati Children's Hospital Medical Center in Ohio compared SpHb and point-of-care (POC) hemoglobin measurements (Abbott iStat) to a standard laboratory hematology analyzer (Abbott Cell Dyn hematology analyzer) in 15 pediatric patients undergoing surgery. Compared to standard laboratory hemoglobin measurements, SpHb and iStat had a similar bias (-0.3 and 0.2 g/dL respectively) and standard deviation (1.1 and 0.5 g/dL, respectively). Researchers concluded that "SpHb offers clinically-acceptable absolute accuracy and very good trend accuracy" and that all significant directional changes in hemoglobin "were indicated by changes in SpHb." Additionally, researchers commented that "SpHb provided earlier indications of directional hemoglobin changes than intermittent tHb values."[1] According to Dean Kurth, Anesthesiologist in Chief at Cincinnati Children's Hospital Medical Center, "These study results indicate that Masimo SpHb has the potential to replace the need for invasive blood draws in infants and children undergoing surgery." SpHb is available as part of Masimo Rainbow SET Pulse CO-Oximetry—the first-and-only technology platform to noninvasively measure blood constituents and fluid responsiveness that previously required invasive procedures, including: total hemoglobin (SpHb), oxygen content (SpOC), carboxyhemoglobin (SpCO), methemoglobin (SpMet), PVI, and acoustic respiration rate (RRa), in addition to the "gold standard" Measure-Through Motion and Low Perfusion performance of Masimo SET oxyhemoglobin (SpO_2), pulse rate (PR), and perfusion index (PI). Masimo SpHb and PVI have been shown in multiple clinical studies to provide accurate, reliable, real-time measurements that help clinicians to proactively monitor and manage hemoglobin and fluid volume levels more appropriately and optimally.

[Reference: 1. F. Jou, C. Kurth, E. Beckman, G.K. Istaphanous. Department of Anesthesiology, Cincinnati Children's Hospital Medical Center. "Absolute and Trend Accuracy of Continuous and Noninvasive Hemoglobin in Pediatric Surgery Patients." Presentation S-401. International Anesthesia Research Society (IARS), Honolulu, Hawaii. *Study Presented at the International Anesthesia Research Society (IARS) Annual Meeting Also Demonstrates Masimo SpHb Provides Earlier Indications of Directional Changes than Intermittent Invasive Hemoglobin Values.]

LOW FLOW

Masimo, the inventor of Pulse CO-Oximetry and Measure-Through Motion and Low Perfusion pulse oximetry, announced research findings, published in the Journal of Perinatology, which show that Masimo perfusion index (PI) accurately predicts low superior vena cava flow (SVC) in preterm, very-low-birth-weight infants--representing a promising method for continuous and noninvasive monitoring of systemic blood flow.[1] SVC flow, a measure of blood flow returning to the heart from the upper body, is useful information in the cardiovascular management of neonates because it helps determine risk for intraventricular hemorrhage, developmental impairments, morbidity, and mortality.[2-4] However, detecting low SVC flow is challenging because current measurement methods are complicated, operator dependent, or can be inaccurate in certain neonatal conditions.[5-6] Masimo PI provides a reliable continuous, noninvasive measure of the ratio of pulsatile blood flow to the non-pulsatile or static blood in peripheral tissue, which provides a rapid, reliable, and cost-effective method to help clinicians assess perfusion and circulatory status. In the study, Dr Takahashi and colleagues at the National Center for Child Health and Development in Tokyo, used the Masimo Radical pulse oximeter and Masimo LNOP NeoPt-L sensor to monitor PI in 24 preterm infants during the first 72-hours following birth. When comparing PI to echocardiography to directly measure SVC, they found that a PI of <0.44 detected low SVC flow (defined as <40ml kg -1 min -1) with good sensitivity (88%) and specificity (86%). A total of eight out of 24 infants were confirmed to have low SVC flow, and PI positively detecting seven--leading researchers to conclude that Masimo PI is a "useful index for detecting low SVC flow in very low birth weight infants born before 32 weeks of gestation" and that "the PI should be evaluated in the cardiovascular management of preterm infants." Masimo Executive Vice President of Medical Affairs Dr Michael O'Reilly, stated, "The current study provides additional evidence supporting the clinical utility of Masimo PI, a reliable noninvasive measure of perfusion. Previous work demonstrated the value of Masimo PI as an early indicator of clinical deterioration in neonates and life-threatening congenital heart disease. Masimo PI has also been shown highly effective in assessing the response to painful stimuli and the

proper placement of epidural and regional anesthesia. These results reinforce the value of Masimo PI to routinely assess circulatory disorders and improve detection and treatment of life-threatening conditions." [References: 1. S Takahashi, S Kakiuchi, Y Nanba, K Tsukamoto, T Nakamura, Y Ito. "The Perfusion Index Derived from a Pulse Oximeter for Predicting Low Superior Vena Cava Flow in Very Low Birth Weight Infants." Journal of Perinatology (12 November 2009). Available online at nature.com; 2. Kluckow M, Evans N. "Low Superior Vena Cava Flow and Intraventricular Haemorrhage in Preterm Infants." Arch Dis Child Fetal Neonatal Ed 2000; 82: F188-F194; 3. Osborn DA, Evans N, Kluckow M. "Hemodynamic and Antecedent Risk Factors of Early and Late Periventricular/Intraventricular Hemorrhage in Premature Infants." Pediatrics 2003; 112: 33-39; 4. Miletin J, Dempsey EM. "Low Superior Vena Cava Flow on Day 1 and Adverse Outcome in the Very Low Birthweight Infant." Arch Dis Child Fetal Neonatal Ed 2008; 93: F368-F371; 5. Kluckow M, Evans N. "Superior Vena Cava Flow in Newborn Infants: A Novel Marker of Systemic Blood Flow." Arch Dis Child Fetal Neonatal Ed 2000; 82: F182-F187; 6. Osborn DA, Evans N, Kluckow M. "Clinical Detection of Low Upper Body Blood Flow in Very Premature Infants Using Blood Pressure, Capillary Refill Time, and Central-Peripheral Temperature Difference." Arch Dis Child Fetal Neonatal Ed 2004; 89:F168-F173.]

SPOTLIGHT ON MONITORING

SITE SPECIFIC

Somanetics' INVOS System's Cerebral/Somatic Oximeter provides site-specific insights on perfusion adequacy and distribution across the brain and body. Its noninvasive OxyAlert NIRSensors emit near infrared light into the microvasculature below, measuring oxy and de-oxy hemoglobin in venous and arterial blood in a 75:25 ratio. This results in a sensitive, real-time measure of venous oxygen reserve, the blood oxygen remaining after extraction by tissues. Bedside monitoring of cerebral and somatic venous oxygen reserve enables proactive intervention to help stop the progression of shock, metabolic dysfunction and other ischemia-related injury. The INVOS System is for patients of any age or size. Contact somanetics.com, (800) 359-7662.

FEATURED PRESENTATIONS

Somanetics Corporation's INVOS System was featured in 24 posters and presentations at the Pediatric Academic Societies (PAS) annual conference. The findings demonstrate adoption and application of Somanetics' technology to improve patient care, clinical outcomes and safety of neonates. Key presentations involving the INVOS System identified: • A strong association between INVOS System cerebral oximetry values and today's commonly used predictors of neurodevelopmental outcomes such as brain MRI, EEG and mental and psychomotor development indices; • The utility of INVOS values to help identify babies with hemodynamically significant patent ductus arteriosus (PDA) and help determine whether medical management or surgical ligation may be best; • The ability to monitor tissue perfusion changes in the gut of neonates with necrotizing enterocolitis (NEC) as an indication of feeding intolerance; • The benefits of correctly identifying intended or unintended effects of drug delivery on cerebral and somatic oxygenation; and • The association between residual lung disease and severe cerebral oxygen desaturations during sleep. The INVOS System provides noninvasive monitoring of regional oxygen saturation (rSO_2) of blood in the brain or other body tissues beneath its sensors. This reflects site-specific perfusion adequacy and—with multi-sensor monitoring—perfusion distribution across the brain and body. This provides a direct, real-time measure of blood oxygenation rather than time-delayed lab results or indirect systemic, whole body measures such as blood pressure and pulse oximetry, which can remain normal when ischemia is occurring at the regional level. In neonates, commonly monitored areas at risk for oxygen deprivation are the brain, abdomen/gut and kidney area. Multiple abstracts demonstrated clinical benefit of the INVOS System in the management of hemodynamics associated with conditions such as necrotizing enterocolitis (NEC) or patent ductus arteriosus (PDA). One abstract showed that tissue perfusion changes as reflected by rSO_2 can be used to predict feeding intolerance and support clinical decision-making about whether it is safe to resume feeds after treatment for medical NEC. PAS abstracts also showed that the INVOS System can help identify oxygen deficits associated with hemodynamically significant PDAs and assist in the treatment decision—medical management versus surgical ligation—by reflecting in real time whether the treatment administered was sufficient to maintain stable hemodynamics and adequate rSO_2. Additional papers demonstrated the INVOS System's value to help guide medical management of hemodynamic stability, and a sleep study explored the possible effect of prone or supine sleep positions on cerebral oxygenation. While no difference was found between the prone or supine position, rSO_2 did show that sleeping preemies with residual lung disease (requiring supplemental oxygen, diuretics or bronchodilators which are used commonly in the NICU) were much more likely than those without to experience cerebral desaturations at levels associated with neurologic injury. The abstracts referenced above can be found at http://www.pas-meeting.org/2010Vancouver/Abstracts/default.asp. Contact somanetics.com.

VITAL SYSTEM

Somanetics' Vital Sync system was designed by physicians for physicians. It provides a more complete view of patient status by allowing clinicians to select and view parameters most relevant to the patient's condition—all on one time-synced bedside display. This spotlights the status and inter-relationships of vital parameters, facilitating early detection of worsening patient condition. Touch-screen interactivity enables easy electronic review of patient data monitored over the course of care. With automatic collection and compilation of multiple metrics and out-of-the-box connectivity, the Vital Sync system is well suited for bedside care, research data aggregation or paperless charting. Contact somanetics.com, (800) 359-7662.

LATEST TECHNOLOGY

The Maico MB11 newborn hearing screening system incorporates the latest technological advances based on years of research. The cost for the supplies to perform an MB11 screening is approximately $0.25 compared to $9.00-$12.00/screening with competitive systems. Using fast rate ABR technology with a unique, CE chirp acoustic stimulus, MB11 stimulates an ABR that is almost two times larger than the response from a traditional click stimulus. This can translate into faster test times. MB11's "green technology" features an integrated, reusable earphone and electrodes, avoiding the exorbitantly high costs and medical waste associated with use of disposable electrodes and ear couplers. Contact maico-diagnostics.com.

TAILORED PRODUCTS

As the industry leader in pulse oximetry, Covidien has tailored products for neonatal patients for more than two decades. Nellcor OxiMax sensors are designed for neonates, including sterile adhesive sensors with LoSat expanded accuracy. LoSat helps clinicians better manage patients in the challenging lower saturation ranges. In addition, the latest signal processing technology effectively monitors infants with weak pulses. • Sensors: Full line including both adhesive and non-adhesive sensors; • SatSeconds Alarm Management: Has shown to reduce non-critical alarms by 60% at a setting of 50*; • Histogram: Allows clinicians to access graphical data for SpO_2 and pulse rate anywhere from 20 seconds to a 48 hour period; • LoSat Accuracy Claim: 60%–80% ±3%, 70%–100% ±2%; • High Sat/Low Sat Alarm Tones; • Neo Mode Monitor Settings: Settings appropriate for the NICU environment; • OxiMax Digital Platform: Digit calibration allows for an expandable platform; • Monitoring upgrades are not needed to access new sensor technologies. [*Brostowicz, H.M. and Rais-Bahrami, K. Oxygen Saturation Monitoring in The Neonatal Intensive Care Unit (NICU): Evaluation of a New Alarm Management Children's National Medical Center Washington, DC. Presented at the 2008 Mid-Atlantic Perinatology conference.] Contact covidien.com.

PATIENT SAFETY

You live and breathe patient safety in the NICU. So do we. As an industry leader in pulse oximetry, Covidien has been tailoring products for neonatal patients for more than two decades. Today you can choose from several Nellcor OxiMax sensors designed for neonates, including sterile adhesive sensors with the Low Saturation expanded accuracy feature. This feature helps you better manage patients in the challenging lower saturation ranges. Plus, our latest signal processing technology lets you effectively monitor wiggling infants with weak pulses. For free continuing education courses on topics such as neonatal skin integrity, check out our Center for Clinical Excellence website at nellcor.com/ccexcellence.

WATCHABLE

Enthermics dual-purpose injection/irrigation fluid warming cabinets feature intuitive controls, rugged construction, and reliable warming. And now a new optional feature ensures even greater temperature accuracy and significant labor savings: WarmWatch, an automatic recording and verifying system. Enthermics fluid warmers equipped with this optional package feature a continuous temperature monitoring system that provides instant confirmation of the chamber temperature. An independent monitoring probe verifies that the chamber reaches and maintains the set-point temperature within +0/-1.1°C (+0/-2°F) accuracy from 37-40°C (98-104°F) and +0/-1.7°C (+0/-3°F) accuracy above 40-66°C (104-150°F). This option also digitally documents the warmer's temperature performance. Digital Documentation offers significant advantages over manually recording temperature set-points. The independent monitoring probe ensures that the actual chamber temperature is recorded, not just the displayed set-point temperature. This data can be downloaded to a USB flash drive and then to a computer at any desired time interval—up to six months between downloads—to provide reliable documentation. Contact (800) 862-9276, ethermics.com.

TWO FROM MASIMO

The Masimo Radical-7 Pulse CO-Oximeter is a 3-in-1 (bedside, handheld, transport) Pulse CO-Oximeter featuring the power and performance of Masimo Rainbow SET Pulse CO-Oximetry. With the first-and-only upgradable technology platform that continuously and noninvasively measures hemoglobin (SpHb), oxygen content (SpOCT), carboxyhemoglobin (SpCO), methemoglobin (SpMet), PVI, and acoustic respiration rate (RRa), in addition to oxyhemoglobin (SpO_2), perfusion index, and pulse rate, the Radical-7 helps clinicians to improve patient safety and clinical outcomes by facilitating early detection of life-threatening conditions and helping guide treatment options. **The Masimo LNOP Blue Sensor** offers a breakthrough sensor specifically designed for cyanotic infants and children who may have congenital heart disease, the Masimo Blue sensor maximizes accuracy in this vulnerable patient population. Proven accurate on cyanotic patients with oxygen saturations as low as 60%, its accuracy and reliability enables better management of cardiac medications and ventilation therapy. Contact masimo.com.

SMART

Philips Children's Medical Ventures offers the SmartMonitor 2 family of event monitors for hospital as well as home use. Available in three configurations, it can be used to measure heart rate, respiration and oxygen saturation levels to aid in step-down or discharge planning, car seat testing, and follow-up care. SmartMonitor 2 is utilized to capture waveforms and to document central apnea, bradycardia, tachycardia, hypopnea and other life-threatening events that may not be recognized and recorded during bedside charting through the use of our proprietary Synergy-E scoring software. Contact chmv.respironics.com.

SPECT-TACULAR

The T-Stat VLS (Visible Light Spectroscopy) Tissue Oximeter provides a continuous, non-invasive and localized measurement, sensitive to regional and global ischemia. Using white LED technology, the T-Stat VLS reports a capillary-weighted oxygen saturation which is closely related to a local venous saturation measure for use during: decreased systemic flow, anemia, increased metabolism and fluid treatment. T-Stat is the first device to be labeled by the FDA as "sensitive to Ischemia" and has been proven in multiple trials as an easy-to-use and reliable tool for assessing the adequacy of oxygen delivery to tissue. Contact spectros.com.

SAFETY AND COMFORT

Radiometer announced that it is expanding the TCM4 platform with several new transcutaneous modules and sensors. The TCM TOSCA module and the TCM CombiM module and sensors increase patient safety, while promoting greater comfort. By linking patient and monitoring information, Radiometer's new TCM CombiM and TCM TOSCA monitors significantly decrease the risk of patient and data mix-ups during continuous transcutaneous monitoring of oxygen, carbon dioxide and saturation in adult, pediatric and infant patients. The new monitors allow the patient ID to be entered into the monitor, while linking monitoring data to a session. This minimizes the risk of patient and result mix-ups, thus improving patient safety. The TCM CombiM measures carbon dioxide and oxygen, whereas TCM TOSCA, compatible with the well-known TOSCA 92 sensor, provides information on carbon dioxide and oxygen saturation. Information is provided continuously and non-invasively. With touch screen technology, the two new Radiometer monitors provide full connectivity to major patient monitoring systems and 48 hours of real-time data

storage. The TCM CombiM configuration also includes two new transcutaneous sensors. The new tc Sensor 84 is a combined oxygen/carbon dioxide sensor, whereas the new tc Sensor 54 is dedicated for carbon dioxide measurements. To ensure optimal patient comfort during non-invasive monitoring, both sensors have a very small surface area and offer multiple choices of application - fixation ring, double-adhesive ring and ear clip - to match different clinical needs. Durable and convenient, these sensors reduce the need for remembraning to once every other week, freeing up valuable time for caregivers. Contact radiometeramerica.com.

PRODUCTS

BABIES FIRST

Dräger, a leading provider of medical and safety technology and services worldwide, including equipment for the NICU, and NICUniversity.org, a web-based medical continuing education center for neonatal practitioners, have joined together to support the launch of Babyfirst.com. Babyfirst.com is a new single destination where neonatal doctors and nurses can exchange information and experiences online—across a range of neonatal care specialties. With content populated by clinicians and renowned experts, the website also offers parents and families of premature babies a trusted resource to gain a better understanding of what they can expect in the Neonatal Intensive Care Unit (NICU), with insight into common terms, procedures, equipment, post-hospital care, and more. Babyfirst.com is a place where clinicians in Labor and Delivery and the NICU can share their expertise and experience, covering key specialties such as thermoregulation, jaundice management, respiratory care, developmental care, neonatal anesthesia, NICU designs, and many other topics including infection control, vital signs monitoring, and nutrition. Acknowledging the importance of parents as part of the healing and growing process, Babyfirst.com also provides resources to assist clinicians in educating parents about the NICU for a healthy collaboration with professionals towards the growth of their babies. Parents and families of premature babies can get quick and easy web access to extensive information about neonatal care, from general descriptions of NICU equipment and their purposes to personal experiences of specialized nurses. Babyfirst.com offers a broad range of content, such as videos of renowned experts explaining the latest NICU procedures, blog and video entries by parents about their own NICU experiences and articles contributed by neonatal nurses and physicians and profiles of "miracle babies" once they have left the NICU. Contact babyfirst.com or draeger.com.

CLEARED

Dräger Medical Systems, Inc, US headquarters of Dräger Medical AG & Co KG, announced that it has received 510(k) clearance from the FDA to market the Evita Infinity V500 in the US. The ventilator is Dräger's latest and most advanced product in its ventilator product line. The Evita Infinity V500 ventilator offers the latest technology in mechanical ventilation for critically ill or injured adult, pediatric, and neonatal patients. Its versatility and range of operation is well suited for acute care facilities as well as university medical centers. The Evita Infinity V500 is a highly advanced ventilation unit for use in modern, acute care respiratory support. High-performance invasive and non-invasive ventilation, comprehensive monitoring and treatment functions, effective O_2- therapy—the V500 delivers advanced care to patients of all ages and acuity levels, including neonates. "The V500 was developed in consultation with key physicians and respiratory therapists alike to offer clinicians a wide array of ventilation therapies required for critical care. Improvements in daily workflow, safety in the ICU, ease of use, and patient comfort are all realized with this new ventilator," said Ed Coombs, MA, RRT and Associate Director of Marketing for Respiratory Care Systems at Dräger Medical, Inc. With a company-wide focus to provide exceptional product support services, Dräger customers will continue to receive support from both field support teams and Intensive Care Online Network (ICON). The company also announced that it has received 510(k) clearance from the FDA to market the Babylog VN500 in the United States. The ventilator is Dräger's most advanced product for neonatal ventilation. The Babylog VN500 ventilator offers the latest technology in mechanical ventilation specifically designed for the special needs of neonates and infants. Its versatility and range of operation is well suited for special care nurseries and pediatric intensive care units. The Babylog VN500 combines important types of ventilation, such as conventional ventilation, nasal CPAP, and oxygen therapy in one medical device. The detachable control panel with 17" touch screen and rotary knob offers extended possibilities of device control and lung function monitoring. "Designed with the clinician in mind, the Babylog VN500 combines the latest in technology coupled with a simplified and easy to use user interface," said Ed Coombs. "After over two decades of experience with the Babylog 8000+, our customers have led the development of the next generation in neonatal ventilation." With a company-wide focus to provide exceptional product support services, Dräger customers will continue to receive support from both our field support teams and Intensive Care Online Network (ICON). Contact draeger.com.

BABI.BUBBLE

B&B Medical Technologies has introduced the first FDA (510k) cleared bubble continuous Positive Airway Pressure (PAP) valve for use with infants weighing <10 kg. The unique design of the new Babi.Plus Bubble PAP Valve 0–10 cm H_2O allows airway pressure to be easily set without the cumbersome and time consuming tasks normally associated with bubble cpap devices. Babi.Plus Bubble PAP Valve provides a safe, accurate and convenient method for delivering CPAP therapy to premature infants to increase end lung pressure above atmospheric in constant flow conditions. The patent-pending Babi.Plus Bubble PAP Valve is adjustable from 1 to 10 cm H_2O with an accuracy of ±1 cm of H_2O using gas flows from 1 to 12 liters per minute. A 360 degree swivel inlet accepts 15 mm OD and 22 mm ID circuit connectors for easy installation to the expiratory limb of the breathing circuit. A fluid level adjustment port allows water or acetic acid levels to be easily maintained without disconnecting the circuit or loss of PAP. The expiratory ports direct gas quietly away from clinicians. Contact bandb-medical.com.

COMMITMENT

After a strong finish in 2009, GE Healthcare IT's Maternal–Child departmental solution, Centricity Perinatal, has surged into 2010. Centricity continues to expand its customer base with several key implementations, adding 12 new customers to its current install base of more than 1500. The latest Centricity Perinatal equipped hospitals and health systems include: Brookwood Medical Center (AL), Carolinas Healthcare System (NC), Fairview Health Services (MN), Gunderson Lutheran Medical Center (WI), Midwest Regional (OK) and Wellstar (GA).

The Centricity Perinatal Clinical Information System supports efficient documentation of mothers and infants throughout the perinatal continuum of care. The product is positioned for a promising year, highlighted by the upcoming release of version 6.9.0. This launch of this latest upgrade continues to demonstrate the strong commitment GE Healthcare has to departmental IT solutions and builds upon the current product's existing capabilities. For five consecutive years, Centricity Perinatal has demonstrated that commitment, in part, by participating in the HIMSS Interoperability Showcase. Centricity Perinatal has demonstrated successful access to and viewing of the mock personal health record created for the event and, of the near 100 eligible unique systems, was the only clinical labor and delivery system to participate in the 2010 event. In addition, Centricity Perinatal served as the host of document source for the IHE (Integrating the Healthcare Enterprise) Labor and Delivery Summary Profile and was the first to implement this within the IHE Patient Care Coordination Domain. GE Healthcare is also proud to have served as a leader and active participant within the IHE organization. Contact centricityperinatal.com.

BORN TOO SOON

The video and production company Paralell Lines is currently producing a video, "born too soon," for public television worldwide, set for distribution in February 2011. Its goal is to to bring to light the specifics of neonatal care to this audience. "Born too soon" will provide audiences with a unique look at the modern treatment of premature babies from several different perspectives, ranging from the parents to the medical specialists—neonatologists, nurse practitioners, nurses, respiratory therapists—to hospital administrators. Intended to be both dramatic and educational, "Born too soon" will track the progress of a cross section of real cases involving newborn babies and the physical and emotional struggle to help them survive and flourish. Each of these cases will be set in a different geographical region and follow the various people involved in the process. Aside from showing the process from each person's point of view, the film will highlight the roles that those working in neonatal care perform on a daily basis, as well as how these roles differ based on the treatment facility. Additionally, the program will look at both the emotional and ethical side of the many decisions these processes entail. Alongside the narrative of individual babies fighting for survival, "Born too soon" will bring to light the differing perspectives on the major issues of neonatology, both from an American and global perspective. Contact forwardintime.com.

REVOLUTIONARY

GEM Premier 4000 is the revolutionary analyzer (BG, Electrolytes, Metabolites, Glu, Lac, Hct, tHb, O_2Hb, COHb, HHb, MetHb, sO_2, BUN, Creat, Total Bili, HCO_3 with integrated CO-Oximetry that quickly provides consistent, accurate, lab-quality results throughout your hospital. Easy-to-use, touch-screen displays make it simple to select and customize parameters. Self-contained cartridges incorporate all components for patient testing and are maintenance-free. iQM automates quality control and continuously detects, corrects and documents to assure quality results and compliance, 24/7, regardless of operator or testing location. GEMweb Plus software enables remote access to any networked analyzer for real-time status updates and supervision of remote locations. Contact ilww.com.

SILICONE-SAFE

NeoMed, Inc introduced its new line of single and dual lumen umbilical vessel catheters. **Features:** Silicone material is well-known as a safe and effective catheter material; flexible silicone material reduces the risk of "mis-tracking" into other vessels during insertion. NeoMed's UAC/UVC products are manufactured with a high-quality 3-way stopcock; the dual-lumen UAC/UVC maintains lumens to the catheter tip. Together with its innovative Catheterization Tray, NeoMed offers a full line of Silicone Umbilical Catheters in both singe lumen and dual lumen designs. Silicone has proven to be a safe and effective material with properties that help reduce risks common with catheterization of blood vessels. Contact neomedinc.com.

INSURANCE

Medela announced the launch of an important new resource, breastfeedinginsurance.com, where new and expectant mothers can access comprehensive information and tools to help them discover if their breastfeeding related expenses, such as breastpump rental/purchase or lactation consultants, are covered by insurance. Many insurance providers offer some coverage for expenses related to providing expressed breastmilk to those infants. The site provides mothers with an important head start on determining if their provider offers coverage and how to access this coverage. To launch the new site, Medela worked with respected insurance experts to develop several reimbursement-related resources, including information about submitting claims and appealing denied claims for services. The site also includes additional sample letters that can help new and expectant parents gain assistance from their employer, healthcare provider and lactation consultant. Downloadable resources available on the site include: Coverage Questions You Should Ask; Tips for Communicating with Your Insurance Company; Understanding the Benefits of Breastmilk; Filing and Insurance Claims; Lactation Consultant Coverage; Appealing an Insurance Claim; and a Quick Coding Reference Guide. Contact medela.com.

DETECTION

Mercury Medical introduced the first full line of CO_2 detectors. The Neo-StatCO_2>Kg is the newest member of the Mercury family of CO_2 detector products. Neo StatCO_2 >Kg is the only CO_2 detector available for babies below 1 kg. Like its other family members, StatCO_2 for patients over 15 kg and the Mini StatCO_2 for patients 1-15 kg, it effectively provides 24 hour continuous performance with breath-to-breath color changes for ET Tube placement verification. Contact mercurymed.com.

EXECUTIVE PROFILE

Covidien

This information is provided by Mark Riters, Director, US Marketing—Patient Monitoring.

Describe your products and their unique features.

In the NICU, clinicians manage conditions such as congenital heart disease and intraventricular hemorrhaging (IVH), while working to prevent overstimulation of underdeveloped nervous systems and conditions such as retinopathy of prematurity (ROP). Overcoming these clinical challenges requires a set of proven tools clinicians can trust to safely obtain accurate, reliable readings of the patients' cardiorespiratory cycles. They rely on: • Sensors that minimize the risk of damaging the

fragile skin of the neonatal patients; • Innovations that help the clinician reduce nuisance alarms; • Proven pulse oximetry technologies that can help clinicians overcome a wide range of challenges, including low saturation; and • Safe, efficient, cost-effective solutions. As the industry leader in pulse oximetry, Covidien has tailored products for neonatal patients for more than two decades. There are several Nellcor OxiMax sensors designed for neonates, including sterile adhesive sensors with LoSat expanded accuracy. LoSat helps clinicians better manage patients in the challenging lower saturation ranges. In addition, the latest signal processing technology effectively monitors infants with weak pulses.

- Sensors: Full line including both adhesive and non-adhesive sensors;
- SatSeconds Alarm Management: Has shown to reduce non-critical alarms by 60% at a setting of 50*;
- Histogram: Allows clinicians to access graphical data for SpO_2 and pulse rate anywhere from 20 seconds to a 48 hour period;
- LoSat Accuracy Claim: 60%-80% ±3%, 70%-100% ±2%;
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- Neo Mode Monitor Settings: Settings appropriate for the NICU environment;
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- Monitoring upgrades are not needed to access new sensor technologies.

Tell us about your educational, technical and support services.

We offer staff in-servicing, free of charge, all shifts, and CE programs, free of charge, online or on site. Technical support is available 24/7 at (800) NELLCOR.

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In the NICU, clinicians need to protect the delicate epidermal tissue of the smallest patients. Research has determined that the use of adhesives is the primary cause of skin breakdown among NICU patients.[1] Covidien offers two sterile, single-patient-use Nellcor SoftCare sensors designed specifically for patients in the NICU—one for neonates and one for preterm infants. Covidien's products provide reliable, accurate readings with secure, comfortable fits, even on the most difficult-to-monitor patients. Our products provide timely information with the necessary context to prevent adverse events and achieve positive results in neonatal care.

Nellcor OxiMax N-600x pulse oximeter, featuring SatSeconds Alarm Management:

- Measurement ranges[2]: SpO_2: 1% to 100%; pulse rate: 20 to 250 BPM; perfusion range 0.03% to 20%.
- Accuracy ranges (neonate to adult)[2]: Saturation (percentage SpO_2) ±1 SD; —60% to 80% ±three digits; —70% to 100% ± two digits (low perfusion); Pulse rate: 20 to 250 BPM ± three digits (low perfusion).
- Alarms: Audible and visual alarms for high- and low-saturation rates and for pulse rate; SatSecond alarm management settings of 10, 25, 50, 100 and OFF; Audible and visual warning indicators for low battery levels; Audible sensor-disconnect alarm and sensor-off alarm; Saturation and pulse rate alarm limit displays; backup speaker with escalating alarm tones.
- Optional accessories: GCX mounting options, interface cables, carrying case.

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ADDENDUM

Covidien recently announced that the Alarm Management System (AMS), designed and clinically proven to help improve patient safety, is now in place in preeminent healthcare facilities globally. After one year on the market, the AMS for the Nellcor OxiMax N-600x pulse oximeter is now in place in medical centers worldwide, with more than 3,000 licenses sold in over 100 hospitals in the US and facilities in Canada, Asia and Europe. The Alarm Management System identifies desaturation patterns indicative of repetitive reductions in airflow, and adds another level of patient safety and medical efficacy. The Alarm Management System with OxiMax SPD technology minimizes nuisance alarms by intelligently monitoring oxygen saturation (SpO_2) levels, a critical measure of respiratory function. Healthcare providers are quickly alerted to potentially dangerous situations—not just drastic drops, but also recurring moderate reductions in airflow, even if the patient has not dropped below the SpO_2 threshold. The system also provides the clinician with a breadth of information about a patient's historical and real-time condition. Covidien also announced research by P.B. Batchelder of Clinimark Labs in Golden, CO, which concluded that the Mallinckrodt TaperGuard endotracheal tube from Covidien provided a more effective seal against fluid leakage than six other tubes studied. The study investigated how well seven cuff designs prevented leakage past the tube cuff. Ten tubes of each design were tested five times, for a total of 50 trials per cuff. The results indicated considerable differences in seal ability. The TaperGuard cuff provided superior performance with an average leak rate of 0.59 grams of water over a five-minute period, while the other cuff designs had leak rates that ranged from 11.19 to 59.18 grams of water in five minutes. By providing a more effective tracheal seal, the TaperGuard tube reduces the risk of microaspiration among intubated patients. Microaspiration refers to aspiration of fluid, secretions and other materials that have leaked past the endotracheal tube cuff and into the lungs, a common problem in intubation that may lead to pulmonary complications, including post-operative pneumonia and ventilator-associated pneumonia (VAP).

Neonatal Lead Poisoning

Arun Aggarwal, MD; Pratibha Ankola, MD

Introduction

Acute /chronic lead poisoning can be threatening to various body organs and possibly life threatening without treatment. Symptoms of lead poisoning include decreased learning and memory, decreased verbal ability, early signs of hyperactivity or ADHD, lower IQ, impaired speech and hearing functions, myalgia or paresthesia, irritability, lethargy, abdominal discomfort, fatigue, difficulty in concentration, tremors, headache, vomiting, weight loss, constipation, paralysis and encephalopathy.[1-13]

Most children who have toxic blood lead levels are asymptomatic at the time of screening. However, population-based studies consistently have shown that blood lead levels greater than 10 mcg/dL affect the cognitive and behavioral development of children. Neurocognitive effects also have been demonstrated at even lower blood lead levels. In utero exposure to lead may adversely affect child's neurodevelopment (measured at 24 months) independent of post-natal blood lead levels.[14-16]

In most cases calcium disodium EDTA is used for the treatment of blood lead levels > 45 microgram/dL. Calcium disodium EDTA increases the urinary excretion of lead through the formation of a nonionizing, soluble chelate. We describe a case of neonatal lead poisoning which was treated with calcium disodium EDTA and the side effect of chelation treatment.

Case Report

Full term appropriate for gestational age male neonate born by normal spontaneous vaginal delivery to a 20 year old G3P2012 woman at 38 weeks of gestation with elevated blood lead levels. Initial maternal lead screening during first trimester revealed a blood lead level of < 3microgram/dL. However rescreening during third trimester showed blood lead levels of 64 microgram/dL with history of maternal ingestion of dirt. Mother was admitted for induction and for starting chelation therapy. Department of health investigation did not reveal any other cause for maternal increase in blood lead levels.

Baby was born with uneventful delivery. Apgar scores were 9 and 9 at 1 and 5 minutes respectively. Baby received vitamin K at birth. Examination of the baby was normal. Immediate venous blood lead levels were sent and baby was placed on cardio pulmonary monitor. Baby was monitored for signs and symptoms of encephalopathy and nephropathy. Urine output remained adequate and base line EKG was normal. Complete blood count (CBC) and reticulocyte count was normal and peripheral smear did not show basophilic stippling. Blood electrolytes, blood urea nitrogen, blood creatinine and liver function tests (LFTs) were normal. Baby was feeding infant formula. Baby's blood lead level was 56 microgram /dL. Baby was started on calcium disodium EDTA with a total daily dose of 1000mg/m2/day (in 4 divided doses), intravenously for 5 days. Baby was on continuous cardio-pulmonary monitoring for detecting any arrhythmias and good urine output was maintained.

During the course of the treatment baby developed blood in the stools and stool guaiac test was positive. Physical examination of the baby was normal, with abdomen soft, non-tender, non-distended with good bowel sounds and no anal fissure. Baby remained afebrile, active and was tolerating formula feeds well. CBC was normal, PT/PTT/INR were within normal limits. Blood culture and stool culture showed no growth. Abdominal X-ray was normal. Baby's formula was changed to alimentum (casein hydrolysate formula) and hematochezia was monitored. There was recurrence of guaiac positive bloody stools and therefore baby was made NPO with IV fluids administration and was given IV antibiotics. On 3rd day feedings were restarted with amino acid based formula. The infusion time of calcium disodium EDTA was increased from 1 hour to 2 hour and thereafter the stools were guaiac negative. After completing treatment for 5 days with calcium disodium EDTA, repeat blood lead level was 20 microgram/dL. At one week of age regular formula feeds were reintroduced which baby tolerated well and stools remained guaiac negative. Subsequently baby's blood lead levels declined gradually to < 3microgram/dL.

Discussion

Lead poisoning during pregnancy is associated with spontaneous abortion, premature birth, maternal hypertension and decreased fetal growth.[16-20] Elevated maternal blood lead levels (BLL) may reflect recent exposure to exogenous lead source and/or mobilization of endogenous bone stores. During pregnancy, when maternal bone stores of calcium are released in to the blood stream to support development of fetal bone structures, bone stores of lead from past exposure may also be released.[21-22] In NYC, approximately 95% of pregnant women found to have elevated BLL are foreign born.[23]

Exposure to high lead levels in utero can have various detrimental effects on the fetus including miscarriage, still birth, premature delivery, low birth weight. Effects on the children include decreased learning and memory, decreased verbal ability, early signs of hyperactivity or ADHD, lower IQ, impaired

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speech and hearing functions, myalgia or paresthesia, irritability, lethargy, abdominal discomfort, fatigue, difficult concentration, tremor, headache, vomiting, weight loss, constipation, paralysis, encephalopathy, learning problems. There is no increase in risk of physical defects with exposure to high lead levels in utero. Children younger than 6 years of age (and particularly those between 12 and 36 months) are more susceptible to the toxic effects of lead than are adults because they have an incomplete blood-brain barrier that permits the entry of lead into the developing nervous system and because they have a greater prevalence of iron deficiency, which is associated with lead poisoning and may permit increased absorption of lead from the gastrointestinal tract. In addition, they are at greater risk of exposure to lead dust because of crawling and hand-to-mouth behavior.[24]

Management of neonates with blood lead levels > 45 microgram/dL include report to department of health, hospitalization of the patient, laboratory tests to confirm blood lead levels and start chelation therapy with calcium disodium EDTA @ 1000-1500 mg/m2/day. Education to parents, nutritional counseling and environmental investigation prior to hospital discharge should be made.[25-28] Monitor lead level every 2 weeks initially, every 1 month for 4 months and every 3-4 months for one year. Continue to check blood lead levels until levels are < 30 microgram/dL. If blood lead level at three weeks is > 45 microgram/dL, infant may be retreated with calcium disodium EDTA as above. Clinicians unfamiliar with chelation therapy in newborns should consult with an expert in chelation for lead poisoning.

Calcium disodium EDTA increases the urinary excretion of lead through the formation of a nonionizing, soluble chelate. It only removes lead from extra cellular compartment. Adverse reactions of calcium disodium EDTA include hypotension, arrhythmias, fever, headache, chills, skin lesions, cheilosis, hypercalcemia, zinc deficiency, gastrointestinal upset, anorexia, vomiting, transient marrow suppression, anemia, mild elevation in liver function tests, renal tubular necrosis, proteinuria, microscopic hematuria, sneezing, nasal congestion and lacrimation.[28]

In our patient, guaiac positive bloody stools developed with the chelation therapy and improved with slow infusion of calcium disodium EDTA and by giving elemental formula during chelation therapy. After completion of chelation therapy baby was reintroduced regular infant formula and tolerated it well suggesting gastrointestinal irritation due to chelation therapy.

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Congenital Afibrinogenemia Presenting as Antenatal Intracranial Bleed

Gopakumar Hariharan, Sivji Ramachandran, Rajiv Parapurath

Abstract

Congenital afibrinogenemia is a very rare inherited coagulation disorder, characterized by virtual absence of plasma fibrinogen (factor I). There are only about 250 cases reported in the world literature.[1] We describe a case of congenital afibrinogenemia which presented as an antenatally detected intracranial bleed.

Case Report

A preterm 29 weeks baby was born of second degree consanguinous marriage to a 28 year old G2A1 mother by elective lower segment cesarean section. Mother was a known case of polycystic ovarian syndrome and was on infertility treatment. Baby was born following intracytoplasmic sperm insertion. She had underwent two intracytoplasmic sperm insertions previously which were both failures. Mother had regular antenatal check ups. Antenatal scan at 29 weeks of gestation showed a large isoechoic intracranial extraaxial collection causing compression of neuroparenchyma and dilatation of the lateral ventricle. A detailed evaluation with a fetal MRI confirmed the finding and showed a fairly large extra axial collection with maximum thickness of 5.7 cms seen on the right with significant mass effect on the ipsilateral cerebral hemisphere, brainstem and cerebellar hemisphere. There was effacement of ipsilateral lateral ventricle and IIIrd ventricle. Significant midline shift was seen with most of the ipsilateral neuroparenchyma pushed towards left causing obstructive hydrocephalus on the left (Fig 1). The collection was homogeneously hyperintense on T1 weighted images. The large extra axial collection suggested hemorrhage on right side with significant mass effect evidenced by the midline shift and hydrocephalus.

Baby was born by elective lower segment cesarean section for fetal indication in view of possible uncal coning. Baby was intubated and ventilated at birth due to poor respiratory efforts.

On clinical examination, she had a large head with wide fontanel. Otherwise clinical examination was unremarkable. There was no obvious external congenital malformations. There was no obvious external bleeding tendency.

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Neurosonogram done after birth showed a large right sided subdural hemorrhage occupying almost the entire right hemisphere extending to midline with gross shift of midline to left. A Plain CT taken postnatally (after draining 50 ml of collected old bleed on day 1 showed extra-axial collection on Rt.side with a mass effect. The brain architecture was distorted with dilated ventricles (Fig 2).

A detailed blood investigation was done to identify the cause. Hemoglobin done at birth was 8.2 mg/dL. C reactive protein, total count, differential count and micro ESR done did not suggest sepsis. Blood culture was reported sterile. PT and APTT done on second day of life was both significantly prolonged. The initial INR was also prolonged (6.36). Platelet count was 1.3 lakhs/cmm.

The various possibilities for bleeding diathesis were considered and evaluated. Disseminated intravascular coagulation and sepsis was ruled out as sepsis work was reported negative and platelet count was normal. The possibility of a coagulation disorder was considered in view of the clinical profile and abnormal coagulation profile. A fibrinogen level was done to rule out the possibility of afibrinogenemia which was reported to be undetectable. In view of the prolonged INR and APTT along with an undetectable Fibrinogen level, the diagnosis of Congenital afibrinogenemia was made.

Baby was managed with Cryoprecipitates. Packed cell transfusion was given in view of low hemoglobin value initially. The fibrinogen activity was 64 on day 2 of life following one infusion of cryoprecipitate. Values above 100 was achieved by 9 days of life and was maintained so with alternate days of cryoprecipitate infusion. The INR and coagulation profile transiently improved with cryoprecipitate, to subsequently revert to the previous prolonged state when stopped. The decision was made to maintain fibrinogen activity above 100 mg/dL (Normal value—200 to 400 mg/dL).

Two subdural taps were done on first and third days respectively which drained liquefied blood. Ophthalmology consultation on day 2 of life showed pale disc with pale retina.

Baby was ventilated for a total of 14 days and extubated once clinical condition stabilized. Cryoprecipitate was stopped from 22nd day of life to see the magnitude of fall in fibrinogen activity. On 25th day of life, Fibrinogen level was detected to be 45 mg/dL. A repeat neurosonogram on 25th day of life showed persistence of subdural hematoma with pressure effect. There was probably

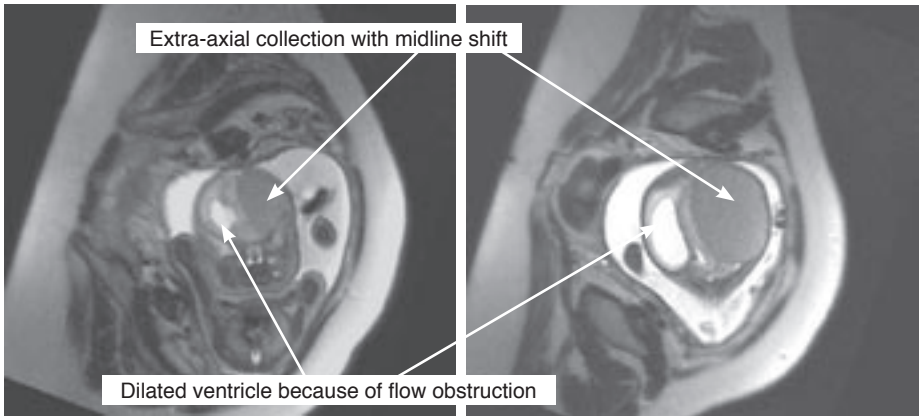

Figure 1. Fetal MRI, T2 weighted coronal section with a mass effect on the right side with mid-line shift to the left side because of sub-dural bleeding.

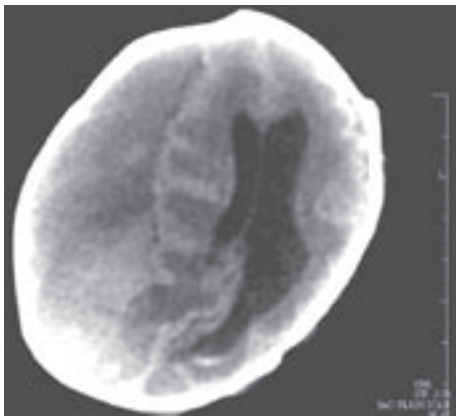

Figure 2. Plain CT taken postnatally (after draining 50 ml of collected old bleed on day 1). The plain CT showing extra-axial collection on Rt.side with a mass effect. The brain architecture is distorted with dilated ventricles.

a fresh episode of bleeding associated with significant mass effect. Supportive measures was given including cryoprecipitate with which the child clinically improved.

Child was discharged after the parents were instructed regarding the need for strict neurodevelopmental follow up. Child was relatively asymptomatic until 3 months of corrected age (6 months chronological age) when she was readmitted with one episode of right sided focal seizures along with poor activity and lethargy. Clinical examination showed raised anterior fontanelle tension. Fibrinogen level done at the time of admission was undetectable. Emergency CT scan showed an acute intraparenchymal bleed in left frontal lobe measuring 5 × 4.8 cm (Fig 3). There was another peripheral bleed adjacent to the larger bleed. Intraventricular extension of bleed was also noted with significant midline shift. The subdural hygroma was seen in right convexity with a maximum thickness of 1.2 cm suggestive of residual old subdural bleed. Seizures was controlled with appropriate anticonvulsants. An external ventricular drainage was done to evacuate the clot. She was given supportive measures and cryoprecipitate and was discharged after 3 days of hospitalization. VEP and BERA done at review at 3 months of corrected age was reported normal. Baby had attained social smile at 5 months of corrected age. She had partial head control at 8 months of corrected age. Babbling was present. Child is under strict neurodevelopmental follow up and stimulation program.

Discussion

Congenital afibrinogenemia is transmitted by an autosomal recessive gene located on chromosome 4 (q26-q28). Partial deficiency of fibrinogen is called hypofibrinogenemia and is a milder disorder. Afibrinogenemia occurs in the homozygous state while hypofibrinogenemia in heterozygotes.[2] Congenital absence of fibrinogen (Afibrinogenemia) was first described in 1920 and has an estimated incidence of 1: 1-2,000,000.[3]

Congenital afibrinogenemia patients may present with bleeding in the newborn period manifesting as hematomas from traumatic delivery. They may also present with hemetemesis, malena or bleeding from the umbilicus. Other manifestations include bleeding in soft tissues, mucosa and following circumcision. Despite having totally incoagulable blood, these patients normally do not have severe spontaneous bleeding, but the case identification is important to prevent more severe bleeding following injuries or surgery.[4] Intracranial hemorrhage is a rare presentation of the condition in a neonate. Antenatal detection of intracranial bleed is still a rarer entity. Intracranial hemorrhage has been described as a frequent cause of death in this disorder.[5-7]

As it is a disorder with the final substrate for formation of the clot missing, results of all screening tests such as clotting time, PT, PTT and thrombin time are abnormal. Platelet functions such as bleeding time, adhesion and aggregation may also be abnormal. Diagnosis is evident by standard fibrinogen assays.

Afibrinogenemic patients have undetectable or nearly undetectable levels of fibrinogen (<10 mg/dL; normal 200-400 mg/dL) by activity-based clotting assays and by measurement of immunoreactive fibrinogen. In the absence of consumptive coagulopathy, an unmeasurable fibrinogen level is diagnostic of the condition.[7] Hemorrhagic symptoms in fibrinogen deficiency are most significant when the plasma level is less than 50 mg/dl.[8,9] Fresh bleeding was noticed in our case, when the fibrinogen fell to 45 mg/dL.

Acute hemorrhagic episodes can be treated with either fresh frozen plasma or cryoprecipitate or fibrinogen concentrate (Cohn fraction I). Each cryoprecipitate bag contains 100 to 150 mg of fibrinogen, and therapy with 100 mg/kg of fibrinogen provides a hemostatic plasma level. The half-life of fibrinogen is 2-4 days and frequent infusions are usually not necessary. However, our patient required frequent transfusions. There was fresh bleeding detected on ultrasonography when cryoprecipitate was stopped temporarily. Recommendations regarding target levels for treating bleeding range from 30-50 mg/dL[10] to 100 mg/dL.[11]

Although prophylactic treatment with regular infusions of cryoprecipitate has been advocated by some,[12] it is not recommended by others for several reasons. This is based on the fact that spontaneous bleeding is very rare and mild. Moreover, there is a potential danger of acquiring infections with regular blood product infusion. Antibodies have been reported to form against fibrinogen with resultant thromboembolic complications, particularly pulmonary embolism.

Acquired hypofibrinogenemia is common in disseminated intravascular coagulation and primary fibrinolysis. The

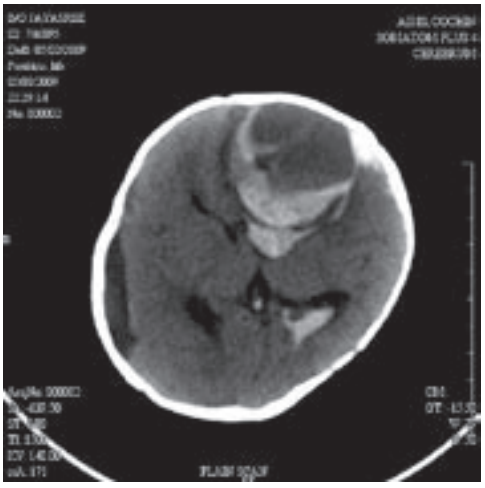

Figure 3. Acute left frontal bleed (At 6 months corrected age).

possibility of acquired afibrinogenemia is unlikely in our case due to its antenatal presentation. A detailed sepsis screen done was unremarkable.

The incidence of spontaneous abortions is high in afibrinogenemic and hypofibrinogenemic females.[13-15] Prepartum and postpartum bleeding are relatively common, and intraabdominal bleeding from ruptured corpus luteal cysts have been reported. We had explained regarding a detailed evaluation of the mother for any Fibrinogen disorders. Maternal Fibrinogen level was reported to be within normal limits. The parents were not willing to do any further genetic work up. We believe that the presence of consanguinity favours the possibility of autosomal recessive inheritance, although a detailed genetic work up was not possible.

Administration of regular infusions of fibrinogen is recommended to maintain pregnancies in afibrinogenemic woman and to reduce the incidence of postpartum hemorrhage.[16,17] Therapy should be initiated as early as possible because fetal loss in the first trimester is frequent. Fetal loss has occurred in some patients with fibrinogen levels above 50 mg/dL as well; therefore, it is recommended that levels be kept above 100 mg/dL through out the duration of the pregnancy.

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Different Fetal-Neonatal Outcomes in Siblings Born To A Mother with Graves-Basedow Disease After Total Thyroidectomy

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Abstract

Introduction: We describe three different fetal or neonatal outcomes in the offspring of a mother who had persistent circulating thyrotropin receptor antibodies despite having undergone a total thyroidectomy several years before.

Case presentation: The three different outcomes were an intrauterine death, a mild and transient fetal and neonatal hyperthyroidism and a severe fetal and neonatal hyperthyroidism that required specific therapy.

Conclusions: The three cases are interesting because of the different outcomes, the absence of a direct correlation between thyrotropin receptor antibody levels and clinical signs, and the persistence of thyrotropin receptor antibodies several years after a total thyroidectomy.

Introduction

Hyperthyroidism occurs in 0.05 to 0.2% of pregnancies. In about 95% of cases it is due to Graves-Basedow disease. In can also be due to Hashimoto's thyroiditis or, less frequently, to toxic adenoma, multinodular toxic goiter, subacute or silent thyroiditis, hydatidiform mole or choriocarcinoma.[1-3]

Neonatal hyperthyroidism develops in about 1 to 2% of babies born to mothers suffering from Graves-Basedow disease or, in a few cases, from Hashimoto's thyroiditis.[4] Neonatal hyperthyroidism is usually a transient disorder. It rarely appears at birth, it is more usual within the first week of life. Sometimes it can be lethal because of the development of heart failure.[3] It is usually caused by IgG antibodies stimulating the thyroid stimulating hormone (TSH) receptors of the thyroid gland, which are called thyrotropin receptor antibodies (TRAb). TRAb are able to cross the placental filter and stimulate fetal and neonatal thyroid function.[5,6] These antibodies can persist several years after thyroidectomy,[7-9] although, after total surgery, they usually decrease until they finally disappear.[9]

We describe three fetal or neonatal outcomes in the offspring of a mother with Graves-Basedow disease. The three cases are interesting because of the different outcomes, the absence of a direct correlation between TRAb levels and clinical signs, and the persistence of TRAb several years after a total thyroidectomy.

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Cases Presentation

The mother was a caucasian Italian woman, diagnosed with Graves-Basedow disease at the age of 14 years. She underwent first subtotal and then total thyroidectomy, and substitutive therapy with L-thyroxine commenced. Two years later, she was treated with radioiodine therapy because of thyroiditis on thyroid remnants. There was no evidence of thyroid tissue on the following scintigraphic evaluations.

Case 1

The first pregnancy occurred six years after the total thyroidectomy and four years after the radioiodine therapy. The mother was on substitutive therapy with L-thyroxine (225 µg/day). TRAb levels were not detected during the pregnancy. A cesarean section was performed at 34 weeks of gestational age (GA), because of intrauterine death of a male fetus. An autopsy was not performed.

Case 2

A year later, the woman became pregnant again. She was still on substitutive therapy with L-thyroxine (225 µg/day) and her hormone levels were within the normal range throughout the whole length of pregnancy. Fetal echocardiographic evaluation was performed one day before the delivery. The report was consistent with mild cardiomegaly and slight sinusal tachycardia, with a fetal heart rate (HR) of 160-170 bpm. TRAb were checked by an enzyme-linked immunosorbent assay (ELISA) with the suspicion of fetal hyperthyroidism. The levels were 32 U/l (normal value [n.v.] <12 U/l). Fetal thyroid ultrasonography was reported to be normal. The following day, the echocardiographic evaluation showed incipient fetal heart failure, severe tricuspid insufficiency, moderate sinusal tachycardia and low amniotic fluid. A ceesarean section was performed at 31 weeks of GA. A female baby was born with an Apgar score of 8-9 and a birth weight of 1870 g. She was transferred to the neonatal intensive care unit. On her 1st day of life (DOL), TRAb were 24 U/l (n.v. <12 U/l). Thyroid hormones and TSH levels (Figure 1) were consistent with neonatal hyperthyroidism (fT3 19.9 pg/ml (n.v. 2.3-4.2), fT4 >75 pg/ml (n.v. 8.5-15.5), TSH 0.03 UI/ml (n.v. 0.35-8)). The baby developed the following clinical signs of hyperthyroidism: considerable weight loss (-12% compared with birth weight), inconsolable crying, irritability and tachycardia at rest (HR 180-190 bpm). Echocardiogram was normal and was not

in agreement with prenatal data. Thyroid ultrasonography results were within the normal range. Both clinical signs and thyroid hormone levels normalized during hospitalization and therapy was not required. The baby was discharged on the 36th DOL. TRAb levels were 2 U/l (n.v. <1.5 U/l).

Case 3

The third pregnancy occurred nine years after total thyroidectomy and seven years after radioiodine therapy. The mother was receiving substitutive therapy with L-thyroxine (225 µg/day). Hormone and TSH levels were within the normal range throughout the whole pregnancy. Lugol's solution (potassium iodine) at the dosage of 8 mg/day was administered to the mother, starting in the 25th week of GA and continuing for 20 days, because of fetal tachycardia. From the 31st week until delivery, methimazole (20 mg/day) was added because of persistent fetal tachycardia. Lugol's solution (8 mg/day) was added during the last two weeks. TRAb levels, checked with a radio immunosorbent test (RIA), were about 400 UI/l at 19 and 29 weeks of GA, respectively (n.v. <10 UI/l). Fetal thyroid ultrasonography and echocardiography were normal. At 33 weeks of GA, a female baby was born by cesarean section, which was carried out due to the persistent fetal tachycardia. The birth weight was 2200 g and the Apgar score was 8-9. Echocardiographic evaluation at birth showed a patent ductus arteriosus with initial overload of left cardiac sections and slight tricuspid insufficiency. All these findings disappeared on the 6th DOL. HR was 160-180 bpm. Thyroid hormones levels were within the normal range and TRAb levels were 35 U/l (n.v. <12 U/l).

A considerable weight loss was detected (-10.5% compared with birth weight).

By the 7th DOL, the baby was extremely irritable with inconsolable crying. At that point, thyroid hormones and TSH levels (Figure 2) were consistent with hyperthyroidism (fT3 5.4 pg/ml (n.v. 2.3-4.2), fT4 34.7 pg/ml (n.v. 8.5-15.5), TSH 0.03 UI/ml (n.v. 0.35-8)), probably due to maternal antithyroid drug clearance. Lugol's solution was started (8 mg/3 times a day). On the 9th DOL, the newborn presented supraventricular parossistic tachycardia (HR 330 bpm). Diving reflex was necessary to reduce HR to 180 bpm. The dosage of Lugol's solution was increased to 24 mg/3 times a day and oral administration of diazepam was necessary, because of a persistent clinical pattern of hyperthyroidism (tachycardia, supraventricular extrasystoles, hyperexcitability, irritability, inconsolable crying and vomiting). On the 13th DOL, propranolol was started (1 mg/kg/day, in 4 daily doses), due to persistent tachycardia. It was withdrawn on the 28th DOL. The baby was discharged at one month old and discontinued Lugol's solution after a week. TRAb levels were not dosable at that point. Thyroid hormones levels were normal (fT3 3.3 pg/ml (n.v. 2.3-4.2), fT4 11 pg/ml (n.v. 8.5-15.5)) at two months of life. Thyroid ultrasonography consistently showed normal results.

Discussion

Newborns of mothers with autoimmune thyroid diseases, especially Graves-Basedow disease and Hashimoto thyroiditis, are at risk of developing thyroid dysfunction. Fetal hyperthyroidism may cause intrauterine growth restriction, intrauterine death, preterm birth, fetal tachycardia and non immune hydrops.[10]

Neonatal clinical signs of hyperthyroidism include: goitre, irritability, periorbital oedema, exophthalmos, craniosynostosis, microcephaly, tachycardia, arrhythmias, cardiac failure, voracious appetite, weight loss, diarrhoea, vomiting, sweating, flushing, hepatosplenomegaly, lymphadenopathy, thrombocytopenia and hyperviscosity.[8]

In our three cases, we report various clinical presentations, from fetal death to neonatal hyperthyroidism with different grade of severity.

In the first case, the pregnancy was not optimally monitored, so fetal death could be a consequence of unknown and untreated fetal hyperthyroidism due to TRAb transplacental passage. It is likely that the circulating TRAb were already present, because they were detected in the subsequent pregnancies and just one year later.

The second pregnancy was well monitored. The mother was treated with L-thyroxine, which ensured a normal thyroid function. The newborn developed signs of a mild neonatal hyperthyroidism (sinusal tachycardia, abnormal thyroid hormones and TSH levels, considerable weight loss, irritability) but they were transient and solved without any therapy.

In the third case, the TRAb of the mother, reported to be at normal levels, seemed to be higher than during the second pregnancy, although the values were not comparable because the different evaluation methods. However, the TRAb levels at birth were similar in the two siblings assayed with the same method.

This suggests that there is not a close correlation between TRAb levels and fetal and/or neonatal clinical features, which indicates that all newborns with TRAb, regardless to their value, should be monitored carefully. After a total thyroidectomy, TRAb levels should decrease, because of the lack of antigen stimulation; one mechanism of TRAb persistence could be microchimerism.

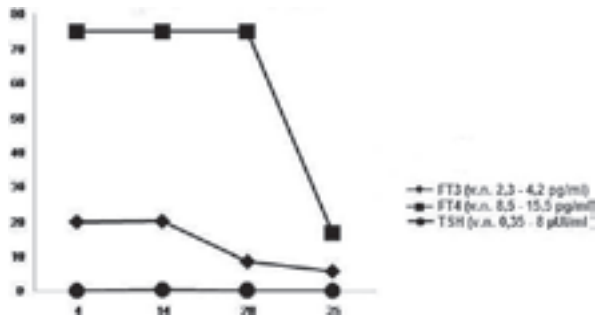

Figure 1 Serum levels of FT3, FT4 and TSH.

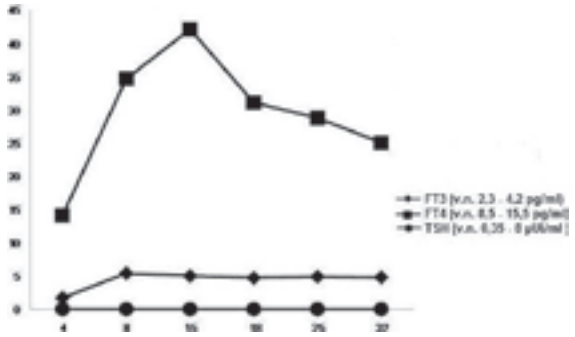

Figure 2 Serum levels of FT3, FT4 and TSH.

During pregnancy, fetal antigens could pass through the placental filter and become triggers for TRAb production.[11] Pregnancy is the most common source of microchimerism. Fetal cells or DNA can persist in women for several years after delivery.[12] Fetal microchimerism could contribute to pathogenesis of autoimmune diseases.[13] In our patient, the first pregnancy (intrauterine death) could have caused the passage of fetal cells and/or antigenic fragments able to induce and maintain TRAb production, even after the total thyroidectomy and the radioiodine therapy. The same mechanism could have occurred between second and third pregnancy.

We would have expected a better neonatal outcome in the third pregnancy because the decrease of TRAb levels. Instead we observed worsening of clinical fetal and neonatal manifestations and an increase of TRAb levels, which were reported to be in the normal range.

Conclusion

Our experience demonstrates that it is difficult to foresee a close temporal correlation between maternal thyroidectomy and fetal and/or neonatal outcome. It is important to consider occurrence of fetal and neonatal hyperthyroidism even several years after a total thyroidectomy. Surveillance of both mother and fetus and/or neonate using a multidisciplinary approach is mandatory.

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Does Opening a Milk Bank in a Neonatal Unit Change Infant Feeding Practices?

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Abstract

Background: Donor human milk banks are much more than simple centers for collection, storage, processing, and distribution of donor human milk, as they cover other aspects and represent a real opportunity to promote and support breastfeeding. The aim of our study is to assess the impact that opening a human milk bank has had on the proportion of infants receiving exclusive breast milk at discharge and other aspects related to feeding children with birth weight < or = 1500 g or < 32 weeks gestation admitted to the neonatal unit.

Methods: The study included babies of < or = 1500 g or < 32 weeks gestation. Fifty infants born from February to July in 2006, before the opening of the human milk bank, and 54 born from February to July in 2008, after its opening, met inclusive criteria. We collected data about days of hospital stay, hours of life when feeding was started, hours of life when full enteral feeding was attained, the type of milk received during admission, and the type of feeding on discharge.

Results: Children born in 2008 commenced feeding 16 hours earlier than those born in 2006 (p=0.00). The proportion of infants receiving exclusive breast milk at discharge was 54% in 2006 and 56% in 2008 (p=0.87). The number of days they received their mother's own milk during the first 28 days of life was 24.2 days in 2006, compared to 23.7 days in 2008 (p=0.70). In 2006, 60% of infants received infant formula at least once in the first 28 days of life, compared to 37% in 2008 (p=0.01).

Conclusions: The opening of a donor human milk bank in a neonatal unit did not reduce the proportion of infants exclusively fed with breast milk at discharge, but did reduce the proportion of infants that received infant formula during the first four weeks of life. Also, having donor human milk available enables commencement of enteral feeding earlier.

Background

Breastfeeding is the normal way to feed infants by providing them the nutrients they need for healthy growth and development.[1-6] Breastfeeding also facilitates the attachment between mother and child, as it requires physical contact and interaction.[7] Artificial feeding is an important risk factor for infant morbidity and mortality, especially for premature children.[8,9] However, mothers do not always have enough breast milk available to feed premature children. In these cases, donor human milk is the best alternative.[1] The benefits of using donor human milk for premature and sick infants in the neonatal intensive care unit are well known. Evidence has demonstrated that donor human milk protects against necrotizing enterocolitis[2-4,10-12] and infections[13] during the neonatal period. Long-term benefits have also been shown, such as enhanced psychomotor developmental indices[14] or reduced cardiovascular risk factors.[15]

The donor human milk bank of the Neonatology Department of Hospital 12 de Octubre in Madrid was inaugurated on 17 December 2007. It is the second milk bank operating in Spain, after the milk bank in the Balearic Islands, and the first one to be opened in a neonatal unit. The usual recipients of donor milk are premature children < 32 weeks gestation or those weighing < 1500 grams, when their mother's milk supply is inadequate to meet the baby's needs. Other potential recipients are infants with feeding intolerance or surgical patients with short gut syndrome.

Before the opening of the milk bank, one of the possible problems to be considered was if the neonatologists would be as supportive as they were before encouraging mothers to breastfeed, once they knew they had human milk at their disposal. On the other hand it could be the mothers who, knowing about the bank, found themselves less motivated to do frequent extractions and all the effort required to breastfeed their children. Therefore, the aim of this study is to assess the impact that opening a milk bank has had on the proportion of infants receiving exclusive breast milk at discharge and other aspects related to feeding children with birth weight < or = 1500 g or < 32 weeks gestation admitted to the neonatal unit. And also whether enteral feeding was started earlier and was fully attained in less time with donor human milk rather or with infant formula.

Methods

We included newborns born in our hospital, with birth weight < or = 1500 g or < 32 weeks gestational age, between 1st February and 31st July of 2006 and in the same period in 2008, when the milk bank was already working. In 2006 and 2008, 61 and 62 infants with these characteristics were respectively admitted. Children whose mothers had no chance to breastfeed due to

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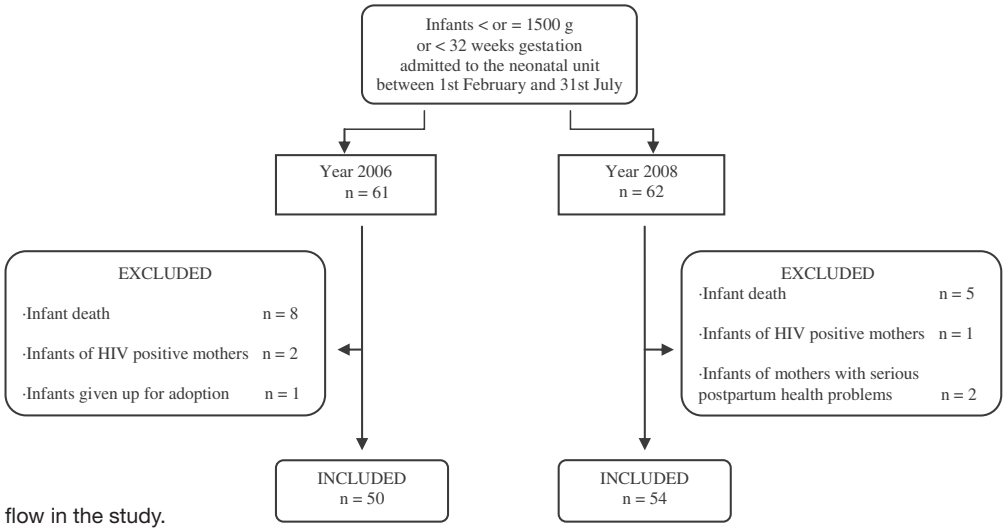

Figure 1. Participant flow in the study.

serious postpartum health problems, HIV infection or because the child was given in adoption, were excluded (3 cases in each period). In 2006, 8 infants (13%) died before discharge and 5 (8%) in 2008. Finally, 50 infants from 2006 and 54 from 2008 were included in the study (Figure 1). The aim of the study was to evaluate the foundation of a human milk bank in a neonatal unit by a before and after study design. In our unit we have concurrent data about the evolution of the infants with birth weight < or = 1500 g or < 32 weeks gestation age, in this study we used the already collected information. The 1st February was selected as the starting date because it is when the bank was fully operating.

For children born in 2006, the enteral feeding administered was their mother's own milk, infant formula or both. In 2008, in addition to the mother's own milk and/or infant formula, donor human milk was also used. When the milk bank was starting up there were few milk reserves, nevertheless, all the children with weight < or = 1500 g or < 32 weeks gestation age were fed with donor milk, at least during the first four weeks of life, if they did not have their own mother's milk or if this was insufficient. Infants received parenteral feeding until full enteral feeding was attained. The criterion for discharge from the unit has not been modified over these years.

We collected data about the following variables: maternal age, previous pregnancies, type of birth, gender, age at gestation, and birth weight. Days of hospital stay, hours of life when enteral feeding was started, hours of life when full enteral feeding was attained, the type of milk received during admission, and the type of feeding on discharge (referring to the type of feeding that they received in the last 48 hours before discharge) were considered as result variables.

We define "exclusive breastfeeding" and "exclusive breast milk" as feeding babies with no other food or liquid, not even water, with the exception of drops or syrups consisting of vitamins, mineral supplements or medicine, apart from breast milk. Besides, we define "partial breastfeeding" and "any breast milk" as feeding infants with breast milk and other sources of energy and nutrients, like an addition of nutritional supplements for human milk. When we talk about "breastfeeding" and "breast milk" the term covers any kind of breastfeeding/breast milk feeding with or without infant formula or other infant food.

During their stay in the neonatal unit, the babies were fed directly from the breast, received their own mother's milk or donor milk by tube or by syringe according to their abilities to feed.

The mothers provided written consent so data for research could be used. The Institutional Review Board of the study centre approved the recruitment methods, the consent process and the study protocol.

A descriptive statistical analysis was performed. Central tendency and dispersion measurements were calculated. For the analytical study, associations were estimated between the different variables collated for the two groups (2006, 2008). A statistically significant association was considered when $p < 0.05$. The statistical test used was the t test and Wilcoxon test for comparison of means and chi-square test and exact Fisher test for categorical variables. The statistical program SAS software (SAS Institute Inc, Cary NC) was used to perform the analysis. Quantitative variables were presented as mean and standard deviation. The relative frequency of the categorical variables were calculated and represented as percentages. The main purpose of the present study was to compare the proportion of infants receiving exclusive breast milk at hospital discharge before and after the opening of the milk bank.

Results

The characteristics of mothers and infants from 2006 and 2008 are compared in Table 1. Regarding the type of birth, 66% of the children included in the study from 2006 and 70% from 2008 (p=0.63) were born by caesarean section and 50% and 59% in 2006 and 2008 respectively, were males. Table 2 shows the proportion of children who received different types of feeding during the first 28 days of life in 2006 and 2008. No child received exclusive infant formula in either 2006 or 2008. Thirty infants (60%) in 2006 and 20 (37%) in 2008 received formula at some time during the first 28 days of life (p=0.01). Table 3 shows the results referring to hours of life until commencing feeding, hours of life when full enteral feeding was attained, and the days fed with the mother's own milk during the first 28 days of life. Twenty-seven (54%) and 30 (56%) infants, received exclusive breast milk 48 hours before discharge (p=0.87) while 43 (86%) and 42 (78%) received "any breast milk" upon discharge (p=0.27), in 2006 and 2008 respectively.

Table 1 Characteristics of mothers and neonates

	2006 (n = 50)		2008 (n = 54)		
	Mean ± standard deviation	Range	Mean ± standard deviation	Range	p-value
Maternal age (y)	28.4 ± 6.4	15 - 41	31.6 ± 5.9	16 - 44	0.01
Previous pregnancy	0.8 ± 1.2	0 - 5	0.8 ± 1.0	0 - 4	1.00
Gestational age (w)	30.9 ± 2.7	25 - 36	30.2 ± 2.2	25 - 35	0.16
Weight of neonate (g)	1285 ± 297	675 - 2120	1291 ± 351	670 - 2210	0.92
Days admission	48.1 ± 22.2	18 - 112	50.6 ± 24.0	17 - 108	0.58
Corrected age at time of discharge (w)	37.7 ± 2.5	33.3-46.9	37.4 ± 2.2	33.7-43.9	0.50

Values are expressed as mean, standard deviation and range.

Table 2 Type of milk received during first 28 days of life

	2006		2008	
	Number of children (n = 50)	%	Number of children (n = 54)	%
[1] Exclusively mother's own milk	20	40	7	13
[2] Mother's own milk + donor milk	0	0	27	50
[3] Mother's own milk + infant formula	30	60	2	4
[4] Mother's own milk + donor milk + infant formula	0	0	18	33
[5] Exclusively infant formula	0	0	0	0
[6] Fortified	15	30	7	13

[1] Infants fed only with mother's own milk directly from the breast or by tube or syringe.
[2] Infants who received donor milk besides mother's own milk.
[3] Infants who received infant formula besides mother's own milk.
[4] Infants who received donor human milk and infant formula besides mother's own milk.
[5] Infants fed only with infant formula.
[6] Addition of a nutritional supplement for human milk.

Discussion

In premature children < or = 1500 g or < 32 weeks gestation, feeding with donor human milk, used as a milk substitute for mother's own milk when it is not available or as an additional supply when mother's own milk is not enough, has not led to a decrease in the proportion of children exclusively fed with breast milk upon discharge from hospital. The total number of days that premature children received their mother's own milk during the first four weeks of life is similar in both time periods. The availability of donor milk has reduced by 23% the proportion of children who receive infant formula at some time during their admission in our neonatal unit.

The percentage of infants receiving exclusive breast milk was reduced from 40% to 13%, because in 2008 donor milk was used when there was not enough milk from their own mothers, whereas in 2006, the infants were fed by parenteral nutrition the first days of their lives to avoid infant formula.

The use of donor milk has dropped the age of commencing enteral feeding by 16 hours. Neonatologists at Hospital 12 de Octubre have always tried to introduce enteral feeding as early as possible, but in very preterm infants whose mothers were willing to breastfeed, they waited for the mother to have enough breast milk to start feeding in order to avoid exposure to infant formula during the first days of life. Now donor human milk is available, this delay is avoided and enteral feeding is started earlier.

This study has had an early onset in order to determine whether the opening of a donor human milk bank is having a negative effect on the proportion of infants receiving exclusive breast milk upon discharge. The objective of our study was to make a self-evaluation of the department and to assess how the professionals work in the promotion and support of breastfeeding in mothers of very premature children. The fact that enteral feeding can be started earlier probably leads to a reduction in the number of hours with a central venous catheter and therefore to a possible reduction in the risk of infection.[16,17]

The rates of breastfed children vary according to the different countries regarded. World Health Organization estimates that only 35% of the infants from all over the world are exclusively breastfed during the first four months of their lives.[1] These low rates are really worrying so different countries are adopting measures, such as The United States in the program "Healthy People 2010",[18] which sets the objective to increase the proportion of mothers who breastfeed their infants to 75% in the early postpartum period and to 50% during at least six months postpartum. There are studies that show that there are higher rates of breastfed children among those who have to be interned in a neonatal unit.[19,20] However, breastfeeding in preterm babies is more difficult because of their impossibility to feed directly from the breast and therefore they are less likely to receive breast milk than term infants.[21]

The proportion of infants exclusively fed with breast milk upon hospital discharge in very premature children in the Hospital 12 de Octubre neonatology department is approximately 55% for exclusive breast milk and 80% if we include any breast milk. Both remained constant throughout the study period. These results are satisfactory; however, we have to offer the same support to mothers who decide to breastfeed their premature children with their own milk, despite having donor milk available.[20]

Donor human milk banks are much more than simple centers for the collection, storage, processing, and distribution of donor human milk, as they cover other aspects and represent a real opportunity to promote and support breastfeeding. The donor human milk bank of Hospital 12 de Octubre works to promote and support breastfeeding and it also encourages the families to follow the kangaroo method, a mother care method

Table 3 Commencement of enteral feeding, full enteral feeding, and days with mother's own milk

	2006 (n = 50)		2008 (n = 54)		
	Mean ± standard deviation	Range	Mean ± standard deviation	Range	p-value
Hours of life at commencement of EF	42.9 ± 26.4	9 - 137	26.6 ± 22.4	3 - 148	0.00
Hours of life at full EF	229.3 ± 190.2	58 - 1235	185.1 ± 117.8	61 - 713	0.16
[1] Days with mother's own milk during 28 days of life	24.2 ± 5.5	7 - 29	23.7 ± 7.3	2 - 29	0.70

Values are expressed as mean, standard deviation and range.

Abbreviation: EF: enteral feeding.

[1] Days that infants received mother's own milk, either exclusively or partially, directly from the breast or by tube or syringe, during the first 28 days of life.

that promotes skin to skin on the mother's chest and therefore facilitates breastfeeding.[22] The revision of the number of babies exclusively fed with breast milk, as we have taken into account in this study, helps to attain the objective of implementing the baby-friendly hospital initiative proposed by UNICEF in our maternal-children's hospitals.[23]

Conclusions

There is very little information on the impact of the opening of a human milk bank in a neonatal unit and how this affects the proportion of children receiving exclusive breast milk at discharge. We believe that this study--in spite of its limitations--is of interest to other units which plan to open a donor human milk bank. We demonstrate how milk banks do not cause reduction in the rates of breast milk feeding. Besides, they help to reduce the proportion of infants that receive infant formula in the first weeks of life and allow them to attain full enteral feeding as soon as possible.

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Neonatal Arterial Iliac Thrombosis in Type-I Protein C Deficiency

Elisabetta Tridapalli, Marcello Stella, Maria G. Capretti, Giacomo Faldella

Abstract

A male infant born by cesarean section at 38 weeks of gestational age (BW 4055 g; Apgar 9-10), in the first two hours of life his right leg became hypovascularizated. Normal values of leukocities, red cells, haematocrit, hemoglobin, platelets. C-Reactive Protein negative. Electrolytes and coagulation tests were normal. Normal vitamin K coagulation proteins levels. Serological tests for TORCH (IgM) and Parvovirus (IgG and IgM) were negative. Sonography showed a reduced blood flow in the iliac artery and reported a 1 cm long vessel thrombosis. From 8 hours of life we administred an intravenous infusion of unfractionated heparin (UFH) 75 UI/Kg for the first 10 minutes then 28 UI/Kg/h. On the 2nd day tests were performed to assess absence of inhibiting-clot factors. The dosage of homocysteine, protein S and antithrombin was normal. FV Leiden and antiphospholipid antibodies were negative. The mapping of G20210A prothrombin's gene resulted normal, whereas the concentration of Protein C was lower than normal: activity 46% (68-150%), antigen 35% (70-150%). The same deficiency was also found in the father. The mother showed normal concentrations. No episodies of thrombosis events were documentated in the family.

The intravenous unfractionated heparin (UFH) therapy was replaced after 64 hours by subcutaneous nadroparin 600 UI twice/day, which was stopped 5 days later when the vessel sonografic images were completely normal. During the hospitalization the infant didn't show bleeding. The child was followed-up yearly until 4 years of age: he was well and had a normal body and mental development.

The final diagnosis is likely to be of a permanent protein C deficiency in heterozygous form. Our case is interesting because the first manifestation was an important thrombosis of large vessel that occurred within a few hours of life in absence of perinatal risk factors, as if it was a homozygous disease, but the patient had a heterozygotic form. In literature few cases are reported of heterozygous forms that became symptomatic, but only in old age.

After a severe first manifestation, a normal and asymptomatic development is uncommon without new thrombotic episodes. In our patient the neonatal thrombosis was the sole event in his life.

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Introduction

In the neonatal period thrombosis is a rare event. In two registers from Canada and Germany[1,2] the incidence of this pathology was respectly 2.4/1000 admission to NICU and 5.1/100000 births. The main causes are the presence of central line, asphyxia, septicaemia, dehydration and maternal diabetes.

Anormalities of antithrombin and the protein C system have been documented in association with spontaneous neonatal thrombotic problems.

Protein C deficiency is a genetic trait that predisposes to the formation of venous or arterial clots.

There are two kinds of Protein C deficiency: type I and type II. Type I deficiency results from an inadequate amount of protein C, that functions normally, but the quantity of protein C present is insufficient to control the coagulation cascade. Type II deficiency is characterized by defective protein C molecules: the protein C level is normal, but it's unable to interact with the other molecules involved in coagulation.

Case Report

A male infant born by cesarean section at 38 weeks of gestational age and with a birth weight of 4,055 g (Apgar Score: 9 at 1' and 10 at 5'), was referred to our NICU because in the first two hours of life his right leg became pale, hypothermic and cyanotic and oxygen saturation was lower than in the other limbs (70-80% vs. 98-100%).

Maternal vaginal scrub was negative for Agalactie group B Streptococcus and maternal screening for the common infections had negative results (HBV negative, HIV negative, CMV immune, Rubella virus immune, Toxoplasma Gondii not immune, Syphilis negative). No disease was referred during the pregnancy.

At birth a single intramuscular dose of vitamin K was administered as antihaemorrhagic prophylaxis on the left thigh. The hypovascularization of his right leg was confirmed, even though he wasn't in immediate danger when he was admitted.

Laboratory studies revealed normal values of leukocities, red

cells, haematocrit, hemoglobin, platelets. (White Blood Cells 13.080/mmc: N 68.5%, L 24.7%, M 3.6%, E 1.2%, B 0.9%; Red Cells 5.660.000/mmc, Hb 19.1 g/dl, Hct 56.2%, PLT 158.000/mmc). C-Reactive Protein negative. Electrolytes and coagulation tests were normal: aPTT-ratio 1.09 range (0.8-1.20); PT% 70% (70-100%); INR 1.27 (0.92-1.30). Our laboratory found normal vitamin K coagulation proteins levels (FII, FV, FVII, FVIII, FIX, FX, FXI, FXII). Serological tests for TORCH (IgM) and Parvovirus (IgG and IgM) were negative. Sonography showed a reduced blood flow in the iliac artery and reported a 1 cm long vessel thrombosis. His heart and other arteries appeared to be normal. Cerebral and renal ultrasound findings were normal. From 8 hours of life we administred an intravenous infusion of unfractionated heparin (UFH) 75 UI/Kg for the first 10 minutes then 28 UI/Kg/h.

On the 2nd day tests were performed to assess presence/absence of inhibiting-clot factors. The dosage of homocysteine, protein S and antithrombin was normal. FV Leiden and antiphospholipid antibodies were negative. The mapping of G20210A prothrombin's gene resulted normal, whereas the concentration of Protein C was lower than normal: activity 46% (normal range 68-150%), antigen 35% (70-150%).

The same deficiency was also found in the father: activity 61%, antigen 50%, but he was asymptomatic. The mother showed normal protein C concentrations. No episodies of thrombosis or other thromboembolic events were documentated in father's family.

The newborn showed both a clinical and sonographic gradual improvement. The intravenous unfractionated heparin (UFH) therapy was replaced after 64 hours by subcutaneous nadroparin 600 UI twice/day, which was stopped 5 days later when the vessel sonografic images were completely normal.

The patient was discharged from the hospital after 10 days with a year long prophylactic 20 mg/day oral dose of aspirin. During the hospitalization the infant didn't show bleeding, the cerebral sonography at the discharge resulted normal. The child was followed-up yearly until 4 years of age: he was well and had a normal body and mental development. Therapy with plasma or protein C was never necessary.

During the observational period the concentration of Protein C was confirmed low: at 1 year of life activity was 46% and antigen was 35%; at 2 years activity 47% and antigen 48%, at 3 years activity 52% and antigen 50%, at 4 years activity 40% and antigen 34%.

Discussion

The protein C levels gradually improve during life.[3] Protein C concentration is 15% of the adult level in the infant, 35% in the premature newborn, 80% in the adolescent and it improves by 4% every 10 years.[4,5]

Protein C deficiency is present in approximately 0.2% of the population. This rate includes asymptomatic people and patients with severe thrombotic disease. Symptoms depend on the genetic mutation on the chromosome 2 q13-q14. People with heterozygous form can usually live all their life without clinical problems. The classical neonatal manifestation of homozygous protein C deficiency is a severe form of thrombosis of the large vessels or a purpura fulminans that occurs within a few hours or days of life, causing tissue necrosis and gangrenous and disseminated intravascular coagulation.[3,6,7]

Treatment of a patient with protein C deficiency depends on the individual patient's risk of thromboembolic disease. In patients with homozygous form the risk of death from thrombosis is imminent. As a result, treatment is based on providing a source of Protein C.[3] This can be done with fresh frozen plasma (FFP) or with human plasma protein C concentrate. At this time there are still no studies that compare the use of the protein C concentrates versus FFP in severe protein C deficiency related thrombosis.

The treatment of deep thrombosis is commonly defined in a bolus dose of unfractionated heparin (UFH) from 75 to 100 U/kg and a maintenance dose of 28 U/Kg/h for newborns or 20 U/Kg/h for children >1 year of age.[8] The few studies on UFH in newborns show that the clearance is faster than that for older children due to a larger volume of distribution.[9,10] Also pharmacokinetic research shows the same different UFH clearance between piglets and adult pigs.[11]

An alternative recommendation is the only supportive care, waiting for anticoagulation if radiologic monitoring show an extension of the thrombosis.[8] Central venous line should be removed if possible.

In our case report the final diagnosis is likely to be of a permanent protein C deficiency in heterozygous form, especially considering the patient's clinical history and father's protein C levels. Our case is interesting because the first manifestation was an important thrombosis of large vessel that occurred within a few hours of life in absence of perinatal risk factors, as if it was a homozygous disease, but the patient had a heterozygotic form. In literature,[6,8,11-14] thought the clinical pattern of heterozygous disease is commonly described as very variable, few cases are reported of heterozygous forms that became symptomatic, but only in old age.

After a severe first manifestation of the thrombosis a normal and asymptomatic development is uncommon without new thrombotic episodes. In our patient the neonatal thrombosis was the sole event in his life. The child has grown well until now without physical or mental problems.

As these patients are often asymptomatic, to perform coagulation tests and the dosage of protein C on parents is the only way to identify newborns with a high risk of fatal thrombotic events. Further epidemiological studies are necessary to asses the real benefit/cost ratio of a parental prenatal screening to diagnose neonatal cases and to begin therapy sooner.

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Nitric Oxide Synthases in Infants and Children with Pulmonary Hypertension and Congenital Heart Disease

Thomas Hoehn, Brigitte Stiller, Allan R. McPhaden, Roger M. Wadsworth

Abstract

Rationale: Nitric oxide is an important regulator of vascular tone in the pulmonary circulation. Surgical correction of congenital heart disease limits pulmonary hypertension to a brief period.

Objectives: The study has measured expression of endothelial (eNOS), inducible (iNOS), and neuronal nitric oxide synthase (nNOS) in the lungs from biopsies of infants with pulmonary hypertension secondary to cardiac abnormalities (n=26), compared to a control group who did not have pulmonary or cardiac disease (n=8).

Methods: eNOS, iNOS and nNOS were identified by immunohistochemistry and quantified in specific cell types.

Measurements and main results: Significant increases of eNOS and iNOS staining were found in pulmonary vascular endothelial cells of patients with congenital heart disease compared to control infants. These changes were confined to endothelial cells and not present in other cell types. Patients who strongly expressed eNOS also had strong expression of iNOS.

Conclusion: Upregulation of eNOS and iNOS occurs at an early stage of pulmonary hypertension, and may be a compensatory mechanism limiting the rise in pulmonary artery pressure.

Introduction

Nitric oxide (NO) plays a central role in the maintenance of normal pulmonary vascular tone and healthy lung function.[1] All 3 isoforms of nitric oxide synthase (NOS) are present in the lungs and contribute to NO production in specific cell types.[2]

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Pediatric pulmonary disease is associated with endothelial dysfunction and consequently reduced NO delivery from the pulmonary vascular endothelium.[3] Moreover there is evidence from experimental models of neonatal pulmonary hypertension that impairment of NOS can generate reactive oxygen species, leading to a further cycle of deterioration of the vascular endothelium.[4] In adults with pulmonary arterial hypertension it has been demonstrated that output of NO is diminished,[5] and that those patients who responded well to therapy had corresponding improvement in exhaled NO.[6] NO status can be improved by administration of inhaled NO which is valuable in the management of infants with pulmonary hypertension.[7-10]

We chose to immunohistochemically investigate changes in NOS expression during the early course of pulmonary hypertension. Studies with experimental models of pulmonary hypertension have shown upregulation of endothelial NOS (eNOS) in the endothelial layer of both large and small pulmonary arteries.[11] Increased expression of eNOS was due to the initiating stimulus (hypoxia) and was not secondary to hyperperfusion.[12] The upregulation of eNOS correlated in time with the development of pulmonary hypertension.[13] In cultured pulmonary endothelial cells, acute exposure to hypoxia also upregulated eNOS.[14] There are several molecular mechanisms through which hypoxia can stimulate eNOS accumulation in endothelial cells, including hypoxia inducible factor[15] and phosphorylated cyclic-AMP response element binding protein (pCREB).[16] Others have shown decreased expression of eNOS during chronic hypoxia in rats[17] and in human endothelial cells.[18] However in patients with pulmonary hypertension, it is less clear what changes in NOS isoform levels occur. In infants with congenital diaphragmatic hernia, it has been reported that pulmonary endothelium levels of iNOS were decreased[19] or unchanged,[20] and similarly that pulmonary vascular endothelium levels of eNOS were decreased[21] or unaltered.[19,20] In adults with primary or secondary pulmonary hypertension, eNOS was reduced in the endothelial layer of small pulmonary arteries[22,23] but increased in plexiform lesions.[22] Given that the clinical studies have used patients with advanced disease whereas the experimental animal studies looked at an early stage of relatively mild pulmonary hypertension, we hypothesised that eNOS is raised initially when pulmonary hypertension is developing but falls at a late stage when endothelium dysfunction becomes severe. The aims of the present study were therefore to immunohistochemically determine the expression of the three isoforms of NOS in the lungs of infants with secondary pulmonary hypertension since they will have been exposed to elevated pulmonary pressure for

Table 1: Patient details

dob	sex	Systolic PA-pressure pre-surgery	PVR dyn	Systolic PA-pressure post-surgery	Systolic PA-pressure after 6-36 months	Qp:Qs	Rp:Rs	Diagnosis	Age at surgery (months)	Heath + Edwards	Rabinovich
26.12.1990	f	75	1178	24	17	7,2	0,01	complete atrio-ventricular septal defect ventricular septal defect, atrial septal	5	2	a
28.03.1991	f		424			5	0,08	defect	6	2	b
20.01.1985	m		388			3	0,10	ventricular septal defect ventricular septal defect, atrial septal	11	2	b
20.03.1984	m		160			1,6	0,11	defect	60	1	a
20.10.1987	f		968			3,9	0,15	ventricular septal defect	12	2	c
03.12.1982	m	83	294	60	11	2,9	0,24	complete atrio-ventricular septal defect	84	1	c
12.08.1988	f	100	2400	30	22	2,6	0,27	complete atrio-ventricular septal defect ventricular septal defect, patent ductus	7	2	c
27.02.1991	f		1425			3,4	0,29	arteriosus, coarctation ventricular septal defect, atrial septal	6	1	a
25.11.1988	f		1855			2,8	0,30	defect	5	1	b
17.01.1985	f	80	2059	25	30	1,5	0,32	complete atrio-ventricular septal defect	14	0	0
14.06.1988	f	75	2222	25	14	2,1	0,32	complete atrio-ventricular septal defect single vessel disease, partial anomalous	5	1	b
09.03.1984	f		1285			1,9	0,33	pulmonary venous drainage	48	2	c
25.05.1990	m		2536			0,71	0,40	thoracic aortic constriction double-outlet right ventricle, ventricular	2	1	b
17.10.1980	m		717			1,9	0,40	septal defect, coarctation	11	3	c
06.04.1987	m		982			2,1	0,40	complete atrio-ventricular septal defect	19	1	c
15.05.1990	m		1883	35		2,3	0,41	ventricular septal defect	7	2	b
13.05.1988	f		1509			1,8	0,43	ventricular septal defect	11	2	0
10.02.1988	f	90	2061	38	18	1,8	0,45	complete atrio-ventricular septal defect	12	2	0
18.05.1990	f		3593			0,83	0,47	complete atrio-ventricular septal defect	4	1	a
22.09.1988	m		3537			1,2	0,50	atrial septal defect, patent ductus arteriosus	2	1	b
31.10.1989	m		2166			1,5	0,52	ventricular septal defect	11	1	b
03.11.1989	m		2617			1,4	0,71	mitral incompetence	11	2	a
05.04.1987	m	100	2135	25	35	1,6	0,71	ventricular septal defect	30	0	?
06.10.1984	f	93	983	75	34	1	0,83	ventricular septal defect	48	4	c
24.10.1988	f	83	2143	35	14	1,5	0,83	complete atrio-ventricular septal defect	6	2	b
25.05.1988	f	110	1888	40		1,3	0,90	ventricular septal defect	3	4	?

(CAVSD: complete atrio-ventricular septal defect; ASD: atrial septal defect; VSD: ventricular septal defect; MI: mitral incompetence); n = 26

a relatively short time and may therefore reveal what happens during the development of pulmonary hypertension.

Methods

Patients: Patients (n=26) had a mean age of 16.9 months (±SEM=4.02, median=11 months, range: 2 months to 7 years) and had cardiac surgery performed between December 1985 and October 1991 at the German Heart Institute, Berlin, Germany. All patients had congenital cardiac defects typically associated with pulmonary hypertension and had a lung biopsy taken during corrective cardiac surgery. Surgery markedly reduced systolic pulmonary artery pressure with further reduction at follow up in patients, from whom data were available (for patient details see Table 1). Informed consent was obtained from the infants' parents, and the study protocol had previously been approved by the local institutional ethics committee.

Table 2: Controls

dob	sex	Age at death (months)	Diagnosis	PH
21.10.1992	f	5	Pulmonary stenosis	no
21.12.1991	m	17	D-transposition of the great arteries	no
04.08.1993	m	2	Hypoplastic left heart syndorme	no
06.04.1993	f	9	Mitochondriopathy	no
28.06.1993	m	10	Sudden infant death syndrome	no
20.07.1995	m	7	Carnitine-Palmitoyl-Transferase-Defect Type I	no
07.04.1996	f	2	Sudden infant death syndrome	no
22.04.1996	f	5	Omenn syndrome	no

(d-TGA: d-transposition of the great arteries; HLHS: hypoplastic left heart syndrome; SIDS: sudden infant death syndrome; CPT-defect: Carnitine-Palmitoyl-Transferase-Defect); n = 8

Control subjects: Control infants (n=8) were chosen from infants and children having died from various non-pulmonary causes, who had an autopsy performed at the Department of Paidopathology, Humboldt University Berlin, Germany. None of these patients had clinical or echocardiographic evidence of pulmonary hypertension nor was there any clinical or radiologic evidence of pulmonary infection. Controls had a mean age of 7.1 months (±SEM=1.75, median: 6 months, range: 2 to 17 months). For control details see Table 2.

Methodology for immunohistochemistry: Lung tissue was supplied as paraffin-embeded tissue blocks. Sections (4 µm) were cut from the blocks, rehydrated and then treated for antigen retrieval by microwave pressure cooking or trypsin incubation. The sections were then treated to block non-specific binding of primary and secondary antibodies and non-specific reaction with chromogens as described previously.[11] Sections were then incubated with the specific antibody for 60 minutes at room temperature (eNOS: catalogue reference 610296, BD Biosciences, UK, used at 1:1000 dilution along with pressure cooking antigen retrieval; iNOS: catalogue reference 610328, BD Biosciences, UK, used at 1:500 dilution along with pressure cooking antigen retrieval; nNOS: catalogue reference 610308, BD Biosciences, UK, used at 1:400 dilution along with trypsin antigen retrieval). Bound antibody was detected using goat anti-mouse IgG conjugated with horseradish peroxidase using a streptavidin-biotin link, and visualized with diaminobenzidine. In negative controls the primary antibody was replaced with pre-immune serum. Sections were counterstained using hematoxylin and viewed by light microscopy.

Staining intensity was quantified as follows: 0=negative; 0.5=faint/blush; 1=mild; 2=moderate. Separate quantification was performed for eNOS in small artery endothelium, small artery media, respiratory epithelium, alveolar macrophages. Antibody dilutions were chosen in order to differentiate between groups i.e. although there is usually baseline expression of eNOS in controls; dilutions were titrated until there was no eNOS expression visible in controls. For iNOS and nNOS, quantification was carried out in the same cell types except that alveolar macrophages and alveolar lining cells were combined. Vessels of an internal diameter of less than 250 µm were regarded as small pulmonary arteries.

Statistics: For each antibody and cell type, the staining intensity of the cardiac patients was compared to the staining intensity of the normotensive patients using the Mann-Whitney-U test. Spearman's correlation coefficient has been calculated to describe the correlation between eNOS and iNOS expression. Statistical significance was assumed at $p < 0.05$.

Results

In all of the lung sections from infants with pulmonary hypertension, thickening of the small pulmonary arteries was evident. In contrast there were no abnormalities of the pulmonary arteries in any normotensive control patients. There was expression of eNOS in the endothelial layer of small pulmonary arteries, the respiratory epithelium, and alveolar macrophages. Expression of eNOS was greatly increased in pulmonary hypertensive lungs compared to control lungs in the pulmonary artery endothelium (Figure 1, Figure 2). However there were no significant differences between controls and patient groups in staining for eNOS in alveolar macrophages and in the respiratory epithelium. Expression of iNOS was found in the small pulmonary arteries, both media and endothelium, the respiratory epithelium, and in alveolar macrophages/alveolar lining cells. There was significant upregulation of iNOS in endothelial cells of pulmonary hypertensive patients compared to control patients, but there were no differences between the cases and controls at any of the other cell types where iNOS was found (Figure 1, Figure 2). Expression of nNOS was very light in all cell types in the lung and was not different between cases and controls (Figure 1, Figure 2).

There was a significant correlation of eNOS and iNOS staining intensity in the pulmonary artery endothelium, such that patients having stronger staining in eNOS also had higher levels of iNOS (Spearman's correlation coefficient 0.72, p=0.0004).

Discussion

Here we report the consistent finding of an increase in eNOS expression during conditions of increased pulmonary vascular resistance secondary to congenital heart disease in infants and children. This upregulation appears to be linked to pulmonary hypertension in that it occurs in the pulmonary artery endothelium, but not in other sites where eNOS is present and nor is there any change in nNOS. We have previously shown increased expression of eNOS in pulmonary endothelial cells in infants with persistent pulmonary hypertension of the newborn (PPHN)[24] and in congenital pulmonary lymphangiectasis.[25]

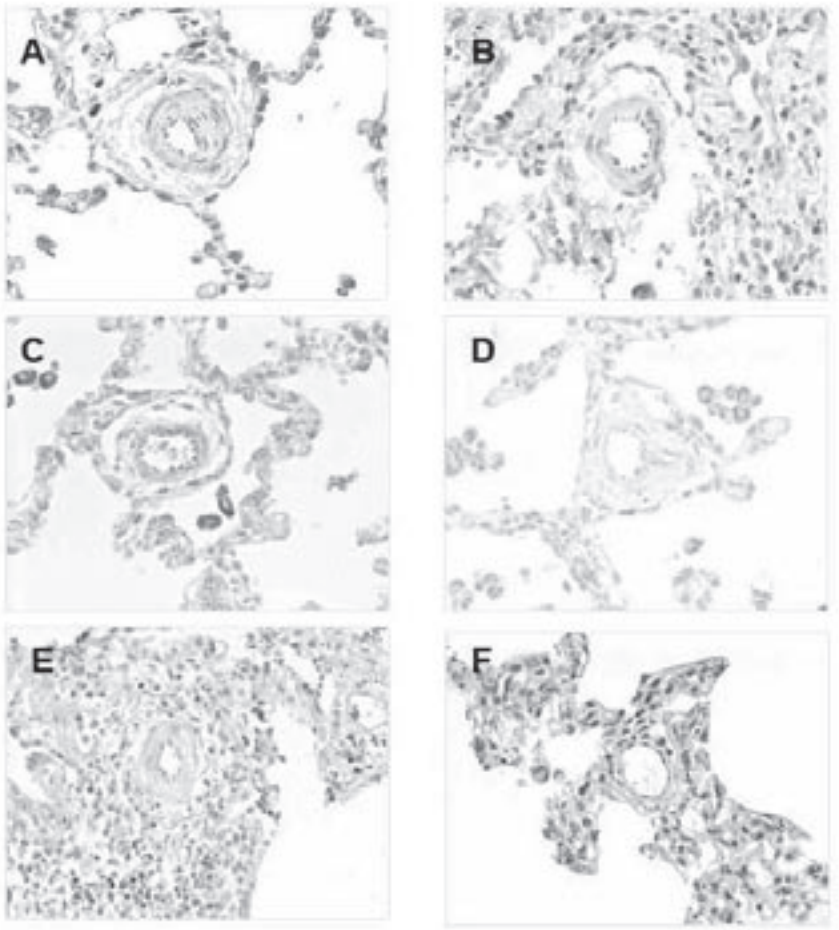

Figure 1. Lungs from infants with pulmonary hypertension (A, C, E) and from control patients of similar age (B, D, F) stained for (A and B) eNOS, (C and D) iNOS, (E and F) nNOS. (A) Cardiac patient small pulmonary artery showing mild endothelial positivity for eNOS. Intra-alveolar macrophages and alveolar lining cells also positive with very mild positivity also noted in media. (B) Small pulmonary artery from control patient showing very mild endothelial positivity for eNOS. (C) Cardiac patient small pulmonary artery showing iNOS positivity in endothelium and media. Intra-alveolar macrophages stained also strongly positive. (D) Small pulmonary artery of control patient showing no significant iNOS positivity. Intra-alveolar macrophages were positive. (E) Cardiac patient small pulmonary artery showing no immunocytochemical positivity for nNOS. (F) Control patient small pulmonary artery showing no positivity by immunocytochemistry for nNOS. × 400.

Previous studies of NOS enzyme expression in patients with pulmonary hypertension have examined either adults with severe pulmonary hypertension of many years' duration, or infants with congenital diaphragmatic hernia who have very severe hypertension. Patients with pulmonary hypertension classified as irreversible have been shown to have higher levels of eNOS expression, particularly in areas of severe vascular lesions.[26] Others found isolated increases in iNOS immunoreactivity but no changes in eNOS immunoreactivity in patients with congenital heart disease and flow-associated pulmonary hypertension.[27] The present study shows upregulation of eNOS and iNOS at an early stage of pulmonary hypertension, in agreement with the rat hypoxic model[11] and in contrast to published studies of end stage disease in pulmonary hypertensive patients.[21-31] This finding is consistent with the hypothesis that increased eNOS is associated with the initiation of pulmonary hypertension (chronic hypoxic model in rats and infants with pulmonary hypertension secondary to cardiac abnormalities) whereas at a late stage there is severe damage to the endothelium resulting in loss of eNOS. The decrease of eNOS expression with longstanding disease in adulthood[23] can be interpreted as the result of secondary damage to the pulmonary vasculature caused by a prolonged period of pulmonary hypertension, resulting in a failing endothelium with reduced production of NO. Additionally there may be other differences between infants and adult patients other than the duration of pulmonary hypertension which may have subtle effects on NOS expression.

The importance of NOS is demonstrated by the finding that mice with eNOS deletion have pulmonary hypertension.[28] However studies of animals that have either deletion or over-expression of eNOS and iNOS reveal that the physiological consequences of alterations in NOS abundance are complex. As expected, agonist contractions and HPV were both inhibited by gene delivery of either iNOS or of eNOS,[29,30] however surprisingly there was no improvement in endothelium-dependent pulmonary relaxation.[29] Deletion of eNOS gene was associated with increased pulmonary artery muscularity, right ventricular hypertrophy and right ventricular pressure, but only in male and not in female mice.[31] Deletion of iNOS was not associated with evidence of pulmonary hypertension, however iNOS transfected mice had increased expression lasting only 7 days making these experiments hard to interpret. Since eNOS deletion mice had upregulation of iNOS[28] it is clear that expression patterns of NOS isoforms are coupled. Thus the over-expression of eNOS and iNOS that we found in infants with pulmonary hypertension suggests but does not prove that this is a compensatory mechanism limiting the rise in pulmonary artery pressure. It is of interest that in our study patients with the more extreme upregulation of eNOS also had greater upregulation of iNOS, suggesting that changes in both isoforms are linked in the process of adaptation to pulmonary hypertension.

Our present data indicate that upregulation of eNOS is not a short term effect as might be anticipated in cases of PPHN. Rather can this increased expression of eNOS persist over months and years as shown in our oldest patients at the age of 5 and 7 years, respectively (Table 1).

Limitations of this study include the lack of enzyme activity data and the subjectivity of the immunohistochemical findings. We have consequently minimized the effect of confounding

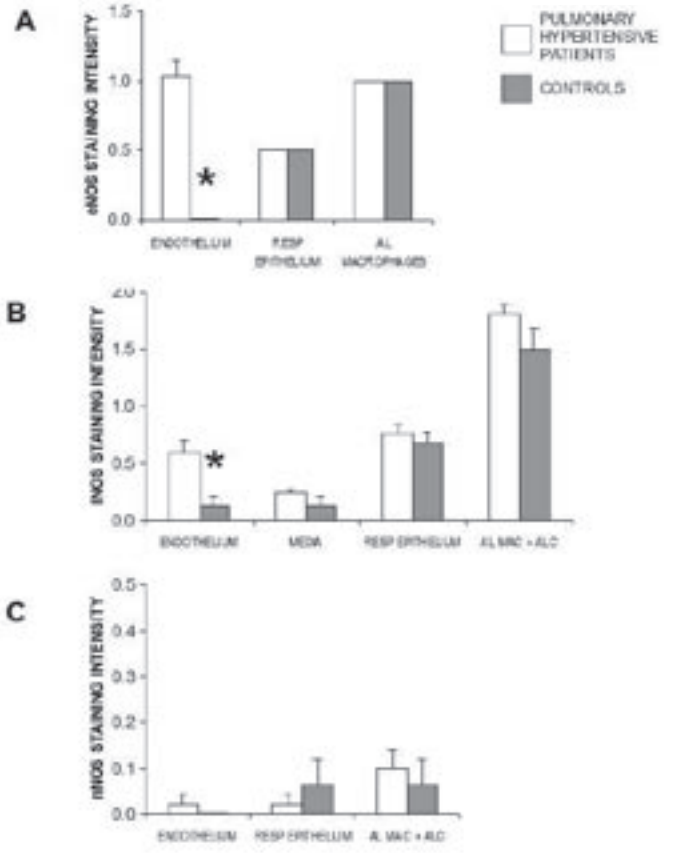

Figure 2. Intensity of staining for (A) eNOS, (B) iNOS and (C) nNOS in lungs from infants with pulmonary hypertension and from control patients of similar age. (A) Staining for eNOS was quantified separately in pulmonary vascular endothelium, respiratory endothelium, and alveolar macrophages of controls and cardiac patients (*p = 0.0001 comparing cases to controls). (B) Staining for iNOS was quantified in pulmonary vascular endothelium, pulmonary vascular media, respiratory endothelium, and alveolar macrophages/alveolar lining cells of controls and cardiac patients (* p = 0.008 comparing cases to controls). (C) Staining intensity for iNOS was quantified in pulmonary vascular endothelium, respiratory endothelium, and alveolar macrophages/alveolar lining cells of controls and cardiac patients. n = 23 cases, n = 8 controls.

factors on the immunohistochemical data by applying strict protocols of quantification of staining intensity. The advantage of immunohistochemical studies is the microtopographic localization of the protein under investigation, which we regard as very important for the specific question of our study. Although protein activity studies would further strengthen the results of our investigation, unfortunately we had only paraffin blocks of lung tissue available thus preventing further protein activity studies.

In summary, we have shown upregulation of eNOS and iNOS in pulmonary endothelial cells at an early stage of pulmonary hypertension in infants with congenital heart disease. Additionally there is co-expression of these two enzymes in pulmonary endothelial cells of these infants. These findings support the hypothesis that infant pulmonary hypertension is different from adult disease and potentially more amenable to the therapeutic effect of anti-proliferative medication and thus prevention of early endstage pulmonary vascular disease.

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Respiratory Syncytial Virus Prevention 2010

The National Perinatal Association (NPA) has just completed a guideline on RSV Prevention. After careful consideration of the literature, we as a board collectively came to the conclusion that there was not an objective, evidence based guideline for the management of RSV risk in all susceptible infants. Although the American Academy of Pediatrics, Committee on Infectious Disease produced a guideline for the 2009 Redbook, there were several departures from accepted evidenced based practice that have caused a great deal of concern within the broader pediatric community and among parents of affected infants. In the course of writing this guideline, we carefully evaluated the recommendations for infants born at gestations 32 to 35 6/7 weeks. It seemed contradictory that while the current data supports an emphasis on the increased risk for the late preterm infant, the Committee on Infectious Disease "redefines" them as "near term" in management of their RSV risk. As with all guidelines, this is not intended to dictate practice but is to be used as a foundation for constructing policies and procedures based on current evidence based data.—*Mitchell Goldstein, MD, President and Chair of RSV Guideline Committee, National Perinatal Association, Alexandria, VA. Dr. Goldstein is also Director, Division of Neonatal Medicine, Citrus Valley Medical Center, West Covina, CA and Associate Professor, Pediatrics, Division of Neonatology, Loma Linda University Children's Hospital, Loma Linda, CA. The members of the Committee who drafted the guidelines are Mitchell Goldstein, MD; Maribeth Sayre, MD; Jack Owens, MD; Munaf Kadri, MD; and T. Allen Merrit, MD.*

I. Issue: While there is a high level of evidence that RSV prophylaxis is effective, some debate remains regarding best strategies for prevention of RSV in neonatal and pediatric patients.[1-3]

II. Background: RSV is the leading cause of re-hospitalization in all children less than 12 months of age for the United States.[4-6] The majority of these hospitalizations occur in otherwise healthy infants. Certain groups of infants and children have higher rates of re-hospitalization including children with Chronic Lung Disease (CLD)/Bronchopulmonary Dysplasia (BPD), Congenital Heart Disease (CHD), and premature infants.[7-14] Treatment options for RSV are limited. Supportive care is frequently the only medical therapy available. The best approach to RSV in at risk groups is prevention. In addition to strategies to minimize exposure to RSV, prophylaxis with RSV monoclonal antibody is effective at decreasing hospitalization.[9,15-19] In patients with CLD/BPD and premature infants born at less than 36 weeks gestational age, prophylaxis decreased hospitalization by 55%; in the subgroup of patients born between 32-35 weeks gestation, hospitalization rates decreased by 80%.[15]

III. Respiratory Syncytial Virus Prophylaxis

A. Prophylaxis to prevent RSV is available as intramuscular monoclonal antibody preparation (palivizumab).[20-21]
B. RSV infection is responsible for significant hospitalizations, morbidity, and mortality in infants less than 24 months of age who have CLD/BPD, Congenital Heart Disease, compromised respiratory or immune systems or who have impaired nutritional status and growth.[16-17,22]
C. Candidates for RSV Prophylaxis: Decisions regarding appropriateness of RSV prophylaxis must be individualized.
   1. Infants or children with CLD/BPD who are less than 24 months of age at the start of RSV season who have required intervention or maintenance therapy for their CLD/BPD within 6 months of the start of the RSV season will benefit from RSV prophylaxis. Other interventions for CLD/BPD may include ongoing use of corticosteroid preparations, methylxanthines, supplemental oxygen, bronchodilators, or diuretics.[12,23-24]
   2. Infants born at 32 weeks or less without CLD/BPD will also benefit from prophylaxis:[25]
      a. Infants born at less than 28 0/7 weeks will benefit from prophylaxis if they are less than 12 months of age at the start of the RSV season. Infants born during RSV season who are less than 12 months of age at the start of the subsequent RSV season are still candidates for prophylaxis.
      b. Infants born between 28 0/7 and 32 0/7 weeks of gestation will benefit most from prophylaxis if they are less than 6 months of age at the start of RSV season.
   3. Birth at a late preterm gestation may merit special consideration.[26-28] However, prophylaxis for infants born at 32 1/7 to 35 6/7 weeks gestation should be reserved for those infants with additional risk factors that increase risk of RSV exposure or morbidity from RSV disease. An RSV relative risk scale has been proposed and may be useful to the practitioner in identifying at risk patients who may benefit from RSV prophylaxis.[29]

The cost of prophylaxis should be weighed against the risk of severe RSV disease requiring hospitalization and associated costs to the family as well as perceived long term consequences.[30-33] A pediatrician or primary care provider is in the best position to assess and interpret relative risk factors. The most consistently identified factors that are associated with increased risk of RSV disease are child care attendance, school-aged siblings, young chronological age at the start of RSV season and maternal smoking; however, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease may also justify concern.[23,34-38] Correlations exist between air quality and respiratory function.[37-48] Thus, environmental air quality assessment is important for these patients with special consideration given to unique circumstances of unwarranted air pollution such as residence near a bus station or industrial plant, or use of a wood or coal burning stove as a primary heat source. Efforts to reduce risk by isolation of the at risk child, smoking cessation strategies for the parents/caregivers, or relocation to an area with cleaner air may not be practical or workable for the immediate term. Certain risk factors may have greater impact based on the level of exposure (ie, one school-aged sibling versus three school-aged siblings in three different schools); however, no particular risk factor has been shown to be unique in its predictive value, and frequently many risk factors may exist simultaneously.[14,46] The greater the number of risk factors, the higher the likelihood of RSV hospitalization.[49] A history of maternal smoking during pregnancy may be augmented as a risk factor by a history of breastfeeding for less than 2 months.[41,50-53] These circumstances must be accounted for in the risk assessment. After assessment of an individual patient, if a provider determines that the patient is at high risk for RSV disease complicated by hospitalization, prophylaxis should be provided.[54]

4. Palivizumab has been shown to be of benefit to patients with congenital heart disease.[16,55-57] The degree and severity of the heart disease may factor into the decision to provide RSV prophylaxis. In order to exclude an infant from receiving palivizumab, the infant must have a documented waiver provided by a board certified pediatric cardiologist that their cardiac defect is hemodynamically insignificant and thereby poses no additional risk for RSV. Children who are in need of or status post cardiac transplantation are in a particularly high risk group and should be given highest consideration for RSV prophylaxis.[55,57] During RSV season, post bypass or ECMO management should include a plan for additional dosing as soon as the infant is stable.
5. Infants with severe neuromuscular disease affecting respiratory function may be candidates for palivizumab prophylaxis, including those with neuromuscular maturational disease common in premature infants.[58] CNS injury prior to, during, or after delivery including but not limited to intraventricular hemorrhage (IVH), hypoxic ischemic encephalopathy (HIE), spinal cord injury, disease of the peripheral nervous system, disease of the neuromuscular junction, and periventricular leukomalacia (PVL) all are considerations for RSV prophylaxis.[22,24,58] IVH, HIE, and PVL may cause cerebral palsy (CP) at a later time. CP alone may be a qualifier for RSV prophylaxis if there is any association with decreased respiratory function.[59-60]
6. Patients with congenital abnormalities of the airways that compromise respiratory function should receive prophylaxis.[8,61-64] This may include persisting wheeze, or disorders of abnormal lung growth. Congenital diaphragmatic hernia is included in this category.
7. Patients with cystic fibrosis and other diseases such as _1-antitrypsin deficiency where there is a genetic basis for changes in the lung milieu may also benefit from prophylaxis.[62,65-66]
8. Immune deficiencies are rare disorders and require collaborative management by pediatricians, infectious disease specialists, and immunologists.[67-68] Although there is no conclusive evidence for a particular disease category, because of the understood high risk of any infectious process, RSV prophylaxis is indicated unless a waiver can be obtained from a board certified pediatric immunologist or infectious disease specialist.

D. Administration

1. RSV prophylaxis should be initiated prior to the onset of the RSV season and terminated at the end of the RSV season.[3,69-70] Although there are regional variations in the United States, RSV outbreaks begin as early as October and decrease between March and May. Providers should review local historical RSV surveillance data to assist in the decision- making process. Some locales in the Southern United States, Hawaii, and Alaska may have high enough incidence of RSV to justify initiation in the late summer months and continuation of monthly prophylaxis into the late spring.[71-74] Although various cost containment models have been proposed to provide relative risk adjustment based on post conceptual age at a specific month during RSV season, there is risk that adequate levels of palivizumab will not be achieved or maintained during months when RSV is widespread.[15,70] Use of an abbreviated schedule of RSV prophylaxis (eg, based on post conceptual age mid season) is contrary to published evidence and FDA approved product indication for palivizumab and is strongly discouraged.[75] Once a child begins RSV prophylaxis for the RSV season, the child must receive palivizumab monthly through the end of the season.[76]
2. Palivizumab 15 mg/kg IM should be given once a month during the RSV season to increased the likelihood of achieving and maintaining appropriate levels for prophylaxis.[20] A dose should be given 24-48 hours prior to discharge from the hospital if the patient meets criteria. The single-dose vial of palivizumab does not contain a preservative. Administration of palivizumab should occur immediately after dose withdrawal from the vial. The vial should not be re-entered.[20]
3. Patients can be re-infected with RSV multiple times during the same RSV season. Thus, monthly dosing should be continued even if the patient is infected with RSV.[20]
4. Fever or other illness including viral syndromes are not contraindications to administration of palivizumab.
5. At present, there are no restrictions on concurrent RSV prophylaxis with any immunization.[77] Immunization with Measles-Mumps-Rubella (MMR) and Varicella vaccines need not be deferred in infants receiving

RSV prophylaxis. RSV prophylaxis should not interfere with Hepatitis B vaccine, Diptheria, Tetanus, Pertussis (DTaP) primary immunization schedule, H. Influenza type B (Hib), seasonal influenza vaccination, Pneumococcal Conjugate Vaccine (PCV), or Inactivated Poliovirus Vaccine (IPV).

6. The safety and efficacy of palivizumab have not been demonstrated for treatment of established RSV disease.
7. Contraindications and Adverse Reactions
   a. Palivizumab should not be used in pediatric patients with a history of a severe prior reaction to palivizumab or other components of this product.[20]
   b. Fever, irritability and injection site reaction are the most commonly reported adverse events.[78]

IV. Nosocomial Infection

A. RSV is horizontally transmitted in the hospital setting and causes serious disease in high-risk infants and young children.
B. The best way to prevent RSV disease is strict adherence to infection control practice, including the use of in hospital screening studies to identify and cohort RSV-infected infants.4 Proper hand washing is of paramount importance.
C. Cohorting of children with suspected RSV disease is not recommended.

Indication	Age of Child	Dosing
Chronic Lung Disease requiring medical management	Less than 24 months at start of RSV season	Monthly during RSV season
Born at < 28 0/7 weeks	Less than 12 months at start of RSV season	Monthly during RSV season
Born at 28 0/7-32 0/7 weeks	Less than 6 months at start of RSV season	Monthly during RSV season
Born at 32 1/7-35 6/7 weeks	Less than 6 months at start of RSV season with provider determined significant risk	Monthly during RSV season
Congenital Heart Disease	Less than 24 months at start of RSV season unless cardiology waiver obtained	Monthly during RSV season
Neuromuscular Disease	Less than 24 months at start of RSV season	Monthly during RSV season
Congenital Abnormalities of the Airways	Less than 24 months at start of RSV season	Monthly during RSV season
Immune Disorders	Less than 24 months at start of RSV season unless infectious disease or immunology waiver obtained	Monthly during RSV season

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Internet-Based Medical Education: A Realist Review of What Works, For Whom and In What Circumstances

Geoff Wong, Trisha Greenhalgh, Ray Pawson

Abstract

Background: Educational courses for doctors and medical students are increasingly offered via the Internet. Despite much research, course developers remain unsure about what (if anything) to offer online and how. Prospective learners lack evidence-based guidance on how to choose between the options on offer. We aimed to produce theory driven criteria to guide the development and evaluation of Internet-based medical courses.

Methods: Realist review—a qualitative systematic review method whose goal is to identify and explain the interaction between context, mechanism and outcome. We searched 15 electronic databases and references of included articles, seeking to identify theoretical models of how the Internet might support learning from empirical studies which (a) used the Internet to support learning, (b) involved doctors or medical students; and (c) reported a formal evaluation. All study designs and outcomes were considered. Using immersion and interpretation, we tested theories by considering how well they explained the different outcomes achieved in different educational contexts.

Results: 249 papers met our inclusion criteria. We identified two main theories of the course-in-context that explained variation in learners' satisfaction and outcomes: Davis's Technology Acceptance Model and Laurillard's model of interactive dialogue. Learners were more likely to accept a course if it offered a perceived advantage over available non-Internet alternatives, was easy to use technically, and compatible with their values and norms. 'Interactivity' led to effective learning only if learners were able to enter into a dialogue—with a tutor, fellow students or virtual tutorials—and gain formative feedback.

Conclusions: Different modes of course delivery suit different learners in different contexts. When designing or choosing an Internet-based course, attention must be given to the fit between its technical attributes and learners' needs and priorities; and to ways of providing meaningful interaction. We offer a preliminary set of questions to aid course developers and learners consider these issues.

The authors are with the Research Department of Open Learning, Division of Medical Education, UCL, London, UK. The authors would like to thank Marcia Rigby for her administrative support; UCL's Interlending and Document Supply Office for their assistance with obtaining manuscripts and the peer reviewers, Jarmila Potomkova and in particular David Cook for their constructive comments. Reprinted from BioMed Central, BMC Medical Education,

Background

The Internet is widely used in medical education. Several previous systematic reviews and two meta-analyses have compared the efficacy and utility of Internet-based education with conventional teaching methods or no teaching. Two main questions face researchers in this field: efficacy (can Internet-based medical education work, and if so what is the "effect size" compared to conventional teaching) and effectiveness (under what real-world circumstances does it actually work, and how might its impact and cost-effectiveness be maximized)?

Cook et al's 2008 meta-analysis addressed efficacy, and concluded that, on average, Internet formats were equivalent to non-Internet formats in terms of learner satisfaction and changes in knowledge, skills and behavior.[8] Their findings indicated that substantial heterogeneity existed and their meta-analysis was unable to account for the complexity of the interactions within their included studies.

In trying to make sense of this heterogeneity we conceptualized educational courses as complex interventions and used the realist review method. Complex interventions consist of multiple human components (teachers, learners etc) that interact in a non-linear fashion to produce outcomes which are highly context dependent. Outcomes in such interventions depend on humans making decisions in a semi-predictable (demi-regular) manner about how to use the resources available to them in the context they find themselves in.

Methods

In this realist review we set out to supplement and extend previous systematic reviews and meta-analyses. In particular we sought initially to [a] explain what sort of Internet-based medical education works, for whom and in what circumstances; [b] produce pragmatic guidance that could be used by developers to optimise the design of their courses and by potential learners to evaluate whether a particular course is right for them; and [c] extend the methodological knowledge base in relation to secondary research in medical education.

The realist approach to reviewing the evidence from complex interventions assumes that no deterministic theories can always explain nor predict outcomes in every context.

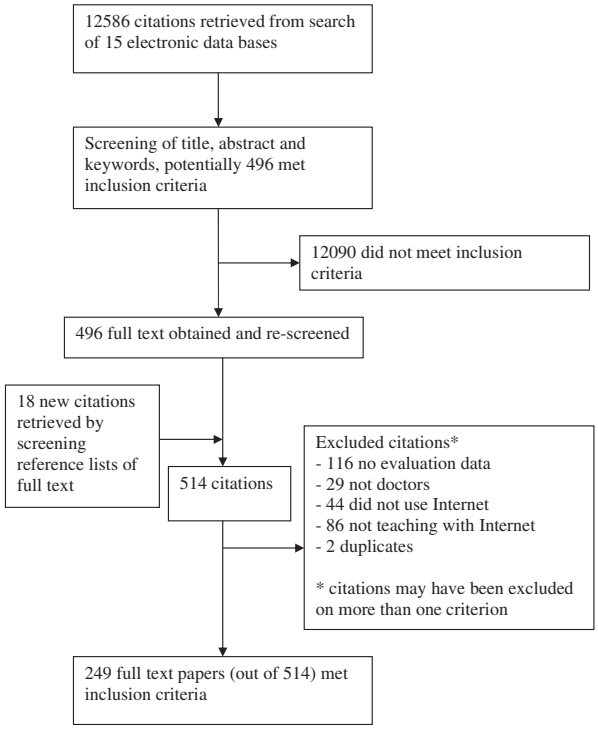

Figure 1. Flow chart of screening process. This figure outlines how we arrived at the 249 full text papers we included in our realist review.

Instead it is based on the principle that, though human agency and interaction is involved, in certain contexts or situations, individuals are likely, though not always certain, to make similar choices about which resources they will use. In other words, particular contexts influence human choice such that semi-predictable reoccurring patterns of behavior ("demi-regularities") occur. Realist review seeks to uncover the underlying theories that explain these demi-regularities by critically scrutinizing the interaction between context, mechanism and outcome in a sample of primary studies.

Table 1. Five questions for developers and prospective learners to ask of an Internet-based course

Technology acceptance

1. How useful will the prospective learners perceive the Internet technology to be?
   For example, in any particular context and compared to what is currently available to them, to what extent will this technology
   a. Increase their access to learning?
   b. Provide consistent, high-quality content?
   c. Be a convenient format in which to receive their education?
   d. Save them money?
   e. Save them time?
   f. Link to course assessment?
2. How easy will the prospective learners find this technology to use?
3. How well does this format fit in with what learners are used to and expect?
   Achieving interactive dialogue
4. How will high-quality human-human (learner-tutor and learner-learner) interaction and feedback be achieved? For example what use will be made of
   a. Structured virtual seminars?
   b. Email, bulletin boards?
   c. Real-time chat?
   d. Supplementary media e.g. video, audio, phone calls, videoconferencing?
   e. Course assessment and feedback on performance?
5. How will high-quality human-technical interaction and feedback be achieved? For example what use will be made of
   f. Questions with automated feedback?
   g. Simulations?

Mechanisms are processes operating within an intervention that describes how the human components use the resources available to them. In particular middle-range theory (that is theory that "involves abstraction... but [is] close enough to observed data to be incorporated in propositions that permit empirical testing.") is specifically sought as their level of abstraction provides a more generalisable explanation of demi-regularities. More than one middle-range theory may explain the influences of context on a mechanism to produce an outcome.

Importantly, realist review methodology acknowledges that within complex interventions there are many dimensions and layers of explanation that warrant exploration. For example, there are human behaviours as well as multiple interactions between the numerous components of the intervention. A realist review does not seek to explain all these layers; it is specifically focused on the demi-regularities in the social (and socio-technical) world which create preconditions for particular human behaviours. To that end, we sought to extract theories from our dataset of primary studies which would explain whether or not an Internet based course was considered a success'and especially whether it produced effective learning. We sought to try to gain insights and explanations that would be generalisable across a whole range of different types of Internet based courses and so theories that focused on specific aspects of such courses (for example only computer mediated conferencing) were not central to our inquiry.

Studies were included if they had any medical students or doctors as learners; used the Internet to support learning; and contained at least one level of evaluation as described by Kirkpatrick. Studies were excluded if the Internet was used for purposes other than learning (eg tracking website use, examinations only, course administration).

We searched 15 electronic databases relevant to medical education from their inception dates to April 2006 using guidance provided by Haig and Dozier. No language restrictions were applied (non-English language papers were translated), and publications of any type were included.

In the first stage of searching, GW screened the title, abstract and subject headings (where available) against inclusion and exclusion criteria. Potentially eligible studies were obtained in full text and re-screened in the second stage. A random subset (200/12586 and 50/514 citations respectively) at each stage was screened independently by TG and disagreements resolved by discussion.

The initial identification of candidate (middle-range) theories in realist reviews is necessarily an iterative and speculative process. Whilst a review team may initially have theories that they believe to be in operation to explain why certain outcomes occur, a key element in realist review is to explore the presence of these "educated guess" theories and where applicable, test their explanatory value. Candidate theories are not considered definitive until they have been tested. Much of the work in realist review involves not only repeatedly questioning the validity of any candidate theory and refining it but also seeking out new candidate theories from included studies if existing ones are found wanting.

We used a variety of methods to derive our list of candidate theories. This included; brainstorming within the review team,

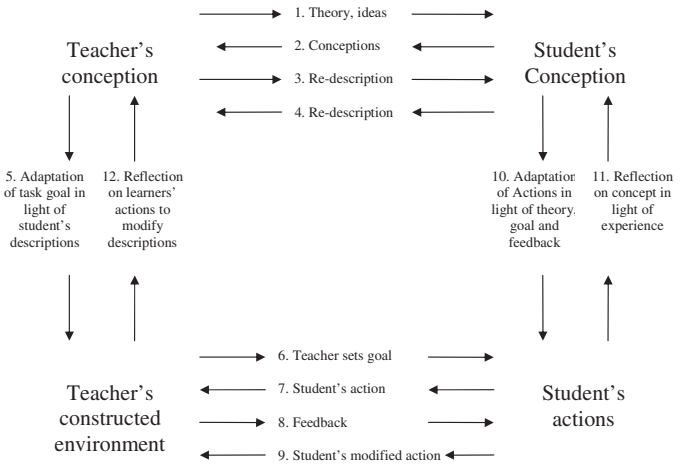

Figure 2. Laurillard's Conversational Framework. This figure is a diagrammatic representation of the all the stages that go to make up the dialogue between a teacher and a student.

browsing through specialist educational library collections, discussions with fellow educators and pursuing references of references. We did not specifically consult individual experts in the field. We iteratively [re-]checked all the included studies against the candidate theories so as to establish which (if any) explained differences in outcomes. In each paper, we sought data to test (affirm, refute or refine) the candidate theory by assessing their relevance and rigour. Throughout our data extraction and synthesis phases, we continually sought out further candidate theories that might better explain the data in the included studies.

In a first phase, study characteristics (eg sample type and size, setting, course objectives) and theoretical contribution (eg, how, why, in what circumstances) were tabulated on an Excel spreadsheet using data domains informed by previous systematic reviews in this field. In a second phase, the NVivo qualitative software was used to index and link relevant sections of text of included articles to our emerging analytic framework. As each included article was read and re-read, we created and iteratively revised codes to capture themes or concepts that might contribute to theory testing. In particular, we sought to identify prominent demi-regularities that might help us to understand Internet-based interventions better. We classified interaction in the online environment according to the criteria of Vrasidas and Glass (in sum, learner-tutor, learner-learner, learner-content and learner-software, the last of these being technical feedback such as automated replies to multiple choice questions).

Data synthesis involved both individual reflection and team discussions that considered the ability of the candidate theories to explain the data reported in empirical studies (especially in relation to any prominent demi-regularities we encountered). The sections of texts from our included studies, which we had coded and captured within NVivo formed the raw materials for our interpretations. We used these sections of texts to see if they were able to confirm, refute or refine our candidate theories. Specifically, we attempted to identify recurrent demi-regularities which might act as barriers or enablers to Internet-based learning and tested the explanatory powers of our initial candidate theories against these. Where candidate theories failed to explain the data we sought new ones, either from the included studies or wider educational or sociological literature. Throughout this process, we deliberately sought out disconfirming data—i.e. data that might refute our provisional candidate theories. In line with realist review methodology, we also used the information we gleaned from our immersion in our included studies to refine our initial review goals.

Results

Figure 1 shows the numbers of included studies at each stage of the review. The raw inter-rater agreement for inclusion/exclusion was 92% (183/200) in the first stage and 84% (42/50) in the second stage. The 249 articles were published in 133 different journals and included a total of 44,591 participants. In all, 20% (49/249) of studies were randomised trials; 66% (165/249) non-randomised controlled studies (usually controlled before and after studies); 7% (18/249) mixed methods and 7% (17/249) not stated. When compared against the study's aim(s) or objective(s), 72% (179/249) reported positive outcomes and 22% (55/249) had mixed findings. In terms of Kirkpatrick's levels of evaluation, 84% (209/249) of studies measured learner satisfaction; 50% (124/249) learning outcomes; 3% (7/249) behaviour change and 0.4% (1/249) patient outcomes.

We initially selected four candidate theories for further testing: Laurillard's conversational framework, Schon's reflective practitioner, Slotnick's how doctors learn and Reeves' effective dimensions of interactive learning. These theories provided only a starting point in our attempt to explain what sort of Internet-based medical education works, for whom and in what circumstances. As we extracted our data, we noted further candidate theories and proceeded to test these as well. Additional candidate theories that we attempted to tested included: Vygotski, Danchak, Schon, Garrison, Dewey and Brookfield, Kolb, Moshman, Eraut, Boettcher, Wenger, Koschmann, Nahapiet and Ghoshal, Socrates Problem Based Learning, Constructivism and adult learning theory/principles.

As no previous realist review had been undertaken in this field, we were initially unclear as to how suitable the data reported in our included studies would be for answering the broad research question goal we had set ourselves. As the review progressed we became aware of various data suitability limitations and the emergence of two prominent demi-regularities prompted us to narrow our review focus to the two candidate theories discussed below. This is an example of progressive focusing, a well-established technique in qualitative research in which the focus of the inquiry is iteratively sharpened by reflection on emerging data.

Technology acceptance: getting learners to log on: At an early stage in this review, our reading and interpretation of the reported data in our included studies showed that educators often faced a substantial barrier of getting learners to use their Internet-based course. This demi-regularity of getting learners to log onto—or engage with—a course was clearly an important factor in explaining the fortunes of such courses. We noted that learners needed to have to have good reasons to engage and that unless they did, the outcomes reported were less favorable. Engagement and acceptance was not explained by any of our initial candidate theories, but we noted that one of our included papers[72] mentioned the value of conceptualising Internet based courses as innovations and specifically Rogers' diffusion of innovations theory. We found that Davis's Technology Acceptance Model, which is derived from Rogers' theory, was a more precise articulation of innovation acceptance when the innovation involved was a technology. Drawing on both Rogers'

and Davis's theories, the attribute of an Internet-based course that provided the most coherent and complete explanation of technology acceptance was the perceived usefulness of the technological medium (in the eyes of potential learners) over an alternative delivery format. From our included studies, we identified that perceived usefulness, or in Rogers' original terminology "relative advantage," included 7 sub-components, representing the contexts that influence whether learners choose to engage with an Internet-based course: access to learning; access to consistent content; links with assessment; convenience; cost saving; interactivity; and time saving.

Overall, 38% (95/249) of our included studies provided some data to support the central importance of perceived usefulness and none provided data to refute it. Two other attributes, perceived ease of use (from Davis's Technology Acceptance Model) and compatibility with the learner's norms and values (from Rogers' original diffusion of innovations theory), also explained some of the variability in acceptance of the Internet medium, and evidence to support these attributes was found in 13% (32/249) and 3% (7/249) of studies respectively. Again, we found no disconfirming studies.

We wanted to provide a set of recommendations that would help course developers and learners make of most of an Internet based course. Thus we converted the three attributes within Davis's Technology Acceptance Model that we were able to test—perceived usefulness, perceived ease of use and compatibility—into three questions (one of which included seven sub-questions, representing the important contextual influences), which are shown in Table 1.

Interaction: building a learning dialogue: The primary studies frequently reported that learners greatly valued courses that allowed them to interact, though this term was rarely defined. This demi-regularity was consistent across different course designs and other characteristics (eg participant type, age, gender). Laurillard's Conversational Framework (Figure 2) was the middle-range theory that explained these data particularly well.[25] This theory is built on the assumption that a learner learns by entering into a dialogue with others (virtual or human) in order to clarify understanding and obtain feedback on performance. Overall, 36% (90/249) of included studies provided some data which supported (and none provided data that refuted) the Conversational Framework.

In our recommendations in Table 1, we have again converted our insights about the importance of interaction and feedback into two questions which remind course developers to think about this issue. The examples that we have provided of how the interaction and feedback might be enabled technically are drawn from our analysis of the methods used in our included studies.

Course-context interaction: An important finding of this review was that "success features" did not seem to be intrinsic to any course but a function of the course-context interaction. One group of learners might perceive the a technologically based course as having very high 'usefulness' while a different group would find the same course much less useful. For example, in studies comparing virtual microscopy (where glass slides were digitised and the features of a traditional light microscope simulated by software) with conventional microscopy, medical student learners were reported as valuing the Internet-based materials much more highly and utilised these more. Features of perceived usefulness included assessment linkage (virtual material was used in exams), consistent high quality content (whereas traditional slides may or may not show the feature concerned); convenience (they did not have to conform to laboratory opening times); cost saving (rental cost of a microscope); and time saving (journey times to the laboratory were cut to zero). The course's ease of use (comments included "doesn't hurt my eyes" "stays in focus") was also highly rated compared to conventional alternatives. However, this same Internet-based application was reported as having little or no perceived usefulness for trainee pathologists, who must learn not merely to evaluate standardised slides in formal examinations but to deal with the inconsistencies and contextual complexities of real slides in the real world.

The above example also suggests that the construct "ease of use" does not operate independently of other course features, especially its perceived usefulness. For example, we encountered studies utilizing virtual textbooks (where text and/or images were digitised and placed online) where despite efforts to ensure the technology was easy to use, learner engagement remained low (eg because the learners perceived that they could access "better" but similar content face to face or in other formats). Conversely, we found a 1996 paper describing a bio-computing course that had been set up to allow teaching expertise to be shared between the few geographically dispersed experts there were in this field. The tutors and highly computer literate students communicated using a very rudimentary and technically complicated email system. Despite these challenges, most students persisted with it and rated their learning experience as positive. It appears that the advantage of being able to learn with otherwise hard-to-reach experts ("improved access to learning") more than made up for the technical limitations of the learning technology.

Discussion

This realist review of 249 primary studies has produced two key findings which are important if somewhat unsurprising. First, Internet-based courses must engage their target group of learners to use the technology. This is likely to occur only if the technology is perceived as useful (eg increases access to learning or saves time) and easy to use, though benefits in the former can outweigh challenges in the latter. Second, interactivity is highly valued by learners. Learners wanted to be able to enter into a dialogue with the course tutor, fellow students and/or a virtual tutorial and obtain ongoing feedback on their understanding and performance.

Course design is an important factor in Internet-based courses, but attention must also be paid to course-context interaction. A pedagogically sound course may prove technically acceptable and produce positive learning outcomes in one group of learners in one context but the same course may be technically unacceptable and/or fail to achieve effective learning in a different context. The skills of learners, course learning objectives and the availability, quality and cost of non-Internet alternatives are particularly important contextual factors.

To our knowledge, this review represents the first use of realist review in medical educational research. It contributes to an emerging field in systematic review, in which qualitative reviews are undertaken to supplement and extend the findings of meta-analyses and other quantitative reviews. The advantage of using both approaches is that the strengths and weaknesses of each

method are complementary. Realist reviews are a type of theory driven qualitative review and so differs in many respects to more quantitative (for example Cochrane) reviews. A discussion of the advantages and disadvantages between these review methods is beyond the scope of this paper and interested readers are directed to Chapter 3 of Pawson's Evidence-based Policy: A Realist Perspective.

The recent meta-analysis by Cook et al provided much-needed evidence that the overall educational impact of Internet-based medical education can be equivalent to that of conventional formats. In their discussion, these authors raised two further questions which they acknowledged had not been addressed by their meta-analysis: "How can Internet-based learning be effectively implemented?" and "When should Internet-based learning be used?" Cook has previously observed that "...the appropriateness of web-based learning as a learning tool will vary upon the instructional context..."—a comment which raises the question of what sort of course is appropriate in what sort of context.

Our review has begun to extend the knowledge base by identifying and refining some of the middle-range theories that explain the how, why and in what circumstances questions about Internet-based medical education. We acknowledge that our progressive focus on two prominent demi-regularities has meant that we have not addressed all aspects of our initial review's goals. However, it is reassuring that the key findings of this review align with, and illuminate, the findings of previous systematic reviews. For example, the quantitative observation that the speed of downloading is associated with learner satisfaction may be explained qualitatively by the 'ease of use' construct within the Technology Acceptance Model (and, more widely, diffusion of innovation theory). Similarly, the observation that dialogue and interaction is associated with improved learner performance is explained qualitatively by the Conversational Framework.

Perhaps more significantly, theory-driven qualitative systematic reviews may also throw light on the reason why there is a lack of association between variables and outcomes seen in quantitative (Cochrane-type) reviews. We suggest that a paradigm shift may need to occur in how interventions that involve human agency should be viewed—namely as complex interventions.

The pursuit of rigor in realist review follows similar principles to the pursuit of rigour in qualitative research more generally. The essence of such research is interpretation, hence key processes are immersion (reading and re-reading texts), reflection, discussion amongst team members, comparison and continuing to seek explanations and test theories until saturation of the data is reached. Our sample included a heterogeneous group of primary studies of different learner groups in diverse contexts, with no restrictions by study design or language of publication; in other words, we had what is known in qualitative research as a "maximum variety sample." This allowed us to explore a wide range of context-mechanism-outcome combinations and use the available qualitative data reported in the primary studies to build and refine theories of how Internet-based learning "works." While we have followed the realist review method and documented the steps we took to arrive at the middle-range theories presented here, we are fully aware that (in common with other qualitative research) this method is subjective and interpretive. Therefore another team reviewing the same literature may arrive at a different set of middle-range theories with which to make sense of this vast field.

We did not consult individual experts in this field and acknowledge that had we done so, we may well have had a wider set of additional candidate theories to test. We did not set out to be all-inclusive in our review but have been able to uncover key middle-range theories that begin to help to explain the fortunes of Internet based courses. We are certain that other middle-range theories will be needed and are important in furthering understanding and believe that there is more work to be done in unravelling the multitude of theories that are in operation within Internet based courses. More specifically, we believe that more theory drive reviews, such as ours and that by Ruiz et al. hold the greatest promise to understanding medical educational interventions.

Whatever review method is used in secondary research, the resulting synthesis is only as good as the primary data on which the synthesis is built. A major limitation we encountered in our review was that many primary studies included only cursory descriptions of their Internet-based educational intervention (eg educational setting, teaching practices and rationale of course design). The paucity of such data placed two important limitations on our review. Firstly, we were not able to test in detail all aspects of our candidate theories. If richer descriptions been reported in our included studies, we would have been able to undertake a more fine-grained analysis of both technology acceptance and interactivity. Secondly, we were aware that a large number of theories exist on how learners learn online and in more traditional settings. In our included studies alone, 17 specific theories were named in 58 articles. However, within the included studies, we could not find sufficient reported detail to enable comprehensive testing of these theories.

Limitations in the type of data, depth and quality of reporting of studies in medical education are well recognised. We strongly recommend that authors of primary studies in this field produce detailed descriptions of the intervention and context as well as quantitative data on satisfaction and impacts, and that journal editors make space for these rich descriptions, since the ability of future realist and other theory driven reviews to extend the knowledge base further will depend on the quality and completeness of the qualitative data gathered and reported.

Conclusion

Based on the findings of this review we suggest a set of questions that educators should address in order to maximise the chance that their Internet-based courses will be perceived as useful and provide an effective learning opportunity, and which prospective learners may use to evaluate whether a course is right for them (Table 1). Given our findings above about the importance of course-context interactions, it follows that the factors referred to in Table 1 cannot be built into courses independently of a consideration of learners' needs and priorities or assessment of other courses available locally and indeed, on the Internet—in other words the course's context. Nor can our guidance be seen as a deterministic 'law of nature' which if slavishly followed will invariably lead to a successful course. The questions in Table 1 are designed to complement existing guidance on course design, and should be seen as part of the entire curriculum design process and not as a substitute for these.

Stillbirths and Hospital Early Neonatal Deaths at Queen Elizabeth Central Hospital, Blantyre-Malawi

Aklilu M. Metaferia, Adamson S. Muula

Abstract

Much of the data on still births and early neonatal deaths from resource-limited settings are obtained via maternal recall from national or community level surveys. While this approach results in useful information to be obtained, often such data suffer from significant recall bias and misclassification. In order to determine the prevalence of stillbirths (SB), early hospital neonatal death (EHND) and associated factors in Blantyre, Malawi, a prospective study of pregnant and post-natal women was conducted at the Queen Elizabeth Central Hospital (QECH), Malawi.

A prospective observational study was conducted between February 1, 2004 and October 30, 2005. Consecutive women attending the hospital for delivery were recruited. Data were collected on the health status of the fetus on admission to labor ward and immediately after delivery, whether alive or dead. Gestational age (GA) and birth weight (BW) and sex of the newborn were also noted. Similar data were also collected on the live births that died in the delivery room or nursery. Data were analyzed using SPSS (Statistical Package for the Social Sciences) statistical package.

A total of 10,700 deliveries were conducted during the 12 months study period and of these deliveries, 845 (7.9%) were SB and EHND. Stillbirths comprised 3.4% of all deliveries; 20.2% of the ante-partum deaths occurred before the mother was admitted to the labor ward while a slightly higher proportion (22.7%) of fetal loss occurred during the process of labor and delivery. Fifty-sex percent of the perinatal deaths (PD) were EHND. The mean gestational age for the perinatal deaths was 34.7 weeks and mean birth weight was 2,155 g (standard deviation=938 g). The majority, 468 (57.8%) of the perinatal deaths were males and 350 (43.2%) were females. Many of the perinatal deaths (57.9%) were deliveries between gestational ages of 20 and 37 weeks. Most (62.7%) of the mothers with a perinatal death had experienced a previous similar incident.

About 3.4% of all pregnant mothers past 20 weeks of gestation ended up in delivering a stillbirth; another 4.4% of the live births died before discharge from hospital, thus, 7.9% of pregnancy loss after 20 weeks (or 500 g estimated weight) of gestation. This is a higher loss when compared to international and regional data. We recommend attention be given to these unfavorable outcomes and preventive measures or intervention for preventable causes be considered seriously. These measures could include the provision of emergency obstetric care, improving access to deliveries by health professionals and resourcing of health facilities such that neonatal viability is promoted.

Background

The rates of stillbirths (SB) and early neonatal deaths (ENND) may be considered as indicators of the quality of ante-partum, intra-partum and neonatal care. Garne has however argued that perinatal deaths are not a good indicator of medical care. Data on the frequency and distribution of adverse birth outcomes are important for planning and execution of maternal and child health care intervention services in developing countries; information on local patterns of SB and ENND will be helpful in improving perinatal care at the local level.

The estimated incidences of SB and ENND vary worldwide based on socio-economic, demographic and clinical profiles. An earlier report from Malawi reported a perinatal death rate of 68.3 per 1000 births; 56% were SB and the remaining 44%, early neonatal deaths. In Kenya, among studied perinatal deaths, antepartum deaths comprised 23%, intrapartum deaths (fresh stillbirth) 38%, and neonatal deaths within 24 hours following birth at 39%. Investigators from Nigeria reported a perinatal mortality rate of 77.03 per 1000 total births; of these 73.5% were SB and the remaining 26.5%, early neonatal deaths.

In low income countries a significant proportion of SB occurs in the intrapartum period and these deaths are commonly attributed to avoidable factors related to inadequate maternity care. In contrast, in developed nations these deaths are largely pre-partal with no apparent cause. Deprived societies in developed nations however, may suffer similar impediments to maternity care and adverse outcomes as are observed in resource-limited nations.

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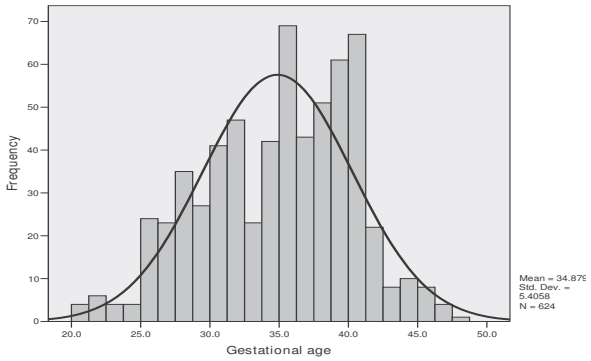

Figure 1. Distribution of gestational ages in weeks among perinatal deaths at QECH 2004-5.

We undertook this prospective observational study to estimate the incidence of SB and END as well as assess how these relate to gestational age, birth weight and sex of the newborn at a referral health facility in Blantyre, Malawi, the Queen Elizabeth Central Hospital (QECH).

Methods

This was a prospective observational study conducted at the Gogo Chatinkha Maternity Unit and the Pediatrics and Child Health Departments at the QECH in Malawi between February 1, 2004 and October 30, 2005. The QECH is a public health facility serving as the referral facility for the southern region of Malawi (population estimated at 5 million), as well as a district hospital for Blantyre (population estimated at 650,000). The Department of Obstetrics and Gynecology at the hospital has often had between 3 and 6 specialist physicians, two to three registrars and 3 to 5 intern medical doctors. There are between two and four nurse midwives for each shift. There are about six pediatricians at the hospital.

The objectives of the study were to estimate the incidence of SB and ENND and assess the gestational age, birth weight and sex distribution of the perinatal deaths observed. During the 12 months study period a total of 10,700 deliveries were conducted at the study center.

Consecutive women presenting for labor and delivery care were enrolled. Data were collected on SB and in hospital ENNDs using a standardized and pre-tested data capture sheet. Maternal and fetal variables of interest including GA, BW, sex of fetus or baby, vital status (dead or alive) were collected by a trained research midwife. Information on live births, but who might have died at home after discharge from the hospital, was unknown. No effort was made to follow-up women in the community who did not present for a postnatal visit.

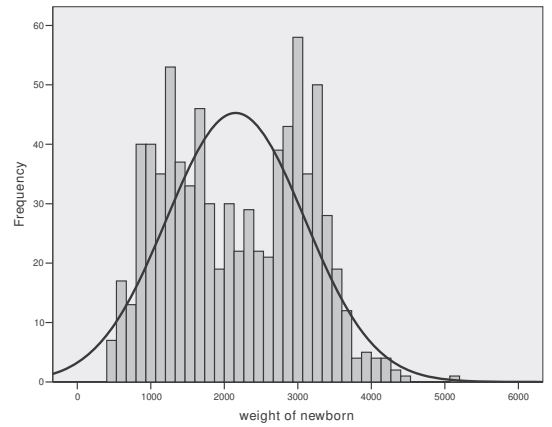

Figure 2. Birth weight (in grammes) distribution of perinatal deaths.

Results

Maternal age ranged between 15 and 45 years with a mean of 23 years (SD=5 years). The majority (89.8%) of the mothers were married and 82% were housewives. Just over half (52%) reported having attended elementary school and 31% had reached secondary school. About one in ten (9%) of mothers did not attend any school and 1.4% had attended higher education. Some 38% of the perinatal deaths had occurred to first pregnancies. The majority, 80% of mothers attended at least two antenatal visits. 15.5% did not.

During the 21 months study period there were 10,700 deliveries of whom 845 (7.9%) resulted in perinatal deaths; 4% (N=363) of all the deliveries were SBs. Of all the perinatal deaths however, these were distributed as 363 (43%) stillbirths and 56% (n=473) neonatal deaths. A total of 171 (47.1%) of the SBs death occurred before admission to labor ward while 52.9% (192) occurred during labor and delivery process. Most of the women (62.7%) with a perinatal death had at least one previous episode of perinatal death. A total of 85.6% (n=723) of the deaths were singleton, 13.3% (n=112) were either or both of twins and the remaining five deaths were triplet deliveries.

ABO blood group and Rhesus factor (Rh) status were determined in only 42 mothers. In 138 (16.4%) mothers (16.4%), VDRL (venereal diseases reference laboratory) for syphilis was done of whom 14 (10.6%) were sero-reactive.

Gestational ages (GA) could be calculated on 72.5% (n=613) of the perinatal deaths based on reported last day of menstrual period and could not be estimated in 27.5% (n=232) of cases. Mean GA for perinatal deaths was 34.7 wks (SD=5.2 wks). The shortest duration of pregnancy recorded was 20 completed weeks; the longest 45.3 weeks. Most (58.9%) of the perinatal deaths were preterm deliveries. Table 1 shows the distribution of the perinatal deaths by gestational age categorized as preterm, term and post term deliveries.

Mean birth weight of the perinatal deaths was 2,155 grams. 56.6% (n=452) of perinatal deaths weighed between 500 and 2,499 g, ie low birth weight; 41.7% (N=333), between 200 g and 3,999 g. The lowest BW recorded was 500 g and the heaviest newborn weighed 5,150 g.

A total of 468 (55.4%) of perinatal deaths were males, while females accounted for 41.4% (350). The male to female ratio at birth for the perinatal deaths was 1.3:1. A total of 723 (85.6%) of the deaths were singleton, 112 (13.3%) were either or both of twins and the remaining five deaths were triplet deliveries.

Discussion & Conclusion

Still births and early neonatal deaths are an important and a fairly common outcome among pregnant and postnatal women at the QECH. We found a SB rate of 34/1,000 births. The perinatal deaths rate that we found may not be representative of hospitals in Malawi. This is because the QECH is a third level health facility which receives high risk referrals. Pregnant women who present to QECH come from the surrounding neighborhoods of the district of Blantyre, health centers and some patients come from the surrounding districts. These are women who

Table 1: Perinatal death by Antepartum, Intrapartum and Neonatal periods in Blantyre, Malawi, 2004-5.

Period of death of fetus or neonate	Frequency (%)
Antepartum	171 (20.4
Intrapartum	192 (23.0)
Neonatal	473 (56.6)
Total	836 (100.0)

are identified either as high risk or already have intrapartal complications that required advanced obstetric care.

The availability of laboratory services to maternity care women can be assessed by examining the proportion of women who accessed VDRL and Rhesus factor assessment among those who experienced a perinatal outcome. The RH factor and VDRL tests should be routinely done, but not always offered to pregnant women in Malawi due to non-availability of laboratory reagents and human resources. Only 5% and 16.4% women had Rh factor and VDRL tests done. This notwithstanding the fact that national maternity guidelines required all pregnant women to have a VDRL test done. Although we did not assess the contribution of syphilis to perinatal death, it is likely to be a leading factor in Malawi. Among the cases who had syphilis assessed with VDRL, prevalence was 10.6%. However, the fact that not all women received laboratory investigations for syphilis, rhesus factors and other tests means that the prevalence estimates for positive test results must be interpreted with caution.

Our study is likely to have underestimated the actual prevalence of prenatal mortality among the cohort that was observed. This is because we did not follow the women into the community. Some of the women may have experienced neonatal deaths after being discharged from hospital. A complete picture could have been obtained if an aggressive follow-up schedule were implemented.

Our findings however are of public health significance, because unlike estimates obtained within intervention studies, we studied the prevalence and the associated features within routine care. These findings are therefore of importance in the design, implementation and evaluation of maternity care improvements at the QECH teaching hospital. However, using routine care in a resource-limited setting as the tool to assess the prevalence and associated factors of perinatal deaths also meant that many other investigations that could explain the deaths were missed. Lack of human resources, laboratory and pharmaceutical supplies and poor adherence to clinical guidelines are likely to be contributors to the high perinatal mortality in Malawi.

We found the prevalence of perinatal deaths among women attending maternity care at a large teaching hospital in Blantyre, Malawi as 9.8%. Many of the deaths were associated with low birth weight and prematurity. This study showed a high rate of pregnancy wastage during pregnancy, labor and delivery process and after birth. We recommend further studies in this setting to assess the effect of intervention aimed to reduced pregnancy wastage in Malawi.

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The Ideal of Equal Health Revisited: Definitions and Measures of Inequity in Health Should Be Better Integrated with Theories of Distributive Justice

Ole Frithjof Norheim, Yukiko Asada

Abstract

The past decade witnessed great progress in research on health inequities. The most widely cited definition of health inequity is, arguably, the one proposed by Whitehead and Dahlgren: "Health inequalities that are avoidable, unnecessary, and unfair are unjust." We argue that this definition is useful but in need of further clarification because it is not linked to broader theories of justice. We propose an alternative, pluralist notion of fair distribution of health that is compatible with several theories of distributive justice. Our proposed view consists of the weak principle of health equality and the principle of fair trade-offs. The weak principle of health equality offers an alternative definition of health equity to those proposed in the past. It maintains the all-encompassing nature of the popular Whitehead/Dahlgren definition of health equity, and at the same time offers a richer philosophical foundation. This principle states that every person or group should have equal health except when: (a) health equality is only possible by making someone less healthy, or (b) there are technological limitations on further health improvement. In short, health inequalities that are amenable to positive human intervention are unfair. The principle of fair trade-offs states that weak equality of health is morally objectionable if and only if: (c) further reduction of weak inequality leads to unacceptable sacrifices of average or overall health of the population, or (d) further reduction in weak health inequality would result in unacceptable sacrifices of other important goods, such as education, employment, and social security.

Introduction

The past decade witnessed great progress in research on health inequities. The standard use of terms is now firmly established among health researchers and policy makers. In the words of Kawachi, Subramanian, and Almeida-Filho, "health inequality is the generic term used to designate differences, variations, and disparities in the health achievements of individuals and groups," "while health inequity refers to those inequalities in health that are deemed to be unfair or stemming from some form of injustice." Researchers and policy makers can now choose their definition of health inequity from a wide menu of views proposed by many scholars in the past decade. Although desired results have not always been achieved, many countries and international organizations have for some time embraced a goal of redressing health inequities by improving the health of populations. The attempt to describe existing health inequities continues, and guidance on how to measure health inequities is now available along with novel measures of health inequities.

Given the explosive growth of interest in health inequities in the past decade, it is interesting that the most widely cited definition of health inequity still is, arguably, the one proposed by Whitehead and Dahlgren in 1991: "Health inequalities that are avoidable, unnecessary and unfair are unjust." The simplicity and all-encompassing nature of this definition are certainly attractive, but it is rudimentary in the light of recent developments in health inequity research. The Whitehead/Dahlgren definition is useful, but not linked to broader theories of justice. For example, health inequalities that are "avoidable or unnecessary" are, presumably, those we as a society could do something about. But are all avoidable health inequalities arising from, say, small differences in income or educational level unjust? Should all non-health inequalities be eliminated if they are associated with inequalities in health? The definition is silent on such important issues.

Moreover, the Whitehead/Dahlgren definition of health equity requires an upgrade given the widespread agreement on both reducing health inequities and increasing overall population health. While normative political theorists disagree as to whether distributive (ie, equity) and aggregative (ie, overall) concerns should be considered simultaneously or separately, policy makers constantly face trade-offs between improving equity in health and increasing the overall health of a population in real life. For example, preventing cardiovascular disease among inner city minorities may be more difficult and costly than among people with higher income and education. The same amount of effort and resources may achieve higher risk reduction among the well-off than the worse-off. But is further improving the health of the well-off,, thereby increasing inequality in health between the well-off and the worst-off, the best policy option? How much weight should policy makers assign to the worst-off if this requires large sacrifices for the better-off? To offer

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much needed guidance to policy makers, health researchers need to combine distributive and aggregative concerns in conceptualizing fairness.

The rapidly developing literature on health inequity measurement is rarely linked to the Whitehead/Dahlgren definition, or indeed, to any definition of health inequity. How we measure health inequities should reflect our view on how we conceptualize health inequities. To put it differently, our view on health inequity should be clear and expansive enough to offer a foundation on which various measures of health inequity can be developed, explained, and used.

The aim of this paper is to propose a pluralist framework of fair health distribution that addresses shortcomings in the definitions of health inequity proposed in the past. Our framework consists of two principles: the weak principle of health equality and the principle of fair trade-offs. The weak principle of health equality offers an alternative definition of health inequity. In developing this principle, it is not our intention to review the immensely rich literature on health equity; rather, we defend an alternative view of health equity that is grounded in general theories of justice. The principle of fair trade-offs supplements weak equality in health, and when integrated the two principles represent a comprehensive and more practical understanding of health inequity—what we prefer to call fair health distribution. Trade-off questions require balancing health equity and overall population health as well as balancing concern for health with concern for other goods.

Equality of what?

Reasoning about distributive justice in health needs to be based on a general and reasonable unit of distribution. The term "health" needs specification. Following Rawls, Nagel, Sen, Parfit and Daniels, we argue that theories of fair distribution should be concerned with individual people's life prospects. In the context of health, a person's overall lifetime prospect in terms of longevity and health-related quality of life is therefore a reasonable choice. Following Gakidou, Murray and Frenk, we could define the unit of distribution as health-adjusted life expectancy (HALE). Another alternative would be to use a similar measure of lifetime health (without adopting the ex-ante perspective) that includes both a time dimension, measured as life years, and a quality of life dimension, understood in terms of morbidity, pain and functioning. Fortunately, such measures of health-adjusted life years (HALYs) exist, although none of them are perfect, for example, quality-adjusted life-years (QALYs) and disability-adjusted life-years (DALYs).

Whatever measure is chosen, it can be linked to more general theories of fair distribution of advantage, such as general economic welfare theory, a Rawlsian theory of justice, or Sen's capability approach. Broome has argued that health is important insofar as it contributes to overall well-being. Daniels has argued that health is important in that it contributes to fair equality of opportunity (whether it is linked to Rawls' theory or more general political conceptions of equal opportunity) Sen has argued that it would be natural to see health, in his view, "escapable morbidity and premature mortality" as elements in the set of "capabilities" that egalitarians should be concerned about.

Daniels' extended notion of equal opportunity is closer to Sen's notion of capability, understood as freedom to pursue his or her objectives, than Rawls' original fair equality of opportunity principle (the original principle was meant to secure access to positional goods such as offices and positions only). It is also interesting to note that if health is seen as an element of people's freedom "to promote or achieve valuable functionings," health has more in common with positive freedom than with resources or utility. In a pluralist framework, equal distribution of freedoms may be assigned a greater weight than aggregative concerns. Freedom is a good everyone has reason to want insofar as it does not interfere with other people's freedom. This means that how we understand health will also influence our views on how to balance competing concerns.

Without taking a stand on which theory is most appropriate, there is room to link health either to a theory of well-being, to a theory of primary goods, or to the capability approach. We suggest that it is acceptable to see health (measured in its most general form as healthy life expectancy) as one intrinsic element in any general conception of advantage linked to a general theory of justice.

A defense of the weak principle of health equity

We distinguish between strong and weak equality. The most straightforward view of health equity is strong health equality, where every person or group has equal health. In the normative literature on inequalities in health, however, there is almost unanimous agreement that strong equality of health is an unattainable and unattractive goal and should therefore be avoided or modified. For example, in a recent summary of the normative literature on this issue, Asada concludes that: "Strict equality for all, however, is not an attractive view for various reasons. For example, it denies personal choice. It would be unrealistically expensive. Moreover, it would be unachievable because some determinants of health are beyond human control. Unlike political liberty, strict equality in health for all would not be a feasible nor agreeable goal."

Brock expresses a similar view in somewhat different words: "[...] some commitment to equality is a central feature of nearly all theory of justice, with most of the dispute being in what respects should people be equal. However, whatever the relevant arguments, strong objections exist to a fundamental commitment to equality in outcomes or conditions, both in general and as the basis for a special concern for the worst off."

Rejecting strong equality of health, the question then becomes when we can reasonably diverge from strong health equality. Below, we will examine four widely held objections to strong equality of health: (1) the levelling down objection, (2) only those inequalities that are social are unjust, (3) individual responsibility, and (4) the problem of biological or technological limitations. On the basis of the examination of these four objections, we defend the weak principle of health equality as a backbone of our proposed framework of fair health distribution.

Leveling down objection

Health economists, Culyer and Wagstaff, in a widely cited article, define an equitable distribution of health care as "simply one which gives rise to an equal distribution of health." They immediately add the following qualification: "Of course, this will almost certainly have to be qualified by a side condition that greater equality cannot be achieved by reducing the health of some as a deliberate act of policy." This qualification is a response to a common objection to strong equality, the levelling

down objection. Parfit has argued that egalitarians should not be concerned about strong equality, but rather be concerned with giving priority to the worst off. No one would argue that we should "blind the sighted to equalize health states with the blind".

Daniels defines the goal of "equity in health" partly in response to the levelling down objection: "One natural way to understand the goal of equity in health--the goal of health egalitarians--is to say that we should aim, ultimately, to make all people healthy; that is, to help them to function normally over a normal lifespan. Pursuing equality means "levelling up"—bringing all those in less than full health to the status of the healthy."

We accept the argument that levelling down is never a good thing, but we hold that equality often is. As we demonstrate in the last section, when weak equality and trade-off considerations are combined properly in a pluralist theory of fair distribution, egalitarians can still promote the value of equality. This argument is grounded on a pluralist moral view. Levelling down will never be judged as a good thing for egalitarians if we adopt a pluralist theory that integrates distributional concerns with overall goodness. Equality is not the only value egalitarians promote, but equality is so important that we should not reject it.

Only those inequalities that are social are unjust

Arguably, the strongest objection historically to defining health equity as strong equality in health has been that health is a natural good and cannot be redistributed by institutions (such as the healthcare system or more broadly, a welfare system) in the same way as income. Many scholars think the distinction between naturally and socially created inequalities is of moral importance. Fairness or justice is concerned only about socially created inequalities, not naturally created inequalities.

This distinction goes back to Rawls, who, more than 35 years ago, distinguished social goods from natural goods and suggested that health should be considered as a natural good. Health cannot be distributed in the same way as political rights or income. Although Rawls' ideal theory did not discuss the distribution of health and health care at all (Rawls famously assumed disease and disability away and stipulated that the parties in the original position are fully cooperating members of society over a complete life), the view of health as a natural good has survived up to this day. From these two assumptions combined (that health is a natural good, and that the parties in the original positions have normal capabilities of their complete lifespan), it follows, for instance, that a severe mental disability is not a concern for justice [Attempts at extending or modifying these assumptions in Rawls can be found in Daniels (1985/2007) and Pogge (1989). Daniels does not build upon Rawls' original assumptions].

Does this distinction between social and natural goods indeed hold, and is it morally relevant and useful? We shall not attempt to review the very interesting debate about the correct interpretation of Rawls' view on this issue, but rather question the factual premise this debate presupposes. In our view, this distinction is irrelevant in thinking about when inequalities in health are unjust.

First, health is primarily a social good. In the world we live in today, the basic institutions of society determine to a large extent the level and distribution of health. According to statistics from the World Mortality Report, life expectancy in many countries has increased by as much as ten years since the early 1970s. This change is mediated through social factors such as economic growth, technology, reduced inequalities, knowledge and investment in public health and health systems. The WHO reports that life expectancy at birth ranges from 77 (for males) and 82 (for females) in Norway to 41 (for both males and females) in Malawi. Natural factors probably play a minor role in explaining this difference. The health of peoples, or nations, is not something given but fundamentally shaped by how societies are organized and how the benefits of cooperation are shared. We know that Malawi is a much poorer country than Norway, and that the social determinants of health (including health care and public health) are unequally distributed between and within the two countries. The literature on the social determinants of health has, convincingly in our view, demonstrated that social factors are dominantly associated with inequalities in health.[39,40] Health is, then, a concern for social justice.

Second, in most cases it is not possible to distinguish between natural and social causes of disease. Diseases, such as cardiovascular disease or cancer, typically result from the complex interaction between genetic and environmental factors (widely understood to include many of the social determinants of health). A person may inherit genes that increase the risk for, say, cardiovascular disease, but this risk is substantially modified by personal behaviour, the environment and culture, and the basic institutional structures in which that person grows up. Singling out one etiological factor as natural and others as social is in practice difficult, if not impossible.

Third, natural and genetic inequalities in health are actually taken seriously in health policy and clinical practice. Convincing arguments are needed to depart from this view. For example, women who have inherited the BRA1 gene that increases their lifetime risk for breast and ovarian cancer by up to 70-80% are typically treated with more concern than others, not less. Indeed, why should genetically inherited disease (caused by the natural lottery) be given less or no priority compared to those who acquire a disease because they live in poverty or lack basic education? Whether risk is associated with unfair social circumstances or is the result of the natural lottery, it affects well-being, opportunities and freedom to the same degree. Disease and risk of disease are not in the same category as the colour of our eyes or beauty in our judgment of social obligations. In clinical practice, no one would consider whether a condition is caused by social or natural factors as a decisive reason for different prioritisation. Practice does not make a thing right, but if we consider principles against well-considered intuitions in reflective equilibrium, this widely held intuition should be considered seriously.

Finally, the implications of the distinction between natural and social factors are counterintuitive and not normatively attractive. Some people have low life expectancy because they are poor, lack education and employment. Others may have low life expectancy, even if not so poor, because they happen to be in a natural setting where there are a lot of malaria-carrying mosquitoes. Should this "natural fact" be a factor against a justice concern? "Freedom from malaria" is one of Sen's paradigmatic examples of what an egalitarian theory should focus on. We agree. If anyone thinks that freedom from malaria should not be a concern for justice, it is probably a mistaken expression of the underlying intuitions that there are some health inequalities we cannot, as a society, do anything about.

Consider the situation in the early 1980s before the existence of HIV was known, before its ways of transmission was known and before antiretroviral treatment was developed. The fact that some people died prematurely from AIDS at that time could not be considered unfair, because the disease was not possible to prevent or treat. Being free from malaria (and HIV today), on the other hand, is a concern for justice because society does have the knowledge and the means to prevent and treat them. In our view, the relevant distinction is whether the institutions of society can respond adequately to a disease or not, which we will elaborate below—not whether the causes are natural or social.

The upshot of this discussion is that most health inequalities should, as a starting point, be considered unjust. The division between health as a natural and a social good is not possible to define. Neither is it morally relevant. [Of course it would be judged unfair if they had been denied access to preventive measures. That many people died prematurely was also a reason to fund HIV research.]

Individuals should have some responsibility for inequality

Another widely held objection to strong health equality is personal responsibility. Temkin, though his work does not focus specifically on health, proposes the following view of which inequalities are of moral concern: "Egalitarians generally believe that it is bad for some to be worse off than others through no fault or choice of their own." Sen also argues that the issue of personal responsibility has some bearing on the issue of health inequalities: "What is particularly serious as an injustice is the lack of opportunity that some may have to achieve good health because of inadequate social arrangements, as opposed to, say, a personal decision not to worry about health in particular. In this sense, an illness that is unprevented and untreated for social reasons (because of, say, poverty or the overwhelming force of a community-based epidemic), rather than out of personal choice (such as smoking or other risky behavior by adults), has a particularly negative relevance to social justice."

Similarly, liberal egalitarian theories of distributive justice argue that a central goal of public policy should be to secure all individuals equal opportunities. All equal opportunity approaches argue that society should eliminate inequalities that arise from factors beyond individual control. One prominent position argues that equal opportunity requires that all inequalities that arise from factors outside the agent's control in the social and the natural lottery, such as a person's natural and genetic abilities should be eliminated, but that inequalities or costs that arise from factors under the agent's control should be accepted.

Applied to the context of health the principle of equality implies that all individuals who make the same choices should be treated as if they were identical with respect to all factors outside their own control. This view holds that natural inequalities (associated with, for example, genetic factors) should be a concern for egalitarian justice.

A common misunderstanding of liberal egalitarianism is that these theories argue that individuals should be held responsible for the consequences of their choice. In the context of health this would imply that all inequalities in health are counted as fair if the agent in question could have avoided bad health outcomes by making different choices. However, the principle of responsibility states that individuals should be held responsible for their choices, not for the consequences of their choices. It is only in the special case where the outcome only depends on the individual's choices and not on any other factors (including the responsibility of society) that this principle implies that individuals should be held responsible for the consequences of their actions. To hold people responsible for the actual consequences of their choice would therefore be to hold them responsible for too much. The implication of the principle of responsibility on the concept of health equality is therefore in practice limited.

Interestingly, health systems of liberal societies generally embody this (correctly understood) principle of responsibility. We discourage people from practising "irresponsible" health behaviors, such as smoking, unsafe sex, and sedentary life styles, through public health and health promotion. For some behaviours, we make people responsible for their action by imposing taxes (eg, tax on cigarettes) or making them illegal (eg, seat belt laws). But our health systems do not treat the reckless and the sensible differently.

Strong equality is unachievable because of limitations of biology and technology

The final objection to strong health equality commonly found in the literature relates to considerations about biological and technological limitations. Many definitions of health inequity proposed by health science researchers suggest that inequalities in health are fair if those inequalities are unavoidable. Whitehead and Dahlgren explicitly incorporate unavoidability in their definition. Similarly, the pragmatic definition of health equity adopted by the International Society for Equity in Health in 2000 focuses on remediability: "Equity in health is the absence of systematic and potentially remediable differences in one or more aspects of health across socially, demographically, or geographically defined populations or population subgroups." Furthermore, though not as explicit as the two definitions above, Gakidou, Murray, and Frenk, in their proposal for measuring health inequities across countries for The World Health Report 2000, consider health inequalities caused by factors amenable to human interventions as unjust.

The concern for unavoidability in the health equity literature echoes the idea of shortfall equality developed by Sen and Anand for the human development index. They are concerned about the fact that some people are more efficient converters of resources or goods to well-being (or health) than others. Anand and Sen explain: "In those cases in which human diversity is so powerful that it is impossible to equalize the maximal levels that are potentially achievable, there is a basic ambiguity in assessing achievement, and in judging equality of achievement (or of the freedom to achieve). If the maximal achievement of person 1 -- under the most favourable circumstances—is , say, $\underline{x}$, and that for person 2 is $2\underline{x}$, then equality of attainment would invariably leave person 2 below her potential achievement."

As an alternative to strong or attainment equality, Anand and Sen defend shortfall equality. This view can most easily be illustrated by reference to gender inequality: There is a commonly observed gender difference in life expectancy of about 2-5 years (researchers disagree about the correct figure), favouring women. In a society where life expectancy is, for example, 60 years for men and women, this equality in life expectancy by sex would be judged equitable if strong equality is the normative standard, while it is inequitable if shortfall equality is the standard.

The key question is: if strong equality is not feasible, should egalitarians be concerned about strong equality or equal shortfall from what is feasible? In short, should we be concerned about all health inequalities (measured from an equal baseline), or only shortfall inequalities (measured from a baseline defined by what is possible)?

We agree with Anand and Sen, that equity concerns inequalities that are avoidable. Although they do not clearly define when we should consider inequalities to be unavoidable, the term often includes limitations of biology, technology or knowledge. Anand and Sen refer to limitations of biology when they defend shortfall equality in the case of men and women as illustrated above. Our view of biological limitations is that, whether they are functional or mental limitations, egalitarians should not count them as legitimate shortfalls. Above, we argued against the view that only those inequalities that are social are unjust. In health policy and clinical practice, we take natural inequalities in health seriously and consider them as important as social inequalities in health. Inequalities due to biology are examples of natural inequalities, and we do not see why gender deserves special consideration among many other biological factors, such as genetics.

It appears reasonable, on the other hand, that egalitarians should be concerned about limitations caused by the level of technology or knowledge available. The implications of this departure from strong equality are probably substantial as technological limitations change over time. To repeat our example from above, using shortfall equality as the standard, people dying prematurely from HIV/AIDS in the early 1980s (before the aetiology of the disease was known) were suffering tremendously, but their tragically reduced life expectancy was not unfair. Given the medical advancement for HIV/AIDS treatment in recent decades, however, the same amount of suffering and premature death now is quite rightly considered inequitable.

We believe the idea of shortfall equality applied to technological limitations reflects a sound principle and well-considered moral intuitions that many people hold regarding equity -although what such limitations entail requires further clarification.

Statement of the weak principle of health equality

The discussion above on four objections to strong health inequality suggests the following. First, health equity should not be improved by "levelling down," that is, making people less healthy. The objection loses force if concern for equality is integrated with concern for average health as required by a pluralist theory of fair distribution. Second, when considering which health inequalities are unjust, distinguishing social and natural factors is morally irrelevant. Third, health inequalities are acceptable if they are derived completely from choices that free and fully informed adults make. But such health inequalities are extremely rare, and in practice, individuals cannot often be held responsible for health inequalities due to choice. Finally, health inequalities are fair if they are associated with technological limitations on further health improvements.

Taken together, we propose a definition of weak health inequality: every person or group should have equal health except when: (a) health equality is only possible by making someone less healthy, or (b) technological limitations exist to further health improvements. In other words, the weak principle of health equality suggests that health inequalities that are amenable to positive human interventions are unacceptable.

Trade-off questions

All definitions of health equity proposed in the past have exclusively focused on health inequalities: among many health inequalities, which ones are unfair? The weak principle of health equality is one partial answer to this question. A definition of fair distribution of health needs to expand its scope beyond health inequalities. Even if the weak principle of health equality is satisfied—every person or group has equal health adjusted for technological limitations to further health improvements—there may be situations where fairness in distribution rejects weak health inequality.

Achieving health equality is an important goal but is only the first step towards a broader pluralist notion of fair health distribution. The next step involves trade-offs with other objectives. In the world of limited resources, defined broadly in terms of, for example, money, time, and talents, to tackle serious issues in our society, how important is it for us to commit to the weak principle of health equality? We divide such trade-off issues into two categories, trade-off between weak health equality and overall health, and trade-off between health and other goods. Together we call them trade-off questions, which form another backbone of our proposed framework of fair health distribution.

Trade-off between weak equality and average

Weak equality of health is morally objectionable when further improvement in weak equality leads to unacceptable sacrifices of average or overall health of the population. This formulation, of course, leaves open the normative question about which trade-offs between weak equality and average health are unacceptable. It is crucial to note, however, that a framework of fair distribution should acknowledge that weak equality is not the only concern. As noted by Sen, equality is not only a complex notion where there is "internal plurality" within the concept itself. Equality can only be properly understood if it is considered together with other key ethical concepts: "The demands of equality cannot be clearly interpreted or understood without taking adequate note of efficiency considerations. The point is not merely that the demands of equality have to be ultimately weighted against the force of competing demands, when present. It is also that the interpretation of the demands that equality makes has to be assessed in the light of other considerations (eg aggregative concerns) that are inter alia recognized. The explicit admittance of other concerns avoids the overburdening of equality with unnecessary loads."

Trade-off questions are important in the context of population-level policies, where the aim is to distribute healthy life years fairly. For example, how much equality of healthy life years between different groups or individuals is a decision-maker is willing to sacrifice, in order to move towards a higher average for all? Or, following Anand: "what amount of healthy life years, if enjoyed equally by everybody, would have equivalent value to a greater average healthy life expectancy?" Equal health here refers to equality in health that is amenable to positive human intervention.

As yet there is no full-fledged principled account of how balancing of this kind can be handled. But economists have suggested a number of indices that attempt to capture the trade-off between weak equal health (or "equity" as the economists call it) and maximizing concerns (efficiency), including the modified Atkinson's index suggested by Anand, and the Achievement index proposed by Wagstaff, which incorporates concerns, such

as (a) aversion to weak inequality of health, (b) a special concern for the worst off individuals or groups, and (c) explicit judgment about the appropriate trade-off between egalitarian concerns (a + b) and maximization concerns. Further investigation is needed to see whether our concerns about fair distributions can be quantified appropriately by these indices. Reasonable quantitative measures coupled with fair processes for making normative choices explicit and legitimate could be used to bridge health policy and the unified framework that we are proposing.

Trade-offs between health and other goods

Weak health equality may also be unfair if further reduction in health inequality would unacceptably increase inequality or reduce aggregate well-being in other domains of concern (such as education, employment, social security, and so on). In other words, some departures from weak equality in health are acceptable with reference to other important social objectives. For example, in a welfare state with publicly financed health care, one may justify limits on the provision of high-cost last-chance chemotherapy with marginal health benefits with reference to improvements in social security for the homeless or in primary education. Although many think that health is special, rightly so in our view, health is partly also a tradeable good.

Health cannot be seen in isolation from other goods, and the interrelation between health and other advantages is of interest theoretically and practically. Weak inequalities in health may be acceptable if we could thereby reduce inequality in other domains more. On the other hand, and this is most often the case, if inequalities in the other domains also increase inequality in health, this may be considered "doubly" unfair. We need a robust theory which integrates health and other substantive goods. Some existing philosophical theories are a good start, as we briefly sketch here. For example, Daniels argues that Rawls' theory of justice provides a unified account of justice that can help explain when social group inequalities in health are unfair: "Health inequalities are unjust or unfair if they result from an unjust distribution of the socially controllable factors that affect health." He suggests that what counts as "an unjust distribution of the socially controllable factors" might follow from Rawls' theory. One problem, however, is that this theoretical framework lacks an index of primary goods that can be used for making trade-offs between health and non-health primary goods.

The Rawlsian framework provides little guidance, Prah Ruger has argued, "when accounts of social and economic justice conflict with accounts of justice with respect to health."[57] As she points out:

"Before giving substantially greater weight to broader socioeconomic policies than to health policies, we need to understand the precise mechanisms through which various factors influence health. We must then determine how to weight different social objectives, once we have this information. In light of existing information on social determinants of health, it would be unwise to prescribe sweeping policies, such as completely flattening of socioeconomic inequalities, in an effort to improve health."

Sen's capability approach provides an alternative framework for evaluating justice. Sen lists five categories of rights and opportunities that are seen as necessary to help "advance the general capability of a person."[44] Poverty is defined as capability deprivation in any of these categories. Sen's list includes: political freedoms; economic facilities; social opportunities; transparency guaranties; and protective securities. Health would probably be subsumed under social opportunities, although transparency guarantees and protective guaranties also include relevant aspects of health-related agency and having good health.[58] This framework links health to a general theory of justice in a way that is interesting. Prah Ruger argues that Sen's approach is superior to Rawlsian analysis in this respect. The capability approach, however, requires that we develop a comparable metric of advantage across various domains.

Concluding Remarks

When are inequalities in health unfair? Answers to this question may be useful for people who want to measure inequalities in health. A definition of health equity may also be useful to people who are concerned about priority setting in health and healthcare.

Our framework of fair health distribution is composed of the weak principle of health equality and the principle of fair trade-offs. The weak principle of health equality offers an alternative definition of health equity to those proposed in the past. The weak principle of health equality maintains the core ideas of the widely popular Whitehead/Dahlgren definition of health equity, and at the same time, it offers a richer philosophical foundation. This principle states that every person or group should have equal health except when: (a) such strong health equality is only possible by making someone less healthy, or (b) technological limitations exist to further health improvements. In short, health inequalities that are amenable to positive human interventions are unacceptable.

The principle of fair trade-offs supplements the weak principle of health equality. The principle of fair trade-offs states that weak equality of health is morally objectionable if and only if: (c) further reductions in weak health inequality leads to unacceptable sacrifices of average or overall health of the population; or (d) further reduction in weak health inequality would result in unacceptable sacrifices of other important goods, such as education, employment, and social security. We believe coupling the weak principle of health equality with the principle of fair trade-offs will offer a fuller view of health equity than the traditional view. A combined pluralist framework is necessary to understand fair health distribution.

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