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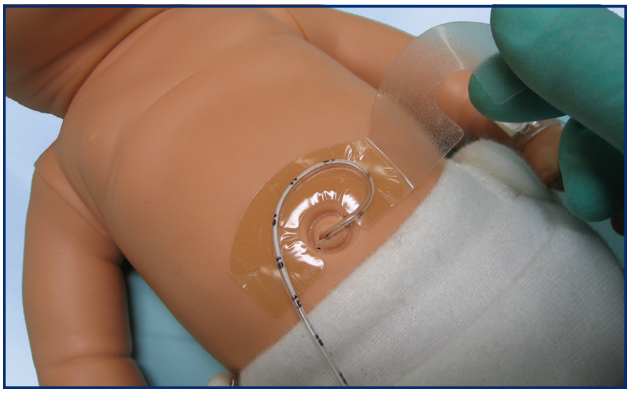

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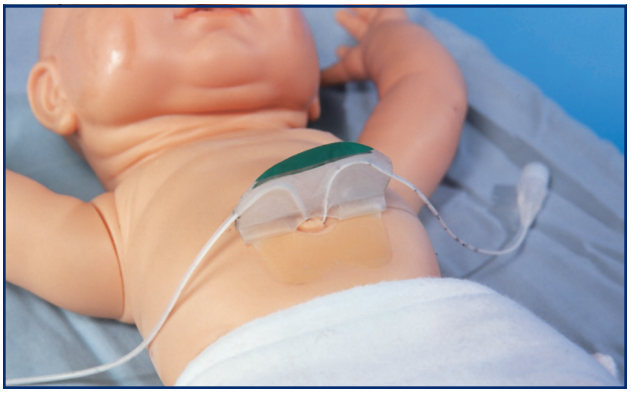

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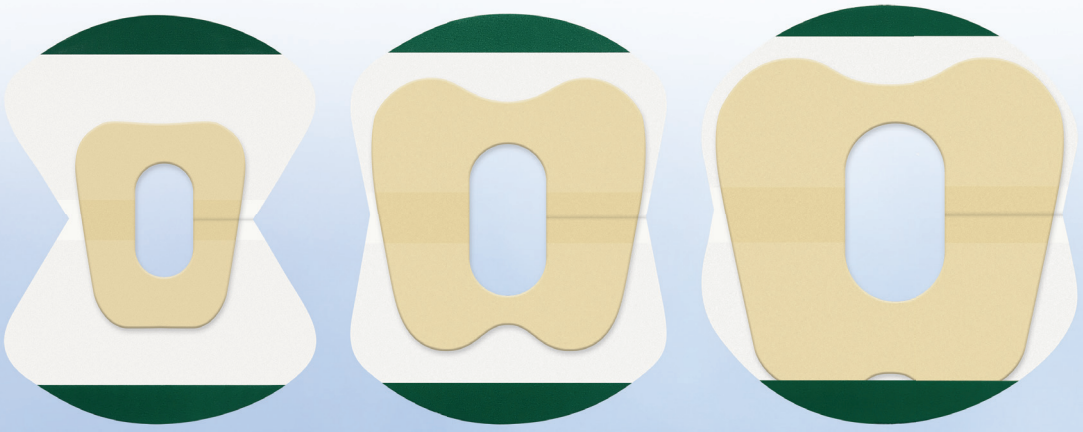

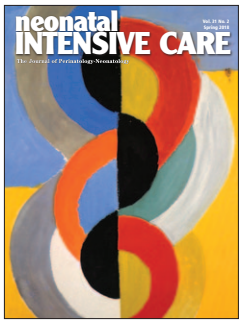

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Generational Loss of Good Bacteria in Baby's Gut Microbiome

Evolve BioSystems announced new research that connects elevated infant fecal pH levels to a profound change in the infant gut microbiome, including the disappearance of a beneficial bacterium that may be key to short and long-term health. Over the past 100 years, the average pH level of a baby's stool, which can indicate the type of bacteria in the baby's gut, has undergone an alarming increase from pH 5.0 to 6.5. The study, published in the American Society for Microbiology journal mSphere, connects this rise in pH to a generational loss of Bifidobacterium, a critical gut bacteria during infancy, and an accompanying increase in a number of harmful bacteria. The complete study is called Elevated Fecal pH Indicates a Profound Change in the Breastfed Infant Gut Microbiome Due to Reduction of Bifidobacterium over the Past Century. A review of 14 clinical studies published between 1926 and 2017, representing hundreds of healthy breastfed infants, showed a change in fecal pH from 5.0 to 6.5 over this time period. The authors attribute this trend to an observed reduction of Bifidobacterium in the infant gut, along with an increase in potentially harmful bacteria such as E. coli and Clostridia, resulting in "dysbiosis," a potentially detrimental imbalance of the gut microbial ecosystem. According to study co-author, Dr Jennifer Smilowitz, Associate Director of the Human Studies Research Program for the Foods for Health Institute at UC Davis, "These alarming changes to the infant gut microbiome and thus, gut environment, may be due to modern medical practices like antibiotics, C-sections, and formula feeding. These are all potentially life-saving medical practices, but have unintended consequences on the infant gut microbiome. As a result, certain pathogenic bacteria—those linked to higher risk of health issues such as colic, eczema, allergies, diabetes and obesity—thrive. The need for clinicians to have a quick and reliable method to determine Bifidobacterium levels in baby's gut, and an effective way to replace the right Bifidobacterium to correct dysbiosis when detected, are the critical next steps for infant health." In December 2017, Evolve BioSystems published results of a landmark clinical trial in mSphere, showing that Evivo, an activated form of B. infantis, produced rapid, substantial, and persistent improvements in the gut microbiome of breastfed infants. Evivo is the only baby probiotic clinically proven to restore the levels of Bifidobacterium to baby's gut, reduce potentially harmful gut bacteria by 80 percent, and return fecal pH to levels seen historically. For more information about Evivo, please visit www.evivo.com.

Inhaled Budesonide May Yield Mixed Results in Premature Infants

Inhaled-glucocorticoid therapy does not appear to boost the longer-term risk of neurodevelopmental disability in extremely premature infants, but might increase mortality, according to a randomized controlled trial. "Thanks to the new study results, neonatologists can now make informed decisions regarding the use of inhaled glucocorticoids for the prevention of" bronchopulmonary dysplasia (BPD), chief author Dr Dirk Bassler, chief of neonatology at University Hospital Zurich said. "When making this decision, they need to carefully balance the risks of potentially increased mortality owing to early inhaled corticosteroids against those of decreased rates of BPD with no effect on neurodevelopment in survivors at 2 years of age." BDP itself is the most common chronic complication of extremely preterm birth. It is associated with higher mortality, growth failure, neurodevelopmental delay and both chronic respiratory and cardiovascular impairment. It can be prevented with systemic glucocorticoids, but those carry a higher risk of neurodevelopmental impairment such as cerebral palsy, and intestinal perforation. So doctors often try

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10940 Wilshire Blvd., Suite 600
Los Angeles CA 90024
Phone: 310-443-4109
Fax: 310-443-4110
E-mail: s.gold4@verizon.net
Web: www.nicmag.ca

Publisher/Editor in Chief
Steve Goldstein

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inhaled glucocorticoids. "Despite much study and progress in neonatology in recent years and some modest improvements in survival, both the incidence and severity of BPD have not changed much. To this day, approximately half of the infants born with a gestational age of less than 28 weeks suffer from BPD," Dr Bassler said. The popularity of glucocorticoid treatment varies widely. It was estimated a few years ago that it was prescribed for about 25% of premature infants in the United States versus about 70% in Japan. The latest findings, reported in The New England Journal of Medicine, are a follow-up to the group's 2015 study in the Journal, which found that while inhaled budesonide lowered the dysplasia risk, it elevated the mortality rate. The new work evaluated data on 629 babies randomly assigned to placebo or budesonide at a corrected age of 18 to 22 months. All were at a gestational age of at least 23 weeks and less than 28 weeks at the time therapy began. In the trial, done at 40 centers in nine countries, the budesonide babies received 400 micrograms of the inhaled drug every 12 hours, with the daily dose reduced to 200 micrograms from day 15 until the babies didn't need respiratory support. Drug treatment ended at 32 weeks. The rate of neurodevelopmental disability — a composite of cognitive delay, deafness, blindness or cerebral palsy — was 48.1% among the 308 budesonide recipients and 51.4% among the 321 who got placebo (P=0.40). The Bassler team also found no evidence that individual elements of that composite scale were affected by inhaled budesonide therapy. Budesonide recipients were more likely to die during the study (19.9% vs. 14.5%, P=0.04). "This is unexpected," Dr Bassler said, and "there is no biologically plausible hypothesis to explain the seeming excess of deaths in treated infants, and the causes of death in our study did not differ considerably between the groups. The mortality findings may be attributed to chance, but we can't be sure about this assumption." He said the results need to be seen in the context of other studies. "There are now updated meta-analyses including our short-term outcomes that address the use of inhaled glucocorticoids as compared with placebo or no intervention," Dr Bassler said. "All updated systematic reviews and meta-analyses found a modest, but significant reduction in the composite outcome of death or BPD at 36 weeks. In these updated meta-analyses, inhaled glucocorticoids were associated with a significant reduction in BPD with no effect on mortality."

Adult Survivors of Preterm Birth Have Smaller Airways

The airways of adult survivors of preterm birth are smaller than those of their peers born full-term, which may help to explain their worse lung function, according to findings. Airway obstruction at rest is a "hallmark finding" in adults who had been born prematurely, Dr Joseph W. Duke of Northern Arizona University in Flagstaff, who helped conduct the study, noted. On average, he added, premature birth is associated with a 20% to 30% reduction in lung function, with expiratory flow limitation (EFL) and reduced inspiratory volume during exercise. Dr Duke and his team used dysanapsis ratio (DR), an indirect measure that accounts for maximal flow, static recoil and vital capacity, to compare airway size in three groups of adults (mean age, 22 years): 14 who had been born at least eight weeks premature and had bronchopulmonary dysplasia (BPD), 21 born at least 8 weeks premature without BPD, and 24 term-born controls matched by age, sex and height. DR was 0.16 for the preterm adults without BPD, 0.10 for the BPD group, and 0.22 for the controls. DR correlated significantly with both peak expiratory airflow at rest (r=0.42) and expiratory flow limitation during exercise (r=0.60). The researchers used two different equations to measure DR, with consistent results: DR was significantly smaller for the preterm adults with or without BPD than for the controls, and those with BPD had significantly smaller DR than those without BPD. Given the findings, standard treatments for asthma and chronic obstructive pulmonary disease, which work by dilating the airways, may not be effective in these patients, Dr Duke noted. "We need to do some studies looking at these traditional medicines to reverse airflow obstruction and see what effect, if any, they have on adult survivors of preterm birth," he said. He

and his colleagues conclude: "The data in the present study suggest that smaller than normal airways explain, at least in part, the lower expiratory airflow rate in PRE (i.e., without BPD) and BPD. The present findings add important information to our understanding of the cardiopulmonary physiology of PRE and BPD."

Air Pollution Tied to Low-Birth-Weight Risk

Air pollution, but not traffic noise, appears to be linked to an increased risk of having low-birth-weight babies, reports a new study from the UK. Previous studies have tied road traffic air pollution to low birth weight. Road traffic produces noise as well as pollution, but studies of noise pollution have had conflicting results, say the authors. "We know that noise is associated with adverse health effects, e.g. sleep disruption, increased blood pressure, and cardiovascular disease, so it could plausibly have an impact on mothers' health in pregnancy and the health of unborn babies," study leader Dr Rachel Smith at the School of Public Health of the Imperial College said. Smith's team wanted to investigate the effect of exposures to both traffic-related air and noise pollution during pregnancy on babies' birth weight. "We found increased risk of babies being born with low birth weight or small for gestational age, at term, to mothers with higher exposure to air pollution from road traffic during pregnancy. We did not see an independent effect of road traffic noise on birth weight," she said. Smith and colleagues used national birth registers to identify over 540,000 live, single, full-term births occurring in the Greater London area between 2006 and 2010. Specifically, the study team was interested in low birth weight (<5.5 pounds) and being born small for gestational age. Mothers' home addresses at the time of birth were used to estimate the average monthly exposure to traffic-related pollutants including nitrogen dioxide, nitrogen oxides, and fine particulate matter, or PM2.5. The researchers also estimated average day and night-time road traffic noise levels. Increases in traffic-related air pollutants, especially PM2.5, were associated with 2% to 6% increased odds of having a low birth weight baby and about 1% to 3% increased odds of a baby being small for gestational age, even after taking road traffic noise into account. The risk associated with air pollution should be considered in context, i.e. the size of the effect of air pollution on an individual baby's birth weight is relatively small compared to the well-recognized effect of smoking, said Smith. "However, at the population level the impact could be large, because collectively more women are exposed to air pollution than are exposed to smoking during pregnancy," she said. There is a limit to what individuals can do to reduce their exposure to air pollution because making major changes to lifestyle, travel or where they live is just not feasible for the vast majority of people. Improving air quality and reducing air pollution in our towns and cities, and thus reducing health impacts of air pollution, requires action by policymakers, said Smith. The study "should increase awareness that prenatal exposure to small particle air pollution is detrimental to the unborn child," Sarah Stock and her colleague wrote. Stock, a researcher at the University of Edinburgh Queen's Medical Research Institute in Edinburgh, UK, said air pollution from traffic is well known to be detrimental to child and adult health. "This study provides further evidence that air pollution from traffic is also harmful to unborn babies. However, it shows that traffic noise is unlikely to be related to low birth weight in babies," Stock, who was not involved in the study said. Pollution should be high on agendas at a local and national level, with pollution control integrated into development planning, said Stock. "Key initiatives include enforcing emission control technologies in motor vehicles; ensuring easy access to affordable and efficient public transport; encouraging walking and cycling; and mandating clean air zones," she said. Unfortunately, women have few options to reduce their risk on a personal level, said Stock. "Avoiding air pollution is difficult, and we have no evidence that lifestyle measures, or wearing protective masks actually reduces chronic exposure to harmful pollutants. We do know avoiding exposure to tobacco smoke is really important. More research in this area is needed to find out the best ways for women to reduce their risk," she said.

Phototherapy Readmissions Studied

Subthreshold newborn phototherapy can reduce the number of readmissions for phototherapy, but as many as 60 newborns could require treatment to

prevent 1 readmission, according to a retrospective study. "I was surprised by how many babies needed to be treated with phototherapy during the birth hospitalization to prevent one from being readmitted," Dr Andrea C. Wickremasinghe from Kaiser Permanente Santa Clara Medical Center, in California, said. "In our unit, we avoid administering phototherapy at bilirubin levels below the phototherapy threshold." Many clinicians use phototherapy for newborns with total serum bilirubin levels (TSB) below established thresholds in order to prevent future readmissions for hyperbilirubinemia and their associated copays and inconvenience to parents. Whether such subthreshold phototherapy has a favorable risk-benefit profile remains unclear. Dr Wickremasinghe's team used data from 16 Kaiser Permanente Northern California hospitals to estimate the efficacy of using phototherapy to treat newborns with TSB levels from 0.1 to 3.0 mg/dL below the appropriate phototherapy threshold during the birth hospitalization, with the goal of preventing readmissions for phototherapy. Among the 25,895 newborns with TSB levels 0.1 to 3.0 mg/dL below threshold, 19.1% received subthreshold phototherapy during the birth hospitalization and 11.3% were readmitted for phototherapy. The mean length of hospital stay, after adjustment for other factors, was nearly 1 day longer (22 hours) for newborns who received subthreshold phototherapy than for those who did not. Significantly fewer newborns that received subthreshold phototherapy (4.9%) than not treated (12.8%) were readmitted for phototherapy. After multivariable adjustment, this represented a 72% decrease, but the overall number needed to treat (NNT) to avoid 1 readmission was 14.1. Factors associated with increased odds of readmission for phototherapy included male sex, lower gestational age, Asian race/ethnicity, assisted vaginal delivery, family history of phototherapy, a qualifying TSB level closer to the phototherapy threshold, lower chronological age at the time of the qualifying TSB level, and exclusive breastfeeding. In contrast, low birth weight, cesarean delivery, direct antiglobulin test (DAT) positivity, and home phototherapy were associated with decreased odds of readmission for phototherapy. The NNT to avoid 1 readmission varied widely according to the newborn's estimated risk of readmission based on these other factors, from 6.3 for those in the highest quintile of risk to 60.8 for those in the lowest quintile of risk. Subthreshold phototherapy during the birth hospitalization also lowered the odds of having a TSB level at or above the phototherapy threshold after discharge. "Phototherapy should be considered a treatment, with the potential for both risks and benefits," Dr Wickremasinghe concluded. "Don't use phototherapy for low-risk infants with bilirubin levels below the phototherapy threshold."

Childhood Stunting Prevention Studied

Treating pregnant women for malaria and other infections reduces the prevalence of childhood stunting, has a positive effect on child development and may lessen neonatal mortality, researchers say. "Stunting is a big global issue and is associated with increased mortality and developmental delay," Lotta Hallamaa of the University of Tampere in Finland said. Hallamaa and colleagues showed in earlier work that intermittent preventive treatment in pregnancy (IPTp) against malaria and reproductive tract infections reduced prevalence of neonatal stunting in Malawi, she said. "This follow-up study shows that gains obtained among children whose mothers received monthly SP (sulfadoxine-pyrimethamine) with two doses of AZI (azithromycin) rather than two doses of SP (alone) during pregnancy were sustained for five years and reflected in the prevalence of childhood stunting, development and possibly post-neonatal mortality," she noted. However, she added, "Even though the results are encouraging, we do not recommend widespread use of broad-spectrum antibiotics as a routine antenatal treatment. This could theoretically lead to problems with antibiotic resistance and cause long-term effects on the microbiota of both the mother and the child." Hallamaa also noted that after the earlier study, World Health Organization recommendations for IPTp changed from two doses to one monthly dose of SP, and recent exploratory IPTp trials suggest other agents may also be effective. Therefore, she stressed, "our results should mainly be considered indicative of a causal role of maternal infections and inflammation in fetal growth restriction and its sustained impact on child growth and development." For the current clinical study, the team randomized 1,320 pregnant Malawian women to receive two doses of SP (control), monthly SP, or monthly SP plus two doses of azithromycin (AZI-SP). The researchers recorded the height or length and mortality of participants' children at seven intervals between 1 and 60 months of age, as well as mental development at 60 months. Throughout the follow-up period, mean child length was 0.4 to 0.7 cm higher at 1 to 12 months of age, the prevalence of stunting was 6% to 11% lower at 12 to 36 months, and the 5-year cumulative incidence of stunting was 13% lower in the AZI-SP group than in the control group. In addition, the mean developmental score was 3.8 points higher in the AZI-SP group than in the control group. Mortality rates during pregnancy and childhood were 13.1% with AZI-SP, 15.1% with monthly SP, and 15.3% with control treatment. Post-neonatal mortality rates were 1.9%, 3.3% and 5.5%, respectively.

Vaccine Touted for Infant Diarrhea

An experimental oral rotavirus vaccine, when given at birth and in two subsequent doses, can reduce the rate of severe and potentially deadly diarrhea by 75%, according to new study conducted among Indonesian babies. Researchers found that while the rate of illness up to age 18 months was 5.6% among babies who received placebo, administering the vaccine within the first five days of birth, followed by booster doses at 8 and 14 weeks, cut that rate to 1.4%. When the vaccine was given a bit later — at eight, 14 and 18 weeks — the rate was 2.7%, meaning it was effective 51% of the time. The study comes at a time when more than 90 million infants worldwide lack access to conventional rotavirus vaccines and doctors are trying to improve the effectiveness of existing products in low-income countries. The World Health Organization has estimated that about 215,000 children under age 5 die each year from a preventable rotavirus infection. The new vaccine, known as RV3-BB, is novel because it comes from a strain of rotavirus that commonly infects babies but doesn't cause symptoms, chief author Dr Julie Bines of the University of Melbourne said. "With this vaccine, because it doesn't cause disease in its natural form, we can be very confident it will be safe in newborns. And it's a novel strategy to give the vaccine at birth." Other rotavirus vaccines aren't given until age six weeks, making babies vulnerable at the beginning of life. The vaccine was developed at Murdoch Children's Research Institute in Melbourne, Australia, where Bines is a researcher. The phase 2b study done in Indonesia because the rotavirus childhood death rate is high — about 10,000 per year among children under 5. The virus also results in more than 200,000 hospitalizations annually, according to the institute. In addition, rotavirus vaccination is not part of the country's immunization program, making it ethical to give some babies placebo. The results were based on 1,588 babies followed for 18 months. Combining the neonatal and

infant groups, the efficacy of the vaccine against severe rotavirus gastroenteritis was 63% compared to placebo.

Obesity Linked to Weight of Birth Moms

Babies born to overweight or obese mothers, either vaginally or via cesarean section, are more likely to become overweight or obese than those born vaginally to normal-weight mothers, a new study has shown. In addition to mode of birth, the presence of microbiota in the infant gut appears to mediate the link between maternal and child overweight status, particularly in cesarean-delivered babies, Hein M. Tun, DVM, PhD, from the Department of Pediatrics, University of Alberta, Edmonton, Canada and colleagues report. The current study adds important information supporting the interdependency of maternal weight status and mode of delivery in forming the "microbial communities of early life," which are linked to offspring weight status, say Giulia Paolella, MD, from the Pediatric Intermediate Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, and Pietro Vajro, MD, from the Department of Medicine, Surgery and Dentistry at the University of Salerno, Italy. Tun and colleagues used sequential mediation analysis (a feature used in other fields but that had not been previously applied to microbiome studies) for their large prospective cohort, which allowed them to successfully examine two original, relevant issues, the editorialists note. First, they identified indirect or mediating effects of infant fecal abundance of Lachnospiraceae bacteria (phylum: Firmicutes) in children with overweight or obesity (OWOB) with a mean age of 3.7 months, born to mothers with OWOB after either vaginal or cesarean delivery. Second, the authors established that maternal body mass index (BMI) and cesarean delivery together affect the composition of the initial microbial communities in offspring with OWOB. This additional insight into the mechanisms behind the mother-to-child transmission of overweight and obesity may ultimately "pave the way to novel strategies for obesity prevention that include the interruption of intergenerational transmission of OWOB from mother to offspring," they add, although they do note some limitations of the study.

LSG Benefits Discovered

Some maternal and perinatal outcomes may be better in obese women who undergo laparoscopic sleeve gastrectomy (LSG) than in their obese peers who are not treated with bariatric surgery, new research shows. Women who underwent the procedure were at lower risk of gestational diabetes mellitus (GDM), excessive fetal growth and cesarean delivery compared to a control group of women matched by pre-surgery body-mass index (BMI), Dr Uriel Elchalal of Hadassah-Hebrew University Medical Center in Jerusalem and colleagues found. The women who underwent LSG were, however, at increased risk for having small for gestational age (SGA) and low-birth-weight babies, the authors report in Obstetrics & Gynecology, online February 5. "Numerous studies have evaluated pregnancy outcomes following bariatric surgery," Dr Elchalal noted. "However, as these studies almost exclusively included patients who underwent either gastric bypass or gastric banding, there is limited information regarding pregnancy outcomes following sleeve gastrectomy, which is now the most commonly performed bariatric procedure in the U.S. and Europe." In their retrospective study, Dr Elchalal and his team compared 119 women (mean age, 32) who had undergone LSG and 119 who had not undergone any bariatric surgery. In the LSG group, the median BMI was 41.7 preoperatively and 28.9 postoperatively. The median time from surgery to conception was 508 days. GDM

occurred in 3.4% of LSG patients and 17.6% of controls; rates of having a large-for-gestational-age newborn were 1.7% and 19.3%, respectively. Less than 1% of the LSG group had a baby weighing more than 4,000 grams, versus 7.6% of the control group. Cesareans were performed in 10% of the LSG group and 20% of the control group. All of these differences were statistically significant. In all, 14.3% of the women who underwent LSG had an SGA infant, versus 4.2% of controls; rates of low birth weight were 12.6% and 4.2% in the two groups, respectively. Both differences were statistically significant. The median hemoglobin level, both in early pregnancy and at delivery, was lower in the post-LSG group than in controls.

NICU Units Adopt Device

SonarMed announced the adoption of the AirWave Monitoring System for NICU patients by two leading children's hospitals in California as part of the Company's controlled-market roll-out: CHOC Children's Hospital (CHOC) and Lucile Packard Children's Hospital Stanford. These additional adoptions demonstrate the Company's building momentum and the critical value provided by the AirWave for real-time, continuous endotracheal tube monitoring. Five hospitals to date have adopted the AirWave, including early adopters Huntington Hospital and Memorial Hermann Southwest Hospital, to help healthcare providers detect intubation issues. As the only cleared airway monitoring system, the AirWave uses unique, patented sound wave technology to provide real-time monitoring and detection of endotracheal tube movement, position and obstruction. "The AirWave is steadily becoming the standard of care for adopting hospitals' NICU patients," said Tom Bumgardner, CEO of SonarMed. "As we continue to partner with high-caliber institutions in our limited market release, we are pleased to offer a clinical solution that addresses a well-known clinical challenge: to notify the clinical staff of complications related to intubated patients, especially premature babies. AirWave monitoring technology has repeatedly alerted NICU staff of arising complications at the moment they start. We thank CHOC and Lucile Packard Children's Hospital Stanford in joining us and we look forward to continued clinical success for each of their patients." "Intubated infants especially are exceedingly fragile and a high level of care is needed to avoid breathing complications," explains Dr Vijay Dhar, medical director, CHOC NICU. "The AirWave allows our neonatologists and respiratory staff to easily understand if the endotracheal tube tip is moving, if there are obstructions blocking airflow and where the tube is positioned to assure proper placement." In addition to increased commercial activities during 2017, SonarMed completed a $3 million Series C financing to support the ongoing controlled market roll-out of the Company's pediatric products, as well as continuing to gather outcomes data from its user case studies.

Risks Found With COX-2 Inhibitors

Late-pregnancy exposure to COX-2 inhibitors appears to be associated with an increased risk of preterm birth, researchers from Canada report. "Our findings show that regardless of whether NSAIDs (nonsteroidal anti-inflammatory drugs), COX-2 inhibitors, or biologics are given for autoimmune diseases or not (taking into account the indication or not), celecoxib is the only one associated with an increased risk of prematurity in singleton live births," Dr Anick Berard from CHU Sainte-Justine and University of Montreal said. Previous studies on the safety of NSAIDs during pregnancy have focused mainly on the risk of miscarriage, birth defects and persistent pulmonary hypertension in the newborn resulting from premature closure of the ductus arteriosus, with little examination of a possible relationship between their use and the risk of preterm birth. Dr Berard's team used data from the Quebec Pregnancy Cohort to quantify the risk of premature birth associated with the use of NSAIDs, COX-2 inhibitors, and biologic agents in the three months before delivery. Among more than 156,000 pregnancies, only 448 (0.29%) were exposed to one of the study medications in the three months prior to delivery, the researchers report in Pain, online January 18. Overall, 7.1% of pregnancies ended before 37 weeks' gestation, including 11.4% of those exposed to NSAIDs or COX-2 inhibitors and 7.1% of those not exposed. After adjustment for potential confounders, including maternal autoimmune disease, only COX-2 inhibitor use during late pregnancy was associated with a significantly increased risk of prematurity (odds ratio, 2.46, based on 10 exposed cases). Celecoxib, in particular, was associated with 3.41-fold increased odds (based on 6 exposed cases). In subgroup analyses, the association between exposure to NSAIDs/COX-2 inhibitors in late pregnancy and the risk of prematurity was evident only among very preterm and extremely preterm deliveries, with no significant association for the risk of moderate to late preterm deliveries. Late pregnancy exposure to disease-modifying antirheumatic drugs (DMARDs) was not associated with an increased risk of preterm birth (based on 28 exposed cases). Early pregnancy exposure to NSAIDs/COX-2 inhibitors was not associated with the risk of prematurity.

Budget Deal Could Help Babies Addicted to Opioids

A US budget deal adopted by Congress includes what advocates call a landmark compromise to provide an estimated $1.5 billion over 10 years to try to keep struggling families together, including those with babies born dependent on opioids. The provision allows assistance on mental health, substance abuse and parenting whenever any child is deemed at imminent risk of entering foster care. It also offers support for relatives who unexpectedly assume responsibility for a child when a parent cannot. The funding is part of a bipartisan budget deal passed by lawmakers which alleviates spending fights that marked President Donald Trump's first year in office, but sets the stage for a battle over immigration and exploding deficits ahead of November's congressional elections. The measure is intended to help newborns whose mothers were addicted to opioids, including heroin, during pregnancy. More than 110 babies died between 2010 and 2015 after being born opioid-dependent and sent home with parents ill-equipped to care for them, a 2015 Reuters investigation found. Senator Ron Wyden of Oregon, the top Democrat on the Finance Committee, said the funding "will usher in the most significant improvements to the child welfare system in decades and provide real help to families to fight the opioid epidemic." The change opens up a new stream of money from a Social Security program now limited to foster care. It allows an estimated $1.5 billion over 10 years to be used to prevent children from entering foster care.

iNO Impacts Studied

Treating extremely premature neonates in respiratory distress with inhaled nitric oxide is not associated with less in-hospital mortality, researchers say. Inhaled nitric oxide (iNO) is increasingly prescribed off-label to affected neonates during the first week of life, despite guidance from the National Institutes of Health and the American Academy of Pediatrics discouraging its use, according to Dr William Carey of Mayo Clinic in Rochester, Minnesota, and colleagues. To investigate further, the team analyzed data from the Pediatrix Medical Group Clinical Data Warehouse on singletons born at 22 to 29 weeks' gestation from

2004 to 2014. Those who required mechanical ventilation for respiratory distress syndrome were included; those with any kind of anomaly were not. Using "rigorous statistical methods," the team matched each patient who received iNO during the first week of life (case patient) to a neonate who had not received iNO before the case patient's iNO initiation age. Neonates "were similar in gestational age, birth weight, degree of illness" and other "important, relevant clinical characteristics," Dr Carey said. Among 37,909 neonates in the study sample, 993 (2.6%) received iNO. The two matched cohorts each contained 971 patients. In the iNO group, 348 died in the hospital at a median age of six days; the remaining 623 were discharged after a median 89 days. Among the matched referents, 325 neonates died at a median age of six days and 646 were discharged after a median stay of 88 days. A total of 171 of the matched referents received iNO therapy at a median age of two days. No significant association was observed between iNO exposure and mortality (HR, 1.08; 95% confidence interval, 0.94-1.25). Exposure to iNO also was not associated with necrotizing enterocolitis, retinopathy of prematurity requiring treatment, chronic lung disease, or periventricular leukomalacia.

Inducing Labor Could Reduce C-sections

Elective induction of labor among low-risk women at 39 weeks' gestation is associated with a reduced rate of cesarean delivery compared with expectant management, results of a large, randomized trial show. Other maternal and infant outcome measures also improved, researchers reported in a late-breaking abstract session here at the Society for Maternal-Fetal Medicine's 38th Annual Pregnancy Meeting. "Our results suggest that policies directed toward avoidance of elected labor induction in nulliparous women would be unlikely to reduce the rate of cesarean delivery on a population level," said first author William Grobman, MD, from the Northwestern University Feinberg School of Medicine in Chicago, Illinois. The multicenter ARRIVE trial, conducted at 41 hospitals in the National Institutes of Health's Maternal-Fetal Medicine Units Network, is the largest randomized trial on the issue to date, involving more than 6100 patients at 41 centers. Overall, the cesarean delivery rate was 18.6% among the 3062 women randomly assigned to elective induction at 39 weeks compared with 22.2% among 3044 women in the expectant management group (RR, 0.84). In addition, maternal adverse outcomes, including preeclampsia and gestational hypertension, were significantly lower in the induced labor group, and neonates in the induced labor group were nearly 30% less likely to experience respiratory morbidity. Other outcomes were similar between the two groups. Guidelines from the American College of Obstetricians and Gynecologists currently say that elective induction may be considered much later than 39 weeks — at 41 weeks — and should be performed at 42 weeks. However, mounting evidence consistent with the new findings is pushing the field toward greater acceptance of elective induction at 39 weeks.

Study Supports Early Postnatal Steroids

New data confirm the value of early low-dose prophylactic hydrocortisone in extremely preterm infants and suggest that those born after placental vascular disease may benefit the most. In the placebo-controlled PREMILOC trial, a low-dose of hydrocortisone administered soon after birth significantly improved survival without bronchopulmonary dysplasia (BPD) at 36 weeks' postmenopausal age (PMA) in extremely preterm

infants. Dr Olivier Baud from University Hospitals Geneva, in Switzerland, and the PREMILOC trialists set out to see whether the magnitude of the hydrocortisone treatment effect on BPD could be related to placental findings. They have presented results of an exploratory analysis of placental findings in 457 of the 523 infants enrolled in the trial. Using standard criteria, the researchers categorized placental histology as normal (27%); inflammatory with chorioamnionitis with or without funiculitis (52%); and vascular with subchorionic thrombosis, infarcts, spindly villi, excess of syncytial knots, basal or marginal hematoma, maternal thrombosis, and decidual arteriopathy lesions (21%). They then correlated placental findings with neonatal outcomes and response to hydrocortisone. Compared with normal placental history, placental inflammation was associated with a significant increased rate of survival without BPD at 36 weeks' PMA (the primary endpoint), independent of gestational age, treatment assignment and sex (adjusted odds ratio, 1.72; P=0.03). Placental vascular disease was not associated with a significant difference in the incidence of the primary endpoint compared with normal placental histology. In terms of response to treatment, the greatest benefit of hydrocortisone compared with placebo was seen in babies born after placental vascular disease, with significantly more of them extubated at 10 days (risk difference, 0.32; P=0.004) and a "similar positive direction" on survival free of BPD (RD, 0.23; P=0.06).

Postnatal CMV Impacts Studied

Premature babies of mothers with cytomegalovirus who pick up the infection from breast milk are unlikely to develop neurological problems in early childhood as a result, according to a Dutch study. Dr Joppe Nijman and colleagues from University Medical Center Utrecht, the Netherlands, note that postnatal cytomegalovirus (pCMV) infection is most often transmitted through fresh breast milk. As a result, breast milk is often withheld or pretreated to avoid CMV transmission to preterm infants. However, the effects of a pCMV infection on neurodevelopment are not well studied. "This study does not show an adverse effect of pCMV infection on neurodevelopment, including hearing in infancy and early childhood. Therefore, measures to withhold fresh breast milk in the neonatal period may not be warranted," the authors conclude. They examined neurodevelopmental outcomes up to age 6 in 356 preterm infants (<32 weeks' gestational age). Forty-nine infants (14%) had pCMV; 307 (86%) did not. At 16 months' corrected age (CA), infected infants actually performed significantly better on the Griffiths Mental Development Scales (GMDS) locomotor scale. At 24 to 30 months CA, the CMV-infected and the non-infected infants did not differ significantly on the Bayley Scales of Infant and Toddler Development, Third Edition, or the GMDS. At age 6 years, infected children scored lower on the Wechsler Preschool and Primary Scale of Intelligence, Third Edition, but average scores were within the normal range, reaching significance only in the subscale of verbal IQ (96 vs. 103 points; P=0.046), which could be attributed to low maternal education and ethnicity, not CMV status, the authors suggest. None of the infected children developed sensorineural hearing loss (SNHL). The researchers say, to the best of their knowledge, this is the largest prospective cohort study to look at neurodevelopmental outcomes of preterm infants with pCMV infection from birth until early childhood. "The results of this study did not show an impaired neurodevelopmental outcome (including SNHL) until 6 years of age in preterm infants with a pCMV infection," they report. The results of this study, they add, "may not justify interventions like pasteurization or freezing or withholding breast milk to prevent CMV transmission in the general preterm population."

Poor Hospital Performance Studied

Blacks and Hispanics have higher preemie morbidity and mortality than whites, and poor performance in the hospital of birth explains 30% to 40% of that disparity, a study by Elizabeth Howell, MD, MPP, from Icahn School of Medicine at Mount Sinai, New York City, and colleagues found. "The real focus here is to try to reduce morbidity in preterm babies and give these kids a chance at a healthier life. This study shines light on the idea that we really need to focus on narrowing disparities when we think about quality improvement. Additionally, these disparities are not just local to New York City. We know that there are infant and neonatal racial and ethnic disparities that have been longstanding in this country," Dr Howell said in a news release. During the last decade, the United States has made strides in improving neonatal care, yet racial and ethnic disparities persist. Some studies have suggested that black newborns die at more than twice the rate of non-Hispanic whites. Research also suggests that black and Hispanic preterm infants are at increased risk for serious birth complications, which can affect the lungs, eyes, intestines, and brain. Such complications can set the stage for health problems throughout life and perpetuate socioeconomic disparities. To investigate whether quality of care contributes to these disparities, the researchers used data from hospital discharges and birth certificates to analyze morbidity and mortality rates in black, Hispanic, and white very preterm infants. The study included 7177 genetically normal infants born between 24 and 31 weeks of gestation at 39 New York City hospitals between 2010 and 2014. The researchers calculated risk-adjusted neonatal morbidity and mortality rates, then used these results to rank hospitals and evaluate differences for black, Hispanic, and white very preterm infants. The overall morbidity and mortality rate was 28% (n = 2011). This rate was significantly higher among black (32.2%; n = 893) and Hispanic (28.1%; n = 610) infants than among white infants (22.5%; n = 319) (two-tailed P < .001). Infants born in hospitals with the highest morbidity and mortality rates had twice the rate of serious complications and death as those born in hospitals with the lowest rates (0.40 [95% confidence interval (CI), 0.38 - 0.41] vs 0.16 [95% CI, 0.14 - 0.18], respectively). Very preterm black (43.4%, 1204 of 2775) and Hispanic (34.4%; 746 of 2168) infants were more likely than white infants (22.9%; 325 of 1418) to be born in hospitals with the highest morbidity and mortality rates (two-tailed P < .001). A large proportion of these disparities was attributed to poor performance in the birth hospital. The fact that white mothers received care at better-performing hospitals explained 39.9% of black-white differences and 29.5% of Hispanic-white differences.

Infant Retinopathy Therapy Studied

Low doses of anti-VEGF therapy with ranibizumab are effective in infants with retinopathy of prematurity (ROP), according to results from the CARE-ROP study. "The CARE-ROP results show that both ranibizumab doses (24% vs. 40% of the adult dose) were equally effective in treating ROP (94% vs. 93% success in per-protocol treated eyes)," Dr Andreas Stahl from University of Freiburg, in Germany, said. "Systemic VEGF levels were not suppressed following ranibizumab treatment." Vascular endothelial growth factor (VEGF) is a main driver of ROP pathophysiology. The anti-VEGF bevacizumab halts progression of severe ROP but suppresses VEGF plasma levels for weeks, raising questions about potential adverse effects on organ

development in infants. Dr Stahl and colleagues evaluated the efficacy and safety of two doses of intravitreal ranibizumab (0.12 mg and 0.20 mg) in a randomized, double-blind trial of 19 infants (38 eyes) with ROP. Sixteen infants completed the trial (three died of causes unrelated to treatment). The proportion of infants without the need for rescue therapy through 24 weeks, the primary endpoint, was 88.9% (8/9) in the 0.12-mg group and 85.7% (6/7) in the 0.20-mg group. No infant with gestational age greater than 25 weeks required rescue therapy. At the final visit, 12 of 20 eyes (60.0%) in the 0.12-mg group and 10 of 18 eyes (55.6%) in the 0.20-mg group had no ROP, and all remaining eyes had ROP stage 1 in the anterior zone II or III. Two eyes that required rescue therapy responded well and had fully resolved ROP at the final visit. Two infants in each group (8 eyes total) had recurrences severe enough to warrant retreatment, and their outcomes at the end of the study were either no ROP or stage 1 ROP in anterior zone II or III. Physiologic vascularization appeared to proceed faster and to reach complete vascularization more frequently in eyes receiving lower doses of ranibizumab. Ranibizumab treatment did not reduce mean VEGF levels in either group.

Neonatal Imaging Subject of New Publication

The National Certification Corporation (NCC) announced the release of their new publication Neonatal Imaging, ISBN 978-0-9890198-2-8. Written by Pediatric radiologists, this full-size, 292-page book has over 300 annotated images. The authors have provided readers with a detailed understanding of imaging, specific to the neonate. Their dedication and commitment to the field is evident in each chapter. Neonatal Imaging discusses the basic principles of common neonatal imaging studies, the pathophysiology of pertinent diseases, and the challenges in reading and evaluating findings. It was written as a resource for skilled clinicians and as a learning tool for students and new providers. Edited by NCC's Executive Director, Robin Bissinger, PhD, APRN, NNP-BC, FAAN and Meryle J. Eklund, MD, Assistant Professor of Radiology and Pediatrics, Department of Radiology and Radiological Science at the Medical University of South Carolina, NCC's new publication Neonatal Imaging provides a foundation for neonatal health care providers, to understand techniques, artifacts and positioning, to relate detailed pathology and interpretation of neonatal radiologic & sonographic images and to differentiate between normal and abnormal findings verses artifact. This book creates a framework for neonatal imaging, providing both basic and challenging issues when reading and interpreting neonatal X-rays & ultrasounds. Neonatal Imaging is a visual learning experience, providing detailed pathology through imaging illustrations and includes over 300 annotated images. Each chapter gives a brief overview of the pathology of disease and provides an in-depth discussion of the concepts and systematic approach to the imaging studies. Neonatal Imaging is broken down into 4 major sections that include the Chest, Abdomen, Head and Renal Systems. Each system is outlined with the specific studies often needed for this patient population. This book includes positioning, techniques, lines and tubes, as well as an understanding of artifacts. All of which must be taken into account when interpreting these studies.

Infant Transport Aided by Generous Grant

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Dr Barbara Warner, a professor of pediatrics and neonatologist at St. Louis Children's Hospital.

History of St. Louis Children's Hospital

At St. Louis Children's Hospital, life-changing medicine happens every day. With its long-standing mission to "do what's right for kids," St. Louis Children's Hospital (SLCH) offers children and families comprehensive services in every pediatric medical and surgical specialty.

The hospital's clinical and community outreach programs touch nearly 95,000 patients each year. In fact, St. Louis Children's Hospital has cared for patients from all 50 states and nearly 80 countries.

Founded in 1879 by eight pioneering women, the hospital opened in a small, rented house with 15 beds. Today, the hospital has grown to a 280-bed, nationally renowned pediatric leader with a commitment to serving the greater community. St. Louis Children's Hospital is an academic medical center, which means our medical staff are faculty members of the top-ranked Washington University Medical School. In addition to world-class patient care, these physicians participate in research and teaching and have received top national honors in their fields. The hospital is also a member of BJC HealthCare, one of the largest nonprofit health care organizations in the United States.

In early 2018, St. Louis Children's Hospital will open a new bed tower that will expand its newborn intensive care unit as part of a 10-year campus renewal project. As part of the expansion, the women and infants program, in partnership with Barnes-Jewish Hospital, will provide families with a higher level of care — a high-risk baby delivered at Barnes-Jewish Hospital can be safely transported to the Children's Hospital NICU in minutes and moms will remain close.

Neonatal Intensive Care: Does your hospital/NICU have any accolades you could share with us?
Dr Barbara Warner: The Newborn Intensive Care Unit (NICU) at St. Louis Children's Hospital recently reached its highest ever census of 100 babies. Our medical providers, nursing and ancillary staff take pride in caring for the sickest and most vulnerable babies in the region. The NICU at SLCH is the only one in the region to offer specialized Neonatal Neurology services and is nationally recognized as a leading provider of cooling therapy for babies with hypoxic-ischemic encephalopathy. The NICU is also a unique provider of Perinatal Behavioral Health for mothers and families of NICU patients, a service provided in a small minority of hospitals nationally.

NIC: How has the equipment purchased with the help of Brave Beginnings grant impacted your NICU/Hospital? Was the Brave Beginnings grant able to ease any financial burdens pertaining to the purchasing of equipment? Explain how.
BW: The Voyager Infant Transport system is used to transport neonates from the labor and delivery suits at the neighboring Barnes-Jewish Hospital (BJH) and from outlying hospitals. Our ability to support community hospitals from where we transport about 50% of our patients is supported by generous funding provided by entities such as the Brave Beginnings Grant. Given the rapid advances in the field of neonatal intensive care, providing state-of-the-art medical care to the most vulnerable of populations requires investment of large amounts of capital for equipment. The cost of purchasing such equipment is prohibitive at times and the NICU and SLCH has to rely on funding from foundations and donors to remain at the cutting edge of patient care.

NIC: What does your NICU hospital do to stay current with research and best neonate practices?
BW: St. Louis Children's Hospital's Newborn Intensive Care Unit ranks highly by all external measures. This is partly because our hospital has been the research partner and pediatric teaching

Dr. Warner and her colleagues work tirelessly, discovering new advancements to treat the littlest patients at St. Louis Children's Hospital.

If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

hospital for Washington University School of Medicine for more than 100 years. Washington University is a leader in NIH funding precisely because it pushes the leading edge of medicine and care ever outward, and our NICU has been the setting for groundbreaking research in Newborn Medicine.

One third of the Human Genome Project was accomplished on our campus and this has also led to numerous research projects in the NICU. We were also the first NICU to deploy a robust, Bedmaster-based, real-time monitoring and data capture system in our NICU, complete with an analytics program that allows our physicians to spot trends leading to potentially catastrophic events far in advance. More than 250 hospitals around the world have adopted these technologies and are now following our progress. We also initiated a research project with Children's Hospital of Philadelphia, Boston Children's and Cincinnati Children's, among others, that reduced unnecessary alarms in the NICU by 30%.

Our NICU has been an incubator for good ideas! For example, the Cool Kids Study was accomplished, in part, on our campus. Our physicians have pioneered many treatments and cures, from the first use of injected insulin in a pediatric setting to identification of a maternal/child genetic link for leukemia in the first three months of life.

NICU nurse, LaToya Daughrity.

The campus at Washington University is ripe with opportunities for CEUs, many in newborn medicine. Clinicians come from around the world to take advantage of the brain trust at Washington University School of Medicine. We also have the Goldfarb School of Nursing on campus, making this a well-rounded medical campus. Our nurses are also excellent teachers and mentors, which is one of the reasons why the hospital continues to achieve Magnet re-designation.

Finally, our culture insists that we remain current. We are inclusive, and we partner with multiple children's hospitals in the sharing of best practices. This will be increasingly important as we add beds to our Women and Infants program, so that mothers with high-risk pregnancies can give birth on campus and their newborns can get some of the world's best medicine close by in our NICU. Increasingly, our Genomics Labs will play a role in driving the care that will improve outcomes for the newborns we treat.


F. Sessions Cole, MD, the Park J. White, MD, Professor and vice chair of the Department of Pediatrics at Washington University School of Medicine is recognized as a driving force behind the success of St. Louis Children's Hospital and its Newborn Intensive Care Unit (NICU).

NIC: Is there a NICU success story that stands out in your mind that you could tell us about?
BW: Yes, we have many success stories, but I will share the story of Tristan, who was born at 22 weeks, weighing only a pound and three ounces. He has had a remarkable journey and after eight months in our NICU, he recently went home. He has been so sick at many points along the way and he clearly has had a will to survive.

Like so many premature babies, just breathing was a huge challenge for Tristan. Even though we had made a lot of advances in terms of being able to improve lung development, it's still not like a full term set of lungs. These babies must be on ventilators and struggle for every breath.

By the time Tristan got to go home, he weighed nine pounds and was holding up his head.

Tristan had a lot of company while he was in the NICU. During one recent week, St. Louis Children's Hospital had the most babies our NICU has ever had at one time. About half of the 100 babies were born premature. Having many babies in the NICU is not necessarily a bad thing: the limit of viability, which is the age a preemie is most like to survive, has dropped by about a month in the past few decades. That means our NICU teams can care for even smaller and younger babies than ever before—but the outcome varies greatly for families.

The biggest issue parents have when they come into the NICU this early and this ill is number one, will my baby survive? And if my baby survives, what will their life look like in the long term? And those are very difficult things to predict. While there have been remarkable medical advances, there are still extraordinary challenges for premature babies and their families.

What happens in the home environment can make a huge difference. Those babies are at an important developmental part of their lives so that early intervention, having services set up for them, even if we're not sure if they will have problems. We know those babies that have appropriate stimulation at home, appropriate services at home, go on and overcome many, not all, but many challenges they would have faced from a neurological standpoint.

Pigtail Versus Trocar Catheter for the Treatment of Pneumothorax in a Premature Infant

Shabih Manzar, MD, Jennifer M Tyson, NNP

Case

Infant was born to a 26-year-old gravida 1, para 1. All antenatal labs including HIV, Hepatitis B, and rapid plasma reagin were negative. There was no history of sexually transmitted diseases. Pregnancy was complicated by premature rupture of membrane (PROM) for > 24 hours and preterm labor. Mother received two dose of betamethasone prior to delivery. She delivered a female infant at 27 weeks of gestation. Apgar scores were 6 and 8 at one and five minutes respectively. Infant's birth weight was 850 grams, head circumference 24.2 centimeters and length of 33.5 centimeters.

On admission to the Neonatal Intensive Care Unit (NICU), physical examination was normal for gestational age. The vital signs showed a temperature of 97.7°F, heart rate of 135 beats per minute, respiratory rate of 49 per minute and blood pressure of 43/23 mmHg. A septic work up was done including complete blood count and blood culture and infant was started on ampicillin and gentamicin. For respiratory support, infant was placed on ventilator and surfactant was given. Infant was then extubated to Bubble CPAP. Chest X-ray (Figure 1) was consistent with hyaline membrane disease. Blood gas on admission was pH of 7.47 pCO_2 of 28 PO_2 of 43 and HCO_3 of 22 on 26% FiO_2. Follow up blood gas after extubation was pH of 7.40 pCO_2 of 37 PO_2 of 43 and HCO_3 of 23 on 30% FiO_2.

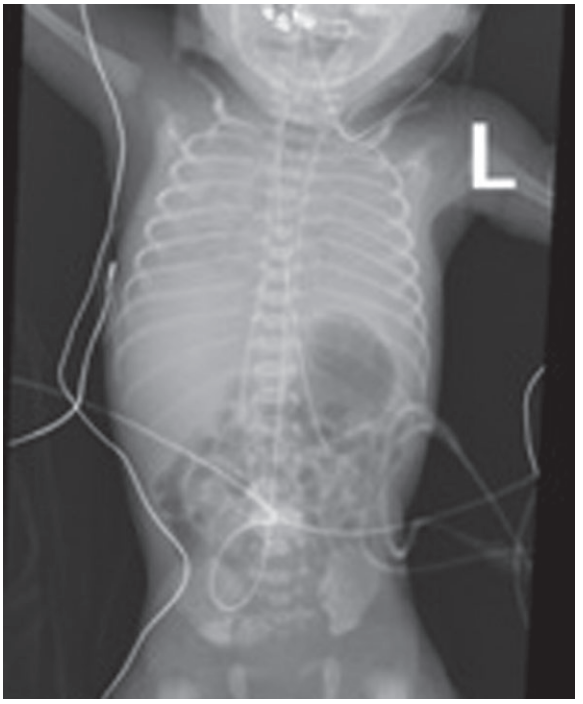

Figure 1. Chest X-ray showing severe RDS

Infant was started on intravenous fluids. At around 48 hours of life, infant respiratory status deteriorated and she was noted to have right sided pneumothorax. An 8 French, Argyle Trocar Catheter, Covidien Inc, USA was inserted with no resolution (Figure 2). Adjustment of the chest tube resulted in some resolution with clinical improvement (Figure 3). However follow up chest X-ray showed reaccumulation of air in pleural cavity. At this point, an 8.5 Fr pigtail catheter, Fuhrman Pleural Drainage Set, Cook Incorp, USA, was inserted using Seldinger technique. This resulted in complete resolution of pneumothorax (Figure 4, 5).

Discussion

Pneumothorax is a known complication in preterm infant who received mechanical ventilation. The air in pleural space cause respiratory distress and cardiovascular instability thereby requiring evacuation. In stable condition with no tension, needle aspiration could be suffice. In smaller air leaks, natural resolution may also occur without intervention or providing oxygen at higher percentages. In neonates excess oxygen can be detrimental therefore a thorocostomy is needed.

Two methods/catheters are used in preterm infant viz. trocar and pigtail catheter. The choice is provider dependent. As noted above that we tried both but we found pigtail catheter more useful in evacuating the pleural air completely. The use of pigtail catheter has been described in literature.[1-3] As far as the cost is concerned Trocar catheter is cheaper (Covidien Argyle Trocar Catheter $12.36 single use while Fuhrman Pleural Drainage Set is $104.95 single use), however pigtail catheter is less traumatic, easy to insert and minimally invasive. Also leur-lock at the distal end of pigtail catheter could be useful in cases of reaccumulation of air. A 3-way stop cork could be attached to this end and air can be aspirated within the closed system. By doing this, the need for second chest tube is avoided.

In conclusion, although both types of catheters could be used in treating pneumothorax in preemies but basing on the case

Neonatal Intensive Care Unit, Rapides Regional Medical Center, 211 Fourth Street, Alexandria, LA 71301, Telephone: 318-769-7160/7791, Fax: 318-769-7473, shabihman@hotmail.com

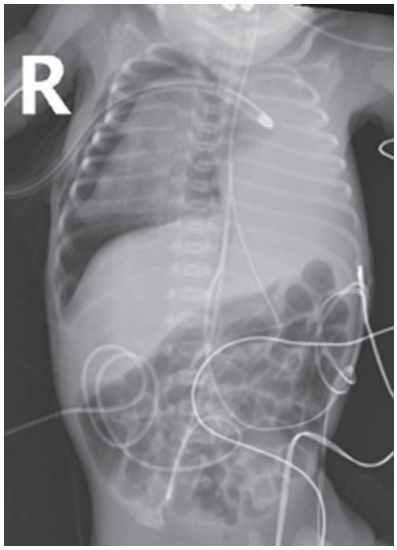

Figure 2. Chest drain in place, pneumothorax unresolved

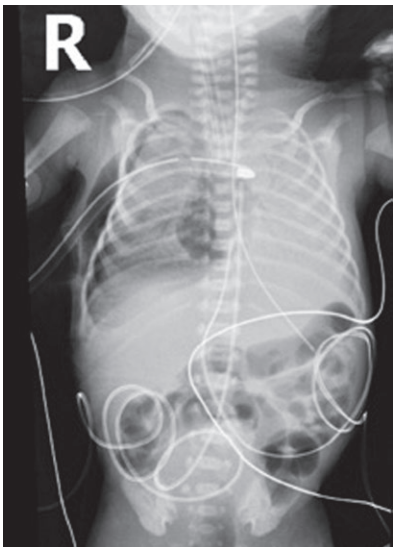

Figure 3. Chest tube adjusted with some resolution in pneumothorax

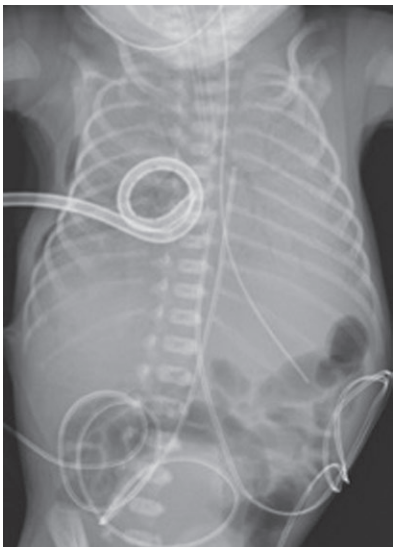

Figure 4. Pigtail catheter inserted with resolution of pneumothorax

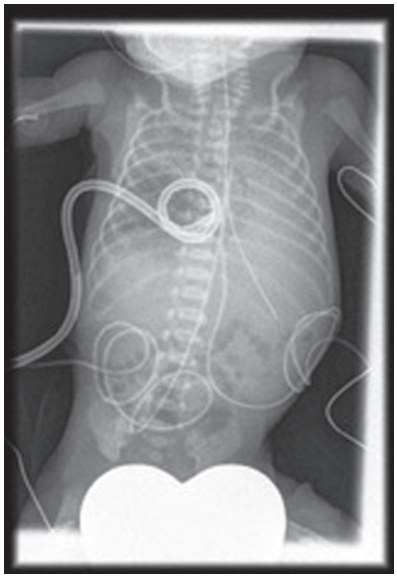

Figure 5. Follow up chest X-ray with complete resolution of pneumothorax

presented and potential advantages, we suggest the use of pigtail catheter as first line technique in the management of pneumothorax. A case series study or randomized study would be needed to make any definitive recommendations.

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Estimating Effective FiO_2 From Flow Rate, Infant's Weight and Oxygen Concentration in NICU

Shabih Manzar, MD

Oxygen (O_2) is the most common drug used in neonatal intensive care unit (NICU). O_2 is frequently given to premature infants via nasal cannula using a flow device. The oxygen delivered to the lungs depends upon many factors, two important ones are the flow rate and concentration of oxygen delivered. However, this delivered oxygen concentration might not be the effective fraction of inspired oxygen. Effective FiO_2 (E-FiO_2) is the actual oxygen concentration delivered to the alveoli.

When oxygen is given through the nasal cannula (NC), it gets mixed with room air (RA) at the nostrils thus affecting the delivered O_2 concentration. Different flow rates would potentially affects the O_2 delivery to alveoli and work of breathing in infant.[1] Therefore, E-FiO_2 is not same as the O_2 delivered by the system.

It is very important to wean delivered O_2 concentration in premature infants. The usual weaning is based on saturation monitor and the respiratory status of the infant. A target saturation of 91-95% is being set to follow as per Support Study.[2] Some units follow a low target as per Schmidt et al.[3] If we know the E-FiO_2 we can wean the infant off oxygen faster. Basing on the earlier study by Walsh et al[4] we develop an excel program model by using which we can very easily estimate the E-FiO_2.

Calculation of E-FiO_2 from excel chart (Excel -Raw):

The rule of thumb:

If the flow rate is ≥ to the weight of the infant, then the E-FiO_2 would be the same as O_2 concentration delivered. For example, if the infant is receiving 40% O_2, infant's weight is 2 kg and the flow provided is 2 Liter per minute or greater, the E-FiO_2 would be 0.40.Estimation formulae are described in literature but they are not accurate for lower flow rates.[5,6] Now let's estimate the E-FiO2 from the following data (Excel-Raw). Example: Infant's weight 1.5 kg, Flow 0.5 (1/2) LPM, O_2 delivered = 30%

Formula:[7]

Using excel sheet 1 (Excel-Raw), calculate the factor. In this case, the factor is 33 (Excel-Solved).

$$
\begin{aligned}
\text{E-FiO}_2 &= 21 + \text{Factor } (O_2 \text{ concentration} - 21)/100 \\
&= 21 + 33\ (30\text{-}21)/100, \text{ using BODMAS rule} \\
&= 21 + 33 \times 7/100 \\
&= 21 + 33 \times 0.7 \\
&= 21 + 2.31 \\
&= 23.31
\end{aligned}
$$

Similarly, by using excel sheet 2 (Excel-Raw), looking at the O_2 concentration corresponding to the factor, will give the corresponding E-FiO_2. As noted that for 30% O_2 factor 33 corresponds to 0.24 (Sheet 1 and 2, Excel-Solved). These calculations were based on the mathematical formulae generated by Benaron and Benitz.[8]

The next phase would be to develop formulae and software program whereby feeding the variables (infant's weight, flow, oxygen concentration and factor) E-FiO_2 could be calculated directly. Once we have that, E-FiO_2 could be incorporated into the display of the commercially available O_2 delivering high flow nasal cannula devices.

In conclusion, the concept of E-FiO_2 should be kept in mind when a preterm infant is weaned on the flow rate of less than the body weight. A tabulated approach could be followed to estimate the effective FiO_2. This approach will help in further weaning and room air challenge earlier than later in these vulnerable premature infants.

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Short Term Neonatology Solution, 3000 July St, Suite 3343, Baton Rouge, LA 70808, Telephone: 630-415-5094, Email: shabih.manzar@neonatologysolution.com

Table 1. Excel-Raw

Factor	21%	22%	25%	30%	40%	50%	100%	Oxygen Conc %
0	0.21	0.21	0.21	0.21	0.21	0.21	0.21	
1	0.21	0.21	0.21	0.21	0.21	0.21	0.22	
2	0.21	0.21	0.21	0.21	0.21	0.22	0.23	
3	0.21	0.21	0.21	0.21	0.22	0.22	0.23	
4	0.21	0.21	0.21	0.22	0.22	0.22	0.24	
5	0.21	0.21	0.21	0.22	0.22	0.22	0.25	
6	0.21	0.21	0.21	0.22	0.22	0.23	0.26	
7	0.21	0.21	0.21	0.22	0.22	0.23	0.27	
8	0.21	0.21	0.21	0.22	0.23	0.23	0.27	
9	0.21	0.21	0.21	0.22	0.23	0.24	0.28	
10	0.21	0.21	0.21	0.22	0.23	0.24	0.29	
11	0.21	0.21	0.22	0.22	0.23	0.24	0.3	
12	0.21	0.21	0.22	0.22	0.23	0.24	0.3	
13	0.21	0.21	0.22	0.22	0.23	0.25	0.31	
14	0.21	0.21	0.22	0.22	0.24	0.25	0.32	
15	0.21	0.21	0.22	0.22	0.24	0.25	0.33	
17	0.21	0.21	0.22	0.23	0.24	0.26	0.34	
18	0.21	0.21	0.22	0.23	0.24	0.26	0.35	
19	0.21	0.21	0.22	0.23	0.25	0.27	0.36	
20	0.21	0.21	0.22	0.23	0.25	0.27	0.37	
21	0.21	0.21	0.22	0.23	0.25	0.27	0.38	
22	0.21	0.21	0.22	0.23	0.25	0.27	0.38	
23	0.21	0.21	0.22	0.23	0.25	0.28	0.39	
25	0.21	0.21	0.22	0.23	0.25	0.28	0.41	
27	0.21	0.21	0.22	0.23	0.25	0.29	0.42	
28	0.21	0.21	0.22	0.24	0.26	0.29	0.43	
29	0.21	0.21	0.22	0.24	0.27	0.29	0.44	
30	0.21	0.21	0.22	0.24	0.27	0.3	0.45	
31	0.21	0.21	0.22	0.24	0.27	0.31	0.47	
33	0.21	0.21	0.22	0.24	0.27	0.31	0.47	
36	0.21	0.21	0.22	0.24	0.28	0.31	0.49	
38	0.21	0.21	0.23	0.24	0.28	0.32	0.51	
40	0.21	0.21	0.23	0.25	0.29	0.33	0.53	
42	0.21	0.21	0.23	0.25	0.29	0.33	0.54	
43	0.21	0.21	0.23	0.25	0.29	0.33	0.56	
44	0.21	0.21	0.23	0.25	0.29	0.34	0.56	
50	0.21	0.21	0.23	0.25	0.3	0.35	0.6	
55	0.21	0.22	0.23	0.26	0.31	0.37	0.64	
57	0.21	0.22	0.23	0.26	0.32	0.38	0.66	
60	0.21	0.22	0.23	0.26	0.32	0.38	0.68	
63	0.21	0.22	0.24	0.27	0.33	0.39	0.71	
67	0.21	0.22	0.24	0.27	0.34	0.4	0.74	
71	0.21	0.22	0.24	0.27	0.34	0.42	0.77	
75	0.21	0.22	0.24	0.28	0.35	0.43	0.8	
80	0.21	0.22	0.24	0.28	0.36	0.44	0.84	
83	0.21	0.22	0.24	0.28	0.37	0.45	0.87	
86	0.21	0.22	0.24	0.29	0.37	0.46	0.89	
100	0.21	0.22	0.25	0.3	0.4	0.5	1	

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Table 2. Excel-Solved

Flow (l/min)	0.7 kg	1 kg	1.25 kg	1.5 kg	2 kg	2.5 kg	3 kg	3.5 kg	4 kg	Weight in kg
0.125 (1/8)	18	12	10	8	6	4	4	4	4	
0.25 (1/4)	36	25	20	17	13	10	8	7	6	
0.5 (1/2)	71	50	40	33	25	20	17	14	13	
0.75 (3/4)	100	75	60	50	38	30	25	21	19	
1	100	100	80	67	50	40	33	29	25	
1.25	100	100	100	83	63	50	42	36	31	
1.5	100	100	100	100	75	60	50	43	38	
2	100	100	100	100	100	80	67	57	50	
3	100	100	100	100	100	100	100	86	75	

Giving Comfort, Giving Back

Deb Discenza

While there are no shortage of support groups for NICU families, sometimes the simplest gesture means the most. Swaddle4Swaddle is a program with great heart and great soul helping families across the United States. I interviewed Swaddle4Swaddle President Tisah Ockey to learn more.

Deb Discenza: How did Swaddle4Swaddle come into being?
Tisah Ockey: Rachel Quarnberg, CEO of Audrey's Bear (www.audreysbear.com) and the founder of Swaddle4Swaddle (www.swaddle4swaddle.org), had a nephew born with several complications and he ended up spending several months in the NICU. She learned, in a small way, how difficult times like that can be for babies and their parents. After getting a few orders from parents and caregivers of babies in NICUs and pediatric cancer centers, she felt a calling to provide these children blankets for free, to help them feel a little more comfortable and to help their parents celebrate the miracle of their child's life.

DD: What a wonderful way to help comfort babies and their families in the NICU. How many swaddles to date have you donated?
TO: To date we have donated over 8,000 swaddles to NICUs and pediatric cancer centers.

DD: How many partners do you have for the blanket distribution?
TO: Currently, Swaddle4Swaddle works with 14 non-profit partners to distribute blankets to NICUs and pediatric cancer centers across the nation (everywhere from California to Boston and Florida to Arizona).

DD: Are you accepting new NICUs for this arrangement? If so, how should they reach out to you?
TO: We are always looking for more non-profit partners to work with and we are actively looking for new partners that work with/donate care packages to pediatric cancer centers. To inquire about becoming a partner with Swaddle4Swaddle, email me at tisah@swaddle4swaddle.org.

DD: Wonderful. Thank you for alerting us to this program.

Deb Discenza is the proud mother of Becky, who was born at 30 weeks and is now 14 years old. Deb is the head of PreemieWorld LLC (www.PreemieWorld.com), co-author of The Preemie Parent's Survival Guide to the NICU, and the founder and leader of the 42,000+ member Inspire Preemie Community (http://preemie.inspire.com).

Abnormalities of Cavum Septi Pellucidi and Vergae

H Cohen, MD, BM Petrikovsky, MD, PhD, D Cohen, MD

Definition
Cavum septi pellucidi (CSP) is a closed cavity in the midline of the transverse plane of the brain. This cavity will normally close when the two leaflets of the septa pellucida come together near term.[1] Septi pellucidi represents two translucent leaflets that extends from corpus callosum to the superior portion of the fornix. The cavum vergae (CV) is a second fluid-filled structure found posterior to the CSP between the corpus callosum and the fornix.[2] CSP and CV are virtually the same structure located respectively anterior and posterior to a vertical plane of the columns of the fornix.

Prevalence
1.4 per 1,000 ultrasound examinations.[3]

Classification
Normal, Dilated, Absent

Etiology
Septi pellucidi begin to develop at 10-12 weeks of pregnancy as a part of the limbic system.[4]

Major principles of diagnosis
It is not uncommon to not be able to visualize the CSP before 20 weeks. If so, patients are asked to return for a follow-up sonogram.[3] CSP is best detected on the median sagittal and the midcoronal sections of the brain. The mean width and anteroposterior diameter of the CSP have been shown to differ significantly between the second and third trimesters. These measurements correlate with gestational age as well as biparietal diameter. CSP closure increases with gestational age. While 90% of premature infants have a cavum septum pellucidum, only 60% of full term infants have an evident CSP. The CV is seen in 100% of fetuses at 28 weeks gestation. CV closure increases with gestational age.

Early presentation
Since septi pellucidi starts to develop at 10-12 weeks of pregnancy, their visualization in the first trimester diagnosis is not expected.

B M Petrikovsky is a Professor of Obstetrics & Gynecology at New York Institute of Technology. H L Cohen is a Chairman of Radiology, Professor of Radiology, Pediatrics, and Obstetrics and Gynecology, University of Tennessee Health Science Center, Radiologist-in-Chief, LeBonheur Children's Hospital.

MRI diagnosis
Septi are low-intensity lines within the high-intensity CSF of T2 weighted imaging.

Prenatal management:
1. Search for associated anomalies
2. Karyotyping, microarray analysis
3. Counselling by pediatric neurologist

Prognosis: An enlarged CSP or CV without other anomalies is of unclear clinical significance.[3] An enlarged CSP has also been reported prenatally in fetuses with 22q11 deletion syndrome, arthrogryposis, polycystic kidneys, cystic hygroma, short stature, hydrocephalus, periventricular calcification, myotonic dystrophy, volvulus, and congenital heart disease.[3-7] The incidence of a large CSP was significantly higher in patients with schizophrenia spectrum disorders compared to controls (odds ratio, 1.59).[6] Schizophrenia has also been highly associated with 22q11 deletion syndrome.[6] Absent septum pellucidum have been reported in association with arachnoid cysts.[4] ASP is associated with De Morsier syndrome, hypothalamic deficiency, and optic nerve hypoplasia. It can be seen in patients with schizencephaly. It can be simulated by a total fenestration from long term hydrocephalus.

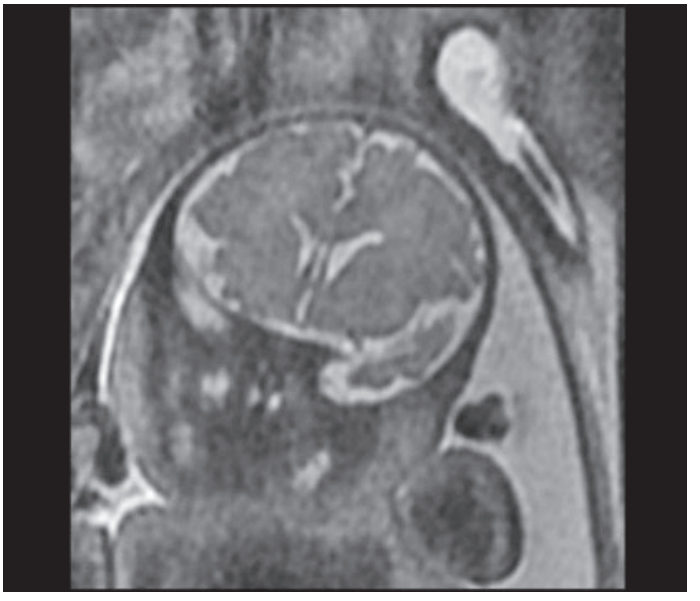

Figure 1. Normal MRI appearance of Cavum Septi Pellucidi

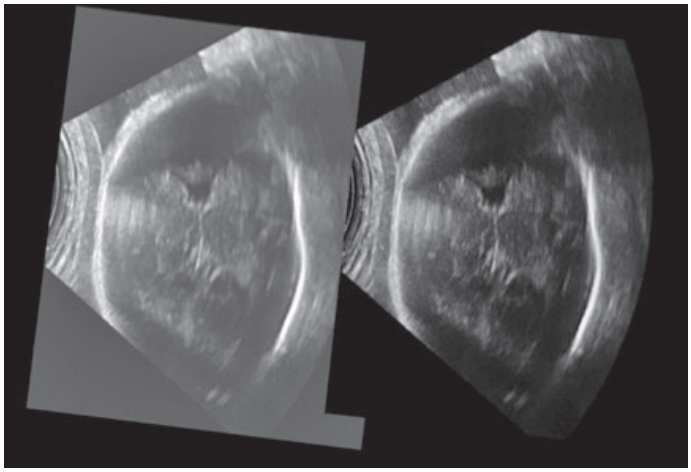

Figure 2. Ultrasound image of absent Cavum Septi Pellucidi

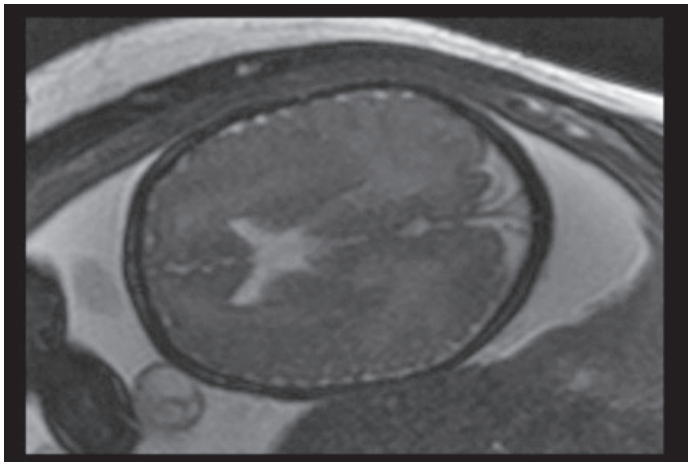

Figure 3. MRI appearance of absent Cavum Septi Pellucidi

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Prenatal Management of Spina Bifida

BM Petrikovsky, MD, PhD, H Cohen, MD, D Cohen, MD

Definition
Spina bifida (SB) is a congenital defect of the spine that results from the failed closure of the neural tube. If only meninges protrude through this defect, a meningocele is present: if neural tissue is involved, it is called a meningomyelocele. SB can occur at any point along the spine, but it is most common in the lumbar and sacral regions.

Classification
Open SB (93% of cases), closed SB (7% of cases).[1]

Prevalence
In the United States, the prevalence of SB is 0.5/1000 births, although there is much variation based on racial and geographic factors.[2,3]

Etiology
SB is a disorder of dorsal induction, with failed closure of the neural tube during the 4th week of embryologic development. Fusion typically begins at the fourth somite and then proceeds rostrally and caudally. If this process is interrupted, neural tube defects can occur in both the cranial and the caudal regions of the neural tube, which may explain the frequent association between anencephaly and meningomyelocele.[4]

Major Principles of Diagnosis
Both obstetrical ultrasound and maternal serum screening have proven to be effective in diagnosing SB. The posterior ossification centers of the fetal spine are usually well visualized by 16 weeks of pregnancy; in a normal spine, they are parallel or converge toward one another. When SB is present, a splaying of the posterior ossification centers can be seen in the transverse plane (Fig. 1), giving the vertebral segment a U or V configuration. At the level of the lesion, the posterior ossification centers are more widely spaced than those in the vertebral segments above and below the defect. SB may be seen in the longitudinal plane, although meticulous individual vertebral body scanning in the transverse plane is required to visualize small defects. If a meningocele or meningomyelocele is present and intact, a bulging sac can be visualized as well.

B M Petrikovsky is a Professor of Obstetrics & Gynecology at New York Institute of Technology. H L Cohen is a Chairman of Radiology, Professor of Radiology, Pediatrics, and Obstetrics and Gynecology, University of Tennessee Health Science Center, Radiologist-in-Chief, LeBonheur Children's Hospital.

Small defects in the spine are difficult to visualize sonographically; however, the frequent association of SB with type II Arnold-Chiari malformation of the brain has greatly enhanced the ability of ultrasound to detect SB. Type II Arnold-Chiari-malformation involves the inferior displacement of a variable amount of cerebellar tissue into the upper cervical spinal canal. Frontal bone flattening or inversion of the cranium (known as the "lemon" sign) and a flattened, centrally curved cerebellum (known as the "banana" sign) are the most specific findings. Other cranial signs, which are seen less often, include ventriculomegaly (which may only be seen after an MMC repair) and a small for gestational age biparietal diameter. Both the "banana" and "lemon" signs have been reported after 12 weeks of pregnancy.

Early Diagnosis
Open SB can be suspected by a detectable marker within the brain — Non-visualization of Intracranial Translucency (IT). IT can be seen as the same mid-sagittal plane of the fetal head as for measurement of NT and assessment of the nasal bone. In normal fetuses the fourth cerebral ventricle presents as an intracranial translucency (IT) parallel to the NT, while in fetuses with open SB there is an absence of the IT.[5,6] At 11-13 weeks the brain stem appears hypoechogenic (dark gray) whereas the IT is anechoic (black).[7]

Prognosis
The legs are lacking any function when the lesions are thoracic or high lumbar (L1-L2). Lower lesions (L3-L5) are usually associated with the possibility for walking with orthopedic devices. Sacral lesions allow for plantar flexion with an ability to ambulate. Bowel and urinary incontinence are frequent problems, however, with higher but specifically lower lesions. In the majority of patients, hydrocephalus develops soon after the closure of the defect.[8] Testing Pavlovian knee reflexes in-utero by the spinal needle used as part of an amniocentesis procedure has been used to predict if a fetus will be able to ambulate.[9,10]

Prenatal Management
Open SB is one of the few conditions where fetal surgery appears beneficial. Candidates for in-utero surgery are patient with singleton pregnancy, myelomeningocele between T1 and S1, a gestational age of 19.0 to 25.9 weeks, and a normal karyotype. Surgery is not indicated if the following are present: associated fetal anomalies, severe kyphosis, risk of preterm birth, a maternal body-mass index of 35 or more, or a previous hysterotomy. As compared with postnatal surgery, prenatal

Ultrasound images of spina bifida
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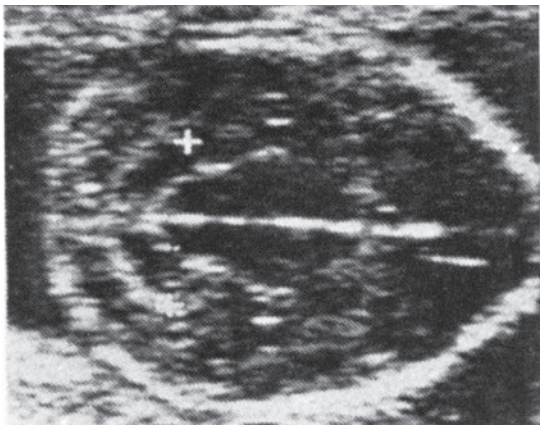
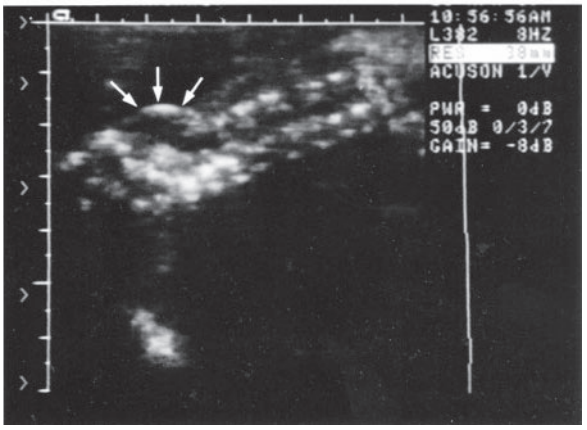


"Lemon" and "Banana" signs



A sacral spina bifida (arrows)

surgery for myelomeningocele performed before 26 weeks of gestation has decreased the risk of death or need for shunting by the age of 12 months and improved scores in a composite measure of mental and motor function.[2] Reductions in rates of shunt placement in the prenatal-surgery group were likely due to the reduction in rates of hindbrain herniation (Chiari II development) as well as the improved flow of cerebrospinal fluid.

Women with pregnancies complicated by fetal myelomeningocele who meet established criteria for in utero repair should be counseled in nondirective fashion regarding all management options, including the possibility of open maternal-fetal surgery.[11] Closed SB has a much more favorable prognosis than the open forms. Indeed, many affected individuals are asymptomatic.[12]

Genetics

Neural tube defects are generally multifactorial in nature. SB has been associated with chromosome abnormalities (trisomy 13, trisomy 18, triploidy, tetraploidy, duplications, deletions, and mosaic trisomies), prenatal valproic acid exposure, maternal diabetes, and maternal hyperthermia.[12-13] SB has been reported in more than 40 malformation syndromes and has been described with increased frequency in monozygotic twins, and cloacal exstrophy.[12,13]

Prenatal evaluation therefore should include a fetal karyotype and a detailed sonogram. Families should be offered the opportunity to meet with a pediatric neurosurgeon. If interested, they may also benefit from visiting SB team clinics and meeting other parents of affected children. The presence of a duplication or deletion in the fetal karyotype should prompt parental karyotypes to rule out a balanced translocation carrier. In the event of a fetal or neonatal demise with multiple anomalies present but normal chromosomes, a complete autopsy should be offered.

Genetic counseling of the family is indicated to review multifactorial inheritance, to determine a parental exposure, to obtain a detailed family history, and to discuss empiric recurrence risks (3 to 5%). High-dose folic acid (4 mg) beginning 3 months before conception may decrease the risk of recurrence by 70% in subsequent pregnancies.

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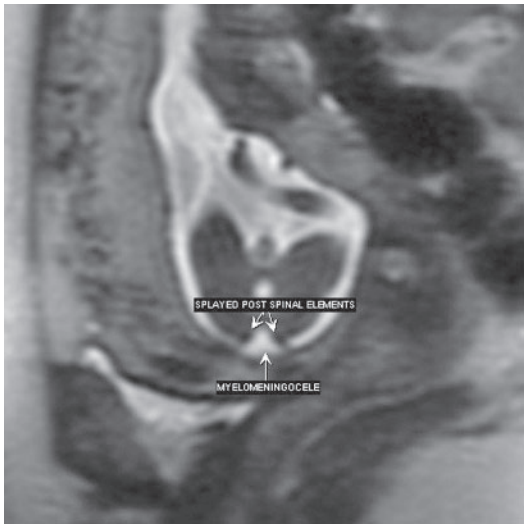
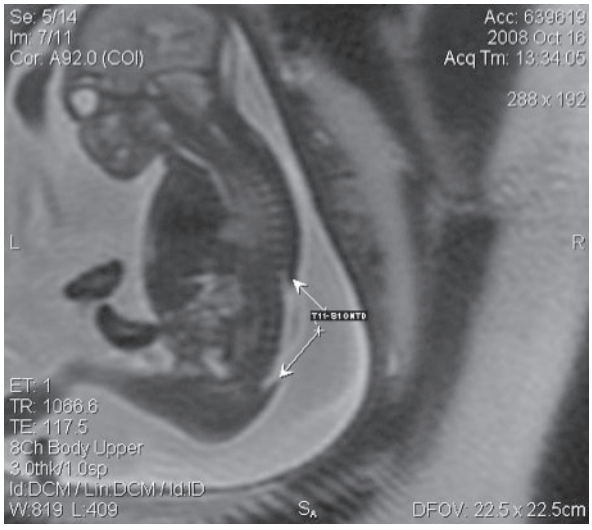
MRI images of open spina bifida





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Benefits of Early Diagnosis of Ventriculomegaly

B M Petrikovsky, MD, PhD, H Cohen, MD, L G Sichinava, MD, DSc

Definition

Ventriculomegaly (VM) is a condition in which the size of the atrium of the lateral ventricles exceeds 10mm.

Prevalence

VM is the most common fetal brain abnormality identified with a prevalence of 0.3 to 1.5 per 1000 live births.[1,2] The incidence of VM without associated anomalies is between 0.39 and 0.87/1000 live births.[2] About 60% of affected fetuses are males.[3,4]

Etiology

VM represents an etiologically heterogeneous group of disorders. It is usually caused by obstruction of cerebrospinal fluids (CSF) flow, with a concomitant increase in intracranial pressure. Isolated VM can be caused by congenital obstruction of the aqueduct of Sylvius. VM can also be caused by an increase in CSF production (choroid plexus papilloma), without obstruction. The VM is termed "isolated" when no other anomalies are detected.

Classification

VM is categorized as mild when the ventricle width is 10 to 15 mm or severe when it exceeds 15 mm.

Major Principles of Diagnosis

The width of the atrium of the lateral ventricle is almost constant from the early second trimester until late in the third trimester. This measurement can be obtained at the level of the biparietal diameter (BPD). The average width is 7.6mm; atrial widths exceeding 10mm suggest VM.[3]

Observation of the choroid plexus is useful in diagnosing VM. The choroid plexus normally fills the atria of the lateral ventricles, and should appear symmetrical in both ventricles. A dangling choroid plexus is seen when the choroid plexus drops to the dependent side of an enlarged lateral ventricle (Fig 1).

To avoid a false diagnosis, certain pitfalls must be considered. It is best to measure the atria of the lateral ventricles in the distal hemisphere. The identification of the choroid plexus within the lateral ventricle and the identification of the lateral wall of the ventricle is important to avoid overestimating the degree of ventricular dilation. One must be aware that the temporal brain normally appears more echopenic than other brain areas and in cases of limited brain penetration may simulate fluid within the ventricle and extension of the ventricular dilation peripherally.[4]

First Trimester Diagnosis

VM in the first trimester is rare in comparison with the second trimester. An enlarged third ventricle or an interruption of the falx can suggest VM in the first trimester.

Prenatal Management

When VM is detected, a meticulous search for both intracranial and extracranial anomalies is essential. Fetal echocardiography is indicated. Spina bifida must be excluded and serial ultrasounds should be taken to monitor for possible progression. If VM is progressive, delivery is recommended as soon as pulmonary maturity is documented, to allow for early neonatal shunting. The benefits of in-uteroventriculoamniotic shunting are doubtful, and this procedure is currently not recommended. Cesarean delivery is recommended only when hydrocephalus is present. VM has been reported in association with ventricular hemorrhage, aqueductal stenosis, arteriovenous malformations, Dandy-Walker malformation, Arnold-Chiari malformation, and more than 40 chromosomal abnormalities. VM is also seen in numerous malformation syndromes, including single-gene disorders and skeletal dysplasias. Associated anomalies are found in 70% to 80% of cases, half of which are extracranial and may not always be accurately detected prenatally. Approximately 25% of prenatally diagnosed cases are associated with chromosomal abnormalities.

Aqueductal stenosis, a common lesion associated with VM,may also develop secondary to intracranial hemorrhage, congenital infections (cytomegalovirus, toxoplasmosis, rubella), or congenital tumors. Familial cases of aqueductal stenosis are consistent with an X-linked pattern of inheritance. In such cases, genetic testing for L1CAM gene mutation should be performed. Abnormalities of the thumb extensors and abductors have been found in 25% of patients with X-linked aqueductal stenosis.

Prenatal evaluation should include a fetal karyotype, TORCH titers, and a detailed sonogram, with particular attention given to the spine and musculoskeletal system. The International Society of Ultrasound in Obstetrics and Gynecology interim guidance on US for Zika virus in pregnancy recommends

B M Petrikovsky is a Professor of Obstetrics & Gynecology at New York Institute of Technology. H L Cohen is a Chairman of Radiology, Professor of Radiology, Pediatrics, and Obstetrics and Gynecology, University of Tennessee Health Science Center, Radiologist-in-Chief, LeBonheur Children's Hospital. L G Sichinava is a Professor of Obstetrics and Gynecology at Moscow University School of Medicine.

Illustrations

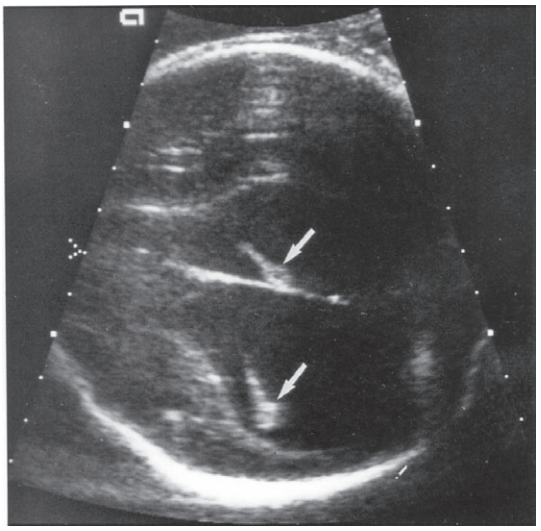

Figure 1. Bilateral dangling of choroid plexus (arrows). From Fetal Disorders, B Petrikovsky, Wiley-Liss. Used with permission.

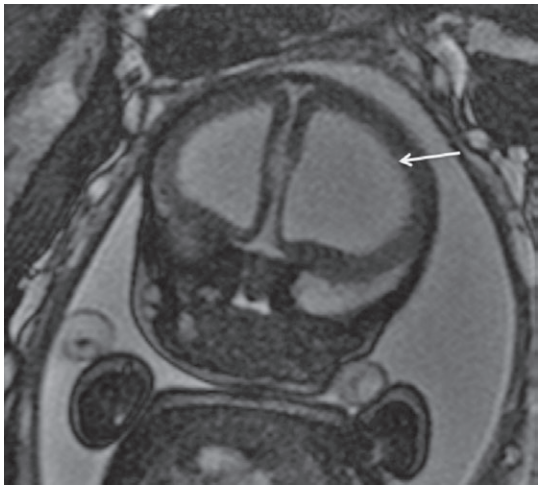

Figure 2. Severe ventricular dilation (arrow) in T2 weighted MRI in the coronal plane.

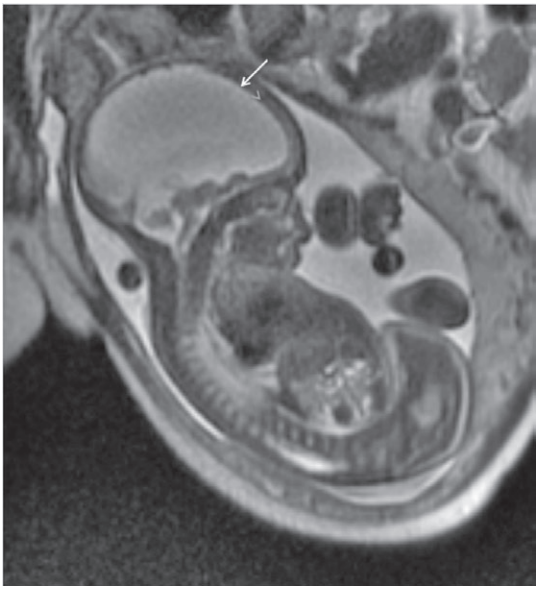

Figure 3. Severe dilation (arrow) of lateral ventricular body on T2 weighted MR in Sagittal plane. Arrowhead points to frontal brain peripheral to the dilated ventricle.

referral to a specialist center for assessment in cases of of fetal brain abnormality, including VM.[5] Although there currently is no evidence of an association between Zika infection and VM, it is possible and should be investigated further especially in cases where clinical suspicion is raised in the context of travel to a high-risk region, clinical or laboratory evidence of disease, or concurrent microcephaly.[6] Fetal MRI should be considered if one is suspicious of associated brain abnormalities, fetal infections, or brain hemorrhages (Fig 2).[7,8] Fetal MRI can be especially helpful in identifying abnormalities not routinely seen on ultrasound, eg, abnormal sulcation, small germinal matrix hemorrhages, schizencephaly, and microphthalmia, among others.[9] MRI is most sensitive technique to detect associated ponto-mesencephalic dysmorphology (ex. 'molar tooth' sign.) Ponto-mesencephalic dysmorphology, if identified, is a profoundly poor prognostic sign even after successful shunting. Families should be offered the opportunity to meet with a pediatric neurosurgeon to discuss neonatal management. In the event of a fetal of neonatal demise, a complete autopsy should be performed. Genetic evaluation of the fetus or newborn by a dysmorphologist will assist in syndrome recognition. The presence of a chromosomal duplication or deletion should prompt the clinician to obtain parental karyotypes to rule out a balanced translocation carrier. If VM is associated with intracranial bleeding, the possibility of fetal alloimune thrombocytopenia should be considered.

Natural History in the Neonate

The newborn presents with a large head or large ventricles seen on a neonatal ultrasound. In the event of an increasing head circumference, ventriculoperitoneal shunting is implemented. All current experience suggests, however, that outcomes depend on associated brain problems and have much less to do with shunting. Patients with associated brain anomalies do poorly, whereas those with otherwise normal brains do better.[10]

Neurodevelopment outcome for isolated VM is variable. Over 85% of neonates will have a normal outcome or minimal developmental delay. Asymmetric bilateral VM may carry a worse prognosis with these children at a significant risk for behavioral disorders. Poor prognostic factors include co-existent anomalies, progressive VM, and female gender. In severe VM, the outcome may still be variable but over 30% of children may develop normally.[10]

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Initiation and Ongoing Clinical Management of an Infant Supported by Volume Guarantee – A Case Study

Robert DiBlasi RRT-NPS, FAARC

The patient is a premature female infant born at 25 4/7 weeks, weighing 452 grams, following premature rupture of membranes at a community hospital. She was supported briefly in the delivery room with CPAP following surfactant administration, and was transferred to a level IV NICU for further care on the second day of life. The infant arrived at the hospital with the neonatal transport team on CPAP with a pressure of 8 cm H_2O and a set FiO_2 of 0.7. The infant was in distress and presented with the following: nasal flaring, intercostal and substernal retractions, and occasional apneic episodes that responded to intermittent tactile stimulation. The chest X-ray showed diffuse bilateral infiltrates and profound hypoinflation, consistent with Respiratory Distress Syndrome (RDS).

Due to the patient's deteriorating respiratory status on high CPAP settings, Non-Invasive Ventilation (NIV) was initiated using the Dräger Babylog VN500.

Initial Settings

Application Mode	NIV
Mode	PC-CMV
PIP	20 cm H_2O
PEEP	6 cm H_2O
Respiratory Rate	20/min
Ti	0.4 s
FiO_2	0.6

Initial arterial blood gas via Umbilical Artery Catheter

pH	7.28
$PaCO_2$	55 mmHG
PaO_2	55 mmHG
HCO_3	19 mmHG

NIV resulted in reduced work of breathing and avoided intubation for this patient. The patient was initially asynchronous with the non-invasive PC-CMV[1] breaths, so the respiratory rate (RR) was adjusted to match every other spontaneous effort being made by the patient (Figure 1).

[1]Pressure Control - Continuous Mandatory Ventilation

Robert DiBlasi RRT-NPS, FAARC is Manager of Clinical Diagnostics and Research in the Respiratory Care Department at the Seattle Children's. Rob is also a Principle Investigator for the Center for Developmental Therapeutics at the Seattle Children's Hospital Research Institute.

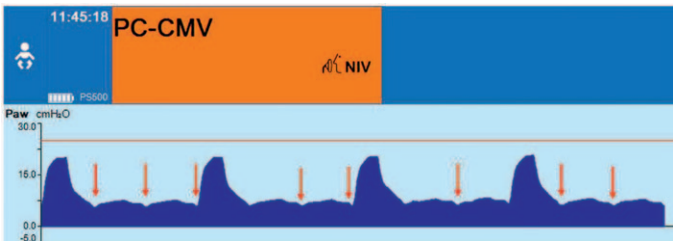

Figure 1. Graphical representation of airway pressure in the patient during NIV with the Babylog VN500

The red arrows in Figure 1 indicate small depressions in the baseline pressure where the patient is making an inspiratory effort. Adjusting the rate to provide fully supported breaths on every other spontaneous effort was useful for improving synchrony in this patient.

The patient failed NIV after 10 hours due to apnea, desaturations, and bradycardia. The chest X-ray (Figure 2) after intubation revealed diffuse bilateral infiltrates consistent with RDS. The patient was given 2 mL/kg Curosurf® for poor compliance (0.5 mL/cm H_2O), refractory hypoxemia, and radiographic evidence of pulmonary atelectasis.

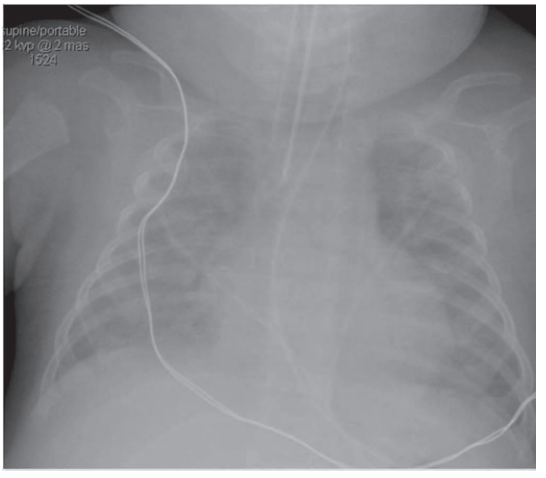

Figure 2. X-ray after intubation

The application mode was changed to "tube" for invasive ventilation. The physician ordered PC-AC[2] with Volume Guarantee (VG) with the following settings: tidal volume (VT) of 4 mL/kg, PEEP of 8 cm H_2O, an inspiratory time (Ti) of 0.3 s, RR 50 /min.

The patient was spontaneously assisting all breaths and was breathing at a rate of 70 / min. The transcutaneous CO_2 levels were 75 mmHg and these values correlated well with the arterial CO_2 levels observed with the last blood gas on nasal CPAP. Upon the physician's request, the Respiratory Therapist (RT) increased the VT to 5 mL/kg to account for the instrumental deadspace of the flow sensor and ET tube. The respiratory rate and CO_2 levels decreased in response to this change and the patient appeared comfortable.

Following this change, an audible ET tube leak could be heard . The ventilator was registering a 50-60 percent leak and an alarm on the ventilator began reading "VT low". This problem was remedied by changing the Pmax setting from 25 to 30 cm H_2O in order to provide enough pressure to allow the tidal volume to be delivered.

Twenty-four hours later, the patient's lung mechanics improved as reflected by lower Peak Inspiratory Pressure (PIP) values. However, the bedside Registered Nurse (RN) expressed concerns that the patient appeared tachypneic and had low PIP values. The bedside RT assured the nurse that this was related to the nursing care and usually the PIP values returned to normal after care was rendered. The RT presented a trend of the pressures and volumes (Figure 3) to the RN. She was then assured that this was a normal function of the ventilator and may be appropriate so that the patient isn't receiving too much pressure and volume during periods of anxiety.

[2] Pressure Control — Assist Control

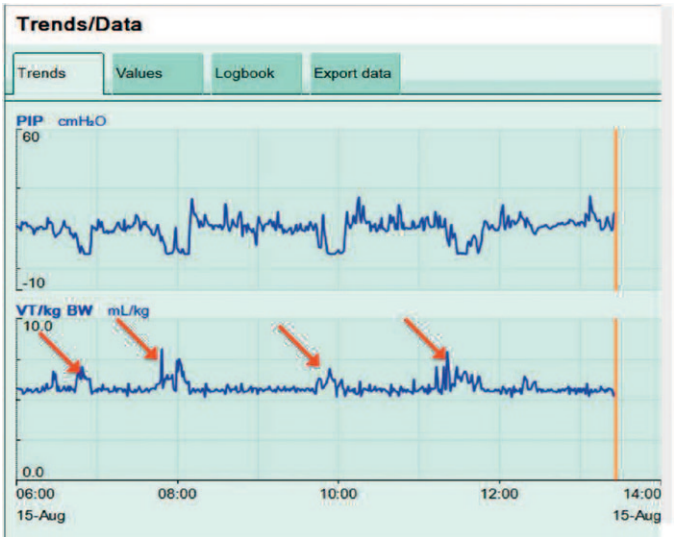

Figure 3: Trend of tidal volume and airway pressure

The trending of pressure and volume show reduced inspiratory pressures due to increased volumes during periods of nursing care (red arrows). The patient's efforts are reduced after nursing care, resulting in smaller volumes and higher PIP values.

A month later, the infant was still supported with the Babylog VN500 in the PC-AC mode with Volume Guarantee activated. The infant gradually started showing signs of increased work of breathing on the ventilator and increased FiO_2 requirement following upsizing of the ET tube.

Settings

Application Mode	Tube
Mode	PC-AC with VG
PIP	7 cm H_2O
Vt	14.4 mL (set)
	17.5 mL (measured)
PEEP	6 cm H_2O
Respiratory Rate	20/min
Ti	0.30 s
FiO_2	0.29

Venous Blood Gas

pH	7.23
$PaCO_2$	68 mmHG
PaO_2	23 mmHG
HCO_3	29 mmHG

Airway graphics revealed consistently low PIP values with tidal volumes greater than that set on the ventilator (Figure 4A). The chest X-ray showed low lung volumes with increasing atelectasis and air bronchograms (Figure 4B) from the previous exam. The patient developed retractions, nasal flaring, and SpO_2 78-89 percent. Breath sounds were reduced in the bases with fine inspiratory crackles throughout.

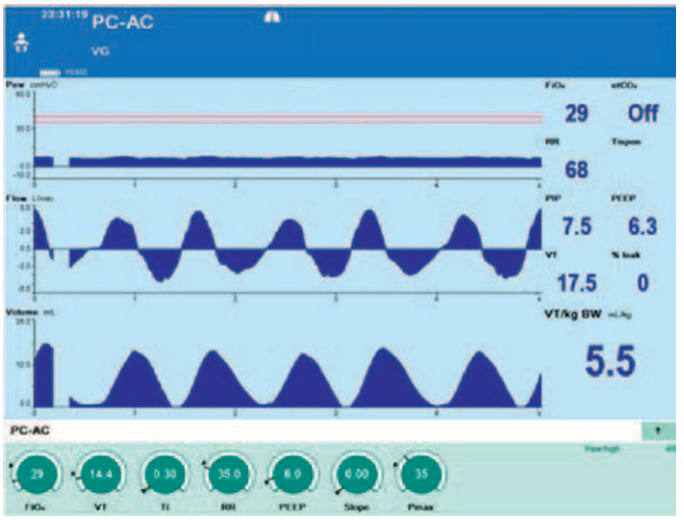

Figure 4A: Inadequate support during PC-AC

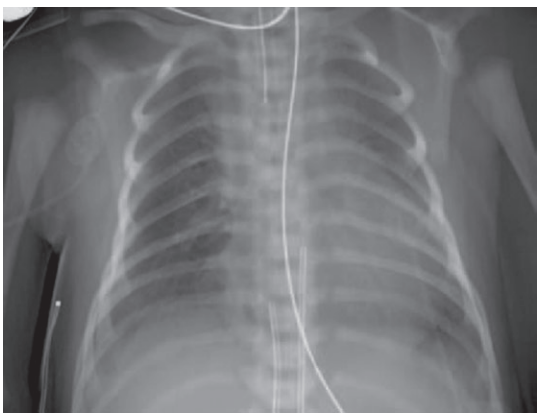

Figure 4B: Strong infiltration constant with atelectasis

Based on the clinical deterioration, the RT chose to assess the appropriateness of the tidal volume setting. The attending neonatologist wanted to place the patient in PC-AC without Volume Guarantee, so that the patient could get a higher level of support. During this time, the NICU team discovered that the dose-calculated weight in the ventilator hadn't been updated in over a month. When the new weight was entered, it became obvious that the patient was only receiving a tidal volume ~3.5 mL/kg. This prompted the team to increase the set tidal volume targeted from 14 to 19 mL. This resulted in an immediate reduction in the observed high levels of work of breathing and increased in PIP values (Figure 5A) as well as radiographic improvement in lung inflation (Figure 5B).

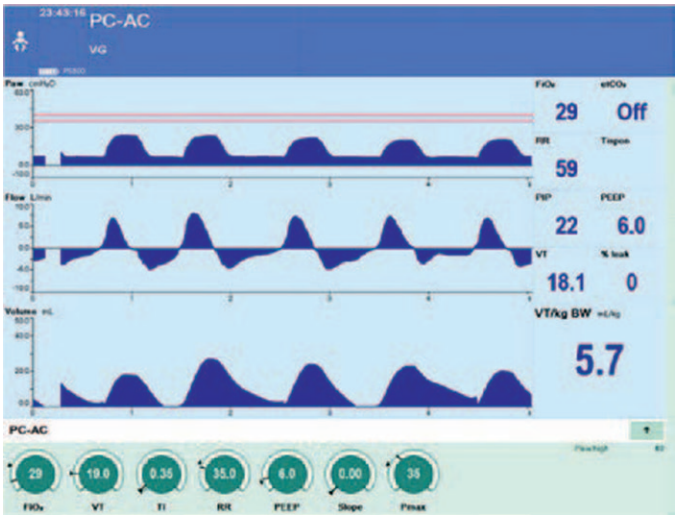

Figure 5A: Airway graphic following setting change

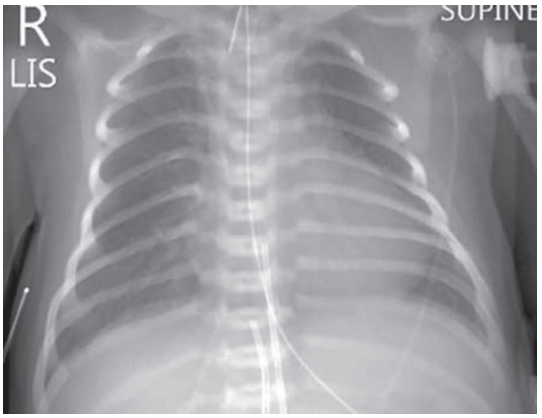

Figure 5B: X-ray following setting change

A week later the PIP values were again reduced to only 1 cm H_2O above the PEEP level during PC-AC with Volume Guarentee. However, with the exception of this time, the patient had normal breathing and acceptable gas exchange. Based on this, the patient was extubated to non-invasive CPAP. Subsequently, five days later, the patient was transferred home utilizing oxygen therapy at 0.5 L/min via nasal cannula.

Meta-analysis of Diagnostic Accuracy of Neutrophil CD64 for Neonatal Sepsis

Jing Shi, Jun Tang and Dapeng Chen

Abstracts

Background: The aim of this study was to systematically evaluate the diagnostic performance of nCD64 for neonatal sepsis.

Methods: Computer retrieval was conducted for the databases of PubMed, Embase, and Springer databases up to March 18, 2015 to select the relevant studies on nCD64 and neonatal sepsis. Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and 95 % confidence intervals (CI) for diagnostic efficiency of nCD64 were pooled. In addition, the summary receiver operating characteristic (SROC) curve was also conducted based on the sensitivity and specificity.

Results: Seventeen studies including 3478 participants were included in this meta-analysis. The overall pooled sensitivity, specificity, PLR, NLR and DOR were 0.77 (95 % CI: 0.74–0.79), 0.74 (95 % CI: 0.72–0.75), 3.58 (95 % CI: 2.85–4.49), 0.29 (95 % CI: 0.22–0.37) and 15.18 (95 % CI: 9.75–23.62), respectively. In addition, the area under the SROC curve (AUC) was 0.8666, and no threshold effect was found based on the Spearman correlation analysis (P = 0.616). Besides, subgroup analysis showed higher sensitivity, specificity and AUC in term infants and proven infection group than those in preterm infants and clinical infection group, respectively.

Conclusions: The n CD64 expression alone is not a satisfactory marker for diagnosing neonatal sepsis with relatively low sensitivity, specificity, PLR and NLR, in spite of relatively high SROC area. Therefore, the n CD64 expression used in diagnosis of neonatal sepsis should be treated with caution.

Keywords: Neutrophil CD64, Neonatal sepsis, Diagnosis, Meta-analysis

Background

Neonatal sepsis is one of the important causes of neonatal mortality. Despite the improvement in management of newborn infant, the mortality caused by neonatal sepsis remains high (~10 %) [1]. It is difficult to diagnose neonatal sepsis during early stage because of the nonspecific and variable clinical symptoms. Blood culture is the current golden standard for confirming the neonatal sepsis. However, the results of blood culture could be available within 24-48 h of culture. Usually, the antibiotics would be discontinued if the blood culture results were negative by 48 h [2, 3]. Moreover, the results are negative in cases with meningitis and pneumonia [4]. There is a high false-negative rate of blood culture [5]. Therefore, considering the limitations of blood culture in neonatal sepsis diagnosis, new biomarkers for early and rapid diagnosis of neonatal sepsis should be developed.

Recently, neutrophil CD64 (nCD64) has been reported as a diagnostic marker of neonatal sepsis, because nCD64 expression is stable for 24 h and can be detected rapidly by flow cytometer with minimal blood volumes [6]. However, the diagnostic accuracy of nCD64 remains unclear due to the large range of sensitivity (0.26–0.95) and specificity (0.62–0.97) in different individual studies [7–9]. Although a metaanalysis has been conducted by Jia et al. in 2013 [10], they combined the results of median monocyte/ nCD64 ratio with nCD64 expression, which might be a source of heterogeneity. In addition, recently new individual studies [11, 12] on this topic have reported conflicting results with Jia et al. [10]. Thus, there is a need to update the exploration. In this study, we performed an updated meta-analysis to systematically evaluate the diagnostic performance of nCD64 for neonatal sepsis.

Methods

Because the data of this manuscript come from the public databases and previous studies, it is not applicable to receive the ethics committee approval or follow the Declaration of Helsinki, and there is no need to get informed consent of patients.

Search strategy

We systematically searched the PubMed, Embase and Springer databases up to 18 March, 2015 with the following search terms: (septicemia or septicaemia or sepsis or infection) and (neutrophil CD64 or nCD64). We also manually searched the printed articles, and the references of the reviews and the included studies.

Inclusion and exclusion criteria

The studies were included if they met the following criteria: 1) exploring the diagnostic value of the nCD64 for sepsis; 2) reporting the babies within 28 days of birth; 3) providing the golden standard of blood culture; 4) giving the number of true positive (TP), false positive (FP), true negative (TN) and false negative (FN). The following studies were excluded: 1) the

The authors are with the Department of Pediatrics, West China Second University Hospital, Sichuan University, No 20 Section 3 South Renming Road, Chengdu, Sichuan Province 610041, People's Republic of China.

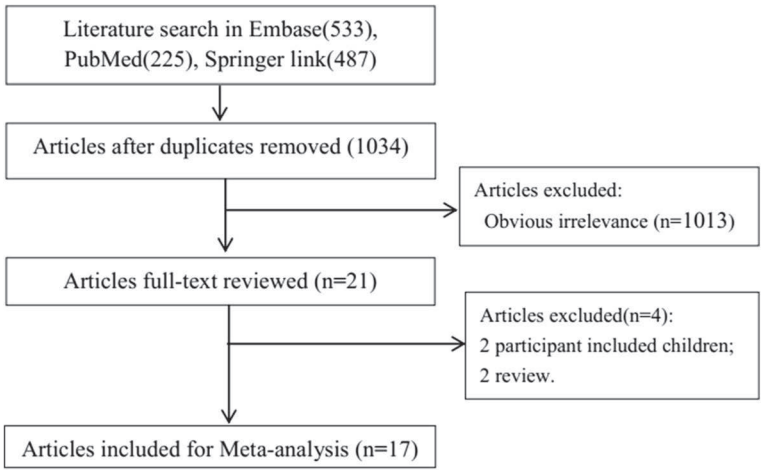

Fig. 1 The process of the study selection

studies were written in a language other than English; 2) reviews, letters and reports.

Data extraction and quality assessment

Two investigators independently extracted the following data using a standard form: name of the first author, publication year, study region, diagnostic golden standard, detection method and cut-off value of nCD64, TP, FP, TN and FN. They exchanged the form after filling out the data extraction. Discrepancies were solved by discussing with each other.

The quality of the included studies was assessed by using a 14-item Quality Assessment of Diagnostic Accuracy Studies (QUADAS) list [13]. Each item was descriptively assessed with yes, unclear or no and scored by 1, 0, -1, respectively [14]. Total scores were produced by plus the scores of each item.

Statistical analysis

The statistical analysis was performed using Metadisc software (version 1.4) [15]. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and 95 % confidence interval (CI) for diagnostic efficiency of nCD64 were pooled. The heterogeneity among studies was evaluated by Cochran Q test and I2 statistic [16]. $P < 0.05$ or $I2 > 50$ % was considered statistically significant and a random effects model was used for pooling the data; otherwise, a fixed effect model was utilized. The summary receiver operating characteristic (SROC) curve was also conducted based on the sensitivity and specificity. The area under the curve (AUC) close to 1 indicated a good diagnostic performance of nCD64 [17].

Threshold effect was assessed using Spearman correlation analysis, and $P < 0.05$ indicated a significant threshold effect [18]. Subgroup analyses based on the diagnosis standard for infection (clinical or proven infection), type of sepsis (early-onset or late-onset), infants (preterm or term) were conducted. Clinical infection means infection suspected on a clinical basis whereas proven infection means culture proven infections with an identified microorganism. In addition, a meta-regression analysis was conducted based on the above variances to explore the sources of heterogeneity.

Results

Study selection

The process of the study selection is shown in Fig. 1. We identified 1,245 studies by the initial search (Embase: 533, PubMed: 225, Springer: 487). Firstly, 211 duplicate studies were removed. Then, by reviewing titles and abstracts, 1,013 studies that did not meet the inclusion criteria were ruled out. In addition, 2 reviews and 2 studies including children population were precluded by reading full-texts. Finally, 17 studies [7–9, 11, 12, 19–30] were included in this meta-analysis.

Characteristics of the included studies

The characteristics of the 17 included studies were listed in Table 1. There were totally 3478 participants involved in this meta-analysis. Nine of the included studies distributed in Asia, 2 in Europe, 5 in America and 1 in Africa. The diagnostic golden standard included clinical test, hematological and biochemical laboratory investigations, and microbiological test-blood culture. The expression of nCD64 was assessed by flow cytometry. As shown in Table 2, the quality of the included studies was relatively high, because most of the total scores ≥ 10.

Pooled analysis

As shown in Fig. 2, the pooled sensitivity and specificity were 0.77 (95 % CI: 0.74–0.79) and 0.74 (95 % CI: 0.72–0.75), respectively. The pooled PLR and NLR were 3.58 (95 % CI: 2.85–4.49) and 0.29 (95 % CI: 0.22–0.37), respectively (Fig. 3). In addition, the pooled DOR was 15.18 (95 % CI: 9.75–23.62, Fig. 4). For all above effect sizes, significant heterogeneities were observed ($P < 0.001$, $I2 > 50$ %). From the SROC in Fig. 4, AUC was 0.8666, and no threshold effect was found based on the Spearman correlation analysis ($P = 0.616$).

Subgroup analysis

The results of subgroup analyses are summarized in Table 3. Higher sensitivity, specificity, PLR, DOR, AUC and Q*, and lower NLR were observed in the proven infection group (0.82, 0.74, 4.14, 30.58, 0.9136 and 0.8461, and 0.17) compared with those in clinical infection group (0.74, 0.66, 2.19, 6.98, 0.8245 and 0.7576, and 0.39). Slightly higher specificity, PLR and NLR, while lower sensitivity, DOR, AUC, and Q were found in the early-onset sepsis, compared with those in the late-onset sepsis. There were higher sensitivity, specificity, PLR and DOR, and lower NLR in term infants (0.80, 0.85, 5.75 and 24.07, and 0.24) compared with those in preterm infants (0.74, 0.69, 2.76 and 7.83, and 0.37).

Meta-regression analysis

Meta-regression analysis (Table 4) showed that the "infants" was

Table 1 Characteristics of included studies

ID	Author	Year	Area	n	Episodes of sepsis	Infected/noninfected	Diagnosis standard	Type of sepsis	Infants	nCD64 analysis	Analysis cut-off	TP	FP	FN	TN
1	Bhandari	2008 [7]	USA	163	293	128/165	Clinical or proven	b	Preterm	FCM	2.30*	90	63	38	102
2	Dilli	2010 [21]	Turkey	109	109	35/74	Clinical or proven	c	Preterm + term	FCM	4.39*	31	11	4	63
3	Genel	2012 [22]	Turkey	119	119	49/70	Clinical or proven	c	Preterm + term	FCM	3.05 MFI	40	16	9	54
4	Groselj-Grenc	2009 [23]	Slovenia	46	46	17/29	Clinical or proven	c	Preterm + term	FCM	1.86*	13	6	4	23
5	Lam	2011 [24]	China	310	310	136/174	Clinical or proven	a	Preterm + term	FCM	6010 $	107	37	29	137
6	Motta	2014 [25]	Italy	129	129	48/81	Clinical or proven	a	Preterm	FCM	2.4*	31	12	17	69
7	Ng	2004 [26]	China	359	359	115/244	Clinical or proven	a	Term	FCM	5500 $	93	46	22	198
8	Ng	2006 [27]	China	298	298	93/205	Clinical or proven	a	Term	FCM	6136 $	73	20	20	185
9	Zeitoun	2010 [30]	USA	98	98	49/49	Clinical or proven	c	Preterm + term	FCM	2.6*	45	14	4	35
10	Du	2014 [11]	China	158	158	88/70	Clinical	a	Preterm	FCM	1010 $	72	21	16	49
11	Elawady	2014 [12]	Egypt	50	50	25/25	Clinical	b	Preterm + term	FCM	46.0	24	0	1	24
12	Layseca-Espinosa	2002 [8]	Mexico	29	29	14/15	Clinical	c	Preterm + term	FCM	#	3	0	11	15
13	Streimish(a)	2014 [29]	USA	684	1156	207/416	Clinical	a	Preterm	FCM	1.63	139	137	68	279
14	Streimish(b)	2014 [29]	USA			204/329	Clinical	b	Preterm	FCM	2.19	159	135	45	194
15	Choo	2012 [20]	Korea	23	23	11/12	Proven	c	Preterm + term	FCM	3.0*	10	2	1	10
16	Elawady	2014 [12]	Egypt	50	50	25/25	Proven	b	Preterm + term	FCM	45.8	24	0	1	25
17	Layseca-Espinosa	2002 [8]	Mexico	34	34	17/17	Proven	c	Preterm + term	FCM	#	5	1	12	16
18	Ng	2002 [9]	China	110	147	37/110	Proven	b	Preterm	FCM	4000 $	35	13	2	97
19	Soni	2013 [28]	India	60	60	24/36	Proven	c	Preterm + term	FCM	2.765*	22	12	2	24
20	Streimish(a)	2012 [19]	USA	649	997	3/577	Proven	a	Preterm	FCM	2.38	3	185	0	392
21	Streimish(b)	2012 [19]	USA			47/370	Proven	b	Preterm	FCM	3.62	35	85	12	285

a, early-onset; b, late-onset; c, early & late-onset; *, CD64 index; FCM, flow cytometric technology; MFI: mean fluorescence intensity; Clinical infection defined as infection suspected on a clinical basis; proven infection defined as culture-proven infection with an identified micro-organism; #, Arithmetic mean + 3 SD of the percentage of CD64 + cells found in normal neonates; $: cAntibody-phycoerythrin molecules bound per cell

the cause of heterogeneity (P = 0.0147) and other variances were not the sources of heterogeneity (P > 0.05).

Discussion

nCD64 can be detected rapidly by flow cytometer with minimal blood volumes [6] and is reported widely to be used in the diagnosis of neonatal sepsis. This meta-analysis showed that the diagnostic performance of nCD64 for neonatal sepsis was not good, because the pooled sensitivity and specificity are not high enough. The PLR and NLR were also not satisfactory. Although the AUC is relatively high, the application of nCD64 for diagnosing neonatal sepsis needs to be cautious.

The pooled sensitivity and specificity of nCD64 were 77 % and 74 %, respectively, which are lower than those of serum procalcitonin (PCT) (81 % and 79 %), although AUC was similar (0.87) [31]. Indicators of nCD64 diagnostic value were lower than CRP (sensitivity 80.8 %, specificity 100 %, AUC 0.90), TNF- α (sensitivity 100 %, specificity 96.6 %, AUC 1) and IL-6 (sensitivity 96.2 %, specificity 89.7 %, AUC 0.97) according data of study of

Table 2 Quality assessment of the included articles

Studies	QUADAS list item													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bhandari, 2008 [7]	+	0	+	+	+	+	+	+	0	0	+	+	0	+
Choo, 2012 [20]	+	-	+	+	+	+	+	+	0	0	+	+	-	+
Dilli, 2010 [21]	+	+	+	+	+	+	+	+	+	0	+	0	+	+
Du, 2014 [11]	+	+	+	+	+	+	+	+	-	+	+	+	0	+
Elawady, 2014 [12]	+	+	+	+	+	+	+	+	+	0	+	0	+	+
Genel, 2012 [22]	+	+	+	+	+	+	+	+	0	0	+	0	+	+
Groselj-Grenc, 2009 [23]	+	0	+	+	+	+	+	+	+	0	+	+	+	+
Lam, 2011 [24]	+	0	+	+	+	+	+	+	+	+	+	+	0	+
Layseca-Espinosa, 2002 [8]	+	0	+	+	+	+	+	-	+	0	+	0	0	+
Motta, 2014 [25]	+	-	+	+	+	+	+	+	+	0	+	0	+	+
Ng, 2002 [9]	-	+	+	+	+	+	+	+	0	0	+	0	+	+
Ng, 2004 [26]	+	+	+	+	+	+	+	+	+	0	+	+	+	+
Ng, 2006 [27]	+	+	+	+	+	+	+	+	+	0	+	+	+	+
Soni, 2013 [28]	+	0	+	+	+	+	+	+	+	0	+	+	+	+
Streimish, 2012 [19]	+	0	+	+	+	+	+	+	0	0	+	+	0	+
Streimish, 2014 [29]	+	0	+	+	+	+	+	+	0	0	+	+	0	+
Zeitoun, 2010 [30]	+	+	+	+	+	+	+	+	0	0	+	0	0	+

Abbreviation: *QUADAS* Quality Assessment of Diagnostic Accuracy Studies. +: YES; -: NO; 0: not clear

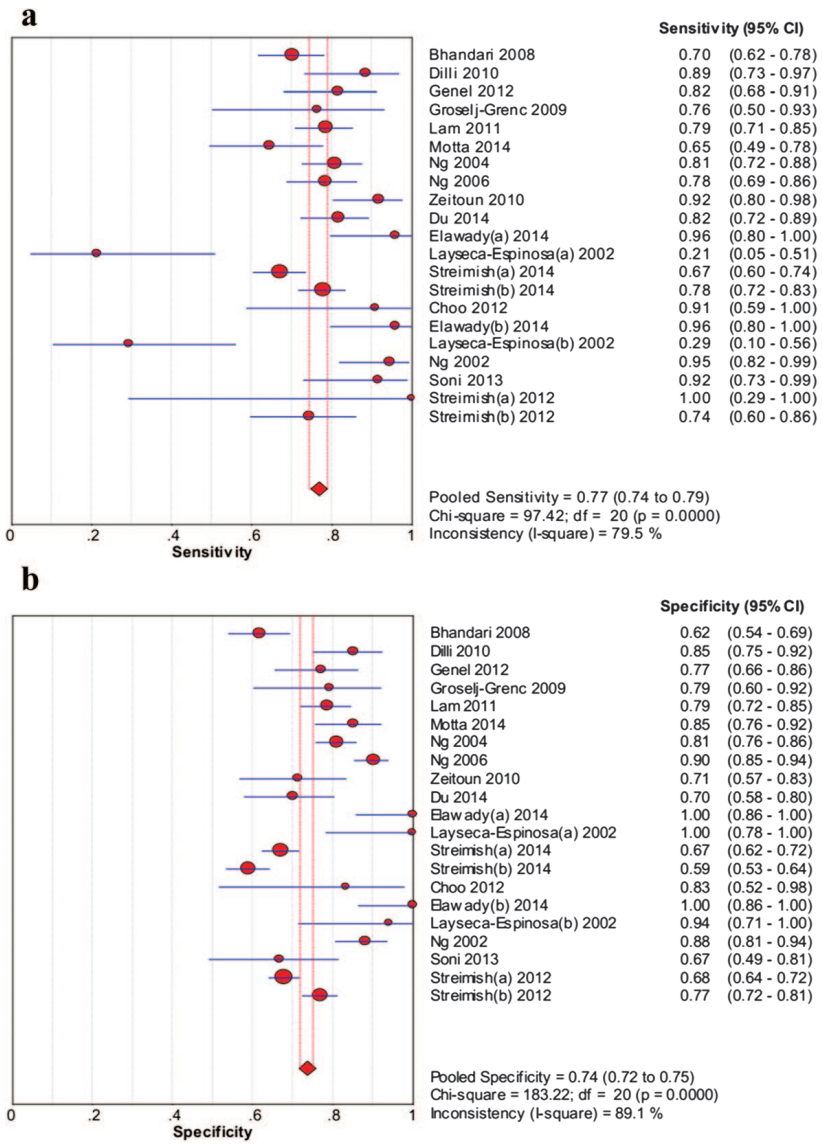

Fig. 2 The forest plots of sensitivity (a) and specificity (b) of neutrophil CD64 for neonatal sepsis diagnosis

Kocabas E et al. [32]. Compared with the novel marker such as presepsin [33–37], nCD64 also showed a lower diagnostic efficiency. Thus, our results indicate that the nCD64 should not be used as a diagnostic marker alone for neonatal sepsis. It can be combined with other diagnostic methods like serum PCT [38] and hematologic scoring system (sensitivity 93 %; specificity 82 %) [39] to improve the diagnostic accuracy. The hematologic scoring system assigns one score for each of seven indexes (abnormal total leukocyte count, abnormal total neutrophil (PMN) count, elevated immature PMN count, elevated immature to total PMN ratio, Immature to mature PMN ratio ≥ 0.3, platelet count ≤ 150,000/mm3, and pronounced degenerative changes in PMNs) with higher scores indicating greater likelihood [39].

The results of the present study are similar with the previous meta-analysis of 12 studies (sensitivity, 78 %; specificity, 81 %; DOR, 21.27; PLR, 4.53; NLR, 0.23; AUC, 0.89.) [10]. Although nCD64 showed relatively high sensitivity and specificity in some included studies with cutoff of 2.3 % [7], 4000 phycoerythrinmolecules bound per cell [9], and 2.6 % [30], respectively, the small sample size and different cut-off may exaggerate the facticity of the results.

nCD64 expressed normally in non-infected neutrophils, but it could be up-regulated by stimulation of bacterial invasion [40]. It has been shown that the expression of nCD64 was not affected by transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS) and other non-infective perinatal events [21]. nCD64 expression in adults is different from newborn neonates. In adults, the expression of nCD64 may be higher in gram-negative sepsis than in gram-positive sepsis [41]. However, this difference has not been confirmed in neonates [21]. Neonates may have less expressed neutrophil to gram-negative bacteria infection. Furthermore, the expression of nCD64 may also been increased in leucocytes in patients with streptococcal infection [42]. All these lead to the lower power of nCD64 in diagnosis of neonatal sepsis.

Identification of the cut-off value of a diagnostic marker is difficult. If the cut-off value is high, the false positive rate may be overestimated. On the contrary, the low cut-off value may lead to overestimation of the false negative rate. Therefore, an appropriate cut-off value is necessary for improving the diagnostic accuracy of nCD64. In this study, cutoff values of nCD64 in included studies are different. Various cut-offs used

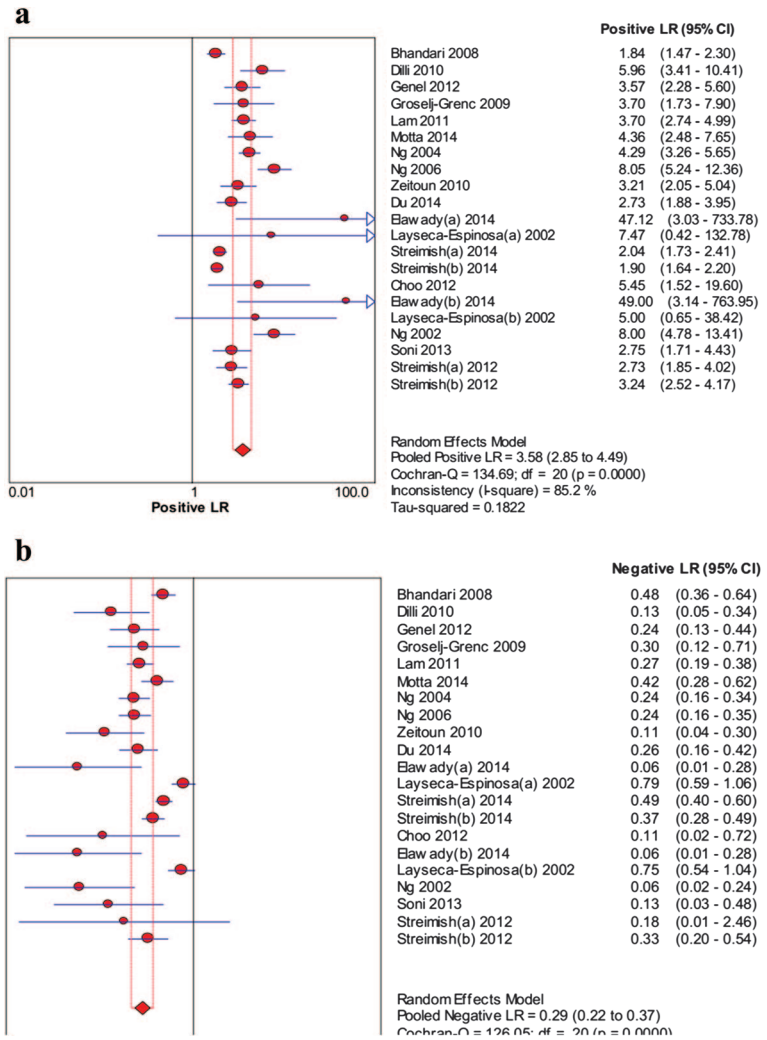

Fig. 3 The forest plots of positive likelihood ratio (**a**) and negative likelihood ratio (**b**) of neutrophil CD64 for neonatal sepsis diagnosis

in different studies might result in a threshold effect which is a cause of heterogeneity [43]. In the present study, no threshold effect was found based on the Spearman correlation analysis (P = 0.616), indicating that the threshold effect is not a cause of the high heterogeneity. The heterogeneity may be explained by the characteristics of the included patients. Some included neonates have other infections, which can also regulate the expression of nCD64. In addition, combination of studies with proven and clinical sepsis, data from preterm with term infants, and studies with early- and late-onset sepsis may also introduce heterogeneity. Therefore, we conducted the subgroup analysis based on these factors. The results revealed

Table 3 Subgroup analyses

Subgroup	Studies	Sensitivity (95 %)	Specificity (95 %)	PLR (95 %)	NLR (95 %)	SDOR (95 %)	AUC	Q*
All	21	0.77 (0.74, 0.79)	0.74 (0.72, 0.75)	3.58 (2.85, 4.49)	0.29 (0.22, 0.37)	15.18 (9.75, 23.62)	0.8666	0.7972
Infection								
Proven	7	0.82 (0.75, 0.87)	0.74 (0.71, 0.77)	4.14 (2.56, 6.68)	0.17 (0.06, 0.52)	30.58 (9.75, 95.88)	0.9136	0.8461
Clinical	5	0.74 (0.70, 0.77)	0.66 (0.62, 0.69)	2.19 (1.72, 2.79)	0.39 (0.25, 0.62)	6.98 (3.68, 13.24)	0.8245	0.7576
Clinical or Proven	9	0.78 (0.75, 0.81)	0.79 (0.77, 0.82)	3.93 (2.81, 5.49)	0.27 (0.21, 0.36)	15.41 (8.76, 27.09)	0.8661	0.7967
Type of sepsis								
Early-onset	7	0.75 (0.72, 0.78)	0.74 (0.72, 0.76)	3.57 (2.49, 5.11)	0.31 (0.23, 0.42)	12.40 (6.40, 24.00)	0.8415	0.7732
Late-onset	6	0.79 (0.75, 0.82)	0.71 (0.68, 0.74)	3.42 (2.11, 5.55)	0.24 (0.14, 0.41)	18.86 (6.82, 52.16)	0.9262	0.8606
Early & late-onset	8	0.78 (0.72, 0.84)	0.79 (0.74, 0.84)	3.65 (2.93, 4.57)	0.26 (0.11, 0.59)	20.43 (12.31, 33.91)	0.8835	0.8140
Infants								
Preterm	8	0.74 (0.71, 0.77)	0.69 (0.67, 0.71)	2.76 (2.16, 3.54)	0.37 (0.30, 0.47)	7.83 (4.84, 12.68)	0.8088	0.7436
Term	2	0.80 (0.74, 0.85)	0.85 (0.82, 0.88)	5.75 (3.08, 10.72)	0.24 (0.18, 0.31)	24.07 (13.17, 44.01)	–	–
Preterm + term	11	0.81 (0.76, 0.84)	0.81 (0.78, 0.84)	3.88 (3.04, 4.97)	0.21 (0.11, 0.41)	22.84 (12.94, 40.29)	0.8853	0.8159

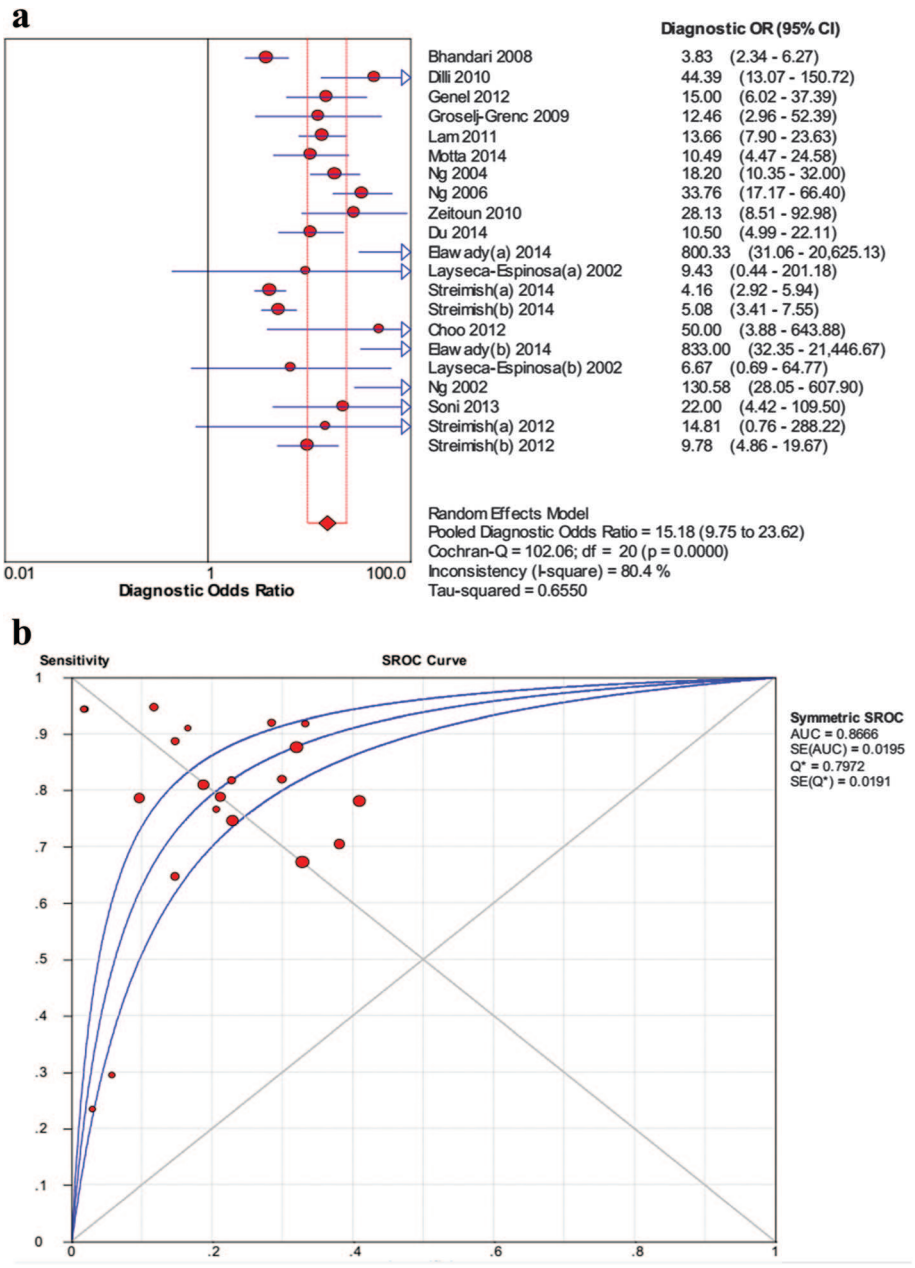

Fig. 4 The diagnostic odds ratio (DOR) (**a**) and the summary receiver operating characteristic (SROC) (**b**) curve

that higher sensitivity, specificity, PLR, AUC and Q* and lower NLR in the proven infection group than those in clinical infection group. There was higher sensitivity, specificity, PLR, DOR and lower NLR in term infants compared with those in preterm infants. No consistent differences in sensitivity, specificity, PLR, NLR, AUC and Q* were found between early-onset and late-onset sepsis. These results indicated that this method is more suitable for term infants than preterm infants, based on proven infection than other clinically suspected infection.

Table 4 Meta-regression

Variances	Coeff.	Std. Err.	*p* - value	RDOR	[95 % CI]
Cte.	1.002	0.729	0.1883	——	——
S	0.094	0.1956	0.6375	——	——
sepsis	-0.319	0.3179	0.3298	0.73	(0.37;1.43)
infants	0.806	0.2946	0.0147	2.24	(1.20;4.18)
diagnosis	0.436	0.2814	0.1406	1.55	(0.85;2.81)

Heterogeneity is a common limitation of metaanalysis, especially in diagnostic meta-analysis. In the present study, meta-regression revealed that types of infants was one cause of the heterogeneity. Although subgroup analysis was performed based on the diagnostic method, types of sepsis (early-onset or lateonset), and preterm or term, the influences of other factors like the cutoff values were not assessed due to the lack of included studies and unavailable data. This reminds the clinical researchers providing more details of the patients in further studies, including the stage and types of neonatal sepsis. In addition, the appropriate and uniform cut-off value of nCD64 should be confirmed in further clinical studies.

Conclusions

In conclusion, the n CD64 expression alone is not a satisfactory

marker for diagnosing neonatal sepsis with relatively low sensitivity, specificity, PLR and NLR, in spite of relatively high SROC area. Therefore, the n CD64 expression used in diagnosis of neonatal sepsis should be treated with caution.

Acknowledgements

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Authors' contributions

JS participated in the design of this study and performed the statistical analysis. DPC carried out the study and collected important background information. JS and DPC drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.
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Making Babies Grow: Necessity and Timing of Human Milk Fortification

Sandra Sundquist Beauman, MSN, RNC-NIC, CNS

There has been recognition for several years now that intrauterine and extrauterine growth vary in premature infants, particularly those born at less than 1500 grams and again, a larger difference for those born at less than 1000 gms.[1] Historically, the growth curves used in the Neonatal Intensive Care Unit (NICU) were growth curves based on normal extrauterine growth. It was realized that this resulted in growth failure, defined as growth that falls below the 10th percentile in comparison to normal fetal growth at the same gestational age.[2] Furthermore, the nutrition provided for these infants could not sustain the expected intrauterine growth. Infants delivered with birth weights in the 50th percentile would fall to the 10th percentile or below quickly. The nutrition provided must allow for rapid cell growth and body development as well as increased caloric use in infants in the NICU. Optimal nutrition must be started immediately after birth and studies have shown that early addition of more protein to the diet results in more lean body mass (less accumulation of body fat) which in turn decreases the risk of obesity, increased blood pressure, insulin resistance and cardiovascular disease later in life.[3] Optimal nutrition and less need for "catch up" growth has also been shown to result in better brain growth and neurodevelopmental outcome[3]. Furthermore, early addition of protein to the diet of premature infants promotes better metabolism and results in less hyperglycemia, a problem for very premature infants who are thought to need more calories for growth. Some studies have shown that post-discharge nutrition that is normal in energy intake but higher in protein intake results in body composition with significantly less body fat at 6 months corrected age.[4,5] While long-term follow up studies are pending, there is reason to believe that this normal energy/high protein diet may result in less risk of a metabolic syndrome later in life.[3]

Nutrition provided in the form of total parenteral nutrition is important in the growth and development of very low birth weight infants. However, nutrition is often delivered enterally within 3 to 4 days after birth and sometimes as early as 1 day. This has advantages in the form of promoting gut maturation, prevention of necrotizing enterocolitis and earlier advancement to full enteral nutrition thus avoiding complications of long-term parenteral nutrition like cholestasis and liver failure.[6] Several studies support the American Academy of Pediatrics Section on Breastfeeding recommendation that human milk is the gold standard for enteral feedings in both term and preterm infants.[7,8] While use of human donor milk is increasingly common in NICUs, scientific evidence demonstrates advantages over bovine formula in most outcomes but still shows mother's own milk as a superior diet.[9,10,11,12] Researchers[12] found that infants fed predominantly human milk (greater than 75%) were at greater risk of poor growth than those fed less human milk and this risk was greatest in those fed donor human milk. From these early reports about suboptimal growth with the use of donor human milk, work has increased around optimal fortification of the milk which may still confer benefits against necrotizing enterocolitis and late onset sepsis.[8,13] All published studies have combined the use of donor human milk and available mother's own milk. Some have reported the percentage of mother's own milk and shown a better effect on growth with greater use of mother's own milk.[8,12]

With the known preference for mother's own milk, both nutritionally and immunologically, there is an emerging body of knowledge about nutrition in this milk. Sauer, Boutin and Kim[14] recently published an evaluation of nutrients in mother's own milk. Clinically, it is assumed that mother's own milk contains 20 calories per ounce. In their analysis, only 34% of the samples were within 10% of the expected level of calories per ounce with the average being 17.9 calories/ounce. Protein and fat content varied significantly as well with more samples below the expected level than at or above.[14] These samples were samples of convenience, ie independent of hindmilk vs foremilk and collected at different times of the day when it is known that nutritional content varies. Other studies have evaluated the macronutrients in preterm, term and donor milk. These were found to have such variability that they cannot be predicted.[15]

There are three types of fortification mentioned in the literature. The most common is standard fortification which means that a standard amount of fortifier is added to a given amount of human milk independent of the nutrient contents of the milk. If growth failure occurs, additional fat, protein or carbohydrates may be added. Other types of fortification are adjustable and target fortification. Adjustable fortification is based on blood urea nitrogen (BUN) levels while target fortification is based on an analysis of the human milk and macronutrients are added to provide targeted intake.[15] It is clear that standard fortification does not always meet the needs of the infants who receive it since researchers found that growth failure persisted even when infants were fed fortified human milk.[16,17] Targeted fortification

Sandra Sundquist Beauman has been a neonatal nurse for her entire career, spanning over 30 years. She is currently a research nurse coordinator at the University of New Mexico and an independent consultant with Medela LLC. She also provides neonatal consultation and continuing education though CNS Consulting.

Study	Sample Size	Type of study	Timing of early fortification	Timing of late fortification	Outcome/Comments
Taheri, P. A., Sajjadian, N., Fargi, M. A., & Shariat, M. (2017). Is early breast milk fortification more effective in preterm infants?: a clinical trial. Journal of Perinatal Medicine, 45(8), 953-957.	N=80 GA 28-34 wks; Birth weight <2 kg	Double-blind RCT	First feeding on day 1	75 mL/kg/day	Growth indices no different at 1 month of age No significant difference in feeding intolerance, NEC or sepsis
Shah, S. D., Dereddy, N., Jones, T. L., Dhanireddy, R., & Talati, A. J. (2016). Early versus Delayed Human Milk Fortification in Very Low Birth Weight Infants–A Randomized Controlled Trial. The Journal of Pediatrics, 174, 126-131.	N=100 Median GA 27.5 – 28 wks Birth weight ≤1500 gms	Prospective randomization	20 mL/kg/day	100 mL/kg/day	No difference in days to full enteral volume No difference in feeding intolerance, NEC or death Protein intake higher in early fortification group
Tillman, S., Brandon, D. H., & Silva, S. G. (2012). Evaluation of human milk fortification from the time of the first feeding: effects on infants of less than 31 weeks gestational age. Journal of Perinatology, 32(7), 525.	N=95 53 EFG 42 DFG	Retrospective pre/ post design	First feeding	50-100 mL/kg/day	Groups did not differ significantly in weight gain. Groups not significantly different in safety outcomes: feeding intolerance, days to full feeds, NEC. Noted incidence of blood stools without NEC in both groups.
Sullivan, S., Schanler, R. J., Kim, J. H., Patel, A. L., Trawöger, R., Kiechl-Kohlendorfer, U., ... & Laroia, N. (2010). An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. The Journal of Pediatrics, 156(4), 562-567.	N=207 HM100=67 HM40=71 Birth weight 500 – 1250 gms	Randomized controlled trial	40 mL/kg/day	100 mL/kg/day	These groups received pasteurized donor human milk-based fortifier added to MOM or donor milk when MOM was not available. No significant differences between these groups in duration of parenteral nutrition, length of stay, late onset sepsis or growth.
Maas, C., Wiechers, C., Bernhard, W., Poets, C. F., & Franz, A. R. (2013). Early feeding of fortified breast milk and in-hospital-growth in very premature infants: a retrospective cohort analysis. BMC Pediatrics, 13(1), 178.	N=206 Median GA 27.6 wks Median BW 915 gms	Retrospective observational		150 mL/kg/day	Evaluated growth r/t standardized feeding protocol that included fortification at 150 ml/kg/day. Trend toward lower weight gain with higher proportion of human milk intake; no significant difference in head circumference growth

is not common due to the difficulty and time involvement in analyzing the nutritional content of the milk. Work is underway to create an instrument that will have the capability to quickly analyze the nutritional content of the milk without using too much of the human milk and thus taking away from milk available to feed to the infant.[18] Since nutritional content may vary from day to day and time of day, analysis would need to be frequent.

The timing of fortification is also important. It is now well-known that early total parenteral nutrition, including micronutrients and protein is important.[1,3,6] Many very low birthweight infants may reach full enteral feeds within 1 to 2 weeks of birth. The traditional timing of adding fortification is when at least 80 to 100 ml/kg/day enteral intake is reached.[19] However, given the variability in human milk nutrients and demonstrated slow growth, it may be advantageous to add fortification earlier. Several researchers have evaluated the risks and benefits of early vs late fortification. Some studies evaluated the addition of early vs late fortification while others were retrospective and evaluated growth based on the established or standard practice of fortification. A meta-analysis of available studies has been attempted but the studies were too dissimilar to be useful as a meta-analysis[20]. The specifics of each study can be found in Table 1. Indeed, when these studies are reviewed, one can see that there is some variability in gestational age and birthweight amongst the studies. Two studies are of a retrospective observational design, one included a change in practice with comparison of infants before and after this change in practice. When comparing the three prospective randomized studies, timing of the early and late addition of fortification is similar but not exactly the same. Outcomes evaluated for these studies were not exactly the same either. Growth was evaluated as an outcome for all of the studies but at different time points. Finally, one of the retrospective reviews evaluated implementation of a standardized feeding protocol that happened to include fortification at a feeding volume of 150 mL/kg/day, a higher volume than any other study.[17] They found that there was a faster weight gain when infants were fed a higher volume of human milk but there was no significant difference in head circumference. This may be addressed by adding fortification at an earlier time point as done in the remaining studies (50 to 100 mL/kg/day). However, in spite of design differences, none of the studies found a higher rate of feeding intolerance (definitions not given in all studies), necrotizing enterocolitis or late onset sepsis (for two of the three studies). Interestingly, and perhaps speaking to the inadequacy of standard fortification practices, early vs late addition of fortifiers to the milk diet did not impact growth significantly in any of the papers reviewed. One author[23] concluded that it was not cost effective to add fortifier to the milk diet early on since there were no advantages to growth. Perhaps the use of more targeted fortification such as mentioned

earlier in this article would address these growth parameters more specifically while also keeping complications like feeding intolerance, NEC and sepsis at a low rate.

In conclusion, there is a recognized need for the addition of fortifiers to a human milk diet, whether using mother's own milk or donor human milk in the very low birth weight infant. The timing of this fortification appears to be safe at an early or late time point in infants who are at risk for feeding intolerance, late onset sepsis and necrotizing enterocolitis. However, it is also known that the use of commercially available fortifiers increases the osmolality of the feeding, which may have an effect on at least the occurrence of feeding intolerance and perhaps, NEC[15]. Therefore, a more precise evaluation of required nutrients may serve to improve growth while avoiding these risks as well as metabolic complications and obesity later in life. As with many practices in neonatal medicine, more research is needed to evaluate both the feasibility and outcomes related to targeted fortification of human milk.

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The Safety and Efficacy of Antifibrinolytic Therapy in Neonatal Cardiac Surgery

Chih-Yuan Lin[1,3], Jeffery H Shuhaiber[1], Hugo Loyola[1], Hua Liu[1], Pedro del Nido[1], James A DiNardo[2], Frank A Pigula[1]*

Abstract

Background: Neonates undergoing open-heart surgery are particularly at risk of postoperative bleeding requiring blood transfusion. Aprotinin has attained high efficacy in reducing the requirement for a blood transfusion following a cardiopulmonary bypass, but is seldom studied in the neonatal age group. The aim of this study was to compare the efficacy and adverse effects of aprotinin and tranexamic acid in neonates undergoing open-heart surgery at a single centre.

Methods: Between October 2003 and March 2008, perioperative data of 552 consecutive neonatal patients undergoing open-heart surgery in Children's Hospital Boston were reviewed. Among them, 177 did not receive antifibrinolytic therapy (Group A); 100 were treated with tranexamic acid only (Group B); and 275 patients received aprotinin with or without tranexamic acid (Group C). Except for antifibrinolytic therapy, the anaesthesiological and surgical protocols remained identical. Postoperative complications and in-hospital mortality were the primary study endpoints.

Results: Body weight and Risk Adjustment for Congenital Heart Surgery (RACHS-1) scores were statistically comparable among the three groups. No statistically significant differences were observed between the duration of hospitalization, chest tube drainage, reexploration for bleeding, and kidney function impairment. In Group C, less blood was transfused within 24 hours than in GroupB. Operative mortality was similar among the three groups.

Conclusion: No further risk and kidney injury were observed in the use of aprotinin in neonatal cardiac surgery, aprotinin demonstrated a reduced requirement for blood transfusion compared with tranexamic acid. Our data provide reasonable evidence that aprotinin and tranexamic acid are safe and efficacious as antifibrinolytic modalities in neonatal patients undergoing cardiac surgery.

1 Department of Cardiac Surgery, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts, United States of America, 2 Department of Anaesthesia, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts, United States of America, 3 Division of Cardiovascular Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

Introduction

Cardiopulmonary bypass (CPB) and cardiovascular surgery activate coagulation, inflammation, and fibrinolysis, which often exert potentially deleterious effects on patient outcome, particularly if CPB is prolonged [1,2]. The use of CPB to repair congenital cardiac defects among neonates often subjects these young patients to wide ranges of physiologic derangement because of immature tissue and organ function in the first month of life. Neonates often experience more pronounced deleterious effects than those seen in large paediatric or adult patients, partially because of the substantial disparity in CPB circuit size [3]. Although haemodilution can produce impaired haemostasis related to both qualitative and quantitative abnormalities in coagulation factors, leading to fibrinolysis [2-6], antifibrinolytics can be helpful in reducing loss and transfusion requirements [7,8].

Aprotinin (Trasylol; Bayer Pharmaceuticals Corporation, West Haven, CT, USA) is a nonspecific serine protease inhibitor that was first used as an antiinflammatory agent in the treatment of acute pancreatitis in the 1960s. The beneficial effects of aprotinin in open-heart surgery reportedly work by inhibiting kallikrein and plasmin, with decreased haemostatic activation, inhibition of fibrinolysis, and preservation of platelet function [9]. In a randomized controlled trial published in 1987, aprotinin was found to reduce blood loss and the need of transfusion in re-do open heart surgery [10]. In the following days, several randomized, prospective, placebo-controlled, carefully performed trials on aprotinin use have indicated a reduced blood transfusion requirement in adult cardiac surgery [11]. By 1993, the Food and Durg Administration (FDA) approved the use of aprotinin in coronary artery bypass grafting for reducing blood loss [12]. Additionally, aprotinin has also reportedly decreased the inflammatory response to CPB, verified by reduced levels of proinflammatory cytokines in aprotinintreated patients [13,14]. In 2008, the results of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) were published [15]. BART was a multicentre, blinded, randomized trial of 2331 high-risk cardiac surgery patients comparing aprotinin with a pair of lysine analog drugs (tranexamic acid and epsilon-aminocaproic acid) owing to concerns of an increased risk of deaths related to aprotinin. From the BART and other observation studies [16-18], aprotinin has been associated with greater risk to benefit ratio among adult populations and the safety concern of aprotinin increased [19]. Consequently, aprotonin was withdrawn and has been clinically unavailable in the United States since 2007. However, because of the biological

Table 1. Preoperative and intraoperative characteristics.

Characteristic	Group ANo antifibrinolytic(n = 184)	Group B Tranexamic acid only(n = 104)	Group C Aprotinin and both aprotinin and tranexamic acid(n = 276)	p-Value
Patients, n	177	100	275	
Male gender, n(%)	105 (59.3)	56 (56.0)	155 (58.4)	0.87
Age at surgery median (IQR) days	6 (4–12)	6 (4–12)	5 (4–8)	0.0036
Weight, mean (SD) Kg	3.06 (0.61)	3.26 (0.56)	3.10 (0.66)	0.0520
Prematurity, n	3	0	10	0.138
RACHS-1 score, median (IQR)	3 (3–6)	3 (3–4)	4 (3–6)	0.2850
Deep hypothermic circulatory arrest, median (IQR) min	32 (13–48)	31.5 (12.5–49)	17 (9–27)	0.0001
CPB time, median (IQR) min	128 (100–158)	142 (116–166)	138 (120–163)	0.0027
Aortic cross-clamp time, median (IQR) min	65 (48–94)	78 (54–99)	71 (57–86)	0.0971

CPB: Cardiopulmonary bypass; IQR: Interquartile range

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and procedural differences between surgery for congenital and acquired cardiac disease, the paediatric experience remains relevant. Aprotinin reportedly decreased the use of blood products and operative time in congenital heart surgery [20]. Additional benefits in congenital heart surgery include improved pulmonary function, particularly in patients undergoing surgical palliation for single ventricle anatomy [21]. However, data regarding the safety and efficacy of aprotinin in neonatal patients are limited.

Tranexamic acid, a lysine analogue, is widely used to reduce blood loss; however, the bloodsparing effect is often considered to be inferior to that of aprotinin [22]. Additionally, the safety of aprotinin has been more extensively studied than that of tranexamic acid. A previous study on paediatric cardiac surgery demonstrated increased susceptibility to seizure after tranexamic acid treatment [23].

The purpose of this study was to determine the safety and efficacy of aprotinin and tranexamic acid in neonatal patients undergoing CPB.

Patients and Methods

The Institutional Review Board of Children's Hospital Boston, Boston, Massachusetts, United States approved this retrospective, nonrandomised cohort study, and the approval included a waiver of informed consent. Data were collected from a retrospective review of prospectively collected data. From October 2003 to March 2008, 552 neonatal patients undergoing 565 cardiac surgical procedures were enrolled in this study. Neonates were divided into three groups: Group A: no antifibrinolytic group (n = 177); Group B: tranexamic acid group (n = 100); and Group C: aprotinin or both aprotinin and tranexamic acid (n = 275). Demographic data were recorded, including gender, weight and age at surgery, and prematurity. Intraoperative information included deep hypothermic circulatory arrest, aortic cross-clamp time, CPB time, use of Risk Adjustment for Congenital Heart Surgery (RACHS-1) scores to assess the complexity of the procedures performed, and duration of hospitalization in days (ICU and ward). Renal function was assessed by measuring pre- and postoperative serum creatinine (Cr). Requirements for extracorporeal membrane oxygenation (ECMO), reoperation for bleeding, blood transfusion within 24 hours and in-hospital death were recorded and analysed. The protocol consisted of administering a bolus of 100 mg/kg of tranexamic acid to the patient after induction of anaesthesia, followed by an infusion of 10 mg/kg/h until the end of the operation, and 100 mg/kg was added to prime the CPB equipment. In the aprotinin group, a bolus of 30,000 KIU/kg of aprotinin was administered to patients after the induction of anaesthesia, followed by an infusion of 10,000 KIU/kg/h until the end of the operation, and 30,000 KIU/kg was also added to the CPB prime.

In all other aspects, the surgical and anaesthesiological protocols remained unchanged. The requirement of a transfusion was considered when the haemoglobin level was < 14 g/dL in cyanotic patients, and < 10 g/dL in noncyanotic patients, or if a patient exhibited clinical signs indicating the requirement for a higher oxygen carrying capacity. Reexploration for mediastinal bleeding was based on clinical signs, including excessive chest-tube output. We did not have a set criteria for exploration regarding chest-tube blood output.

Chart reviews consisted of preoperative, intraoperative and postoperative data collection. Preoperative data included patient demographics: age, gender, weight, prematurity (defined as < 36 wk gestation), and presence of a major noncardiac structural anomaly. Cardiac diagnosis and surgical procedure were recorded. All neonates were assigned a RACHS-1 score [24]. Neonates with a combination of cardiac surgical procedures were assigned the RACHS-1 score of the highest risk procedure and the combination of procedures was treated as an independent variable. Preoperative baseline creatinine (Cr) was also recorded. Intraoperative data included the use of aprotinin or tranexamic acid, CPB time, aortic cross-clamp time, and deep hypothermic circulatory arrest time. Postoperative data were used to assess specific outcomes. Postoperative Cr levels were recorded at 24 hours. Biochemical acute kidney failure was defined as an increase in serum creatinine levels to double or more than the preoperative level. We also recorded the time to tracheal extubation and the duration of the intensive care unit stay, the duration of chest-tube drainage, the use of ECMO and mortality before hospital discharge.

The data included in our manuscript represents an entirely clinical data base obtained from the department of surgery databases, without the reliance of administrative databases, and included discrete information not available in previous publications.

Table 2. Postoperative characteristics and morbidity/mortality.

Characteristic	Group ANo antifibrinolytic(n = 184)	Group B Tranexamic acid only(n = 104)	Group C Aprotinin and both aprotinin and tranexamic acid(n = 276)	p-Value
Total blood transfusion within 24 h, mean (STD) ml	39.8±47.0	47.7±51.0	32.0±40.0	0.011
ICU LOS, median (IQR) days	11 (7–19)	13 (9–20)	11 (9–18)	0.6395
Hospital LOS (days), median (range)	16 (12–28)	19(12–34)	16(16–26)	0.2575
Chest tube drainage (days), median (range)	4 (1–63)	4(1–63)	4(1–44)	0.5324
Acute kidney injury, n (%)	16 (8.7%)	10 (9.6%)	31 (11.2%)	0.655
Reopen chest, n (%)	9 (4.9%)	7 (6.7%)	10 (3.6%)	0.4270
ECMO support, n (%)	2 (1.1%)	0 (0%)	7 (2.5)	0.1690
Hospital mortality, n (%)	29 (15.8%)	8 (7.7%)	28 (10.1%)	0.072

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Data analysis

The three groups of patients were compared using the preoperative, intraoperative, postoperative complications results. Collected data were summarized descriptively and compared between each two of the three groups. The Shapiro-Wilk test was used to assess the normality distribution assumption. Data were described using means and standard deviation, and comparisons were performed using an analysis of variance and a posthoc test if appropriate. Nonnormally distributed data were compared using the Kruskal-Wallis equality-of-populations rank test and a posthoc test for multiple comparisons, as described in Siegel and Castellan [25]. Categorical data were analysed using Fisher's exact test. Outcome data was presented using Kaplan-Meier survival curves with a comparison between types of antifibrinolytic therapy by using a log-rank test. A multivariable logistic regression model was used to evaluate the association between antifibrinolytic therapy and death adjusted for a previously described set of covariates. The goodness of fit was evaluated using the Hosmer-Lemeshow chi-square. All statistical analysis was performed using the STATA/IC 10.1 (STATA Corp, College Station, TX, USA) software and statistical significance was assessed at the .05 level.

Results

Male patients predominated in all three groups. The demographic and intraoperative data are listed in Table 1. Weight and the percentage of prematurity were comparable across the three groups and no significant difference was observed in the RACHS scores. The K-W test indicated that the median deep hypothermic circulatory arrest (DHCA) time in Group C was significantly lower than that in Groups A and B (P = .00010). The median CPB time differed significantly among the groups (P = .00275): between the control and tranexamic acid groups (P = .005419), and the control and aprotinin groups (P = .00063). The total blood transfusion within 24 hours after surgery (excluding reoperation for bleeding) varied among all three groups (P = .0011) (Table 2). Chi-square analysis revealed no statistical differences in the incidence of acute kidney injury among the three groups (P = .655), and the odds ratio for death was similar (Table 3). The estimated survival functions for death and being reoperationfree between the antifibrinolytic therapy groups were also similar (P = .2841 and .2897) (Fig 1).

Discussion

Congenital heart disease (CHD) has long been associated with coagulation abnormalities [26], including platelet abnormalities [27] and fibrinolysis [28]. To overcome these adverse effects, attempts have been made to modify these effects with both lysine analogue, antifibrinolytics, and aprotinin. Aprotinin is a broad-spectrum serine protease inhibitor that protects platelets by preventing their activation on CPB [29]. Previous reports focusing on aprotinin in patients with various congenital heart diseases who underwent cardiac operation have consistently revealed a decrease in postoperative blood loss [30]. However, there is no definite conclusion regarding the efficacy of

Table 3. Adjusted effect of antifibrinolytic therapy on odds ratio for death.

Risk factor	OR	P value	[95%CI for OR]
None	1.00*		
Transexamic Ac	0.27	0.092	0.06–1.23
Aprotinin	0.31	0.357	0.02–3.62
Gender(female ref)	1.27	0.720	0.33–4.79
Age at surgery	1.05	0.240	0.96–1.16
Days in Hospital	0.77	0.001	0.67–0.89
Days in CICU	1.35	<0.001	1.16–1.57
Cross-clamp Ao	0.96	0.039	0.93–0.99
CPB temp	1.21	0.012	1.04–1.41
CPB time	1.02	0.020	1.00–1.05
RACHS-1 level 1–2	1.00*		
RACHS-1 level 3	1.28	0.816	0.15–10.4
RACHS-1 level 4	0.73	0.831	0.04–12.6
RACHS-1 level 6	7.31	0.084	0.76–69.9
Creatinine pre-post	3.74	0.385	0.19–73.9
Transfusion < 24h	0.98	0.200	0.97–1.00

*Reference group of the following OR.

Hosmer-Lemeshow chi^2 (8) = 3.73Prob > chi^2 = 0.8805

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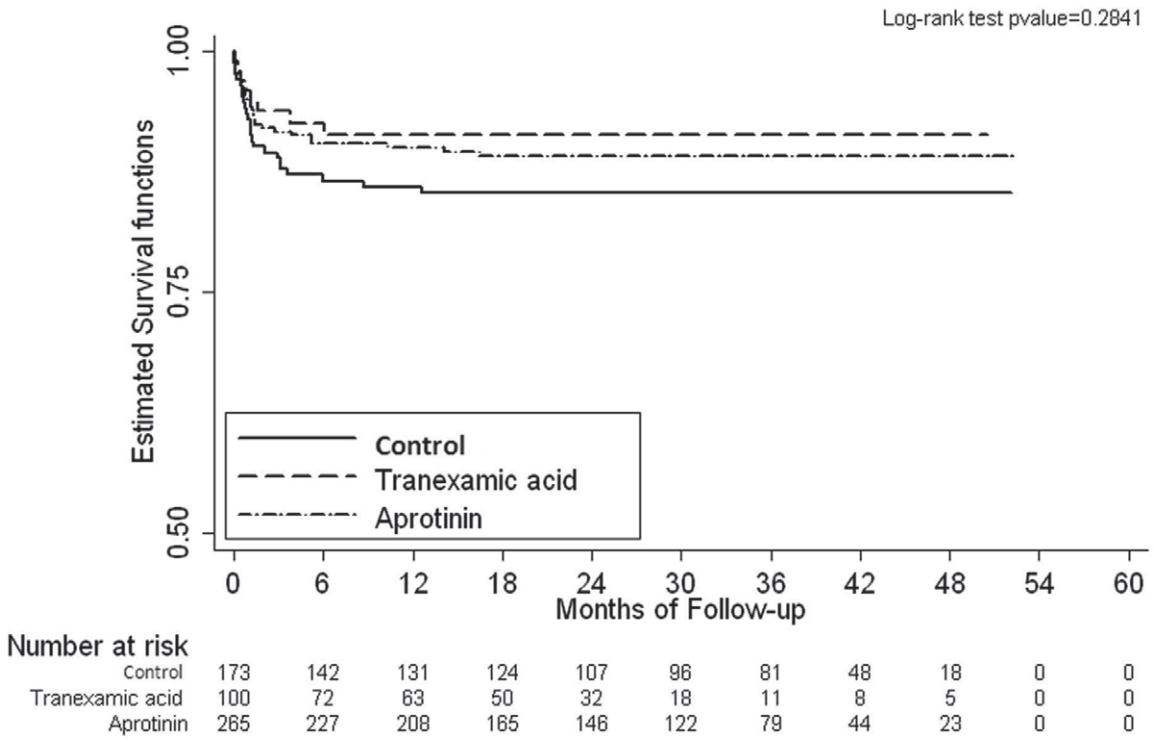

Fig 1. Kaplan-Mier survival curve.

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antifibrinolytic therapy in neonatal patients undergoing cardiac operation. Because analyses of the effects on paediatric cardiac operations have been hampered by various confounding factors, undefined transfusion triggers, various dosing protocols and institutional preference, information regarding the efficacy of aprotinin in neonates remains limited and occasionally conflicting [31,32]. In our study, using specified transfusion triggers, blood transfusion within 24 hours was significantly less common among those who received aprotinin (32.0 ± 40.0 mL) compared with the other two groups (P = .011) (39.8 ± 47.0 mL in Group A and 47.7 ± 51.0 mL in Group B).

Numerous studies have reported findings demonstrating increased mortality and renal failure in cardiac surgery patients [15,19]. Aprotinin was suspended at the FDAs request and removed from the market in 2007. Some publications suggested that the withdrawal of aprotinin has been detrimental to patients undergoing cardiac surgery due to increased adverse outcomes and use of blood products [33-35], but others found a relatively minimal influence in clinical practice [36]. However, no randomized multicentre study has demonstrated any robust adverse events in a paediatric group, particularly among neonates undergoing cardiac surgery [37-40]. Because of the concern that children undergoing congenital heart operations are more prone to bleeding than adults are [41], tranexamic acid is considered the second most suitable alternative to antifibrinolytic therapy. Schindler et al. reported that aprotinin can be replaced with tranexamic acid because of the equal blood sparing effects, but they also indicated that the evidence accumulated at present remains insufficient to clearly estimate the benefits and risks associated with the use of tranexamic acid in congenital heart surgery [42]. In addition to its antifibrinolytic property, aprotinin might exert an attenuating effect on the inflammatory response to CPB. This effect can be particularly beneficial to neonates who often exhibit a marked inflammatory reaction and capillary leak syndrome during CPB [43]. In a study conducted by Hsia et al. with the aim of exploring the effects of aprotinin or tranexamic acid on proteolytic and cytokine profiles in infants after cardiac surgery, the expression of proinflammatory cytokines and associated matrix metaloproteinases was reduced in an aprotinin group compared with a tranexamic acid group [44]. Two currently published reports also demonstrated that aprotinin attenuates postoperative expression of pro-inflammatory factors and inflammatory gene expression whereas tranexamic acid does not [45,46]. Theses results were consistent with prior studies of cardiac surgery patients [13,14,47-49].Because of the retrospective form of the present study, we lacked data for specific biomarkers of inflammation. However, from the clinical parameters of postoperative recovery outocmes such as chest-tube drainage, duration of stay in the intensive care unit, duration of hospitalization and in-hospital mortality indicated no statistically significant differences among the three groups, suggesting that the potential antiinflammatory effect of aprotinin was clinically negligible.

One of the major side effects of aprotinin therapy in neonatal patients is renal injury. Renal injury has been extensively studied in aprotinin, because it is appropriated by the brush border of the renal tubules after filtration that has caused concerns regarding the potential for renal toxicity [50]. The possible effects of aprotinin on renal function have been both experimentally and clinically described (e.g. decreased kinin synthesis, diminished renal blood flow and glomerular filtration rate, and reversible tubular overload) [51]. In adult cardiac surgery patients, Wagener et al. observed that the use of aprotinin was associated with both an increased risk of acute renal injury and an increase of urinary neutrophil gelatinase-associated lipocalin, which is a sensitive marker for renal injury [52]. The adverse effects of aprotinin varying with the age of patients remains unsubstantiated. In a

cohort study presented by Backer et al. that examined aprotinin safety in congenital heart operations, no association was observed between aprotinin use and acute renal failure, dialysis requirement, neurologic complication or mortality [53]. Another large-scale study involving 35 children's hospitals also concluded that the use of aprotinin in congenital heart operations is safe without increased mortality or dialysis [54]. However, in a recently published study by Leyvi et al. [55], higher odds of acute renal injury were observed, compared with ε-aminocaproic acid, suggesting that the established concerns for adults with adverse kidney effects treated using aprotinin are also applicable to paediatric patients. In our study, postoperative creatinine levels after 24 hours were significantly higher than preoperative creatinine levels in all three groups. However, no evidence was found for the progression to renal failure or dialysis following administration of either aprotinin or tranexamic acid.

From the accumulated evidence, aprotinin effectively reduces blood loss and the need of blood transfusion associated with heart surgery and currently in Canada and the EU, Health Canada, and the EMA believe the benefits of aprotinin outweight its risks in isolated CABG surgery [56,57]. Wilder et al also demonstrated that aprotinin had significantly lower intraoperative transfusion requirements, surgical reexploration, renal injury and shorter surgical times in neonate heart operations [58]. These studies clearly illustrate the need for further large-scale randomized, well-designed with adequately grouped clinical trial to investigate the safety and efficacy of aprotinin in cardiac surgery.

The present report demonstrates single center data analysis that is unique and important with clinical significance. The limitations of this study include retrospective design, omitted variable bias in the database, lack of strictly defined transfusion triggers, lack of some direct measures of inflammation markers, possibility of type 2 error which is related to the power. Additionally, some factors including median cardiopulmonary bypass time and deep hypothermic circulatory arrest time may influence coagulation and fibrinolysis and thus confound the data interpretation.

Conclusions

In conclusion, our study demonstrated that neonates who received aprotinin benefited from the blood-sparing effects without increasing the risk of acute renal injury and other adverse clinical outcomes. The data provide reasonable evidence that aprotinin and tranexamic acid are safe and efficacious as antifibrinolytic modalities in neonatal patients undergoing cardiac surgery.

Author Contributions

Conceived and designed the experiments: CYL FAP. Performed the experiments: CYL JHS. Analyzed the data: H. Loyola H. Liu. Wrote the paper: CYL JHS FAP. Data analyses and critical revision: PN JAD.

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1. American Academy of Pediatrics. Breastfeeding and the Use of Human Milk. Section on Breastfeeding. [originally published online February 27, 2012]. Pediatrics. DOI: 10.1542/peds.2011-3552

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