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neonatal INTENSIVE CARE

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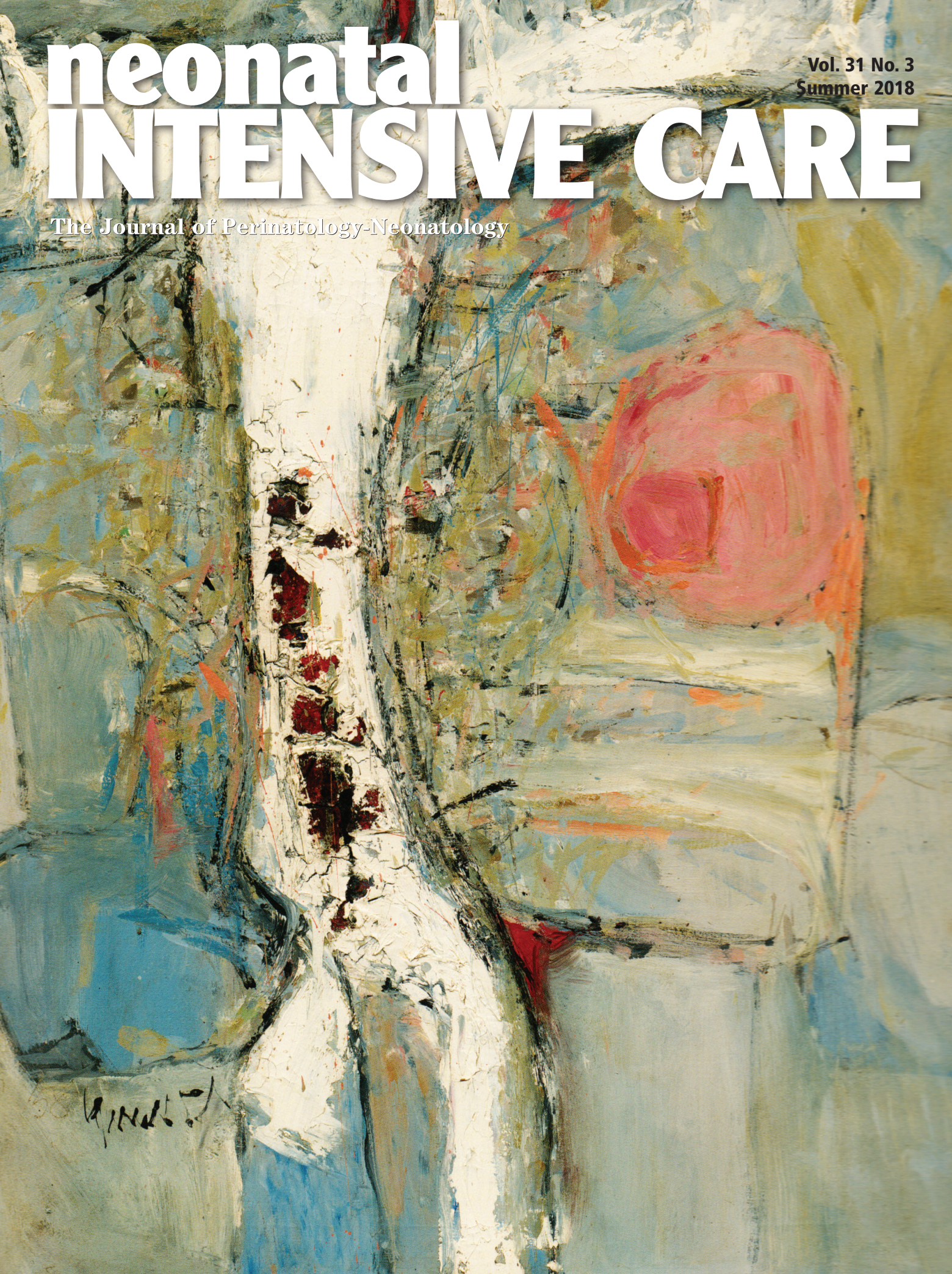

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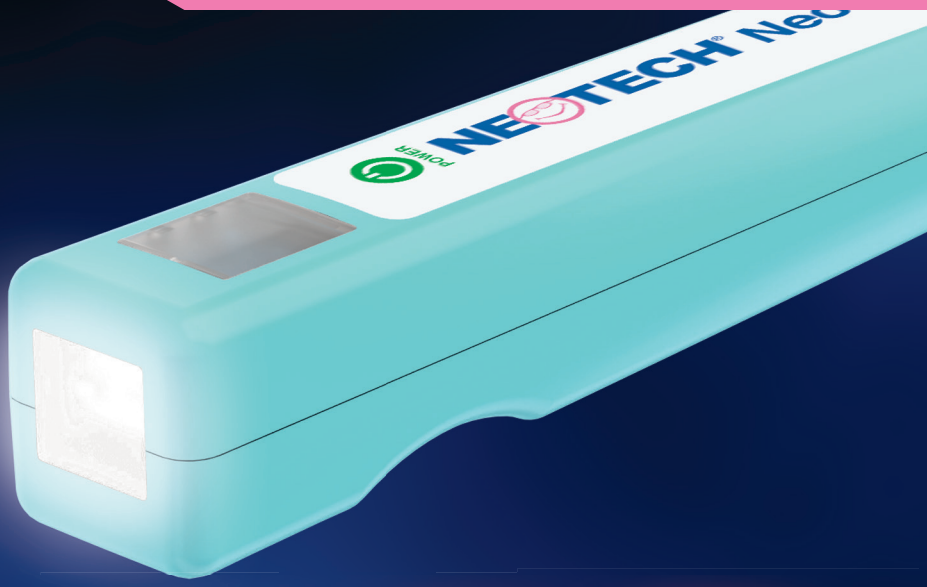

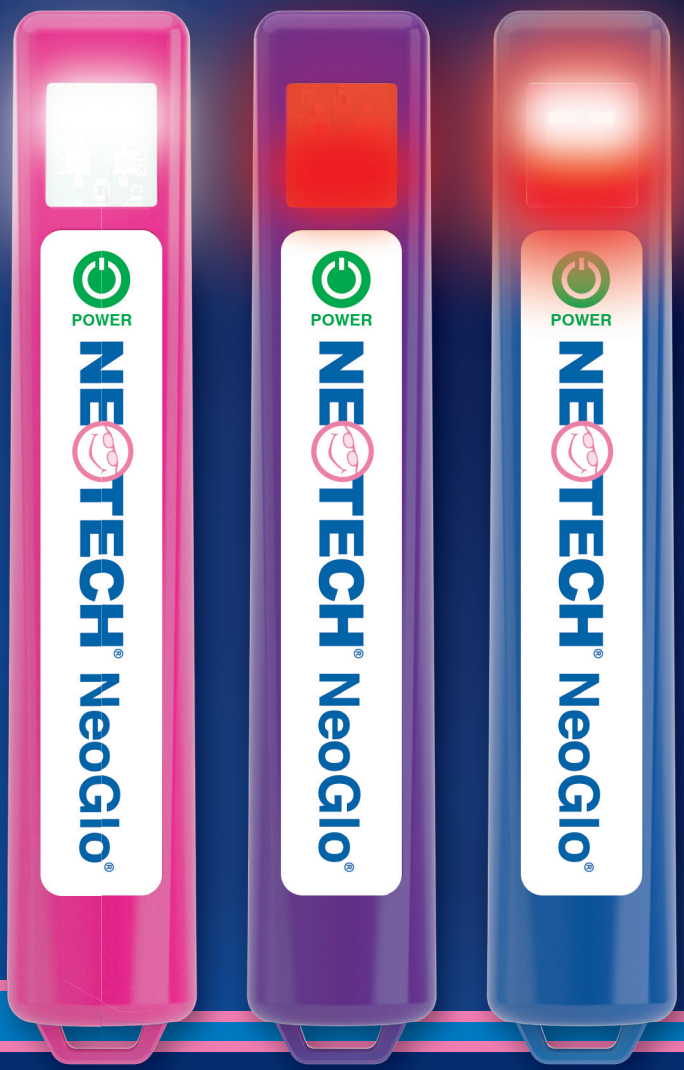

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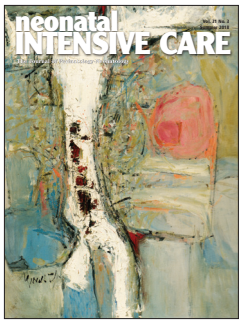

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News

☐ Summer 2018

Baby Steps to Home Updated

The National Association of Neonatal Nurses (NANN) released a 2018 update to Baby Steps to Home, a series of downloadable online handouts created to standardize the discharge pathway neonatal intensive care unit (NICU) nurses use to educate parents about their baby's condition and prepare them to take their baby home. This free discharge planning resource is the only of its kind, providing English and Spanish-speaking families with the information needed to navigate their NICU experience and reduce apprehension as they prepare for life beyond the NICU. The update offers 12 modules comprised of 109 handouts that cover topics that range from breastfeeding to car seat safety, revisions to 85% of the original handouts, and 19 new nurse and parent handouts. New topics include: Newborn screening and critical congenital heart defects screening; postpartum depression; 6 new diagnoses, such as neonatal abstinence syndrome and microcephaly; 6 new medications, such as methadone and keppra; new section on procedures, including circumcision and lumbar puncture; updated and expanded resources section.The 2018 update of Baby Steps to Home was led by Rebecca South, BSN RNC-NIC and Suzanne Staebler, DNP APRN NNP-BC FAANP FAAN. "Going home with a neonate after days or months in the NICU is a stressful time for family members," South says. "It's an honor to contribute to an evidence-based resource that impacts so many lives—not just our patients, but their caregivers as well." Baby Steps to Home handouts are editable so nurses can add patient-specific notes. NANN encourages hospital systems, healthcare institutions, and neonatal nurses to share Baby Steps to Home with families of patients in their care.

RSV Trial Reaches Milestone

Novavax, Inc. announced it has reached a significant milestone in the Prepare Phase 3 clinical trial of its respiratory syncytial virus F protein recombinant nanoparticle vaccine (RSV F Vaccine) for infants via maternal immunization. Enrollment has reached approximately 4,600 participants — at least 3,000 have received the RSV F Vaccine. Prepare is a global, pivotal Phase 3 clinical trial of the RSV F Vaccine, in healthy, third-trimester pregnant women, which initiated in December 2015. The primary objective of the Prepare trial is to determine the efficacy of maternal immunization with the RSV F Vaccine against medically significant RSV-positive lower respiratory tract infection (LRTI) in infants through a minimum of the first 90 days of life and up through the first six months of life. "Reaching this enrollment target for the Prepare trial is a significant milestone in the advancement of our RSV F Vaccine franchise," said Stanley C. Erck, President and CEO of Novavax, Inc. "RSV remains an urgent global unmet medical need due to the mortality and morbidity associated with RSV disease in infants and the absence of a vaccine to prevent such disease. We look forward to completing the interim analysis of the Prepare trial as this is the next step on the path to filing marketing applications in the U.S. and Europe for the first-ever RSV vaccine." Novavax will initiate a prespecified interim efficacy analysis for the Prepare trial after the last infant born to the approximately 4,600 women enrolled in the trial has been followed for six months. Novavax expects to report on the interim data in the first quarter of 2019. Assuming successful interim analysis results, the trial would be concluded without further enrollment and Novavax would file a biologics license application (BLA) with the U.S. Food and Drug Administration (FDA) and a marketing authorization application (MAA) with the European Medicines Agency (EMA) by the first quarter of 2020. With Fast Track designation previously granted by the FDA, the Novavax RSV F Vaccine could potentially be eligible for priority review of the BLA, which reduces the standard FDA review by four months. In December 2017, Novavax conducted an informational analysis

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related to the prevention of medically significant RSV-positive LRTI in a subset of 1,300 infants from the Prepare trial. This analysis allows Novavax to conclude that the vaccine's potential observed efficacy in this subset group is in the range of 45% and 100%. The Prepare trial is supported by a grant of up to $89.1 million from the Bill & Melinda Gates Fund. This grant supports development activities, product licensing efforts and World Health Organization prequalification of the RSV F Vaccine. RSV is the most common cause of lower respiratory tract infections and the leading viral cause of severe lower respiratory tract disease in infants and young children worldwide, with estimated annual infection and mortality rates of 64 million and 160,000, respectively. In the US, RSV is the leading cause of hospitalization of infants. Despite the induction of post-infection immunity, repeat infection and lifelong susceptibility to RSV is common. Currently, there is no approved RSV vaccine available.

Device Promises Comfort to Secure Nasal Prongs

Baby Head Band and Circuit Bumpers from Respiralogics are intended to secure the nasal interface during oxygen therapy, nCPAP or NIV therapy. The Baby Head Band is made of breathable, non-latex foam that absorbs and wicks away moisture leaving the scalp and skin dry. The soft material of the head band allows it to conform to even the tiniest of heads while maintaining the circuit position. The soft outer covering of the Baby Head Band allows for easy head movement while holding the nasal prongs and circuit stable. The new reversible Circuit Bumpers secure and stabilize the position of the inspiratory and expiratory limbs to the soft outer side of Head Band while providing optimal positioning for infants of all shapes and sizes. The Head Band and Circuit Bumpers work in conjunction with neonatal/pediatric ventilator circuits and oxygen therapy tubing. Benefits include: fashioned to provide a comfortable fit for all infants; sized by head circumference for easy and quick application; Reversible Velcro Bumpers allow for secure attachment and minimize pressure points; allows caregivers to freely move infant without interrupting therapy; opened at the crown for fontanel checks and to accommodate scalp vein IVs; available in four sizes for very low birth weight up to 10 kg infants; Single Patient Use, non-latex material. Designed for use in NICU, PICU, surgery and clinics for stable positioning of nasal interface.

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Device to Help Neonates With Dosing Difficulties

NeoMed announced the launch of the new NeoConnect DoseMate DL (Directional Long) — an innovative and ergonomic solution for gentle, direct oral medication administration with an ENFit syringe. This new, patent-pending pharmacy accessory is ideal for dosing oral medications directly to the patient's cheek or back of the mouth. The soft, pliable cannula features a smooth, rounded tip, which is optimal when administering oral medication into a patient's mouth. Not only does the inventive design mitigate concerns over placing threaded syringe tips into a patient's mouth, it also provides patient comfort during direct oral administration without introducing a choking hazard. Dosing accuracy is a key component of the DoseMate DL design. Similar to its DoseMate counterpart, the DoseMate DL minimizes priming volume and helps prevent fluid accumulation in the syringe's moat, which complies with the Global Enteral Device Supplier Association's (GEDSA) August 2016 position statement. Ben Davis, Vice President of Engineering and Product Development, said, "Not only does the DoseMate DL satisfy a clinical need not previously addressed with other ENFit systems, but it also represents an improvement in care compared to what was available with legacy systems." "The addition of the DoseMate DL to our ENFit accessories portfolio contributes to our mission of supporting the specialized feeding and medication dosing needs of the low birth weight, neonatal, and pediatric patient populations. We are very pleased to release a new product focused on patient comfort, while following clinical best practices. The DoseMate DL is yet another effective accessory that will help minimize protocol changes for clinicians as the global transition to ENFit continues," stated NeoMed President, Aaron Ingram. For ordering information, contact your local sales representative, visit www.neomedinc.com, or call 888-876-2225.

Gestational Diabetes Tied to Hypoglycemia Even in Low-Risk Neonates

Babies born to mothers with gestational diabetes are at high risk of hypoglycemia and should be screened for the condition within the first 12 hours of life, researchers say. "Some guidelines recommend screening all neonates born after a pregnancy complicated by gestational diabetes mellitus, while others recommend screening only those with abnormal birth weight or insulin-treated gestational diabetes mellitus," said Dr Leon de Wit from University Medical Center at Utrecht University in the Netherlands. "In this study, we show that low-risk neonates are as equally prone to hypoglycemia as high-risk neonates," he said. Dr de Wit and colleagues studied 506 term neonates born to mothers with gestational diabetes from 2013 through 2015. Gestational diabetes was controlled by diet (77.5%) or with insulin (22.5%). Neonatal blood glucose levels were measured at 1, 3, 6, 12 and 24 hours after birth. Neonatal hypoglycemia was defined as severe if the blood glucose level was less than 36 mg/dL, and as mild if it was between 36 mg/dL and 47 mg/

dL. Whether the mother's disease was controlled by diet or insulin, rates of mild hypoglycemia were similar (33% vs. 35%, respectively; P=0.66), as were rates of severe hypoglycemia (20% vs. 21%, P=0.79). Overall, 17.2% of newborns were above the 90th percentile for birth weight. Although these infants had the highest risk for hypoglycemia, 78.6% of neonates with hypoglycemia had a birth weight <90th percentile. More than 95% of all hypoglycemia occurred within 12 hours after birth. "Considering the potential severity of the detrimental effects of neonatal hypoglycemia in light of the relatively simple screening procedure and treatment, we propose routine blood glucose screening for neonatal hypoglycemia within the first 12 hours of life in all neonates after gestational diabetes mellitus, regardless of maternal insulin use or neonatal birth weight," said Dr de Wit.

Telemedicine Useful in Detecting Retinopathy of Prematurity

Telemedicine has similar accuracy to ophthalmoscopy in detecting clinically significant retinopathy of prematurity (ROP), researchers say. "ROP is a leading cause of childhood blindness in the U.S. and throughout the world, yet it is often difficult to find qualified ophthalmologists to care for infants with this disease," Dr Michael Chiang of Oregon Health and Science University (OHSU) in Portland said. "Telemedicine has potential to improve the quality, accessibility, and cost of ROP care," he said. Many previous studies have looked at whether telemedicine is useful for diagnosing ROP, he noted. "However, to my knowledge, all of those previous studies have assessed the accuracy of telemedicine by assuming that a traditional in-person eye examination gives the 'correct' answer." Dr Chiang and colleagues examined the eyes of 281 premature infants (mean gestational age, 27 weeks; 54% boys) at seven neonatal intensive care units in the US and Mexico. Each examination consisted of one eye undergoing binocular indirect ophthalmoscopy by an experienced clinician followed by remote image review of wide-angle fundus photographs by three telemedicine graders. A total of 1,553 eye examinations were classified using both ophthalmoscopy and telemedicine. No difference was found in overall accuracy between the two for the detection of clinically significant ROP; however, on average, ophthalmoscopy had slightly higher accuracy for the diagnosis of zone III and stage 3 ROP. Specifically, ophthalmoscopy and telemedicine each had similar sensitivity for zone I disease (78% each); plus disease (74% vs. 79%, respectively); and type 2 ROP (stage 3, zone I, or plus disease: 86% vs. 79%). Ophthalmoscopy was slightly more sensitive in identifying stage 3 disease (85% vs. 73%).

Neonatal Caffeine Therapy for Apnea of Prematurity Has Long-term Benefits

Neonatal caffeine therapy for apnea of prematurity is associated with improved visuomotor, visuoperceptual and visuospatial abilities in adolescence, according to follow-up data from the Caffeine for Apnea of Prematurity (CAP) trial. More than half of preterm babies suffer apnea of prematurity and are treated with caffeine therapy, which has been demonstrated to boost survival rates without neurodevelopmental disability and to reduce the rate of cerebral palsy and cognitive impairment in toddlers. "Previous research has demonstrated that neonatal caffeine therapy is effective in the treatment of apnea of prematurity and has long-term benefits for gross-motor skills. This is the first study to investigate long-term neurobehavioral outcomes as a result of neonatal caffeine therapy," Dr Peter Anderson from Monash University in Melbourne, Australia, said. "We

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found that caffeine therapy has no adverse effects on long-term neurobehavioral outcomes, and may have selective benefits for visuomotor, visuoperceptual, and visuospatial abilities," he said. Dr Anderson and colleagues investigated the effects of neonatal caffeine therapy on neurobehavioral outcomes at age 11 in 870 children born weighing 500 g to 1250 g with apnea of prematurity who participated in the double-blind randomized placebo-controlled CAP trial. In a paper online, they report that neurobehavioral outcomes at age 11 were "generally similar" for children who received caffeine and those who received placebo as part of the trial. However, the caffeine group performed better on tests of fine motor coordination (mean difference, 2.9; P=0.01), visuomotor integration (mean difference, 1.8; P<0.05), visual perception (mean difference, 2.0; P=0.02), and visuospatial organization (mean difference, 1.2; P=0.003), the researchers report. "General intelligence, attention, and behavior were not adversely affected by caffeine, which highlights the long-term safety of caffeine therapy for apnea of prematurity in very low birth weight neonates," they write. "Thus, we found specific benefits of neonatal caffeine therapy in the visuomotor domain and no evidence of harmful effects on neurobehavioral outcomes up to 11 years of age." The researchers also note that the benefits of caffeine therapy on fine motor coordination and visuomotor integration are in line with prior data from the CAP trial showing reduced risk for motor impairment at 18 months, 5 years and 11 years, improved fine motor coordination at 5 years and lower rates of developmental coordination disorder (DCD) at 5 years.

Transilluminator Introduced

Neotech Products announced the release of the NeoGlo 2.0 and the NeoGlo Sleeve. After the successful launch of the NeoGlo Transilluminator in 2017, Neotech received product input from clinicians and end users on how to make the product even better. They heard their feedback and from it came the NeoGlo 2.0 and the NeoGlo Sleeve. The NeoGlo 2.0 features a new light setting, upward facing white and red lights on at the same time. This provides the user with a fourth option to aid in the examination of soft tissue. The NeoGlo 2.0 also features three new colors: Bright Pink, Aqua, and Violet, to compliment the existing colors of Rose, Blue, Silver, Black, and White. "Neotech takes the time to listen to feedback from clinicians. This feedback births changes throughout all of our product lines. Without this valuable feedback we would not be able to advance our technology for the benefit of the user," said Sara Dimmitt, Manager of Business Development. Along with the new NeoGlo, Neotech is releasing the NeoGlo Sleeve. The NeoGlo sleeve is a disposable, protective cover designed to help keep the NeoGlo clean and protect against bodily fluids. The NeoGlo Sleeve is durable, disposable, and features a self-sealing flap. "With infection control being a top priority in the hospital, we wanted to create something that was a quick, easy solution to add a layer of protection for the NeoGlo," Dimmitt said.

Individualized Guidance Needed on Sex in High-Risk Pregnancies

Recommendations on sexual activity restriction during high-risk pregnancies should be individualized based on a patient's obstetric history and comorbidities, as well as the fears and emotional needs of the patient and her partner, according to a new evidence review. About one in 10 pregnancies among US women end in preterm birth (PTB), Dr Sally MacPhedran of Case Western Reserve University School of Medicine in Cleveland notes in her report, online March 20 in Sexual Medicine Reviews. Women with complicated pregnancies that increase PTB risk are typically told to restrict or abstain from sexual activity, she adds. "However, the restriction is most commonly 'pelvic rest,' which is not defined in terms of what specific sexual acts are to be avoided or are permissible," Dr MacPhedran states. "In particular, pelvic rest does not address whether orgasm needs to be limited in pregnancy. This vague restriction on all sexual activity leaves patients confused and disappointed." Sexual activity could contribute to preterm labor through three mechanisms, according to the author: endogenous prostaglandin release and prostaglandins in semen causing cervical ripening; release of oxytocin causing uterine contractions; and direct contact with the cervix or lower uterus causing trauma. Dr MacPhedran offers the following recommendations on restriction of sexual activity during pregnancy for women with different types of pregnancy complications, based on her review of the evidence: Past PTB, without short cervix or other risk factors: No restriction. Short cervix with bleeding, increased contraction frequency or intensity, or further shortening of cervical length: Avoid any sexual activity with or without orgasm that causes perceived or painful contractions. Prophylactic cerclage placement: Avoid penetrative sex for at least two weeks. Afterwards, non-penetrative activity "need not be discouraged," and modified penetrative activity can be permitted after a discussion with the patient and her partner. Premature rupture of membranes: Avoid oral sex and vaginal penetration due to the risk of infection. Placenta previa: Avoid penetrative sexual acts or sexual activity leading to perceived or painful contractions. Stable, chronic placental abruption: avoid sexual activity that results in bleeding, but sexual activity need not be limited unless it results in "frequent, intense, or painful uterine contractions." Uncomplicated multiple pregnancy: No restriction.

Adverse Pregnancy Outcomes More Likely With Hypertension History

Women with a history of chronic hypertension are three to five times more likely to have a poor pregnancy outcome than women without past hypertension, even if their blood pressure is normal before 20 weeks gestation, found a retrospective cohort study. The highest risk occurred among women taking antihypertensive medication, but even women not taking medication (but with a history of chronic hypertension) had triple the risk for stillbirth, neonatal death, respiratory support, low Apgar score, seizures, or cord blood acidemia, although the findings were limited by a nongeneralizable population and some underpowered measures. "Although the incidence of stillbirth increased across exposure groups 1.3% [control] vs 1.9% [hypertension history but no medication] vs 2.9% [hypertension with medication] this trend was not statistically significant (P=.06) nor was it significant in adjusted analyses," write Mallory Youngstrom, MD, from the Department of Gynecology and Obstetrics at Emory University in Atlanta, Georgia, and colleagues. "The incidence of neonatal death (measured only in those with liveborn neonates) increased across the exposure groups (P=.03), but in adjusted analyses, the increased odds was only significant for women receiving [antihypertensive] medication." Compared with women without a history of hypertension, women taking antihypertensive medication also had significantly increased risks for preeclampsia, severe preeclampsia, preterm birth, and an infant small for gestational age after adjustments, but women with a history of hypertension not taking medications did not. The researchers first identified all singleton births from 2000 to 2014 at the University of Alabama at Birmingham in which the mother had a history of chronic hypertension. They then compared outcomes among

830 women with a history of chronic hypertension but blood pressure under 140/99 mm Hg before 20 weeks gestation with those of 476 women without chronic hypertension. Mothers with higher blood pressures were excluded, as were pregnancies with fetal anomalies and mothers with any major medical problems besides hypertension and diabetes. Among the 830 women with a history of chronic hypertension, 74% (618 women) were taking hypertension medication; the other 26% (212 women) were not. Renal disease and diabetes were more prevalent among these women, who also tended to be older and have more obesity than the control group. The primary outcomes of stillbirth, neonatal death, respiratory support at birth, seizures, an Apgar score of 3 or less, and arterial cord blood with a pH below 7 were collapsed into a composite outcome. In addition, preeclampsia, infants small for gestational age, and preterm birth before 37 and 34 weeks gestation were recorded as secondary outcomes.

Low Birthweight Tied to Lower Visual Acuity Decades Later

Individuals with low birthweight (BW) are more likely to have lower visual acuity and a higher myopic refractive error in adulthood, according to a new study from Germany. The study was part of a single-center, population-based observational cohort study that included 15,010 participants ages 35 to 74. Of those, 8,369 individuals were able to report their birthweights and were then divided into three groups based on low (<2,500 g), normal (2,500-4,000 g) and high birth weights (>4,000 g). The low-BW group had significantly lower visual acuity compared with the normal-BW group, though there were no difference between the normal-BW and high-BW groups, according to Dr Achim Fiess of the University Medical Center of the Johannes Gutenberg University Mainz and colleagues. Analysis of spherical equivalent suggested that the high-BW participants were more hyperopic, the team reports in the British Journal of Ophthalmology. Those in the low-BW group were also significantly more likely to have myopia more severe than -3 diopters or -6 diopters. Participants with high BW were less myopic than were those with normal BW. Hyperopic refractive error exceeding 3 or 6 diopters was significantly associated with the high-BW group. There was no association between BW and astigmatism.

Watchful Waiting Reasonable for Well-Appearing Infants of Mothers With Chorioamnionitis

Careful monitoring without empiric antibiotics appears safe for well-appearing infants born to mothers with chorioamnionitis, researchers report. "In the current era of maternal group B streptococcus (GBS) screening and intrapartum antibiotic prophylaxis, the risk of early-onset sepsis is very low in well-appearing late-preterm and term infants, even if perinatal risk factors are present," Dr Adam Frymoyer from Stanford University, in California, said. "Due to this low risk, treatment approaches that rely on the empiric use of antibiotics will result in frequent, unnecessary, and potentially harmful antibiotic exposure in many uninfected infants." In an effort to reduce unnecessary antibiotic use, Lucile Packard Children's Hospital Stanford updated its approach by focusing on clinical monitoring and examination to determine the need for antibiotics and laboratory testing in well-appearing, late-preterm and term infants born to mothers with chorioamnionitis. Infants who remained well-appearing during the first 24 hours after birth were transferred to room in with the mother until discharge. If they developed clinical signs that were concerning for sepsis, then laboratory evaluation

and/or antibiotics were initiated, at the discretion of the treating physician. Dr Frymoyer's team reports the impact of this quality improvement (QI) effort after the first 15 months of implementation in a paper online March 29 in Pediatrics. Of the 277 initially well-appearing, chorioamnionitis-exposed infants, 245 (88.4%) did not receive antibiotics during their hospitalizations, and 229 (82.7%) never had laboratory testing for early-onset sepsis. The remaining 32 infants (11.6%) later developed signs and/or symptoms that were concerning for infection, and all had laboratory testing and were treated with empiric antibiotics. There were no true-positive blood or cerebrospinal fluid cultural results in these infants. Among all neonates born at or after 34 weeks' gestation, the proportion exposed to ampicillin or gentamicin during the first three days after birth decreased from 12.3% before implementation of the updated policy to 5.5% after implementation, a 55% reduction (P<0.001). If a neonatal sepsis calculator (NSC) score of >1.54 per 1,000 at birth had been used as a criterion for treatment, an additional 64 infants would have received antibiotics. Waiting to incorporate clinical findings during the first 24 hours of life into the NSC score would have resulted in antibiotic recommendations similar to actual antibiotic use in this group, with agreement for 93.1% of infants.

Impaired Left Ventricular Response to Exercise Seen in Adults Born Preterm

Adults born preterm showed blunted left ventricular (LV) functional responses to moderate-intensity exercise stress, despite normal LV function at rest, in a prospective observational study. As a result, their LV ejection fractions and cardiac output were significantly lower at both 60% and 80% of peak exercise capacity compared with responses in comparable adults who had been born at term. Also, the lower the gestational age at birth in the preterm group, the greater was their LV-functional impairment at exercise. The findings were independent of birth weight, maternal health history, and adult health status and suggest that "preterm-born young adults have a reduced myocardial functional reserve that might help explain their increased risk of early heart failure," Adam Lewandowski, DPhil, University of Oxford and John Radcliffe Hospital, United Kingdom, said. They also complement earlier research from his group and others suggesting that adults born preterm have increased LV mass and reduced LV volumes, adjusted for body size, he said in an emailed comment. Altogether, the structural and functional abnormalities seen in preterm-born adults constitute a "unique phenotype" compared to other types of cardiomyopathy, according to Lewandowski. "There's no immediate cause for alarm, as most preterm-born individuals will not go on to develop heart failure as adults," he said. "However, the more we start to understand how the heart works differently in people born preterm, the better we can start to implement primary prevention steps, including reducing cardiovascular risk scores and developing a healthy lifestyle."

Effective Options for Treating Patent Ductus Arteriosus

High doses of oral ibuprofen are most effective for closure of hemodynamically significant patent ductus arteriosus (PDA) in preterm infants, but treatment may not be necessary, according to a systematic review and meta-analysis. "Higher doses of oral or intravenous ibuprofen and oral acetaminophen are significantly better than the traditionally used standard doses of intravenous ibuprofen or indomethacin if one decides to close

a hemodynamically significant PDA," said Dr Souvik Mitra from Dalhousie University and IWK Health Center, in Halifax, Canada. "Conservative management may be an equally viable option, as current evidence does not suggest that it worsens outcomes," Dr Mitra said. There are several effective therapies for hemodynamically significant PDA, so clinicians are faced with the question of what should be the ideal choice of pharmacotherapy, if any. Dr Mitra's team undertook a systematic review and network meta-analysis of 68 randomized clinical trials comparing 14 different variations of placebo, indomethacin, ibuprofen and acetaminophen for the treatment of hemodynamically significant PDA in preterm infants. The overall PDA closure rate in all studies combined was 67.4% with treatment and 38% in the placebo or no treatment group, the researchers report. A high dose of oral ibuprofen was associated with significantly higher odds of PDA closure versus a standard dose of intravenous ibuprofen (199 more closures per 1,000 infants) or a standard dose of intravenous indomethacin (124 more closures per 1,000 infants). A high dose of intravenous ibuprofen, oral acetaminophen, and a standard dose of oral ibuprofen all had higher rates of PDA closure, compared with a standard dose of intravenous ibuprofen. In the network meta-analysis, a high dose of oral ibuprofen was ranked as the best treatment option for PDA closure and for reducing surgical PDA ligation. For reducing the need for repeat pharmacotherapy, a high dose of intravenous ibuprofen and oral acetaminophen ranked highest.

More Preemies Developing Motor Impairments

More than one-third of extremely premature and underweight babies have cerebral palsy or other motor impairments that can make it hard for them to do basic things like ride a bike or use a fork, an Australian study suggests. Researchers examined data on children in Victoria, Australia, who were born at less than 28 weeks gestation or weighing less than 1,000 grams (2.2 pounds) during three time periods: 1991-1992, 1997 and 2005. The proportion of these babies who had cerebral palsy or other motor impairments by age 8 climbed from 23 percent at the start of the study to 37 percent by the end. While the study wasn't designed to assess why this is happening, it's possible that children born with developmental deficits today have fewer opportunities to move around and stimulate their brains to help improve their motor skills, said lead study author Alicia Spittle, of the University of Melbourne and the Murdoch Children's Research Institute in Australia. "It could be that with increases in technology and screen time, along with less children actively commuting to school (e.g. walking, biking) that children are getting less active and this is affecting their overall motor skills," Spittle said. For the current study, researchers focused on almost 1,200 extremely preterm or underweight infants who were born without lethal abnormalities. The proportion of these babies who survived to age 8 increased from 54 percent at the start of the study to 64 percent by the end, aided by advances in medical technology, researchers report. However, motor impairments also became more common over time in a comparison group of full-term babies in the study, accounting for 2 percent of babies initially and rising to 7 percent by the end. That suggests the increase in motor impairments among extreme preemies is not a result of better survival in the more recent periods.

US Infant Mortality High Even for Full-term Babies

Infant mortality rates for full-term babies vary across the US, but all states are worse than many European countries, a new study suggests. Previous research has found babies more likely to die in the U.S. than in other developed and affluent nations, but the current study offers fresh evidence that this is true even for infants born at the very end of pregnancy when they should have excellent survival odds. Across the US, infant mortality rates for full-term babies were 50% to 200% higher than in Austria, Denmark, Finland, Norway, Sweden and Switzerland, the study found. The two main reasons for the higher U.S. mortality were "congenital malformations, which patients cannot really do much about other than ensuring adequate screening during pregnancy, and high risk of sudden unexpected deaths in infancy, which should largely be preventable through appropriate sleeping arrangements," said study co-author Neha Bairoliya of the Harvard Center for Population and Development Studies in Cambridge, Massachusetts. Bairoliya

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and colleagues studied more than 10 million U.S. infants born between 2010 and 2012 at full-term, that is, between 37 and 42 weeks gestation. Out of every 5,000 full-term births, 11 babies died before age 1, researchers reported March 20 online in PLoS Medicine. Overall, more than 7,000 full-term babies die each year in the US, and researchers estimate that infant mortality could be reduced by about 4,000 deaths if all states achieved the mortality levels of the best-performing state for each cause of death. At the state level, infant mortality rates ranged from 6.45 deaths for every 5,000 full-term births in Connecticut to nearly 19 deaths for every 5,000 in Mississippi.

High-Flow Oxygen Improves Infant Bronchiolitis Outcomes

High-flow oxygen therapy was associated with improved outcomes among hospitalized infants with bronchiolitis treated outside intensive care units (ICUs) in a multicenter, randomized trial. Compared with infants treated with standard oxygen therapy, roughly half as many infants in the high-flow oxygen group required escalation of care (12% versus 23%), and there was no significant difference between the two groups in the incidence of adverse events. Bronchiolitis is the most common reason for hospital admission among infants worldwide, and in the U.S. it is responsible for an annual $1.7 billion in hospital costs. High-flow oxygen therapy is increasingly being used outside the ICU to provide respiratory support for infants, children, and adults with respiratory diseases. The new study, published online in the New England Journal of Medicine, is among the first to examine the treatment's safety and efficacy outside the ICU in infants with bronchiolitis, said the study's senior researcher, Andreas Schibler, MD, of the University of Queensland in South Brisbane, Australia.

Phthalate Exposure in NICUs Tied to Altered Neurobehavioral Performance in Neonates

Exposure to phthalates in neonatal intensive care units (NICUs) is associated with alterations in attention and social response that could lead to neurobehavioral problems in childhood, researchers in New York City suggest. "Phthalates are endocrine disruptors. Although their mechanism of action in relation to behavioral outcomes is not definitively known, in vitro studies show that phthalates interact with sex receptors in the brain known to impact behavioral function," Dr Annemarie Stroustrup of Icahn School of Medicine at Mount Sinai said. "Infants with higher phthalate exposure in our study demonstrated improved or more mature behavioral performance," she said. "Taken at face value, this could be seen as a positive outcome, particularly in the short-term." "However," she explained, "research with other children has shown that environmental causes of more rapid neurodevelopment early in life can lead to behavioral problems later in childhood." "As premature infants are known to be at heightened risk of attention problems later in childhood, and as this risk is not directly attributable to specific prematurity-related illness," she noted, "we worry that phthalate exposure in the NICU could contribute to long-term behavioral adverse outcome in premature infants." To investigate, Dr Stroustrup and colleagues prospectively studied 64 premature newborns with a birth weight of <1500g (3lb 5 oz). They analyzed 164 urine specimens for phthalate metabolites using high-performance liquid chromatography/tandem mass spectrometry and administered the NICU Network Neurobehavioral Scale (NNNS) prior to NICU discharge. As reported online March 5 in PLoS ONE, various analyses showed associations between phthalate biomarkers and NNNS performance, as well as the intensity of medical interventions. Specifically, the sum of di(2-ethylhexyl) phthalate (DEHP) metabolites was associated with improved performance on the NNNS Attention and Regulation scales. Certain biomarker mixtures also were associated with improved NNNS performance. Further, more intense medical intervention was associated with higher DEHP metabolite exposure.

Tenofovir Fails to Add Extra Hepatitis B Protection for Vaccinated Newborns

Adding tenofovir disoproxil fumarate (TDF) to an aggressive treatment strategy fails to give extra protection to newborns at risk for contracting hepatitis B virus (HBV) from their infected mothers, according to a study at 17 public hospitals in Thailand. The drug or placebo was given to 331 infected women from 28 weeks of gestation until two months postpartum. All newborns were also given both hepatitis B immune globulin and the first dose of hepatitis B vaccine at birth, with booster vaccine doses at 1, 2, 4 and 6 months. None of the babies in the tenofovir group became infected. But the rate was so low in the control group - with three infections among 147 babies by the six-month mark - that the difference between the two groups was not statistically significant (P=0.29). "No maternal or infant safety concerns that were considered by the investigators to be related to the maternal use of TDF or that occurred after the discontinuation of TDF were identified, but the sample size was small," writes the research team, led by Dr Gonzague Jourdain of Chiang Mai University in northern Thailand. "No significant differences in infant growth were detected between the two groups."

News continued on page 17…

SPOTLIGHT ON MONITORING

Simpler Method for Bedside Pressure Measurement

Respiralogics introduces GiO 1 Digital Pressure Gauge for real-time display of airway pressure. The GiO provides a simple method for bedside pressure measurement in an easy-to-read digital display. There are no complicated buttons or display screens with the GiO. Start with two buttons and unlock the possibilities. The GiO Digital Pressure Gauge can be used in a wide range of applications and clinical settings. GiO is backlit for ease of reading in minimal light environments. Battery operated; GiO has an auto power off feature to extend the life of the lithium battery. GiO 1, with pressure measurement between 0 to 30 cmH2O, is specifically designed for both non-invasive and invasive infant/neonatal applications. Portable and compact, GiO can conveniently accomplish your pressure monitoring needs at the bedside as well during transport. The GiO Pressure Gauge is packaged complete with hydrophobic filters, pressure line, elbow connectors and straight leur connector. Individual patient pressure line and replacement filter kits are available for bedside use. The GiO Pressure Gauge is available in different pressure ranges for large pediatric and adult applications. Visit www.respiralogics.com for all Respiralogics products and information.

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A Mother's Perspective on the Impact of a Tracheostomy While in the NICU

In this feature, Kristin King, PhD, CCC-SLP, Vice President of Clinical Education and Research with Passy-Muir, Inc, interviews a mother and NICU Parent Advisor about the impact of having a newborn, who required a tracheostomy, and the education needed to learn about tracheostomy care and use of a bias-closed, no-leak speaking valve. This interview is with Krysten Kendall, mother of a NICU graduate and NICU Parent Advisor at Nationwide Children's Hospital.

Prevalence of Complications During Pregnancy

The birth of a child is a much-anticipated and exciting time for parents. However, the birth plan that parents typically have in mind for a new addition to their family does not always proceed as planned. A study investigating the prevalence of complications and healthcare costs during pregnancy found that a total of 46.9% of women had at least one pre-specified pregnancy complication; the most commonly observed were fetal abnormality (24.7%) and early or threatened labor (16.3%).[1]

Harrison and Goodman (2015) considered the epidemiologic trends for the NICU and reported that in 2012 there were 43.0 NICU admissions per 1000 normal-birth-weight infants (2500-3999 g), while the admission rate for very low-birth-weight infants (<1500 g) was 844.1 per 1000 live births. The authors indicated that during the 6-year study period overall admission rates increased from 64.0 to 77.9 per 1000 live births in all birth weight categories.[2] During their study period, newborns admitted to a NICU were larger and less premature than seen in previous years; however, no trends were identified for weight based on gestational age or the use of assisted ventilation. These numbers are significant in that the occurrence of neonates needing assisted care in the NICU is increasing. With that increase comes differences in care management and parents' interactions and bonding with their child.

Reasons for Tracheostomy in Neonates

Despite advances in the care of critically ill neonates, extended mechanical ventilation and tracheostomy are sometimes required. A retrospective study by Overman et al (2013) reviewed the records of 165 infants over a ten year period who required tracheostomy and ventilator support. They reported from their review that in infants with extremely low birth weight (< 1000 g) the primary diagnosis requiring airway intervention was Bronchopulmonary Dysplasia (95.4%).[3] In infants with very low birth weight (>1000 g), the incidence for a single diagnosis was highest for uncomplicated congenital heart defect (45.3%) but when combining such diagnoses as tracheomalacia, subglottic stenosis, and others, upper airway obstruction became the primary reason (82%).[3]

A study by Isaiah et al (2016) investigated causes for tracheostomy in the NICU and was consistent with the Overman et al report. This study reported that the indication for tracheostomy showed a reversal from disease toward obstructive pathologic mechanisms.[4] Their findings suggest that advancements in NICU care for infants with lung disease are progressing so that the primary indication for a tracheostomy is changing.

Tracheostomies circumvent anatomical and physiologic obstructions to provide access to ventilation and, in turn, provide neonates with life-sustaining airway support when born with acute or chronic airway obstruction, neurologic impairment, or pulmonary insufficiency. To perform a tracheostomy in a neonate is a complex procedure but is performed with relative frequency. A review of recent literature suggests that about half of all pediatric patients who receive a tracheostomy are younger than 1 year of age.[5]

Because a tracheostomy can impair an infant's ability to communicate and bond with caregivers, some facilities pursue the use of a bias-closed, no-leak speaking valve (Passy Muir®

Colin in infancy at the hospital (left) and shortly before decannulation while at home (right). Photos submitted.

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

Tracheostomy and Ventilator Swallowing and Speaking Valve (PMV®) to restore access to vocalizing, crying, and airflow through the upper airway. Use of the PMV has been shown in research with adults to improve: secretion management, cough, swallowing, communication, lung recruitment, and weaning, among other benefits. Unfortunately, there is a paucity of research specific to neonates and use of the speaking valve; however, some medical facilities, such as Nationwide Children's Hospital, have instituted policies to allow use of the PMV with infants and report benefits from bonding to improved weaning and decannulation.

This interview provides the perspective of one mother who has experienced the NICU on multiple levels and discusses the impact of having a neonate who required a tracheostomy. She shares her experiences from receiving education to independence in care. Not only is she the parent of a child who spent his first few months in the NICU, required a tracheostomy and used a speaking valve, she also works as a NICU Parent Advisor at Nationwide Children's Hospital, providing support to other parents experiencing similar circumstances.

Kristin King, PhD, CCC-SLP: Hi, Krysten. Your son, Colin, spent time in the NICU, had a tracheostomy, and Passy Muir Valve. Could you share some information about Colin's diagnosis and what lead to his being in the NICU?

Krysten Kendall: When I was 25 weeks, my water broke, so Colin spent the next 7 weeks in utero without fluid to help develop his lungs. It was also discovered that there was an issue with attachment; so even when there was fluid, there wasn't a lot of room for him. Colin was diagnosed with Bronchopulmonary Dysplasia which led to his need for a trach. Colin was born at 32 weeks on Christmas day, 2013. I had spent the last 7 weeks admitted to Magee Women's Hospital in Pittsburgh, PA due to preterm premature rupture of the membranes (PPROM).

Colin was initially intubated at birth due to a right pneumothorax but was extubated to high flow by the next evening. He even was on the small nasal cannula just a few days later. However, his respiratory status quickly declined, and he eventually ended up on the oscillating ventilator for several days, then progressed to the conventional vent. Due to inability to extubate or even lower his vent settings, they decided to transfer us to Children's Hospital of Pittsburgh UPMC. After several tests, including a CT Scan and Pulmonary Function Test (PFT), Colin was started on bronchodilators and steroids and they were able to start weaning his vent settings. After a failed extubation, the attempt only lasted 5 days, they determined that the next step should be a trach placement as they did not know how much longer Colin would need breathing support. We agreed, and the trach was placed the next day.

Kristin King, PhD, CCC-SLP: What information were you provided in the beginning to prepare you about how the tracheostomy would affect Colin's recovery, communication, and feeding and swallowing?

Krysten Kendall: Before Colin got his trach, I really had no idea what a trach even was. All you think of are those anti-smoking commercials. So, I wasn't sure exactly what to expect. When they first brought up the fact that Colin may need a trach, I started doing research online about babies and children with trachs and learned a little more about how it worked. The medical team told me that he would not be able to make much sound but that it shouldn't affect his feeding and swallowing.

Kristin King, PhD, CCC-SLP: When were you and Colin first introduced to the Passy Muir Valve? What information were you provided as to how the Valve worked and when Colin would use it?

Krysten Kendall: We were first told that there was a speaking valve that he could use when we were still at the Children's Hospital in Pittsburgh, PA, then again when we transferred to Nationwide Children's Hospital in Columbus, OH. The attending physicians brought it up almost immediately, saying he wanted to start Colin on the speaking Valve.

Shortly after our arrival in Columbus (on 4/9/14, he was born 12/25/13), our speech therapist brought the Passy Muir Valve to his room to do the testing with Colin to see if he could tolerate using the Valve. The test showed that Colin could in fact tolerate using the PMV, and our speech therapist explained how the Valve worked, where to attach it, how to clean it, and how we would start by working up slowly to using it on Colin, so as to not push him too much. She also told us to remove the Valve when Colin was sleeping or when he was not constantly being watched. The first time we put it on him, he was happy and made some sounds (which was music to his mama's ears!).

I will say, it was one of the best days in the NICU that I'd had in a long time when I finally got to hear my baby making sounds again, even if he was crying. He tolerated it very well, and we then even started using it during physical therapy (PT) and feeding. They let Colin use the Valve if someone was in the room with him. I was there pretty much all day during the day, so he started wearing it for long stretches of time and then started making appropriate [vocal] sounds.

Kristin King, PhD, CCC-SLP: Why was it important to you to have Colin access the Passy Muir Valve at such a young age?

Krysten Kendall: It was important to me to start using the PMV so early because I didn't want Colin to be behind developmentally in speech. I was also told that it would help him wean faster off the ventilator and help him while eating.

Of course, the biggest highlight of the Valve was being able to hear my baby again after months of not hearing him. I'm not sure how much the Valve helped his weaning process, but I like to think it really helped him as he weaned so quickly from needing the ventilator to just oxygen (the whole process took about 7 weeks) after he started using the Valve. Also, and this is a bit selfish, but I just wanted to be able to hear my baby laugh, babble, and even cry.

Kristin King, PhD, CCC-SLP: What was it like as you transitioned from one facility to another with Colin and learned the changes in his care?

Krysten Kendall: Colin was born in Pittsburgh and spent a few months in their children's hospital, where he received his trach at 41 weeks gestation. We loved the hospital in Pittsburgh and are so thankful for them, however, coming to Nationwide Children's was the best thing we could have done for our son.

The NICU in the hospital in Pittsburgh was much smaller than NCH's, and they just didn't have the space to keep babies long-term. Pittsburgh's [original] plan was to get Colin transitioned to a home vent, and we would wean from home. When we came to Nationwide, the doctors informed us that they planned to get Colin weaned to Cool Mist Collar at 30% O2 before we went home. That came as a bit of a shock because that meant a long NICU stay, and I wasn't sure how long it would take to wean him. In hind sight, I am so thankful that they were able to wean him off support before sending him home because it made our lives so much easier. Colin was very stable by the time we brought him home.

Kristin King, PhD, CCC-SLP: What advice would you offer a parent or caregiver going through a similar experience of changing hospitals during the early stages of care?

Krysten Kendall: My advice is that the changes are sometimes hard when you move to a new facility because you're used to the way things were, but these changes could ultimately be for the best for your baby.

Kristin King, PhD, CCC-SLP: Can you share a little of what life has been like during his first years of life and learning to live with a tracheostomy?

Krysten Kendall: I tried to make life for my son as normal as possible when he had his trach; I didn't want him to miss out on anything. There were times when it was stressful, but things got easier and easier, especially when he was able to tolerate wearing the Passy Muir Valve all day and then when he transitioned to capping.

He was our first child, so we didn't know life without having to change trach ties, suction, and take care of other medical needs. We brought him pretty much everywhere when he had his trach: the zoo, pool, trips to Pittsburgh, baseball games, hockey games, and the list goes on. We didn't let the fact that he had a trach hold us back from doing what we would do, if he had been typical.

We were discharged July 14, 2014. At home, we used the PMV all day and would even let him fall asleep wearing it before we switched him over to cool mist. He really started talking on his first birthday, just kind of out of the blue, using 'B' sounds and 'M' sounds. It was awesome for us. Over the next year and a half, he developed very appropriate in speech, thanks to the Passy Muir Valve. I would have people tell me that they had kids the same age and they didn't talk as well as he did, so that alone is a huge testament that early placement of the PMV is so important. I always tell people that the PMV is my favorite invention of all time. My son would not be where he is today without it.

Kristin King, PhD, CCC-SLP: What is it about your story with Colin and having a tracheostomy that you would want to be sure other parents and caregivers know and understand?

Krysten Kendall: What I make sure parents here at Nationwide know when I tell them about the Valve is that not all babies can tolerate using it at first, but hopefully, as they grow bigger and stronger, they can begin to use it. I also tell parents to use it as often as they can so that their baby can appropriately develop their speech.

I always tell parents that when Colin would have his developmental testing done, he would always test highest in speech thanks to using the Passy Muir Valve.

It is always a big concern of parents that they won't be able to hear their baby when they get a trach. It was a big concern of mine as well, so introducing the Valve was one of the biggest highlights of our NICU stay. I always tell people that the PMV is one of my favorite inventions of all time because it gave my son his voice. He would not be who he is today without the PMV.

Kristin King, PhD, CCC-SLP: Could you provide an update and brief description of how Colin is doing now?

Krysten Kendall: Colin is doing great. He got his trach out on 4/25/2016. Our biggest hurdle now is just getting him to eat like a typical kiddo. Right now, he will eat his food as long as it is pureed and gets most of his liquid through his g-tube. Just this past Monday, Colin started an intensive feeding program at Nationwide Children's Hospital. We hope that this will help him with his eating and drinking skills and our goal is that he will have his g-tube out by kindergarten

Kristin King, PhD, CCC-SLP: It is so good to hear how well Colin is doing and the progress he has made. Lastly, could you share how your experiences led you to your role as a NICU Parent Advisor?

Krysten Kendall: I am part of the support team for families as someone who has been in their shoes. We do a Pizza Night every Thursday night where we invite all the NICU families to attend and meet other people who are in the same position. I work a lot with families with babies with trachs to talk about discharge and what to expect when they get home. They appreciate talking with someone who knows what they are going through. A lot of times I'll get a request from a doctor, social worker, or the case manager to talk with a family when it has been recommended that their baby receive a trach to answer any questions they may have from someone who has had a baby with a trach. I started working at Nationwide Children's Hospital in August of 2016, about 4 months after Colin's trach was removed.

Krysten and Colin's journey from birth to childhood took unexpected turns with the NICU stay and learning about aspects of care that are not in the life of a typical, full-term infant. Krysten shared that it is a continual learning process as a parent and that while the journey may not be what was initially anticipated, it is still extraordinary. Earlier intervention in the NICU, with introduction of a bias-closed, no-leak speaking valve, may provide access to more vocalizations and other benefits related to use of the upper airway.

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Biologics in Pregnancy Safe

Using biologics to treat autoimmune disease during pregnancy does not appear to increase the risk for preterm birth or infants born small-for-gestational-age (SGA), according to a new study. "While we examined all biologics used in the cohort, [tumor necrosis factor]-alpha inhibitor biologics (94%) were the most common, and as such, our results mostly apply to these biologics and less so to those that are not TNF-alpha inhibitors," write Nicole W. Tsao, a PhD candidate at the University of British Columbia Faculty of Pharmaceutical Sciences in Vancouver, Canada, and colleagues. "Indeed the population-based setting of this study lends more generalisability to the results," and the statistical methods used allow for better control of confounding compared with traditional modeling methods, "thus contributing to better understanding of the use of biologics in the pregnant population," the authors write. "Our study represents an important contribution to the accumulation of evidence on the safety of the use of biologics in pregnant women, which may lead to increased prescriber comfort and patient acceptance, decreased uncertainty and improved maternal and neonatal outcomes in this population," they add. Given the pathophysiology of autoimmune disease, with cytokine and chemokine dysfunction, and the role of the immune system during pregnancy, pregnant women with autoimmune disease activity have a higher risk for adverse maternal and neonatal outcomes, research shows. Abnormally increased TNF-alpha in particular, along with other cytokines, has been linked to "pregnancy complications including preterm delivery, fetal growth retardation, early and unexplained spontaneous abortions and miscarriages," Tsao and colleagues explain. The researchers used population-based administrative data from more than 4 million British Columbian residents, including 305,351 women with pregnancies during the study period. They compared the outcomes of 8607 pregnancies in 6218 women with autoimmune diseases, from January 2002 through December 2012.

Standardized Protocol May Improve Care of Opioid-addicted Neonates

Statewide implementation of a standardized protocol to treat neonatal abstinence syndrome (NAS) in Ohio neonatal ICUs appears to have reduced the duration of opioid exposure as well as the length of hospital stay in opioid-exposed newborns. "The ability to spread a complex protocol across 54 hospitals statewide is a testament to the urgency of the opioid epidemic as well as to the power of rigorous quality improvement (QI) science and collaborative work," researchers with the Ohio Perinatal Quality Collaborative. NAS has increased significantly in the U.S. and no treatment standards exist, leading to marked variation in management, Dr Michele Walsh, from Rainbow Babies & Children's Hospital in Cleveland and colleagues note in their article. They developed a standardized protocol for pharmacologic and nonpharmacologic care of infants with NAS. The pharmacologic protocol includes standardized guidelines for scoring NAS, triggers for initiation of treatment and a stringent weaning protocol. The non-drug care bundle emphasizes compassionate trauma-informed care for the mother and infant and keeping mother and infant together (swaddling/kangaroo care, feeding on demand, etc.). In Ohio NICUs between January 2014 and June 2015, compliance with the nonpharmacologic bundle improved from 37% to 59%, and the pharmacologic bundle improved from 59% to 68%. Among 3,266 opioid-exposed infants, 48% received pharmacologic treatment for NAS symptoms, and this rate did not change much across the study period. Regardless of the opioid used to manage NAS, the length of treatment decreased from 13.4 to 12.0 days and the length of stay decreased from 18.3 to 17 days. "Although the 1.3-day, 9% reduction in both measures is smaller than the 20% effect desired as the aim of the collaborative, it was both statistically significant and clinically important, given the large number of infants who experienced NAS: an overall reduction of 2,041 hospital days," the researchers write. The researchers say other states and institutions treating opioid-exposed infants may benefit from considering this pharmacologic and nonpharmacologic care model for NAS.

The Benefits of Swaddle Bathing with the Turtle Tub

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Linda M. Roche, BSN, RNC-NIC, Clinical Coordinator, Neonatal Intensive Care Unit, UMass Memorial Medical Center.

Neonatal Intensive Care: How long have you been working in the NICU?
Linda M. Roche: I have been a nurse in the NICU my entire career over 25 years from my early years as a nursing assistant. I have worked in many institutions — mainly in Level III NICUs as well as newborn nursery, pediatric and cardiac ICUs — across the country from Massachusetts to Hawaii.

NIC: How did you bathe the infants prior to learning about swaddle bathing with the TurtleTub?
LR: The sponge bath in the baby's isolette or crib was the first method of bathing that I learned from my preceptor or a bath in a small hospital basin.

NIC: Who did the bathing?
LR: The nurse typically performed the bath as part of her night shift routine of bathing, weighing and changing the linens.

NIC: How did the baby respond to your previous way of bathing?
LR: Generally, it was stressful experience for the baby and not well tolerated. Babies would often cry, squirm in response to being cold and wet. The nurse often would do it quickly as it was an unpleasant experience which burned many calories and depleted baby's energy.

NIC: Why did you decide to change your bathing method?
LR: I attended a conference my first few years as a nurse and spoke with a developmental care specialist. She introduced me to the technique of swaddled bathing and explained the rationale behind it. It made sense to me. Everything we do as nurses has an effect on the baby and it is crucial to look at things from the baby's perspective. Developmentally supportive care focuses on observing the baby's cues and responding in a way that promote stability. I incorporated this new idea into my practice at the bedside and observed a remarkable difference in the way the baby was able to be calm and content. As nurses we thrive on learning new ways of doing things that improve the care we provide our babies. It is always evolving as we learn from each other and share ideas.

NIC: What were you trying to accomplish by changing bathing methods?
LR: My hope was to improve the baby's experience and turn bathing into a pleasant and positive experience. We are discovering that these early experience both positive and negative directly affect baby's brain development. What we do now matters. As caregivers, we recognize the impact we have on these fragile babies long after they leave the NICU. It was also important to decrease the calories burned to foster growth and development. Baby's often have little reserve after stressful events which leave them little energy to devote to other things such as successful breastfeeding. We also wanted to role model for parents and demonstrate ways to be involved in hands-on care.

Photo submitted.

"The Developmental Care Team is committed to providing individualized developmentally supportive care to all infants in our NICU with the understanding that the care we provide greatly impacts the ability of the infant to achieve his or her developmental potential. Developmentally supportive care impacts brain development and has lifelong implications. How we interact with infants in large part impacts how they will develop and who they will become. The bedside nurse has a unique role in providing life-saving medical care while simultaneously supporting and protecting quality of life." The team supports and encourages the swaddled bathing technique.

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

NIC: And did swaddle bathing with the TurtleTub accomplish those goals?
LR: This technique certainly achieves the goals.

NIC: How did the babies respond to bathing in the TurtleTub?
LR: The babies loved it. It was pleasant and positive. They were either in a quiet and alert state, dozing or in a light sleep. Their bodies were relaxed and they were calm and content. The wrapping offers the containment and the boundaries that they prefer. Babies that are experiencing withdrawal from opioids are often irritable, difficult to console and hypertonic. This technique is so beneficial in helping them soothe and gives them a sense of security. One Dad said, "This is amazing! No tears. He slept through the whole thing!"

NIC: What surprised you the most about swaddle bathing with the TurtleTub?
LR: It is such a simple technique but highly effective. It is a wonderful tool that provides meaningful touch. Meaningful touch is important for all babies no matter what their gestational age. So much of the touch that is done in the NICU is uncomfortable and even painful so it is important that each baby receives meaningful, positive touch from his or her parents and staff as often as possible. The NICU environment increases the risk of developmetal delays in cognition, hearing and language development so techniques that support and encourage proper development are important.

NIC: Have parents been able to bathe their infants with the TurtleTub? If so, what has been their response?
LR: Yes. We support family-centered care and encourage parents to be involved in all aspects of their babies care. We have a conversation with our parents about this and hand out an information sheet on how to perform a swaddle bath and encourage them to watch the video. Nurses are there to assist them the first time. Parents are so pleased to be able to bathe their baby without all the stress of a traditional bath causes. Parents say that they are more confident in handling their baby and now look forward to bath time. They feel more bonded and attached as they get to know their unique baby. They are pleased to have the opportunity to not only clean the baby but comfort them as well. It gives them a sense of pride as they share special time together to interact and make memories.

NIC: How did the rest of the staff feel about changing bathing practices?
LR: An educator from the company came to my unit and gave in-services to the staff and provided resources we needed to successfully launch the program. Staff have warmed up to the idea once they see the positive effect it has on the baby and family. It takes time to change our practice and incorporate new ideas into daily routines. As nurses we are vigilant and mindful about improving the care we provide each family.

NIC: Would you recommend other hospitals to swaddle bathe with the TurtleTub? If so, why?
LR: Definitely. The technique is effective and the TurtleTub swaddle bath system is wonderful.

Breastmilk is Medicine – The Role Of The Mother-Baby Nurse in the NICU Infant-Mother Dyad

Kiersten LeBar, DNP, MMHC, CPNP-AC

The American Academy of Pediatrics and World Health Organization recommend exclusive breastfeeding for at least the first six months of life.[1,2] Additionally, the Healthy People 2020 report recommends a target of 82% of infants receiving exclusive human milk at the time of discharge from the hospital and that 60% of these infants continue to receive exclusive human milk until 6 months of age.[3] According to the Centers for Disease Control and Prevention, approximately 81.1% of women initiate breastfeeding yet only 22.3% continue to provide exclusive human milk at 6 months of age.[4]

Hospitalized infants, including those born preterm, are at the highest risk for not receiving human milk for the following reasons including maternal/infant separation, long hospitalizations, maternal knowledge and confidence deficit, insufficient supply and delayed onset of lactogenesis stage II.[8-10,16] In 2012, the American Academy of Pediatrics recommended that all preterm infants be fed human milk because of these infants' special needs.[1] Human milk provides important immunological, nutritional, and developmental benefits leading to a decrease in the short- and long-term morbidities associated with being born preterm.[11,12] Within the neonatal intensive care unit (NICU) population human milk has been shown to decrease the incidence of feeding intolerance, necrotizing enterocolitis (NEC), infections, chronic lung disease, retinopathy of prematurity, developmental and neurocognitive delays, length of stay and hospital readmission rates post discharge.[12] The benefits of human milk feedings in the very low birth weight (VLBW) population have been shown to be dose dependent, therefore increasing the duration of breastmilk use for infants in this population is imperative to improve their short- and long- term outcomes.[5-7]

Dr. LeBar is the advanced practice provider team manager for the Neonatology Intensive Care Unit at Monroe Carell Jr. Children's Hospital. She leads advanced practice providers (APPs) in the Neonatal Intensive Care Unit (NICU), facilitating highly specialized, safe, and efficient care. Dr. LeBar is a board-certified Acute Care Pediatric Nurse Practitioner and has practiced in the neonatal/pediatric critical care setting for 14 years. Prior to joining Vanderbilt, Kiersten was a nurse practitioner in the NICU at Duke University Medical Center. She has also served as nurse practitioner team lead at The Children's Hospital of Philadelphia in the Neonatal/Infant Intensive Care Unit, as well as at the NICU at The Hospital of The University of Pennsylvania. Dr. LeBar received her Master of Science in Nursing degree in Pediatric Acute/Chronic Care from The University of Pennsylvania. She earned a Doctorate of Nursing Practice (DNP) from Duke University and a Masters in Management or Healthcare from Vanderbilt University.

Nurses are critical to the initiation, promotion, and protection of breastfeeding.[5,13-14] During the first 14 days it is imperative to support mothers so they can establish and maintain a good milk supply. Labor and delivery and mother-baby nurses spend a significant amount of time with the mothers of infants admitted to the NICU, during this most critical time frame. Because of this they have the unique opportunity to play a vital role in improving the outcomes of NICU patients. Skin-to-skin or kangaroo care, early breastmilk expression, and the development of an expression regimen are important ways labor and delivery and mother-baby nurses can assist mothers.

Inadequate breastmilk production is one of the most common reasons mothers decide to stop breastmilk expression.[15] Early breastmilk expression within 1 hour of delivery has been shown to increase duration of lactation and decrease time to the onset of lactogenesis II. In one randomized control trial, mothers of VLBW infants were noted to be more likely to be lactating at 3 weeks, 6 weeks, and at time of discharge if they initiated pumping within 1-3 hours of birth. Additionally, mothers who pump more than 6 times per day have been found to have increased milk production.[16] Compelling research by Meier,[17] Torowicz[18] and Post[19] has identified that use of a double electric breast pump in the first days post-birth outfitted with Initiation Technology™ results in increased milk production.

Continued adequate production of human milk relies on emptying the breasts completely at a routine interval. Simultaneous expression of both breasts not only has been demonstrated to cut down on the amount of time during a pumping session, but research has shown that this method leads to increased prolactin levels, that result in increased milk volumes. In low risk infants, pumping durations of at least 100 minutes per day has been correlated with increased volumes.[15] The addition of hand expression in combination with use of a double-electric breast pump can be effective in collecting initial quantities of colostrum. Mothers who pump 6 times or more per day have been found to have increased milk production.[16]

Skin-to skin care is the first important step maternity nurses can take to support the mother-infant breastfeeding dyad for the NICU patient. Each mom has a unique microbiome and bacteria from the maternal GI tract translocate into breastmilk via the enteromammary pathway. This pathway allows the infant to tell the mother's body to make good bacteria to fight the bacteria present in the NICU environment. Mothers should be encouraged and supported to perform kangaroo care with their infant, as this

action had been associated with mothers more often producing milk volumes greater than 500ml per day, which is considered adequate to maintain nutritional demands of a neonatal infant.[15] Additionally, studies suggest that how long a mother holds her infant on a daily basis, how often kangaroo care occurs on a weekly basis, and whether or not kangaroo care was started within the first week greatly affect the volume of human milk mothers are able to express.[20]

Bedside nurses working within the labor and delivery and mother-baby units are in a prime position to help improve the outcomes for patients admitted to the neonatal intensive care unit. Skin-to-skin or kangaroo care, early breastmilk expression, and the development of an expression regimen by nursing staff help to set NICU mother's up for long-term success.

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Mucus Degradation and Gut Microbes: Maintaining Gut Barrier Function in the Preterm Infant

Tracy Shafizadeh, PhD

The gut epithelium acts as a barrier

The neonatal gut is rapidly colonized after birth by bacteria it encounters from its environment.[1] One of the major purposes of the gut epithelium is to prevent the translocation of these bacteria to the body and bloodstream. Complex cell-to-cell interactions and interlocking proteins that hold the epithelium together (tight junction proteins) help regulate this barrier.[2] While gut epithelial cells themselves play a role as a physical barrier, they also secrete antimicrobial factors and mucin which help keep bacteria in the gut away from the epithelium itself. Antimicrobial proteins, like defensins and antibodies, are secreted to enhance the barrier effect. Mucus also plays a critical role in helping to keep bacteria at a friendly distance and allow for diffusion of nutrients from the lumen to epithelial cells.[3]

The breakdown of intestinal barrier function is a major way by which pathogens invade the gut tissue, and long-term breakdown of gut barrier function (e.g. a "leaky gut") plays a role in many diseases such as infectious enteritis, inflammatory bowel disease, Crohn's disease, and neonatal bowel diseases including necrotizing enterocolitis (NEC).[3] While the etiology of NEC remains unclear, immature gut host defenses and intestinal dysbiosis are thought to play a critical role.[4] In the preterm infant, intestinal development continues to take place postnatally, and optimizing intestinal barrier function may be key in preventing diseases such as NEC.

In the preterm infant, intestinal development continues to take place postnatally, and optimizing intestinal barrier function may be key in preventing diseases such as NEC.

The gastrointestinal tract is the main system involved in the uptake of nutrients and water, and simultaneously serves as an essential barrier against harmful substances and pathogens from the environment. As part of this defense system, the large intestine is comprised of an inner mucus layer that separates the commensal bacteria from the host epithelium, and an outer, looser mucus layer that serves as the natural habitat for the commensal bacteria.[3] Components such as immune cells, the intestinal microbiota, and anti-microbial peptides all interact across this mucus barrier—safely away from the gut epithelium.

Mucus as a key part of the gut barrier

Mucus itself is made up of glycoproteins (mucins), which are proteins modified by the addition of O-glycan groups made up of complex sugars.[5] Normally, a healthy gut epithelium secretes a thick mucus barrier between 150-300 microns thick in the large intestine that is continuously shed and replenished by secretion of new mucins. Therefore, a lack of sufficient protein in the diet can reduce the secretion of mucins and the thickness of the mucus barrier. Especially in infants whose diets contain insufficient protein, such as preterm infants, this could contribute to the prevalence and severity of infection.[6]

Colonization by B. infantis EVC001 helps to reduce the abundance of mucus degrading taxa like Bacteroides and, in concert with an exclusive human milk diet, help protect the mucus barrier in the gut.

Bacteria in the gut often break down mucus when dietary fibers are inaccessible.[5] This breakdown releases sugars from the complex mucus glycoprotein, which attract potential pathogens. The consumption of these released sugars has been shown to play a role in both *C. difficile* and *Salmonella* infections, and the diffusion of these sugars creates a gradient that bacteria can follow toward the gut epithelium to cause infection.[7] However, only some species of bacteria can actually break down mucus. Among others, *Bacteroides* and *Akkermansia* are the primary mucus degraders in the human gut, along with some species of *Bifidobacterium*, such as *B. bifidum*.[8] These bacteria secrete enzymes that break apart the mucin glycan from the mucin protein and then consume the degraded sugars released from the protein, which thins the mucus barrier in the process. Among healthy adults, this represents a small burden on available energy, but in infants — and especially hospitalized infants — this could be a major contributor to energy deficits and blunt the efficacy of nutritional interventions on growth.

Protecting the mucin barrier

In contrast, key infant-associated gut microbes like *Bifidobacterium longum* subsp. *infantis (B. infantis)* do not break down mucus. Recent clinical studies have shown that colonization by *B. infantis* EVC001 helps to reduce the

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abundance of mucus degrading taxa like *Bacteroides* and, in concert with an exclusive human milk diet, help protect the mucus barrier in the gut.[9] These recent clinical studies show that colonization of the infant gut by *B. infantis EVC001* helps reduce the abundance of taxa which thrive on the breakdown of mucin glycans and produce compounds like lipopolysaccharide (LPS, or endotoxin) which trigger inflammation in the gut. *B. infantis* is highly efficient in metabolizing oligosaccharides found in human milk (HMO). This is advantageous in multiple regards, including increasing the production of acetate and lactate, which effectively lowers the intestinal pH and inhibits the growth of pathogenic bacteria.[10] These biochemical changes elicited by *B. infantis* are thought to be mechanisms by which *B. infantis* colonization reduces the abundance of mucus degrading bacteria and promotes a protective environment in the infant intestine.

There is a unique but limited opportunity immediately following birth during which the infant gut microbiome is established. In the absence of protective infant-adapted bacteria, such as *B. infantis*, there is optimal opportunity for mucin-degrading pathogenic bacteria to colonize the infant gut. Common medical interventions, such as C-section delivery and antibiotic administration has limited the transfer of *B. infantis* from mother to infant over the last century, which has led to the absence of this bacterium in the majority of infants born in developed counties today. To ensure colonization with this beneficial bacterium, and to inhibit growth of mucus-degrading pathogens, early supplementation with an activated form of *B. infantis*, such as the clinically studied strain *B. infantis* EVC001, is a safe and effective method of creating a protective intestinal environment in newborns.

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Update on Holoprosencephaly

B M Petrikovsky, MD, PhD, H L Cohen, MD, D Cohen, MD

Holoprosencephaly (HPE) is a brain anomaly in which the prosencephalon (the forebrain of the embryo) fails to develop into two hemispheres. Formation of the forebrain and the face begins to occur in the fifth and sixth weeks of pregnancy.

Classification

HPE is a spectrum of disorders often divided into 3 types: alobar, semilobar, and lobar HPE. Alobar HPE, the most severe form (Fig. 1), in which the brain fails to separate, is usually associated with facial anomalies of variable severity, which may include an absent or abnormally positioned nose (proboscis) and a single midline eye (cyclopia). Semilobar HPE, in which the brain's hemispheres is partially divided, is an intermediate form of the anomaly (Fig. 2). Lobar HPE, in which there are a number of findings which indicate some diverticulation of the ventricular system and separation of the brain into two hemispheres, is the least severe form (Fig. 3). Syntelencephaly, is the term used for the middle interhemispheric variant of HPE (MIHV), in which the posterior frontal lobe and parietal lobe are not properly separated, but the rostrobasal forebrain is normally separated.

Prevalence

Prevalence is less than one in 10,000. It is higher when fetuses from terminated pregnancies are included and is found in as many as 50 per 10,000 aborted embryos.[2]

Etiology

The etiology of HPE is multifactorial: Chromosomal and genetic abnormalities, teratogen exposure, and/or syndromic association have all been described as causes. Standard karyotyping will find a chromosomal abnormality, classically trisomy 13, in 24%-45% of all HPE cases. At least 10% of those with a "normal" karyotype have a microdeletion or duplication.[1-3] Although the division between alobar, semilobar and lobar HPE is a spectrum without clear cut borders, major principles of differential among the 3 are reflected on table 1.

Early presentation

HPE had been reported between 10 and 14 weeks on the basis of abnormal facial morphology and absence of the "butterfly" sign.[4,5] Right and left choroid plexuses on the axial view of the head resembles the shape of a butterfly and are referred to as the "butterfly sign". The falx cerebri is seen in the midline.[3,4] By the time of the second-trimester scan, the diagnosis of alobar HPE should be straightforward. A hallmark of all forms of HPE is the absence of the cavum septum pellucidum. If the face is normal, an inability to demonstrate a normal cavum septum pellucidum may be the only hint that there is severe brain malformation. If a normal cavum septum pellucidum is not demonstrable on routine obstetric sonographic images, careful follow-up is essential with endovaginal ultrasound, three-dimensional volume acquisition sonogram, and fetal MR imaging, depending on the available expertise.[3]

Genetics

Many noncraniofacial anomalies may be seen with HPE. The most common are: genital defects (24%), postaxial polydactyly (8%), vertebral defects (5%), limb reduction defects (4%), and transposition of the great arteries (4%).[2] There are at least 13 known HPE-associated genes, but there is no strict genotype-phenotype correlation.[6] Identification of a specific mutation responsible for HPE may confer considerable recurrence risks (approaching 20%) in a clinically normal family.[7] One of the most important sources of centralizing signals during forebrain development is the sonic hedgehog gene. Despite the proven usefulness of genetic mutation screening, nearly 75% of

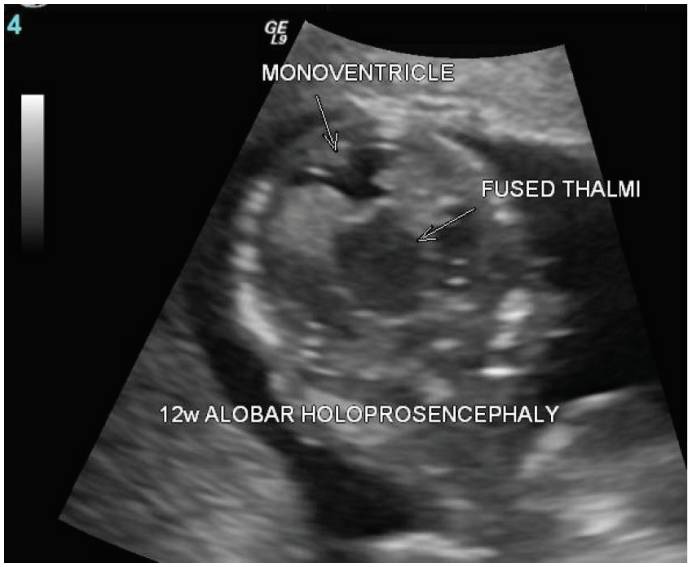

Figure 1

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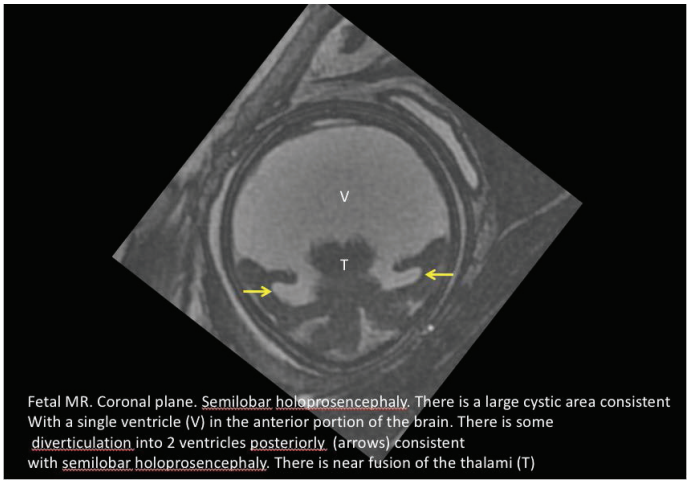
Table 1

Brain Structures	Alobar	Semilobar	Lobar
Olfactory bulbs/tracts	Fully or partially absent	Present	Present
Corpus Callosum	Absent	May be partially seen	Normal or incomplete
Interhemispheric Fissure	Absent	Present posteriorly	Present
Thalamic Nuclei	Fused	Partially Fused	Separated
Third Ventricle	Absent	Incomplete	Often incomplete
Facial malformations	Often Severe	Mild or absent	Usually absent



Fetal MR. Coronal plane. Semilobar holoprosencephaly. There is a large cystic area consistent With a single ventricle (V) in the anterior portion of the brain. There is some diverticulation into 2 ventricles posteriorly (arrows) consistent with semilobar holoprosencephaly. There is near fusion of the thalami (T)

Figure 2

HPE cases with normal chromosomes do not have identified mutations. Multiple autosomal recessive syndromes are associated with HPE; these include Smith-Lemli-Opitz syndrome, Meckel syndrome, and hydrolethalus syndrome.[8] Maternal diabetes (potentially increasing the risk 200-fold), alcohol consumption, cigarette smoking, and retinoic acid have all been listed as possible causes of HPE.[9,10]

Figure 3

Neonatal history and prognosis

HPE is not uniformly lethal. Survival depends on the severity of the brain and facial malformations, and the presence of chromosomal abnormalities.[3] Among euploid patients with HPE, there is an inverse relationship between the severity of the facial phenotype and the duration of survival. None of the surviving children with alobar HPE could sit or speak.[11] About 50% of children with all Alobar HPE die within 5 months of birth. More than 50% of children with semilobar or lobar HPE were alive at 1 year of age.[12] Of those with lobar HPE, about 50% are able to walk and can speak single words. About half of children with HPE have at least one seizure; about 40% require long term anticonvulsant therapy. Most children with HPE have cerebral palsy. Swallowing problems are common in the more severe forms, placing these children at risk for recurrent respiratory problems.[3]

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Disorders of the Posterior Fossa: Dandy-Walker Cyst, Dandy-Walker Continuum, Persistent Blake's Pouch, and Mega Cisterna Magna

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Definitions and Etiology

The spectrum of findings in the posterior fossa includes Dandy-Walker Cyst (DWC), Dandy-Walker Continuum (DWC), persistent Blake's pouch, and mega cisterna magna. In a persistent Blake's pouch, the vermis of the cerebellum is fully formed, but neither the pouch, itself, nor the foramina of Luschka fenestrate leading to a dilated fourth ventricle and limited egress of cerebrospinal fluid into the subarachnoid space. In a Mega Cisterna Magna, the vermis of the cerebellum is fully formed, but the fenestration of Blake's pouch and the foramen of Luschka is only mildly deficient allowing small expansion of the cisterna magna but not enough to cause vermian elevation or hydrocephalus.[1]

DWC is an abnormality in development of the brain that is characterized by the partial or complete agenesis of the cerebellar vermis, cystic dilation of the fourth ventricle, and as a result, an enlarged posterior fossa and an elevated tentorium. The term Dandy-Walker variant usually refers to the partial absence of the cerebellar vermis without enlargement of the posterior fossa.[1]

Incidence

DWC is the most common malformation of the fetal cerebellum with an incidence of 1 in 5000 births.[2]

Major Principles of Diagnosis

Complete or partial agenesis of the cerebellar vermis can be seen in fetuses with DWC. In complete agenesis of the vermis, there is lateral splaying of the cerebellar hemispheres at either side of the cystic communication between the cisterna magna and the fourth ventricle. The cisterna magna is enlarged, as is the fourth ventricle. When the defect is limited to the inferior portion of the vermis, a normal-appearing cerebellum will still be seen in some views. The defect can be demonstrated by angling the transducer posteriorly and inferiorly, so the communication between the fourth ventricle and cisterna magna can be visualized. A posterior fossa arachnoid cyst can mimic the appearance of DWC, particularly if the arachnoid cyst is located in the midline.[3] Such a cyst can distort and displace the cerebellum anteriorly, but the cerebellar hemispheres and vermis will be normally developed. Unlike DWC, arachnoid cysts do not communicate with the fourth ventricle. They are rarely associated with prenatal hydrocephalus or other anomalies. At times, the global imaging of MRI may have an advantage over sonography in its better visualization of the cerebellum, itself and in its often easier determination of the position of the torcula, important points in recognizing the classic Dandy-Walker cyst, where there is "torcula-lambdoid inversion".[4]

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Early Diagnosis

DWC has been diagnosed as early as 14 weeks with endovaginal ultrasound.[4]

Classification

Abnormalities of the posterior fossa consist of the classic Dandy-Walker cyst and the other DWC entities including a persistent Blake's pouch cyst (intact vermis and normal torcula), and Mega Cisterna Magna (cisterna magna ≥ 1 cm, normal appearing cerebellum), as well as rhomboencephalosynapsis (a small fused cerebellar hemispheres and a severely deficient vermis), and finally posterior fossa arachnoid cyst (cystic mass which may have a distorting effect on the cerebellum).[3,5]

Natural History

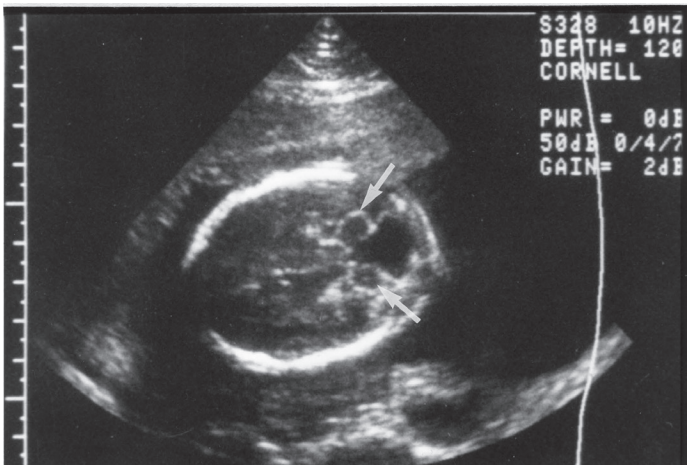
Intrauterine evolution of posterior fossa fluid collections is common. There is frequent disappearance of Blake's pouch cyst and Mega Cisterna Magna. The Dandy-Walker cyst, posterior fossa expansion may occur only later in gestation. Cerebellar hypoplasia may manifest only in the third trimester.

Prenatal Management

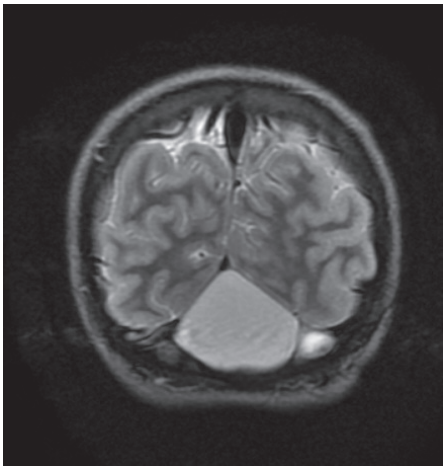
Once DWC is suspected, a meticulous search for both associated intracranial and extracranial anomalies is warranted. An associated absence of the corpus callosum has been reported in 7 to 19% of cases of DWC.[5] Associated cardiac, genitourinary, skeletal, gastrointestinal, and facial abnormalities have also been described. Fetal echocardiography is, therefore, recommended. Serial sonography, obtained every 3-4 weeks, helps to assess growth and allow a search for hydrocephalus. Delivery should take place in a tertiary-care facility.

Genetics

A total of 18 chromosomal abnormalities have been reported in fetuses with DWC, including duplications, deletions, trisomies, and triploidy.[6] DWC is also a feature of more than 70 fetal malformation syndromes, including Walker-Warburg and Meckel-Gruber. DWC has been associated with maternal diabetes.[6] Other



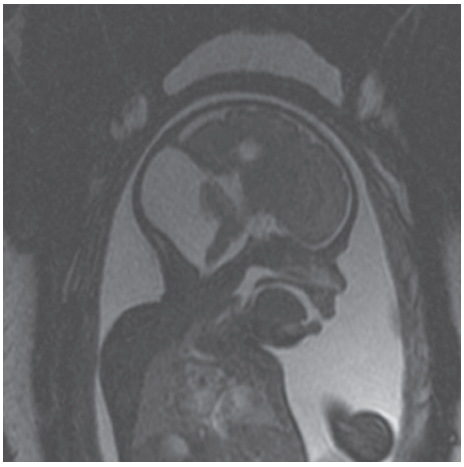
Splaying of the cerebellar hemispheres (arrows) and communication of the fourth ventricle with the cisterna magna (from Fetal Disorders, B Petrikovsky. Wiley-Liss, used with permission).



MRI image of Arachnoid cyst simulating Dandy-Walker Cyst.

teratogens including retinoic acid, warfarin, and congenital infections (cystomegalovirus and rubella) have been implicated.[7] Recurrence of isolated, nonsyndromic DWC is rare; the empiric recurrence risk is 1 to 5%.[2]

Prenatal evaluation should include a fetal karyotype; TORCH titers; and a detailed sonogram. Families should be offered the opportunity to meet with a pediatric neurosurgeon to discuss neonatal management. In the event of a fetal or neonatal demise, a complete autopsy should be performed and should include a fetal radiograph. 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 parental karyotypes to rule out a balanced translocation carrier.



MRI image of Dandy-Walker Cyst.

Mutations in ZIC genes (on chromosome 3) have recently been implicated in a wide variety of congenital malformations, including DWC, holoprosencephaly, neural tube defects, and heterotaxy.[6]

Neonatal Outcome

Outcome largely depends on the presence of associated brain malformations, e.g., agenesis of corpus callosum. Patients with DWC, however, are more likely to be hypotonic and ataxic secondary to the abnormal vermis. Some patients may have only mild clumsiness and are able to lead a normal life, including riding bicycles and enjoying athletic activities. The structure of the vermis appears crucial in predicting neurological outcome. If the vermis contains at least two fissures, three lobes, and a fastigium, the majority of affected children will do well. If the vermis is malformed, dysplastic, presenting with only one fissure or no fissure at all, the patient in this group may suffer from mental retardation.

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Maternal Use Of Selective Serotonin Reuptake Inhibitors During Pregnancy Is Associated With Hirschsprung's Disease In Newborns – A Nationwide Cohort Study

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Abstract

Background: Hirschsprung's disease is a rare condition caused by congenital malformation of the gastrointestinal tract affecting 1:5000 children. Not much is known about risk factors for development of Hirschsprung's disease. Two clinical cases of hirschsprung's disease led to an investigation of the association between maternal use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy and development of Hirschsprung's Disease in the newborn child. The study examined a nationwide, unselected cohort of children born in Denmark from 1 January 1996 until 12 March 2016 (n = 1,256,317). We applied multivariate models to register-based data to estimate the odds ratio of Hirschsprung's disease, adjusting for possible confounders. The studied exposure period for SSRIs were 30 days prior to conception to the end of the first trimester.

Results: In the main exposed cohort the prevalence of Hirschsprung's disease was 16/19.807 (0.08%) compared to 584/1.236.510 (0.05%) in the unexposed cohort. In women who redeemed a minimum of one prescription of selective serotonin reuptake inhibitors, the adjusted odds ratio for development of Hirschsprung's disease was 1.76 (95% CI: 1.07–2.92). In women who redeemed a minimum of two prescriptions, the adjusted odds ratio for Hirschsprung's disease was 2.34 (95% CI: 1.21–4.55).

Conclusions: Our data suggest that early maternal use of selective serotonin reuptake inhibitors is significantly associated with the development of Hirschsprung's disease in the newborn child. Treatment of depression during pregnancy always has to be weighed against the risks posed by untreated maternal depression. Our results have to be confirmed in other studies.

Keywords: SSRI, Congenital malformation, Hirschsprung's disease, Developmental biology, Enteric nervous system, Paediatric gastroenterology

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Background

The use of selective serotonin inhibitors (SSRIs) during pregnancy has increased significantly during the last two decades [1–3] and an increased risk of adverse birth outcomes has been reported, [4, 5] including neonatal complications [5], and groups of congenital heart and gastrointestinal malformations [4, 6–12]. Other studies have not found an increased risk of malformations [13–15].

Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter, which is important for the development of the enteric nervous system, and the migration of neural crest cells to the bowel wall during the first trimester [16–18]. SSRI intake during the first trimester might inhibit this process resulting in Hirschsprung's disease (HD). HD is a congenital malformation with aganglionosis of the enteric plexuses of the bowel wall that extends from the anal canal and proximally affecting a variable length of the colon. The clinical picture is ileus with megacolon or intractable constipation, which necessitates surgery in infancy or childhood [19] resulting in severe consequences of impaired bowel function with a mixture of constipation and in faecal incontinence in early life and later [20].

During the last decade the incidence of HD has doubled [21, 22] and since only a minority of HD cases have a known genetic aetiology, further investigation into non-genetic risk factors of HD is warranted [23].

The aim of the present study was to investigate the association between maternal prescription of SSRI in the period of 1 month prior to conception to the end of first trimester of pregnancy and having a child with the diagnosis of HD. To examine this association we used nationwide Danish register data.

Methods

Setting

A population-based nationwide cohort study was conducted using data from Danish health registries. The uniform organization and unrestricted access to a tax-funded universal healthcare system for all Danish residents, allowed us to use a population-based study design. We used the Danish National Patient Registry (NPR) [24], the Danish Medical Birth Registry (MBR) [25], the Nationwide Prescription Database [26], and the Central Personal Registration system [27]. All registries were linked using the civil registration number. All Danish residents are assigned a civil registration number at birth or when taking residence

Table 1 Characteristics of the exposed and unexposed cohorts. The exposed cohort was divided according to number of redeemed prescriptions of selective serotonin-reuptake inhibitors (SSRI's): minimum of one prescription, limited to one prescription, and minimum two prescriptions. Total number of children, *n* = 1.256.317

	SSRI prescriptions redeemed a minimum of one time (*n* = 19,807)	SSRI prescriptions redeemed one time only (*n* = 11.351)	SSRI prescriptions redeemed minimum two times (*n* = 8.456)	No prescriptions of SSRIs (*n* = 1.236.510)
Maternal age				
≤19	308 (1.6%)	184 (1.6%)	124 (1.5%)	18.039 (1.5%)
20–24	2.645 (13.4%)	1.530 (13.5%)	1.115 (13.2%)	145.031 (11.7%)
25–29	5.764 (29.1%)	3.234 (28.5%)	2.530 (29.9%)	415.536 (33.6%)
30–34	6.678 (33.7%)	3.779 (33.3%)	2.899 (34.3%)	437.740 (35.4%)
≥35	4.412 (22.3%)	2.624 (23.1%)	1.788 (21.1%)	220.164 (17.8%)
Maternal smoking status				
No	13.384 (67.6%)	7.838 (69.1%)	5.546 (65.6%)	946.853 (76.6%)
Yes	5.656 (28.6%)	3.095 (27.3%)	2.561 (30.3%)	186.807 (15.1%)
Missing	767 (3.9%)	418 (3.7%)	349 (4.1%)	102.850 (8.3%)
Sex of child				
Male	10.249 (51.7%)	5.862 (51.6%)	4.387 (51.9%)	601.949 (48.7%)
Female	9.558 (48.3%)	5.489 (48.4%)	4.069 (48.1%)	634.561 (51.3%)
Parity				
1	8.792 (44.4%)	4.912 (43.3%)	3.880 (45.9%)	545.646 (44.1%)
>1	11.015 (55.6%)	6.439 (56.7%)	4.576 (54.1%)	690.864 (55.9%)
Birth year				
1996–2001	1.972 (10.0%)	1.033 (9.1%)	939 (11.1%)	387.716 (31.4%)
2002–2007	6.077 (30.7%)	2.976 (26.2%)	3.101 (36.7%)	376.939 (30.5%)
2008–2011	6.787 (34.3%)	3.952 (34.8%)	2.835(33.5%)	240.952 (19.5%)
2012–2016	4.971 (25.1%)	3.390 (29.9%)	1.581 (18.7%)	230.903 (18.7%)

in Denmark, and this unique identifier was unambiguously used to link data on an individual level.

Study population

The study population included all live born children identified by the Medical Birth Registry [25] with a valid civil registration in Denmark from 1 January 1996 until 12 March 2016. By using information on the gestational age and delivery date, the date of conception was assessed for all children in the study population.

Data sources

Established in 1977, the NPR includes records of all discharges from Danish hospitals and since 1994 all outpatient visits. Information in the NPR includes patients' civil registration numbers and up to 20 discharge diagnoses based on the International Classification of Diseases (ICD-10 from 1994 onward) [24, 28]. The MBR consists of information on all births in Denmark since 1973 including pregnancy-related information i.e. gestational age, birth outcomes, and information on the mother, maternal civil registration number, maternal age, smoking status and parity. In 1997 the coding of maternal smoking was expanded to include possible registration of maternal smoking cessation during pregnancy. As this change was done during the study period, we reduced the complexity of the variable maternal smoking to yes (including any

Table 2 Odds ratio (OR) estimates for Hirschsprung's Disease from logistic regression models, crude and adjusted OR with 95% confidence interval (CI) for occurrence of Hirschsprung's Disease based on all live births in the period of 1 january 1996 until 12 March 2016

	SSRI prescriptions redeemed a minimum of one time	No prescriptions for SSRIs	Crude OR (95%CI)	Adjusted OR[a] (95%CI)
Child born with Hirschsprung's Disease	16/19.807 (0.08%)	584/1.236.510 (0.05%)	1.71 (1.04–2.81)	1,76 (1.07–2.92)
	SSRI prescriptions redeemed one time only	No prescriptions for SSRIs	Crude OR (95%CI)	Adjusted OR[a] (95%CI)
Child born with Hirschsprung's Disease	7/11.351 (0.06%)	584/1.236.510 (0.05%)	1.31 (0.62–2.75)	1.33 (0.63–2.83)
	SSRI prescriptions redeemed a minimum of two times	No prescriptions for SSRIs	Crude OR (95%CI)	Adjusted OR[a] (95%CI)
Child born with Hirschsprung's Disease	9/8.456 (0.11%)	584/1.236.510 (0.05%)	2.25 (1,17–4.36)	2.34 (1.21–4.55)

[a]Adjusted for maternal age (≤19, 20–24, 25–29, 30–34, ≥35), maternal smoking (yes/no), sex, of child (male/female), parity (1/<1), calendar year of birth (1996–2001, 2002–2007, 2008–2011, 2012–2016)

Table 3 Odds ratio (OR) estimates for Hirschsprung's Disease from logistic regression models, crude and adjusted OR with 95% confidence interval (CI) for occurrence of Hirschsprung's Disease based on all live births in the period of 1 january 1996 until 12 March 2016. All women with prescriptions 3 months prior to time of conception of antiepileptic, antidiabetic, antipsychotics, anxiolytic and tricyclic antidepressants are excluded from the population

	SSRI prescriptions redeemed a minimum of one time	No prescriptions for SSRIs	Crude OR (95%CI)	Adjusted OR[a] (95%CI)
Child born with Hirschsprung's Disease	13/16.395 (0.08%)	561/1.207.989 (0.05%)	1.71 (0.99–2.96)	1.76 (1.01–3.07)
	SSRI prescriptions redeemed one time only	No prescriptions for SSRIs	Crude OR (95%CI)	Adjusted OR[a] (95%CI)
Child born with Hirschsprung's Disease	6/9.663 (0.06%)	561/1.207.989 (0.05%)	1.34 (0.60–3.00)	1.38 (0.61–3.09)
	SSRI prescriptions redeemed a minimum of two times	No prescriptions for SSRIs	Crude OR (95%CI)	Adjusted OR[a] (95%CI)
Child born with Hirschsprung's Disease	7/6.732 (0.10%)	561/1.207.989 (0.05%)	2.24 (1.06–4.72)	2.32 (1.10–4.90)

[a]Adjusted for maternal age (≤19, 20–24, 25–29, 30–34, ≥35), maternal smoking (yes/no), sex, of child (male/female), parity (1/<1), calendar year of birth (1996–2001, 2002–2007, 2008–2011, 2012–2016)

smoking and smoking cessation during pregnancy), no (no smoking whatsoever) [25].

The Danish Medicine Agency maintains a nationwide prescription database for all reimbursed drug prescriptions issued from Danish pharmacies. The database includes for each prescription, patients' civil registration number, medication dosage, package size, date of reimbursement and drug classification code, according to the anatomical therapeutic chemical (ATC) classification system [29]. As only prescription drugs are registered in the Nationwide Prescription Database, over-the-counter-sale is not included. However, SSRI are only available by prescription in Denmark. The Central Personal Registration system consists of information on civil registration number, death and immigration.

Exposed cohort, children born of women exposed to SSRI

Main cohort

For the children in the study population, information was collected on maternal prescriptions of SSRI (ATC: N06AB03, N06AB04, N06AB05, N06AB06, N06AB08, N06AB10) from 30 days before conception to end of first trimester (end of 12th week of pregnancy). The main exposed cohort, thus, included children of women who had filled one or more prescriptions from 30 days before conception to end of first trimester.

Sub-cohort I

Sub-cohort I was defined as all children in the main cohort where the mothers filled one single SSRI prescription from 30 days before conception to end of first trimester.

Sub-cohort II

Sub-cohort II was defined as all children in the main cohort where the mothers filled two or more SSRI prescriptions from 30 days before conception to end of first trimester.

Unexposed cohort, children born of women not exposed to SSRI

The unexposed cohort constituted all children included in the study population where mothers did not fill prescriptions of SSRI from 30 days before conception to end of first trimester.

Outcome

Outcome information was obtained from the NPR and defined as any child with a diagnosis of HD (ICD-10: DQ431) from 1 January 1996 until 12 March 2016.

Information on possible confounders

From the Maternal Birth Registry (MBR) [25], we obtained information on the age of the mother (≤19, 20–24, 25–29, 30–34 ≥ 35 years) at the time of delivery, parity (one or more than one pregnancy), sex of the child, maternal smoking during pregnancy (yes/no), and calendar year of birth (1996–2001, 2002–2007, 2008–2011, 2012–2016).

Statistical analysis

We constructed contingency tables for the main study variables according to the exposed and unexposed cohorts. We used logistic regression analyses to compute crude and adjusted odds ratio estimates (prevalence odds ratio with 95% confidence intervals [95% CI]) for HD following maternal use of SSRI relative to no maternal use of SSRI. These analyses were performed for the main cohort, sub-cohort I, and sub-cohort II, all relative to the unexposed cohort.

Adjustment was made for maternal age (≤19, 20–24, 25–29, 30–34 ≥ 35 years), maternal smoking status (yes/ no), parity (one or more than one pregnancy), sex of the child, and calendar year of birth (1996–2001, 2002–2007, 2008–2011, 2012–2016).

Sub-analysis

To exclude an underlying effect of other maternal disease that might be associated with malformations and use of SSRI we performed a sub-analysis. We excluded children from the exposed and unexposed cohort where the mothers had reimbursed prescriptions for any of the following medications: antiepileptic drugs (ATC: N03A), antidiabetic drugs (ATC: A10), antipsychotic drugs (ATC: N05A), anxiolytics (ATC: N05B), and tricyclic antidepressants (ATC:N06AA) 3 months prior to conception and until the end of 12th week of pregnancy. Again we used logistic regression analyses to compute crude and adjusted odds ratio estimates for HD following maternal use of SSRI, and included in the model were the same covariates as in the main analyses.

All calculations were performed using STATA Release 14.0 (StataCorp, College Station, TX, USA).

Results

A total of 1.256.317 children were included, and of these, 19.807 children were born by women who had filled one or more prescriptions of SSRIs 30 days before conception to the end of

the first trimester. Sub-cohort I included 11.351 children born by women who had filled only one SSRI prescription within30 days before conception to the end of the first trimester, and sub-cohort II included 8.456 children born by women who had filled two or more SSRI prescriptions within 30 days before conception to the end of the first trimester. A total of 1.236.510 children were born by mothers who were not exposed to SSRI 30 days before conception to the end of the first trimester. The characteristics of the exposed and unexposed cohorts are shown in Table 1, and the basic characteristics were similar according to mother's age at delivery, sex of child and parity. Maternal smoking was more frequent in the main exposed cohort (28.6%) compared to the unexposed cohort (15.1%).

In the main exposed cohort we found that 16 out of 19.807 (0.08%) of the children had a diagnosis of HD, and among the unexposed cohort 584 out of 1.236.510 (0.05%) had HD, corresponding to an adjusted OR for HD of 1.76 (95% CI 1.07–2.92) (Table 2). In sub-cohort I (only one redeemed prescription), 7 out of 11.351 (0.06%) had a diagnosis of HD (corresponding to an adjusted OR for HD of 1.33 (95% CI 0.63–2.83) (Table 2). In children in sub-cohort II (a minimum of two redeemed prescriptions), 9 out of 8.456 (0.11%) had a diagnosis of HD, and the adjusted OR for HD was 2.34 (95% CI 1.21–4.55) (Table 2).

In our sub-analysis we excluded women with prescriptions of antiepileptic, antidiabetic, antipsychotics, anxiolytic and tricyclic antidepressants, and a total of 16.395 children were born by women who had filled one or more prescription of SSRI 30 days before conception to the end of the first trimester. A total of 1.207.989 children were born to women not exposed to SSRI. The basic characteristics were similar between the exposed and unexposed (Additional file 1). A total of 13 children were born with HD out of 16.395 (0.08%), corresponding to an adjusted OR for HD of 1.76 (95% CI 1.01–3.07) (Table 3). In sub-cohort I, a total of 6 children had HD out of 9.663 (0.06%) corresponding to an adjusted OR for HD of 1.38 (95% CI 0.61–3.09). In sub-cohort II, a total of 7 children had HD out of 6.732 (0.10%), corresponding to an OR for HD of 2.32 (95% CI 1.10–4.91) (Table 3).

Discussion

The results of our study demonstrated a significantly increased risk of HD after maternal exposure to SSRI. The analyses indicated that only one redeemed prescription for SSRI was associated to a 1.3 fold increased risk of HD, and a minimum of two redeemed prescriptions was associated to a 2.3 increased risk, indicating a dose-response relationship between SSRI and development of HD.

A review of the literature did not yield any previous studies that demonstrated an association between maternal use of SSRIs and HD. The majority of population-based studies examined different groups of congenital malformations [4, 6–10] and none have had specific focus on the association between HD and SSRIs. The aetiology of various congenital malformations differ, and the clustering of gastrointestinal malformations in one group for analyses may render previous studies unable to show a specific association between SSRIs and HD. HD is a rare disease (1:5000 live births) and most of the previous studies may lack the statistical power to find significant associations between maternal use of SSRI and specific malformations [4, 6, 8, 13, 14].

The strengths of the present study were that it was based on nationwide registers and included information on all children in Denmark during the study period. We had no loss to follow up which prevents selection bias. The information on maternal drug exposure was based on prescriptions and not on patient recall therefore eliminating recall bias. Information on the outcome (HD) was collected independently of the exposure status and thereby preventing information bias. In Denmark, HD is treated in one of two national centres and internal review of the HD diagnosis from one of these centres (Odense University Hospital), verified that all HD diagnoses from the NPR was given on the basis of histopathological examination of rectal biopsies or surgical specimens (unpublished data). The validity of the diagnosis of HD is therefore considered high. In our study we had access to a complete nationwide prescription database, ensuring that all mothers could be classified according to the possible prescriptions for SSRIs during the pre-conception period and during early pregnancy. The data in the prescription database are of high quality as previously documented [30]. Furthermore it is strength that we, in sub-analyses, were able to eliminate a possible confounding impact of other maternal underlying diseases that at least in the theory could be associated to congenital malformations. In sub-analyses, we thus excluded women using medications for epilepsy, diabetes, and those who used antipsychotics, anxiolytics and tricyclics antidepressants; and we found that our results were robust as the results from the sub-analyses were similar to our main analyses. With regard to possible confounders, we were able to take into consideration several possible confounders, but the impact of these was limited as the crude and adjusted risk estimates were similar. Overall, the external validity of our study is considered good and applicable to other populations.

Possible limitations of this study were lack of information on drug compliance. We used prescription data as a proxy for drug intake. Previous studies in pregnant women indicated a high rate of compliance in the use of antidiabetic, antibiotic and thyroid medication [31–33].

Patient compliance of antidepressant treatment in Denmark has previously been estimated to 80% [34] and similar findings were found in a Swedish study based on patient interviews (83%) [35]. Any potential misclassification of exposure due to patient non-compliance would, however, tend to underestimate our risk estimates. A high degree of non-compliance could therefore mask a true association. In addition, we did not have enough data to look into the impact of specific types of SSRI. The few number of children born with HD among exposed women did not allow us to give results according to specific types of SSRIs. In a cohort study like this, it may be difficult to isolate the effects of drug treatment, and in case of a statistical significant association (as in our study), it is necessary to consider whether the result is influenced by residual or unmeasured confounding. We had no opportunity to adjust our analyses for severity of underlying depression, and it is unknown whether maternal depression may predispose to HD. An association between major congenital malformation and depression has not been documented [36–38] and HD-associated genes do not match genes associated with depression [39, 40]. Development of the enteric nervous system is dependent on epigenetic stability [41] and maternal depression is associated with epigenetic changes within the DNA of the offspring, including a gene encoding a trans membrane serotonin transporter that regulates the intrasynaptic reuptake of serotonin. This would lead to less intrasynaptic 5-HT, the exact

opposite effect of an SSRI, which increases intrasynaptic 5-HT [42]. Other studies did not find epigenetic changes related to maternal depression [43].

HD phenotypes can arise from different genotypes [44] and the genes associated with the most common type of HD (short-segmented HD) are likely to have possible environmental interactions [39, 45]. While discussing confounding by indication in relation to depression and HD it is therefore important to note that depression during pregnancy may be associated with poor nutrition, obesity, smoking, alcohol, and drug abuse [37, 38]. These risk factors can influence the development of the enteric nervous system (causing HD, but the relation between environmental risk factors and HD is not well documented [21, 46]. Maternal smoking has been linked to an increase in gastrointestinal malformations [47], but no association between smoking and HD has been found [48]. One study has reported that vitamin A deficiency (as a proxy for poor nutrition) can impair development of the enteric nervous system and cause a HD-like condition in mice [49]. This is interesting since folic acid supplement compliance during pregnancy is poor especially in young, smoking women with low levels of education [50]. No information on nutritional habits including supplement of vitamins were included in the present study. Maternal obesity may increase the risk of HD [48], but it was not possible to include this information in this study.

Conclusions

Our data suggest that use of SSRIs in the period of 30 days before conception to end of the first trimester is associated to an increased risk of HD. We cannot rule out that our results might be influenced by unknown confounders, and we do not know whether the increased risk of HD might be associated to specific types of SSRIs. Our results need to be confirmed in other settings, and in the future we need data on a possible impact of specific types of SSRIs. Treatment of depression during pregnancy always has to be weighed against the risks posed by untreated maternal depression during pregnancy, but restrain should be shown in fertile women, who do not use effective contraceptive measures or are planning to become pregnant.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to Danish data protection law. Datasets can be made available from the corresponding author on reasonable request and under condition of prerequisite approval of the Danish Health authorities.

Authors' contributions

NSW: conception, funding, design, interpretation of results, manuscript writing. NJ: data collection, data analyses, interpretation of results, manuscript editing. LPM: assistance with data analysis, interpretation of results, manuscript editing. NBM: funding, design, data collection, assistance with data analysis, interpretation of results. QN: conception, funding, interpretation of results, manuscript editing. All authors edited and approved the final version.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by the Danish Data Protection Agency (j.nr. 15/43761). According to Danish law, no ethical approvals of register-based studies are necessary.

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Incidence, Clinical Features, And Implications On Outcomes Of Neonatal Late-Onset Sepsis With Concurrent Infectious Focus

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Abstract

Background: Neonatal bloodstream infection (BSI) is the most important cause of morbidity and mortality in the neonatal intensive care unit (NICU). Although most neonatal BSIs are primary bacteremia, some are associated with a focus of infection. This distinction is not well characterized.

Methods: All patients with neonatal late-onset sepsis (LOS) between January 2006 and December 2013 were enrolled. LOS was categorized as a BSI with a concurrent focus of infection if LOS occurred before or within 24 h after the diagnosis of a specific infectious entity, and as "primary bacteremia" if no concurrent focus of infection was identified. Data concerning demographics, hospital course, microbiology, and outcomes were compared via univariate and multivariate analyses.

Results: Of 948 episodes of neonatal LOS, 781 (82.4%) were primary bacteremia, whereas 167 (17.6%) were associated with a known focus of infection, including meningitis (n = 51, 5.4%), ventilator-associated pneumonia (VAP) (n = 36, 3.8%), catheter-related bloodstream infections (n = 57, 6.0%), and necrotizing enterocolitis (NEC) (n = 21, 2.2%). The majority of NEC-associated BSIs were caused by gram-negative bacilli (85.7%). Group B streptococcus accounted for nearly one-third of all meningitis cases (29.4%). Although sepsis-attributable mortality was comparable between primary bacteremia and neonatal BSIs with a focus of infection, neonatal BSIs with meningitis, VAP, and NEC had significantly higher rates of infectious complications. The independent risk factors of sepsis-attributable mortality were infectious complications (Odds ratio [OR] 6.98; 95% confidence interval [CI] 3. 64–13.39, $P < 0.001$); history of one or more than one previous episode(s) of BSI (OR 2.40 and 7.40; 95% CI 1.21–4.74 and 3.70–14.78, $P = 0.012$ and <0.001, respectively); and underlying secondary pulmonary hypertension in neonates (OR 4.77; 95% CI 1.91–11.96, $P = 0.001$).

Conclusions: A considerable proportion of neonatal LOS can be associated with known infectious foci in the NICU. The microbiologic etiology of neonatal LOS with a concurrent focus of infection is significantly different from that of primary bacteremia. Neonatal BSIs with concurrent meningitis, VAP, or NEC are significantly more likely to have infectious complications. This association independently leads to sepsis-attributable mortality.

Keywords: Bacteremia, Neonates, Catheter-related bloodstream infection, Late-onset sepsis, Risk factor

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Background

Bloodstream infection (BSI) is the most common nosocomial infection in the neonatal intensive care unit (NICU) [1, 2], and accounts for the most important cause of morbidity and mortality after these neonates have survived the perinatal insults and complications of extreme prematurity [3, 4]. Neonates with certain underlying chronic comorbidities are more likely to have severe infection or die after BSI [5, 6]. Factors predisposing to morbidity or mortality after neonatal BSI include prolonged use of a central catheter and/or ventilation, recurrent nosocomial infections, and possibly, immunosuppression caused by the use of broad-spectrum antibiotics [3–5]. Similarly, concurrent neonatal BSIs with infectious complications are often more severe, and sometimes may require surgical intervention [7, 8].

Our recent study has demonstrated that concurrent meningitis and ventilator-associated pneumonia were independent predictors of treatment failure in neonatal BSI [6]. Bizzarro et al. also showed that infants with necrotizing enterocolitis (NEC)-associated BSI are significantly more likely to die than are those with post-NEC BSI and NEC without BSI [9]. An episode of BSI with concurrent infectious focus may impose greater therapeutic challenge, and adequate infectious source control plays an important role in optimizing treatment response. There have been several studies in adults that investigated BSI with concurrent skin and soft tissue infection, bacteriuria, gastroenteritis, or pneumonia [10– 14], but the epidemiology and outcomes of neonatal BSIs with a concurrent infectious entity are poorly characterized. Therefore, we conducted a retrospective cohort study to determine the risk factors for, specific microbiology of, and clinical implications of neonatal BSI with a concurrent focus of infection.

Methods

Study setting, subjects and ethics

The Chang Gung Memorial Hospital (CGMH) is a tertiary-level medical center in a university-affiliated teaching hospital

Table 1 Pathogens causing a total of 948 episodes of primary bloodstream infection (BSI) and 123 episodes of BSI with specific infectious focus in the neonatal intensive care unit

	Neonatal BSIs with specific infectious focus (total *n* = 167)					Primary bacteramia (total *n* = 781)
	Meningitis (total *n* = 51)	Ventilator associated pneumonia (*n* = 36)	CLABSI (*n* = 57)	Necrotizing enterocolitis (*n* = 21)	Others[c] (*n* = 7)	
Gram-positive organism						
Coagulase-negative *Staphylococcus*	4 (7.8)	0 (0)	25 (43.9)	3 (14.3)	1 (14.3)	332 (42.5)
Staphylococcus aureus	9 (17.6)	9 (25.0)	11 (19.3)	0 (0)	4 (57.1)	89 (11.4)
Enterococcus species	2 (3.9)	1 (2.8)	1 (1.8)	0 (0)	0 (0)	22 (2.8)
Group-B streptococcus	15 (29.4)	1 (2.8)	0 (0)	0 (0)	0 (0)	10 (1.3)
Streptococcus pneumoniae	0 (0)	1 (2.8)	0 (0)	0 (0)	0 (0)	2 (0.2)
Viridan Streptococcus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.2)
Gram-negative organism						
Klebsiella pneumoniae	5 (9.8)	6 (16.7)	5 (8.8)	3 (14.3)	0 (0)	72 (9.2)
Klebsiella oxytoca	0 (0)	1 (2.8)	1 (1.8)	0 (0)	0 (0)	22 (2.8)
Escherichia coli	7 (13.7)	3 (8.3)	2 (3.5)	8 (38.1)	1 (14.3)	59 (7.5)
Enterobacter cloacae	1 (2.0)	1 (2.8)	1 (1.8)	0 (0)	0 (0)	21 (2.7)
Enterobacter aerogenes	0 (0)	1 (2.8)	1 (1.8)	1 (4.8)	0 (0)	13 (1.7)
Pseudomonas aeruginosa	2 (3.9)	2 (5.6)	1 (1.8)	1 (4.8)	0 (0)	10 (1.3)
Acinetobacter baumannii	1 (2.0)	3 (8.3)	1 (1.8)	1 (4.8)	0 (0)	36 (4.6)
Serratia marcescens	2 (3.9)	1 (2.8)	2 (3.5)	2 (9.5)	0 (0)	6 (0.8)
Others[a]	2 (3.9)	1 (2.8)	1 (1.8)	0 (0)	0 (0)	8 (1.3)
Fungus						
Candida albicans	1 (2.0)	0 (0)	4 (7.0)	2 (5.6)	0 (0)	18 (2.3)
Candida parapsilosis	0 (0)	0 (0)	1 (1.8)	0 (0)	0 (0)	13 (1.7)
Other *Candida* spp.	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	11 (1.4)
Polymicrobial microorganisms[b]	0 (0)	3 (8.3)	0 (0)	2 (9.5)	1 (14.3)	35 (4.5)

CLABSI central line-associated bloodstream infection
[a]Including *Citrobacter freundii* (3), *Stenotrophomonas maltophilia* (3), *Hafnia alvei* (2), *Neisseria meningitidis* (2), *Chryseobacterium meningoseptium* (1) and *Flavobacterium* (1)
[b]Indicating two or more microorganisms were recovered from the same blood culture set
[c]Including osteomyelitis (2), septic arthritis (2), upper limbs cellulitis (2), and urinary tract infection (1)

in northern Taiwan. The CGMH's NICU has three units that include a total of 49 beds equipped with mechanical ventilators, and 28 beds in special-care nurseries. All babies under 34–35 weeks gestation or birth weight < 2 kg or >5 kg, and those with any clinical signs of respiratory distress or cardiovascular, gastrointestinal, or neurological problems requiring surgical or intensive treatment were eligible for admission to this NICU. We identified all episodes of cultureproven BSI in the NICU of CGMH between 1 January 2006 and 31 December 2013. All BSIs identified were "late-onset", defined as a positive blood culture occurring at >72 h of life [1, 4, 15]. This study was approved by the institutional review board of Chang Gung Memorial Hospital, with a waiver of informed consent because all patient records and information were anonymized and de-identified prior to analysis.

Data retrieval and study database

For more than ten years, the NICU at CGMH has had an electronic database maintained by a full-time nurse specialist dedicated to following neonates from birth (or admission if the neonate was transferred from another hospital) until discharge or death. The NICU database contains information on basic demographic data, perinatal insults, and complications of prematurity, a summary of the patient's hospital course, chronic comorbidities, and discharge diagnosis. Utilizing this database, we characterized in detail the course of every episode of BSI, including the clinical manifestations, laboratory results, microbiological data, concurrent focus of infection, treatment, infectious complications, and outcomes. The severity of illness was evaluated at the time of greatest severity during the course of BSI using the neonatal therapeutic intervention scoring system (NTISS) [16].

Definitions

An episode of BSI was defined according to the presence of clinical sepsis and the identification of pathogens, which included any bacteria isolated from at least one blood culture and not consisting of saprophytic skin flora [17]. *Corynebacterium* spp., *Propionibacterium* spp., *Penicillium* spp., and *Diphtheroids* spp. were considered contaminants in blood cultures, and were excluded from consideration. For coagulase-negative staphylococci (CoNS), the diagnosis of BSI required clinical signs of sepsis, and a blood culture positive for CoNS. The indicated treatment for CoNS BSI included intravenous antibacterial therapy for at least 5 days after the date of the blood culture (or until death) [1, 4]. We defined all concurrent infectious foci, including NEC, ventilator associated pneumonia (VAP), central line-associated bloodstream infection (CLABSI), and meningitis according to the U.S. Centers for Disease Control and Prevention's (CDC's) National Healthcare Safety Network (NHSN) definitions [8, 18–20]. Only cases with NEC ≥ stage IIA in modified Bell's criteria (definite

Table 2 Episodes of neonatal bloodstream infections stratified according to primary bacteremia and bacteremia with various foci of infection

Characteristics	Neonatal BSIs with specific focus of infection (total *n* = 167)					Primary bacteremia (*n* = 781)
	Meningitis (*n* = 51)	VAP (*n* = 36)	CLABSI (*n* = 57)	NEC (*n* = 21)	Others[b] (*n* = 7)	
Demographic characteristics						
Birth body weight (g), median (IQR)	2375 (1405–2905)**	960 (820–1600)**	1267.5 (911–2680)	1480 (1065–2040)*	2330 (1600–2700)*	1240 (880–1880)
Gestational age (weeks), median (IQR)	35.0 (30.0–38.0)**	27.0 (25.0–31.0)**	29.5 (27.0–37.0)	29.0 (27.0–34.0)	37.0 (32–38)**	30.0 (27.0–34.0)
Male sex, n (%)	30 (58.8)	21 (58.3)	29 (50.9)	10 (47.6)	5 (71.4)	405 (51.9)
Onset of BSI (day), median (IQR)	33.5 (17.8–60.3)	30 (20–58)*	25 (17–45.5)	19 (12–43)**	42 (11–73)	28 (17.0–53.0)
Perinatal history						
Low Apgar score at 5 min (≦ 7)	13 (25.5)**	22 (61.1)**	26 (45.6)	5 (23.8)**	2 (28.6)**	351 (44.9)
Perinatal asphyxia	6 (11.8)	13 (36.1)**	4 (7.0)	2 (9.5)	0 (0)	62 (7.9)
Underlying chronic conditions[a]						
Congenital anomalies	2 (3.9)	2 (5.6)	4 (7.0)	0 (0)	2 (28.6)	55 (7.0)
Neurological comorbidities	23 (45.1)**	5 (13.9)	3 (5.3)	1 (4.8)	1 (14.3)	91 (11.7)
Complicated congenital heart disease	0 (0)	0 (0)	3 (5.3)	0 (0)	0 (0)	32 (4.1)
Acyanotic CHD with heart failure	0 (0)	1 (2.8)	3 (5.3)	0 (0)	0 (0)	17 (2.2)
Bronchopulmonary dysplasia	9 (17.6)	23 (63.9)**	15 (26.3)	6 (28.6)	2 (28.6)	243 (31.1)
Pulmonary hypertension	1 (2.0)	1 (2.8)	3 (5.3)	0 (0)	0 (0)	23 (2.9)
Gastrointestinal pathology	0 (0)	1 (2.8)	4 (7.0)	3 (14.3)	0 (0)	54 (6.9)
Renal	1 (2.0)	1 (2.8)	2 (3.5)	1 (4.8)	0 (0)	25 (3.2)
Cholestasis[b]	4 (7.8)	9 (25.0)	13 (22.8)	6 (28.6)	4 (57.1)**	147 (18.8)
Clinical septic symptoms						
Fever (temperature > 38 °C)	33 (64.7)	8 (22.2)	26 (45.6)	6 (28.6)	4 (57.1)	319 (40.8)
Apnea ± bradycardia and/or cyanosis	31 (60.8)	32 (88.9)	40 (70.2)	16 (76.2)	5 (71.4)	528 (67.6)
Abdominal distension ± feeding intolerance	31 (60.8)	27 (75.0)*	27 (47.4)	21 (100)**	5 (71.4)*	457 (58.5)
Tachycardia	15 (29.4)	5 (13.9)	13 (22.8)	6 (28.6)	1 (14.3)	177 (22.7)
Hyper- or hypoglycemia	14 (27.5)	14 (38.9)	11 (19.3)	8 (38.1)	1 (14.3)	206 (26.4)
Septic shock	8 (15.7)	11 (30.6)*	6 (10.5)	9 (42.9)**	2 (28.6)	126 (16.1)
Disseminated intravascular coagulopathy	8 (15.7)*	5 (13.9)	3 (5.3)	5 (23.8)*	1 (14.3)	62 (7.9)
Laboratory parameter						
Leukopenia (WBC count <4000/uL)	12 (23.5)	6 (16.7)	5 (8.8)	9 (42.9)**	3 (42.9)**	127 (16.3)
Leukocytosis (WBC count >20,000/uL)	14 (27.5)	14 (38.9)*	13 (22.8)	5 (23.8)	4 (57.1)**	217 (27.8)
WBC shift to left (immature WBC ≧ 20%)	10 (19.6)	7 (19.4)	3 (5.3)	7 (33.3)**	1 (14.3)	89 (11.4)

Table 2 Episodes of neonatal bloodstream infections stratified according to primary bacteremia and bacteremia with various foci of infection *(Continued)*

Anemia (hemoglobin <11.0 mg/dL)	22 (43.1)	23 (63.9)**	26 (45.6)	13 (61.9)**	2 (28.6)	291 (37.3)
Thrombocytopenia (platelet <80,000/uL)	16 (31.4)	21 (58.3)**	19 (33.3)	11 (52.4)**	1 (14.3)	267 (34.2)
Metabolic acidosis	12 (23.5)	15 (41.7)**	6 (11.8)	10 (47.7)**	1 (14.3)	139 (17.8)
Prolonged PT and/or aPTT	12 (23.5)	11 (30.5)	12 (21.1)	11 (52.4)**	1 (14.3)	196 (25.1)
Sequences of BSI during hospitalization						
1st episode	41 (80.4)	27 (75.0)	42 (73.7)	19 (90.5)	4 (57.1)	584 (74.8)
2nd episode	7 (13.7)	6 (16.7)	12 (21.1)	1 (4.8)	2 (28.6)	126 (16.1)
3rd (or greater) episode	3 (5.9)	3 (8.3)	3 (5.3)	1 (4.8)	1 (14.3)	71 (9.1)

All data were expressed as number (percentage %), unless indicated otherwise
NTISS neonatal therapeutic intervention scoring system, *IQR* interquartile range, *SD* standard deviation, *BSI* bloodstream infection, *NSD* natural vaginal delivery, *C/S* cesarean section
*$P < 0.05$; **$P < 0.001$; *P* values are the comparisons between BSIs with specific infectious focus and primary bacteremia
[a]Indicating the presence of chronic conditions or comorbidities at onset of bloodstream infection, and some patients had >1 underlying chronic conditions. Each patient with an underlying chronic condition is compared with those without that specific condition
[b]Indicating direct bilirubin ≥1.5 mg/dL or more than 50% of the total bilirubin

NEC) were enrolled, and clinically defined VAP cases were considered [8]. An episode of BSI was defined as "BSI with concurrent infectious focus" if the onset of BSI (defined as the timing of the first positive blood culture was drawn) was accompanied with a specific infectious entity, i.e. meningitis, VAP, or NEC, otherwise, this BSI was categorized as "primary bacteremia". In this definition, the onset of BSI was always within 24 h (before or after) of the diagnosis of a specific infectious entity.

A patient was said to have an episode of clinical sepsis if the patient had a positive blood culture and was treated with antibiotic therapy for 5 or more days (or was treated for a shorter period if the patient died) and had at least two of the following clinical symptoms of sepsis: fever or hypothermia, hyper or hypoglycemia, apnea or tachypnea, frequent oxygen desaturation with an increased requirement for ventilator support, bradycardia and/or cyanosis, feeding intolerance, abdominal distension, seizures, decreased motor activity, skin mottling, and hypotension [1, 4]. The microbiological assay system in our hospital is a matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) system (Bruker's flagship FLEX series) [21].

The diagnosis of all co-morbidities of prematurity, including respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), broncho-pulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and peri-ventricular leukomalacia (PVL) was based on the latest updated diagnostic criteria [22]. Congenital anomalies included either documented or undocumented syndromes, chromosomal abnormalities, and genetic or metabolic disorders, but not simple cleft palate or polydactyly. Persistent BSI or fungemia was defined as three or more consecutive positive blood cultures, at least 48 h apart, during a single episode of sepsis [23].

Infectious complications were defined as a new-onset focus of infection, empyema, abscess, venous thrombosis, or vegetation directly related to bacteremia or major organ dysfunction within 1 week after the onset of bacteremia. Empiric antibiotic therapy was considered inappropriate if the treatment regimen did not include at least one antibiotic active in vitro against the infecting microorganisms, administered within 24 h of blood culture collection. For patients who died during hospitalization, the cause of death was recorded according to the clinician's assessment. Sepsis-attributable mortality was defined as death of a neonate within 3 days after the onset of sepsis or death from of infectious complications or clinically progressive deterioration following the onset of BSI.

Statistical analysis

Descriptive data all episodes of neonatal BSI were expressed as mean and standard deviation (SD) or median and IQR (interquartile range), where appropriate, for continuous data and absolute number and percentage for dichotomous data. Infecting organisms responsible for BSI in infants with infectious entities associated and primary BSI were compared via χ^2 analysis and presented as unadjusted OR with 95% CI. If an infant had multiple episodes of sepsis, each episode was considered as an independent event.

In univariate analyses, continuous data were analyzed using the Kruskal-Wallis and Mann-Whitney U tests, where appropriate. Dichotomous data were analyzed using χ^2 test and Fisher

Table 3 Treatment and outcomes of neonatal bloodstream infections among the three CRP groups

	Neonatal BSIs with specific infectious focus (total *n* = 167)					Primary bacteremia (*n* = 781)
	Meningitis (*n* = 51)	VAP (*n* = 36)	CLABSI (*n* = 57)	NEC (*n* = 21)	Others[#] (*n* = 7)	
NTISS score, (mean ± SD)	15.4 ± 5.1	19.8 ± 4.0**	16.8 ± 4.0	19.0 ± 6.5**	14.7 ± 6.1	16.9 ± 4.5
Ventilator requirement						
Prolonged invasive intubation (≥ 7 days)	14 (27.5)	22 (61.1)**	19 (33.3)	8 (38.0)	2 (28.6)	287 (36.7)
High frequency oscillatory ventilator	0 (0)	14 (38.9)**	3 (5.3)	4 (19.0)*	0 (0)	71 (9.1)
Inadequate antibiotic treatment within the first 24 h	10 (19.6)*	8 (22.2)	17 (29.8)	7 (33.3)	4 (57.1)**	217 (27.8)
Outcomes						
Infectious complications	18 (35.3)**	10 (27.8)**	6 (10.5)	5 (23.8)**	0 (0)	68 (8.7)
Sepsis attributable mortality	5 (9.8)	4 (11.1)	3 (5.3)	3 (14.3)	1 (14.3)	53 (6.8)

The *P* values are the comparisons between neonatal BSIs with infectious focus and primary bacteremia
*$P < 0.05$
**$P < 0.001$

exact test, where appropriate. A *P* value <0.05 was considered statistically significant. BSI-attributable mortality was assessed as the dependent variable in a multivariate logistic regression model. This model incorporated variables identified in a univariate regression model with a *P* value of <0.10. Estimates were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were performed using SPSS version 21.0 (SPSS, Chicago, IL, USA).

Results

A total of 948 episodes of BSI were identified in 732 infants during this study period, of which 781 (82.4%) were primary bacteremia and 167 (17.6%) had a specific focus of infection. The incidence rate of neonatal BSI during this study period was 3.71 per 1000 neonate-hospital days. Among those with concurrent infection, 51 (45%) BSIs had meningitis, 36 (23%) were VAP, 21 (23%) were NEC, and 57 (28%) were CLABSI. Other uncommon foci of infection included osteomyelitis (2), septic arthritis (2), upper limbs cellulitis (1), and urinary tract infection (1). Among these 167 BSIs with a focus of infection, five (3.0%) had more than two infectious foci. The microbiology of BSIs with concurrent infection was distinctively different from that of primary bacteremia (Table 1). The majority of NEC-associated BSIs were caused by gram-negative bacilli (85.7%) and group B streptococcus accounted for nearly one-third of all meningitis cases (29.4%). More than half cases of VAP- and CLABSI-associated BSIs were attributable to gram-negative bacilli (61.1%) and gram-positive pathogens (64.9%), respectively.

Demography, hospital course, underlying chronic comorbidities, and treatment for all neonatal BSIs with concurrent infection were evaluated comparing with primary BSIs (Table 2). Neonates with BSIs concurrent with meningitis had a significantly higher birth weight and later gestational age than neonates with primary bacteremia, whereas neonates with BSIs concurrent with VAP had a significantly lower birth weight and gestational age than neonates with primary bacteremia. Neonatal BSIs with concurrent NEC and neonatal BSIs with concurrent VAP tended to occur earlier and later than primary bacteremia, respectively. VAP associated BSIs were more likely to occur in neonates with low Apgar score (≤ 7) at five minutes and in those with perinatal asphyxia.

Table 4 Risk factors for sepsis-attributable mortality in neonatal bloodstream infections with and without a focus of infection

Variables	Univariate analysis		Multivariate logistic regression analysis	
	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Gestational age (weeks)	0.95 (0.90–1.01)	0.126	-	-
Inappropriate antibiotics	1.64 (1.01–2.73)	0.048	1.05 (0.57–1.94)	0.872
Presence of infectious complications	6.19 (3.61–10.62)	< 0.001	6.98 (3.64–13.39)	< 0.001
Sequence of bloodstream infections				
1st episode	1 (reference)		1 (reference)	
2nd episode	2.90 (1.57–5.41)	0.001	2.40 (1.21–4.74)	0.012
3rd (or greater) episode	8.53 (4.63–15.71)	< 0.001	7.40 (3.70–14.78)	< 0.001
Underlying pulmonary hypertension	8.11 (3.58–18.35)	< 0.001	4.77 (1.91–11.96)	0.001
Underlying neurological comorbidities	2.80 (1.59–4.93)	< 0.001	1.89 (0.99–3.61)	0.053
BSIs with and without infectious focus				
Primary bacteremia	1 (reference)		-	-
With concurrent meningitis	1.05 (0.34–3.21)	0.937	-	-
With concurrent ventilator-associated pneumonia	1.27 (0.38–4.20)	0.699	-	-
With necrotizing enterocolitis	2.84 (0.64–12.57)	0.169	-	-
With concurrent CLABSIs	1.07 (0.34–3.75)	0.918	-	-

CLABSI central line-associated bloodstream infection, *OR* odds ratio, *95% CI* 95% confidence interval

The underlying chronic comorbidities were not significantly different between primary bacteremia and BSIs with a concurrent focus of infection, except that VAP-associated BSIs and meningitis were more likely to occur in neonates with BPD and neurological comorbidities, respectively. In addition to GBS meningitis, other gram-positive-cocci-associated meningitis occurred mostly in neonates with congenital or acquired hydrocephalus as a complication of ventriculoperitonal shunt or extraventricular drainage. All episodes of primary bacteremia, as well as neonatal BSIs with concurrent meningitis, VAP, or CLABSI were evenly distributed as first episode of LOS or recurrent episode of LOS; however, there were only two cases of BSI with concurrent NEC occurring as a recurrent episode of LOS.

The clinical presentations of neonatal BSI with meningitis and CLABSIs were mostly comparable to those of primary bacteremia; however, NEC-associated and VAP- associated BSIs had more severe clinical symptoms, including more septic shock, disseminated intravascular coagulopathy, thrombocytopenia, anemia, and metabolic acidosis. Appropriate antibiotics were administrated in 72.2% of cases of primary bacteremia within 24 h of onset, which was similar to the rate in cases of neonatal BSIs with concurrent VAP, NEC, and CLABSIs.

Neonatal BSIs with concurrent VAP and NEC had significantly greater severity of illness, judged by NTISS scores (Table 3). Neonates with VAP-associated BSIs were more likely to require prolonged invasive intubation (≥ 7 days) and to experience respiratory failure under a high-frequency oscillatory ventilator. Neonatal BSIs with concurrent meningitis, VAP, and NEC had significantly higher rates of infectious complications than did primary bacteremia. The sepsis-attributable mortality rates were comparable between primary bacteremia and BSIs with a concurrent focus of infection.

Table 4 shows univariate comparisons of neonatal BSIs with sepsis-attributable mortality versus those without. None of neonatal BSIs with concurrent meningitis, VAP, or NEC was associated with significantly higher rates of sepsis-attributable mortality. Underlying secondary pulmonary hypertension (due to severe BPD), neurological comorbidities, presence of infectious complications, and history of one or more previous episode(s) of neonatal BSI were significantly associated with a higher risk of sepsis-attributable mortality. In multivariate logistic regression, the presence of infectious complications (Odds ratio [OR] 6.98; 95% confidence interval [CI] 3.64–13.39, $P < 0.001$), history of one or more previous episode(s) of BSI (OR 2.40 and 7.40; 95% CI 1.21–4.74 and 3.70–14.78, $P = 0.012$ and <0.001, respectively), and underlying secondary pulmonary hypertension (OR 4.77; 95% CI 1.91–11.96, $P = 0.001$) were independent predictors of sepsis-attributable mortality.

Discussion

In this study, we found that the majority of neonatal late-onset BSIs were primary bacteremia, and only 17.6% were associated with a specific focus of infection. To our knowledge, this is the first investigation of neonatal BSIs

with concurrent onset of nosocomial infections. Not surprisingly, the microbiologic profile of neonatal BSI concurrent with a specific focus of infection was significantly different from that of primary bacteremia. In contrast to previous studies documenting that patients with NEC-associated BSI and GBS meningitis have higher mortality rates than do those with bacteremia [9, 24], we found that a concurrent focus of infection did not directly contribute to case mortality. Instead, a concurrent focus of infection was associated with a significantly higher rate of infectious complications, and the associations finally lead to sepsis attributable mortality.

The overall incidence of culture-positive meningitis, VAP, NEC, and the distribution of organisms in this cohort was similar to other studies [9, 24–26]. Although neonates with concurrent VAP and NEC seemed more severely ill, the insignificant influence of neonatal meningitis, VAP, and NEC on sepsis-attributable mortality can be explained partially by the small sample size. Our previous studies showed that neonates with fungal BSI and multidrug-resistant gram-negative bacteremia have a significantly higher mortality rate [1, 5]. Because these pathogens usually caused primary bacteremia in this study, the sepsis-attributable mortality was comparable between primary bacteremia and bacteremia with concurrent infectious focus. Furthermore, our aggressive treatment strategies for neonatal NEC, as well as meningitis and VAP, could possibly reduce the mortality rate of these disease entities [1, 2, 5, 6].

Although our study extended over a relatively long period of time, there were very few variations in practice and all collections of data showed similar results (data not shown). The sepsis-attributable mortality rates in our cohort, both in the primary bacteremia group and in the group with BSI with a concurrent focus of infection, were much lower than those reported in other studies [9, 27]. For neonatal BSIs with meningitis, the case fatality rate of our cohort was comparable to that reported in some recent studies [24, 28, 29]. Previous studies have shown worse outcomes in preterm or small for gestational age infants [28–30], but this was not documented in our study. It is therefore likely that the presence of underlying chronic comorbidities contributed to mortality [1, 6], both in primary bacteremia and neonatal BSIs with a concurrent focus of infection.

A recent study found that infants with blood-cerebrospinal fluid (CSF) concordance were more likely to have indicators related to increased severity of illness [26]. Because neonatal meningitis is inevitably associated with significantly higher rates of mortality and morbidity [6, 7, 31], the relatively lower sepsis-attributable mortality of neonatal BSI with meningitis in this cohort highlighted the importance of aggressive treatment. Based on this result, the clinicians should consider treating the primary bacteremia and controlling the infectious focus at the same time once a focus is identified. The antibiotic regimens and treatment duration of neonatal bacteremia with concurrent meningitis or NEC are supposed to be adjusted to the presence of infectious complications.

CLABSI is an important source of neonatal BSI. In this study, we applied strict diagnostic criteria for CLABSI [18]. CLABSI was diagnosed only in neonates from whom the catheter was removed at the time of or soon after the onset of the episode of BSI, and in whom culture of the catheter tip was positive for the same organism that was cultured from the blood. Cultures are imperfect, and sometimes the catheter was removed after empiric antibiotics had been administrated. Therefore, we may have inadvertently missed patients who, in fact, had an unidentified focus of infection in the catheter. Furthermore, some CLABSIs were treated with the catheter in situ, which led

to an underestimate of the true incidence of neonatal BSI due to CLABSIs. Nonetheless, it is clear that in almost all demographics, clinical characteristics, treatment, and outcomes neonatal BSIs due to CLABSIs were comparable to those details in primary bacteremia.

The presence of certain underlying chronic comorbidities may increase the risk of secondary bacteremia. In our cohort, only neurological comorbidities and BPD predisposed neonates to higher rates of meningitis and VAP, respectively. The frequency of secondary bacteremia in neonates with nosocomial infections other than BSIs was low [32, 33], but it should be considered when there are clinical symptoms lasting more than 48 h or when signs or symptoms of sepsis have reemerged.

The sources of neonatal BSIs were identified in only 17.6% episodes in this cohort. It has been proven that the sources of neonatal BSIs are most commonly from epidermis colonization and gram-negative bacilli penetration of bowel mucosa, for gram-positive cocci and gram-negative bacilli, respectively [34, 35]. Because not all infected catheters were removed for bacterial culture at onset of BSIs, the percentage of neonatal BSIs with concurrent CLABSI in this cohort may be underestimated.

The microbiological assay system is MALDI-TOF in our institute, which has the advantage of rapid identification and reliable microbiological results [36, 37]. However, the disadvantage of this method is the lacking tests of antibiotic resistances; therefore, additional antibiotic susceptibility testing was required in our institute.

This study has some limitations. This was a retrospective, single-center cohort study, which inevitably restricts its generalizability compared with that of a prospective, multicenter study. We applied the definition of single positive blood culture for CoNS with clinical symptoms, which possibly resulted in an over-estimate of the burden of CoNS-related bacteremia. Subgroup analyses were limited by sample size, and some episodes of BSIs with a focus of infection may have been treated with antibiotics while awaiting blood culture results. The delay in identifying a specific focus may have resulted in sterilization of the CSF, sputum, or catheter tips. Blood cultures were ordered as clinically indicated, and the pathogens might not have been identified in some patients with infectious sources. Further, the identification of concurrent infectious was based on clinical judgment, which can be subjective.

Conclusions

Our data suggest that neonatal BSIs with a concurrent focus of infection is not rare, and is associated with increased severity of illness and a higher rate of infectious complications. At the initial presentation of neonatal BSI, systemic evaluation should be performed to identify a possible source of infection after blood cultures are obtained. In the support and recovery phase of neonatal BSIs with a concurrent focus of infection, especially in cases with VAP, meningitis, and NEC, efforts to limit the risk of infectious complications and prolonged hospitalization are necessary, because infectious complications are independently associated with in-hospital mortality.

Abbreviations

BPD: Bronchopulmonary dysplasia; BSI: Bloodstream infection; CDC: Centers for disease control and prevention; CI: Confidence interval; CoNS: Coagulase negative staphylococcus; CRBSI: Catheter-related bloodstream infection; CRP: C-reactive protein; CVC: Central venous catheter; ESBL: Extended-spectrum β-lactamase; GBS: Group B streptococcus; GPC: Gram-positive cocci; IQR: Interquartile range; MALDI-TOF: Matrix-assisted laser desorption ionization time-of-flight; NEC: Necrotizing enterocolitis; NICU: Neonatal intensive care unit; NTISS: Neonatal therapeutic intervention scoring system; OR: Odds ratio; PVL: Periventricular leukomalacia; RDS: Respiratory distress syndrome; TPN: Total parenteral nutrition; VAP: Ventilator associated pneumonia

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Availability of data and materials

The manuscript detailing where the data supporting the findings in this study can be found if requested.

Ethics approval and consent to participate

This study was approved by the institutional review board of Chang Gung Memorial Hospital, with a waiver of informed consent because all patient records and information were anonymized and de-identified prior to analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Disease Burden And Antimicrobial Resistance Of Invasive Group B Streptococcus Among Infants In China: A Protocol For A National Prospective Observational Study

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Abstract

Background: Group B Streptococcus (GBS) is a cause of neonatal sepsis, pneumonia, and meningitis that can lead to neurological sequelae in infants less than 3 months of age. The GBS disease burden is not known in China, therefore it cannot receive major attention. The main objectives of this study are the evaluation of the incidence of neonatal GBS infection, GBS case-fatality ratio, its serotypes and genotypes, bacterial resistance, clinical treatment and outcomes in China.

Methods: We are conducting a nation-wide, population-based, multi-center, prospective, observational cohort study in China from May 2016 to December 2017. Eighteen large urban tertiary care hospitals from 16 provinces were selected that cover the eastern, southern, western, northern and central regions of China. Meanwhile, we retrospectively collected data and GBS strains from January 2015 to April 2016 from selected hospitals. The incidence rate per 1000 live births will be defined as the total number of confirmed GBS cases born in the selected hospitals divided by the number of live births in the hospitals during the study period. All GBS cases detected in selected hospitals will be used to calculate the case-fatality ratio and for the typing analysis. GBS isolates will be serotyped using the Strep-B-Latex® rapid latex agglutination test for serotyping of Group B streptococci. Multi-locus sequence typing (MLST) will be performed by sequencing the internal fragments of seven house-keeping genes. Antimicrobial susceptibility will be tested per interpretive standards established by the Clinical and Laboratory Standards Institute. The presence of the common resistance genes ermA, ermB, mefA, tetI, tetO and tetM will be tested by PCR.

Discussion: We are conducting the first national study to estimate the invasive GBS disease burden and antimicrobial resistance of GBS among infants in China. Study findings will provide important evidence for improving clinical practice to ensure timely diagnosis of GBS disease and decisions for preventive measures. Surveillance of antimicrobial resistance will promote the rational use of antimicrobials.

Trial registration: The study was retrospectively registered at http://clinicaltrials.gov on June 13, 2016. It was granted a registration number of "NCT02812576".

Keywords: Group B streptococcus, Incidence, Case fatality ratio, Serotype, Genotype, Antimicrobial resistance, Resistance gene

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Background

Group B Streptococcus (GBS) is a cause of many neonatal infectious diseases including sepsis, pneumonia and meningitis. Although antimicrobial prophylaxis has significantly reduced the incidence of GBS infection, the mortality rate remains high [1–3]. Furthermore, it is estimated that approximately half of GBS cases have moderate or severe neurological consequences [4, 5]. Infant invasive GBS disease is usually divided into two phases based on age at presentation. Early onset disease (EOD)

occurs within 0–6 days of birth, late onset disease (LOD) occurs within 7–90 days of birth. The predominant risk factor for EOD is colonization by GBS of the maternal gastro-intestinal or genitourinary tracts [6].

There is currently no GBS vaccine available. Thus, prevention of prenatal GBS remains a massive challenge. The Centers for Disease Control and Prevention (CDC) in the United States (US) recommended guidelines for Intrapartum Antibiotic Prophylaxis (IAP) in 1996 [7], and the preventive measures of IAP are based on either culture screening (prenatal colonization of GBS) or a risk-based strategy (colonization with GBS, gestational age < 37 completed weeks, and longer duration of membrane rupture, among others). These guidelines were updated in 2002 [8] and 2010 [9], and have recommended universal culture-based screening of all pregnant women at 35–37 weeks of gestation since 2002, reducing the incidence of EOD in the US and other high-income countries [10–12].

Currently, there are no standard guidelines for GBS screening and prevention in China. To our knowledge, few hospitals perform IAP following a risk-based strategy, however, almost no hospital strictly follows the US CDC guidelines. Moreover, no program exists to monitor the prevalence of GBS infection. Nevertheless, two previous studies in China (Beijing and Shenzhen) revealed that GBS is a leading cause of neurological sequelae and high mortality in infants [13, 14]. Similarly, a previous pilot study conducted in two urban hospitals demonstrated a total incidence (0.28/1000 live births) of EOD and LOD among infants, however, this study suffered from underestimation [15]. In addition, further analysis of GBS strains from the pilot study found a new multi-drug resistant cluster of GBS caused by serotype III in China [16]. However, these studies were not truly representative of a large population of China due to the small sample-size restrained areas.

Hence, there is an urgent need for nationwide surveillance data. This will determine the national disease burden and provide surveillance of antimicrobial resistance. The findings of this study will provide strong evidence to improve clinical practice and will be a milestone in the development of precise, optimal preventive measures. Additionally, data pertaining to antimicrobial resistance in this disease will be helpful for the development of future rational antimicrobial-prescribing guidelines. This nationwide, population-based epidemiological data of GBS disease will aid the assessment of prospective interventions, such as antimicrobial prophylaxis and future vaccine development nationally or globally. These data will be helpful for the allocation of health funds to curtail disease and future research.

Methods and analysis

Study objectives

We have designed a suitable study with excellent research and ethical protocols for a better understanding of the disease burden and antimicrobial resistance of invasive GBS in China.

Fig. 1 Selected hospital locations throughout China. This figure indicates that the eighteen large urban tertiary hospitals from 16 provinces provide good coverage of the eastern, southern, western, northern and central regions of China. It also demonstrates the study sample has good representativeness.

The target population includes infants aged from 0 to 90 days. The possible outcomes are given as follows:

1. Incidence
2. Case-fatality ratio (CFR)
3. Susceptibility to specific antimicrobials
4. Spread of GBS types:
   (1) Serotyping
   (2) Genotyping
5. Detection of common GBS antimicrobial-resistance genes

Study design and setting

We are conducting a national population-based, multicenter, prospective, observational cohort study in China. As hospitals in China do not have a fixed catchment service area, we chose cities where study hospitals are located near dense populations to ensure maximum coverage. Considering the expected low overall incidence of GBS infection among infants, and the challenge of identifying GBS cases in Chinese primary health care institutions lacking appropriate professionals and laboratory equipment, we set five specific inclusion criteria for site selection: (1) A study hospital must be a large, urban, tertiary hospital; (2) a hospital must have adequate research capabilities and facilities to conduct the study, such as adequate laboratory facilities and competent staff for the identification, processing and storage of GBS isolates; (3) a hospital must have enough time to devote to this study; (4) a hospital must be willing to participate in this research; and (5) according to the geographic regional divisions of China, at least one hospital must come from each region as follows: Northeast China (NE), North China (NC), Northwest China (NW), East China (EC), Central China (CC), South China (SC), and Southwest China (SW). Following a preliminary screening, in which a number of hospitals did not meet at least one of the above criteria, we ultimately selected 18 hospitals from 16 provinces of China to obtain a representative sample. The locations of the 18 hospitals provide greater coverage of the regions of China (Fig. 1).

Among these, 12 hospitals are large maternity and children's hospitals, providing both obstetric and pediatric care service, and 5 are considered large, complete hospitals. One is exclusively a children's hospital.

The period of the prospective study runs from May 2016 to December 2017. To complete the retrospective study, data will be collected from clinical charts, hospital and laboratory records specifically from January 2015 to April 2016.

Sample size

The actual incidence of GBS disease in China is currently unknown. From previous global reports, we have assumed a total incidence (EOD and LOD) of 0.53 cases per 1000 live births [17]. The expected number of GBS cases may therefore be 127 per 240,000 expected live births within the 18 months of the prospective study period.

Study population

This study may include:

1. Infants born in a selected hospital, which we refer to as "inborn cases".
2. Infants born in a non-selected hospital who go to a selected hospital for treatment, which we refer to as "out-born cases". Inclusion criteria:
   (1) Positive culture for GBS from one or more normally sterile sites, such as blood and CSF.
   (2) Younger than 90 days old at the time of GBS confirmation.
   (3) Written informed consent of parents or legal guardians.

Study procedures and participant recruitment

All selected hospitals were given a clinical protocol to evaluate and investigate the infected neonates. Identification of GBS cases is based on uniform diagnostic criteria. For any infant presenting with clinical symptoms or signs consistent with suspected GBS cases, including but not limited to fever, poor feeding, breathing problems, heart rate and blood pressure abnormalities, reduced movement, fussiness, bluish-colored skin, seizures, limpness or stiffness, a blood culture is minimally required before antimicrobial administration. Upon laboratory confirmation from at least one of the normally sterile sites, the investigator will contact the parents or guardians of the GBS (+ve) infant for acquisition of consent if the case meets the inclusion criteria. Laboratory personnel are required to monitor the existing electronic lab records system weekly to ensure capture of all GBS cases. All GBS isolates from selected hospitals

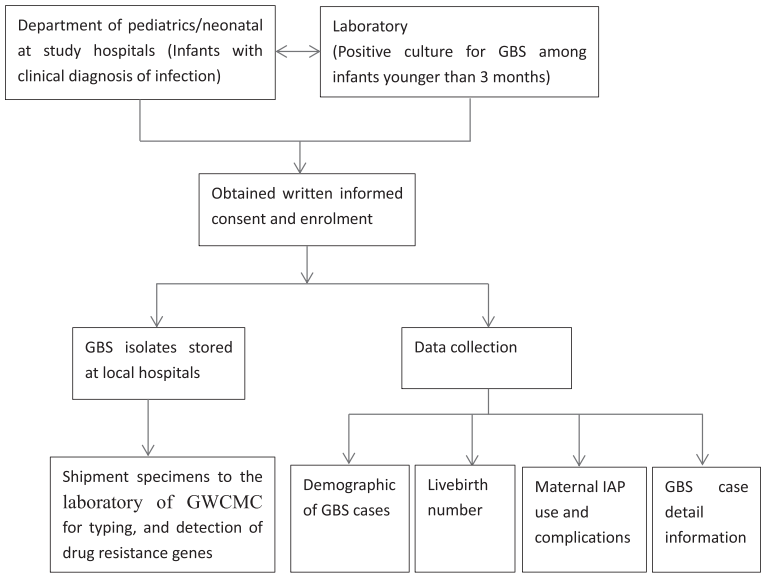

Fig. 2 Overview of the study procedures and subject enrollment. This figure describes the study procedures and the enrollment process

will be centralized and analyzed at the Joint Commission International certified laboratory of Guangzhou Women and Children's Medical Center (GWCMC) (Fig. 2).

GBS culture and identification

Isolation, cultivation and identification of GBS strains will be determined in local laboratories. Sterile samples will be inoculated in culture bottles (BioMerienx, French) or (BD BACTEC™) and incubated with automated blood culture systems. GBS strains will be grown at 37°C in 5–10% CO_2 in trypticase soy agar supplemented with 5% sheep's blood for 18–24 h, according to the manufacturer's instructions.

Preparation of frozen stocks of GBS isolates

With a sterile swab, a sweep of colonies (5 cm^2 or 20–50 colonies) will be collected and the bacteria will be suspended in 1.8 ml cryovials containing 1 ml STGG (Skim milk, Tryptone, Glucose, Glycerol) medium (prepared as per appendix below) by rotating the swab while pressing it against the side of the tube to release the bacteria into the medium. Frozen stocks will be prepared in duplicate, with one to be stored locally as a backup. GBS strains will be cultured in local hospitals and centralized for serotype and genotype analysis in the lab of GWCMC. A laboratory manual will be provided to the laboratories of selected hospitals to provide guidance in the preparation, storage and shipping of samples.

Serotyping by latex agglutination

GBS strains will be serotyped using the standard Strep-B-Latex® rapid latex agglutination method (Statens Serum Institute, Hillerød, Denmark).

Multi-locus sequence typing analysis

Polymerase chain reaction (PCR) products, the genomic DNA of GBS, will be purified and bidirectionally sequenced (Beijing Genomics Institute). Multi-locus sequence typing (MLST) will be performed by sequencing the internal fragments of seven house-keeping genes (adhP, pheS, atr, glnA, sdhA, glcK and tkt). MLST will be performed using primers that were described for S. agalactiae MLST. (as detailed at: http://pubmlst.org/sagalactiae/info/primers.shtml).

Alleles and sequence types (STs) of all GBS isolates will be determined by comparing the sequences with those in the S. agalactiae MLST. (as detailed at: http://pubmlst.org/sagalactiae/).

Antimicrobial susceptibility test

Antimicrobial susceptibility of GBS isolates to 5 antimicrobials (penicillin G, ampicillin, cefazolin, clindamycin, and erythromycin) will be determined using the AST-GP67 (VITEK 2 COMPACT) or manual K-B method at local hospitals, as per interpretive standards established by the Clinical and Laboratory Standards Institute. In addition, detection of resistance genes will be performed in the GWCMC lab. The presence of the common resistance genes ermA, ermB, mefA, tetI, tetO and tetM will be investigated by PCR. The primer and PCR conditions require the modification of previously described methods [18, 19].

Data management and statistical analysis

For infants enrolled in this study, data are collected using a paper case report form (CRF) by the investigator, who will sign and date. The CRF collects the variables listed in Table 1.

Training regarding completion of these forms will be provided to the investigators. Data from paper CRFs will be entered into a computer database.

Descriptive analysis will be provided for variables including age, gender, birth weight, gestational age, hospitalized duration, antimicrobial usage, and outcome at discharge, among others, categorized by selected hospitals, regions and by disease onset for comparison. The number of GBS cases will be reported overall, by site, onset of disease, and GBS typing. The incidence rate, expressed per 1000 live births, will be computed as the total number of confirmed GBS cases born in the selected hospitals divided by the number of livebirths in the study hospitals during the study period. The case-fatality ratio will be expressed as the percentage (%) of cases of GBS in this study where the outcome recorded at discharge is "died" among GBS cases identified in selected hospitals. For both the incidence rate and case-fatality ratio, 95% confidence intervals (CI) will be calculated using the Wilson interval method.

Ethical considerations

The protocol, informed consent form (ICF), CRF and other relevant study documents were reviewed and approved by the Xi'an Jiaotong University's Research Ethics Committee and the Medical Ethical Committees of selected hospitals.

We will obtain voluntary informed written consent from parents or guardians for study inclusion. We will provide the information orally and written in an understandable format regarding the study. Parents / guardians of the subjects have the opportunity to ask about details of the study regarding participation and withdrawal from the study. The investigators will provide a copy

Table 1 List of variables in the Case Report Form

Category	Items	Measures
Infants	Demographic information	Birth hospital, date of birth, gender, birth weight, and gestational age
	Clinical information	Date of onset of first symptoms, child's admission date, symptoms, and diagnosis
	Laboratory information	Date of sample collection, culture site, culture result, whether patient received antimicrobials prior to sterile sample collection
	Antibacterial therapy	Antimicrobial susceptibility results, antibacterial agent's name, dose, and duration
	Discharge results	Discharge date, outcome and sequelae
Maternal	Demographic information	Maternal age, mode of delivery
	Clinical information	Risk factors/complications of pregnancy during or after delivery
	Laboratory information	GBS screening and result
	Antibacterial therapy	Antibacterial treatment information

of the signed informed consent to the subject and will maintain the original form at the local site.

For each enrolled subject, we will assign a unique study identification number. The CRF and other study documents do not include any identifying information to maintain confidential records of the participants.

Dissemination

We anticipate that the results of this study will be relevant for health professionals including clinicians, laboratory personnel and relevant preventive policy-makers. Hence, we will disseminate the findings of this study through different channels, such as scientific articles in international peer-reviewed journals and presentations at high-level national and international conferences. Preparation of the study results will be in accordance with the current guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). (as detailed at: http://www.strobe-statement.org/.)

Discussion

GBS disease has not been well-recognized or documented in China. This is the first national study to explore the invasive GBS disease burden and antimicrobial resistance among infants in China to address this significant research gap.

First, robust data will provide basic evidence for medical care personnel and the public to improve knowledge of GBS infections.

Second, the improvement of awareness will be helpful for the control of GBS infections, thereby reducing mortality. In addition, this is necessary for the improvement of clinical practices to ensure timely and correct diagnosis of GBS disease.

Third, key information from the surveillance of antimicrobial resistance will support guidelines for rational prescribing attitudes for antimicrobials.

Fourth, the serotyping results will be vital for future GBS vaccine selection in China.

Finally, the findings from the 18 selected hospitals located in different geographical regions will provide information from large hospitals disseminated throughout all Chinese regions; this might facilitate different prevention measures for invasive GBS infections.

There are several limitations to this study. Selection bias is one potential limitation. GBS cases born in nonselected hospitals cannot be included until they seek any sort of therapy at a selected hospital. Disease onset may occur after discharge from the hospital, and once the family has moved out of the catchment areas of study hospitals, it will be difficult to enroll the GBS case. To minimize this risk, the selected hospitals are major tertiary hospitals with good facilities and medical services and are the preferred hospitals when an infant is sick.

Secondary or primary health care institutions and rural hospitals are not included in this study. Therefore, this will lead to the limiting of the representativeness of the findings from this study to urban China.

Several small variations at each study site for blood collection, volume and blood culture systems may have minor effects; therefore, we have provided uniform protocols to each selected hospital, and GBS strains will be centralized in GWCMC for typing analysis.

Abbreviations

CDC: Centers for Disease Control and Prevention; CFR: case fatality ratio; CI: confidence intervals; CRF: case report form; EOD: early onset disease; GBS: Group B Streptococcus; GWCMC: Guangzhou Women and Children's Medical Center; IAP: intrapartum antibiotic prophylaxis; ICF: informed consent form; JCI: Joint Commission International; MLST: Multi-locus sequence typing; PCR: polymerase chain reaction; ST: sequence types; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Availability of data and materials

This is a study protocol for an observational study. No data can be shared currently.

Author's contributions

WJ, YF and HL conceptualized the study and contacted study sites based on the hospital selection criteria. WJ drafted the proposal. WJ, MMA and AHJ drafted the final manuscript. HL, ZJ, AW, XM, XQ, CG, YZ, XF, JL, SS, LJ, JL, SY, ZL, GL, QL and DG contributed to the study oversight, management, co-ordination and implementation. All authors reviewed and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study protocol, informed consent form (ICF), case report form (CRF) and other study documents were approved by the Xi'an Jiaotong University's Research Ethics Committee and the Medical Ethical Committees of all involved hospitals. Written informed consent will be obtained from parents or legal guardians of GBS-infected infants for enrollment in this study.

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Use Of Ranitidine Is Associated With Infections In Newborns Hospitalized In A Neonatal Intensive Care Unit: A Cohort Study

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Abstract

Background: The inhibition of gastric acid secretion with ranitidine is frequently prescribed off-label to newborns admitted to neonatal intensive care units (NICU). Some studies show that the use of inhibitors of gastric acid secretion (IGAS) may predispose to infections and necrotising enterocolitis (NEC), but there are few data to confirm this association. This study aimed to compare the rates of neonatal infections and NEC among preterm infants (<37 weeks gestation) hospitalised in a NICU exposed or not to treatment with ranitidine.

Methods: A retrospective cohort study was conducted with all consecutive preterm newborns admitted to a NICU between August-2014 and October-2015. The rates of infection, NEC, and death of newborns exposed or not to ranitidine were recorded.

Results: A total of 300 newborns were enrolled, of which 115 had received ranitidine and 185 had not. The two groups were similar with regard to the main demographic and clinical characteristics. Forty-eight (41.7%) of the 115 infants exposed to ranitidine and 49 (26.5%) of the 185 infants not exposed were infected (RR = 1.6, 95%CI 1.1–2.2, p = 0.006). The late onset (>48 h) blood culture positive infection rate was higher in the group exposed to ranitidine than in the untreated group (13.0% vs. 3.8%, p = 0.001). There was no significant association between the use of ranitidine and NEC (Bell stage >II) (p = 0.36). The mortality rate risk was 4-fold higher in infants receiving ranitidine (16.5% vs. 8.6%, p < 0.001).

Conclusion: Ranitidine use in neonates was associated with an increased risk of infections and mortality, but not with NEC.

Keywords: Ranitidine, Neonates, Infection, Necrotising enterocolitis, Mortality

Background

Infections are the major cause of mortality in preterm newborns worldwide [1, 2]. It is well established that the gastric acid secretion is an important non-immune defence barrier for infants against invading pathogens [3, 4]. Although some studies have shown that the use of inhibitors of gastric acid secretion (IGAS) may predispose to infections [5–8] and/or necrotising enterocolitis (NEC) [7, 9], few data are currently available to confirm this association [10]. In addition, most of these studies are based on industrialised countries and there is very limited information on whether these patterns also apply to low- and middle-income populations, where the burden of infection is often highest. Due to the perceived safety and efficacy in older populations, the IGAS therapy has been commonly prescribed off-label in Neonatal Intensive Care Units (NICU) [11, 12]. In this context, we compared the rates of hospital infections, mortality, and NEC between preterm newborns exposed or not to ranitidine therapy admitted to a NICU in Sergipe, Brazil.

Methods

Study design and populations

We performed a retrospective cohort study to compare rates of hospital infections among premature neonates hospitalised in a NICU who were exposed or not to ranitidine treatment in the Nossa Senhora de Lourdes Maternity (NSLM). This maternity unit is located in Aracaju, Sergipe-Brazil and it is the high and medium-risk obstetric reference unit for the state of Sergipe. In 2014, approximately 370 births occurred per month in NSLM.

All consecutive neonates with a gestational age < 37 weeks, born at NSLM and with at least five consecutive days hospitalized in the NICU, between August 2014 and October 2015, were eligible for the study. Neonates born from mothers with trans-placental infection potential (i.e. human immunodeficiency virus, syphilis, hepatitis, toxoplasmosis, rubella and cytomegalovirus), patients with congenital malformation (i.e, hydrocephalus, intestinal atresia, gastroschisis, meningoencephalocele, hydronephrosis), and patients with genetic syndromes were excluded.

The sample size was calculated to detect an absolute difference of 20% in the infection rate between newborns exposed or not to ranitidine treatment, with $\alpha = 5\%$ and 90% power. We hypothesised that a neonate exposed to ranitidine would be more likely to be infected (30% and 10% of patients exposed or not to ranitidine, respectively) [7]. A sample size of 300 newborns was required and evaluated, of which 115 were exposed to ranitidine and 185 were not. None of them were excluded.

Outcomes

The primary outcome analysed in the study was the rate of infections in preterm infants exposed or not to treatment with

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Table 1 Association of maternal and neonatal characteristics in patients who used or did not use ranitidine in a Brazilian NICU, 2014–2015

Variable	Not exposed to Ranitidine *n* = 185	Exposed to Ranitidine *n* = 115	*p*-value
Maternal and prenatal care information			
Age mother, mean (SD)	25.0 (7.2)	24.5 (6.8)	0.53[a]
> 6 visits prenatal care, n (%)	56 (30.3)	34 (29.6)	0.89[b]
Hypertension, n (%)	16 (8.6)	13 (11.3)	0.45[b]
Diabetes Mellitus, n (%)	1 (0.5)	1 (0.9)	0.73[b]
Gestational diabetes, n (%)	1 (0.5)	1 (0.9)	0.73[b]
Caesarean section delivery, n (%)	95 (51.4)	47 (40.9)	0.08[b]
Characteristics of the neonates			
Male, n (%)	88 (47.6)	60 (52.2)	0.44[b]
Twins, n (%)	31 (16.8)	19 (16.5)	0.95[b]
Gestational age, median (IQR)	32 (31–34)	32 (30–33)	0.26[c]
Birth weight (g), median (IQR)	1474 (1163–1863)	1410 (1150–1810)	0.29[c]
Apgar score at 1 min, median (IQR)	7 (5–8)	7 (5–8)	0.24[c]
Apgar score at 5 min, median (IQR)	9 (8–9)	8 (8–9)	0.16[c]
Devices used by the neonate			
Duration of mechanical ventilation (d), mean (SD)	2.0 (3.3)	5.5 (7.2)	<0.001[a]
Duration of umbilical catheter (d), mean (SD)	1.9 (2.6)	2.8 (2.7)	0.007[a]
Duration of central catheter peripherally inserted (d), mean (SD)	4.0 (6.0)	7.2 (8.2)	<0.001[a]
Duration of orogastric tube (d), mean (SD)	19.9 (15.3)	11.9 (9.3)	<0.001[a]
Duration of parenteral nutrition (d), mean (SD)	3.0 (4.3)	5.9 (5.4)	<0.001[a]

d days, *SD* standard deviation, *IQR* interquartile range
[a]T-Student test
[b]Chi-Square test
[c]Mann-Whitney U test

ranitidine. Secondary outcomes were the occurrence of NEC (Bell stage >II), mortality, and hospital stay.

The Brazilian Ministry of Health criteria [13] were used to define nosocomial infection and its types. Therefore, nosocomial infection was defined as a late onset infection starting after 48 h of life. Based on the site of infection, it was further classified as follows: a) pneumonia was determined by clinical signs, such as apnoea, tachypnoea, grunting, bradycardia or tachycardia, wheezing or snoring associated with radiological findings with suggestive signals of pulmonary involvement by infectious agents (persistent infiltrate, consolidation and cavitation) and abnormal laboratory tests; b) meningitis was defined by the cerebrospinal fluid of the microorganism isolation and/or the use of antimicrobial therapy for meningitis by the assistant doctor; c) urinary tract infection (UTI) was defined by the presence of signs and symptoms suggestive of infection associated with positive urine culture; and d) late onset sepsis was considered when there were suggestive signs of infection and a positive blood culture for microorganisms not colonizing the skin. Presumed late onset sepsis was defined by the presence of suggestive symptoms of infection associated with altered laboratory tests (white blood count increase with young neutrophils and positive PCR) and negative blood culture. NEC and Bell stage were decided on the basis of standardised clinical and radiologic criteria [14, 15].

Data collection

Research assistants collected data from the medical records of newborns, using a pre-defined form, regarding: personal information of the mother; background of the obstetrician; gestational age (GA); birth weight and height; Apgar score; occurrence of infections and/or NEC; presence and duration of intensive care invasive procedures (mechanical ventilation (MV), central catheter peripherally inserted (CCPI), umbilical catheter (UC), parenteral nutrition (PN), orogastric tube (OT); indications, timing and dosage of ranitidine treatment; antibiotic therapy; use of corticosteroid; results of laboratory tests; age in days to discharge or death.

Data analysis

Categorical variables were described using frequencies and percentages. Pearson's Chi-square or Fisher Exact Tests were used to compare the categorical variables association. The normal distribution of the scores was verified using the

Table 2 Association of the use of devices between patients who developed nosocomial infection and those who did not in a Brazilian NICU, 2014–2015

Variable	Infection		*p*-value[a]
	Yes	No	
Duration of mechanical ventilation (d), mean (SD)	3.6 (5.3)	3.3 (5.4)	0.60
Duration of umbilical catheter (d), mean (SD)	2.5 (2.5)	2.2 (2.7)	0.46
Duration of central catheter peripherally inserted (d), mean (SD)	5.4 (7.1)	5.2 (7.1)	0.82
Duration of orogastric tube (d), mean (SD)	16.7 (13.0)	16.7 (14.0)	0.96
Duration of parenteral nutrition (d), mean (SD)	4.8 (5.1)	3.8 (4.7)	0.09

d days, *SD* standard deviation
[a]T-Student test

Table 3 Nosocomial infection prevalence in premature neonates admitted to a Brazilian NICU in 2014–2015

Variable, description	Not exposed to Ranitidine	Exposed to Ranitidine	*p*-value
	n = 185	*n* = 115	
Overall infection, n (%)	49 (26.5)	48 (41.7)	0.006[a]
Sepsis confirmed, n (%)	7 (3.8)	15 (13.0)	0.003[a]
Pneumonia, n (%)	10 (5.4)	16 (14.0)	0.01[a]
Urinary tract infection, n (%)	0 (0.0)	3 (2.6)	0.03[b]
Fungal infection, n (%)	6 (3.2)	3 (2.6)	0.74[b]

[a]Chi-Square test
[b]Fisher's exact test

Kolmogorov-Smirnov test. The T-Student or Mann-Whitney tests were used to assess any differences in the study variables between the groups, respecting the distribution symmetry. We calculated the relative risk (RR) and 95% confidence interval (CI). We controlled for possible confounding variables using a backwards stepwise modelling, retaining variables that had a p-value smaller than 0.05. Analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL USA) and STATA 12.0 (STATA Corp., College Station, TX, USA).

Results

A total of 300 neonates admitted to the NICU were enrolled in the study. Of these, 115 (38.3%) used ranitidine, mostly due to episodes of regurgitation, and 60 (52.2%) and 29 (25.2%) due to prophylaxis or treatment of stress ulcer, respectively. 185 neonates represent the control group of patients not exposed to ranitidine. The main demographic and clinical characteristics of both groups were similar, as shown in Table 1. However, neonates, who received ranitidine, were more likely to undergo more interventions and procedures, such as mechanical ventilation [Mean (SD), 5.5 (7.2) vs 2.0 (3.3), p < 0.001], umbilical catheter [2.8 (2.7) vs 1.9 (2.6), p = 0.007], central catheter peripherally inserted [Mean (SD), 7.2 (8.2) vs 4.0 (6.0), p < 0.001], and parenteral nutrition [Mean (SD), 5.9 (5.4) vs 3.0 (4.3)] than neonates who did not receive ranitidine. Additionally, we explored whether the long-term use of these devices was associated with nosocomial infection in neonates and we observed that the use duration of these devices was not associated with a risk of infection (Table 2). Although there is no association between device duration and infection, we performed a multivariate analysis to control for confounding variables because of its clinical relevance and we found that ranitidine was independently associated with a risk of infection (Additional file 1: Table S1).

Neonates who received ranitidine were more likely to have nosocomial infection (RR: 1.6, 95% CI = 1.1–2.2, p = 0.006), confirmed sepsis (RR: 3.4, 95%CI: 1.4–8.2, p = 0.003), and pneumonia (RR: 2.6, 95%CI: 1.2–5.4, p = 0.01) (Table 3). The median (IQR) between the first dose of ranitidine and infection outcome was 6 (3–8) days. The most used route of administration was intravenous (104, 90,5%), and the mean (SD) dose was 1.1 (0.33) mg/kg/day. Only 11 (9,5%) used ranitidine by oral administration and the mean (SD) dose was 3.75 (0.9) mg/kg/day.

Twenty-one (7%) cases of NEC were reported in the patient groups during the study period and ranitidine use was not significantly associated with necrotising enterocolitis (RR = 1.4, 95%IC: 0.6–3.3, p = 0.36).

The mortality rate was significantly higher in neonates who received ranitidine (RR 3.9, 95%CI: 2.1–7.3, p < 0.001). Furthermore, hospitalisation was longer in those exposed to ranitidine (Median (IQR), 36.0 (19.0– 59.0) vs 24.0 (14.5–38.0), p < 0.001).

Discussion

Despite a lack of sufficient evidence demonstrating the safety and efficacy of IGAS use by preterm newborns [10], these drugs have been widely prescribed in an offlabel manner to treat prophylaxis or therapy of stress ulcers and gastroesophageal reflux disease (GERD) in NICU. The use of these drugs and its consequences for preterm newborns have raised important questions. However, the majority of the studies evaluating its safety have been performed in developed countries. We performed a retrospective cohort study in order to compare the rates of hospital infections and NEC between preterm newborns exposed or not to ranitidine treatment, admitted to a NICU in a poor area of Northeastern Brazil. In accordance with studies from developed countries, our results showed an association between ranitidine use and an increased risk of infection [6–8, 16, 17] and mortality [7]. However, there was no significant association between the use of ranitidine and NEC.

Gastric acid secretion is one of the main non-immune defenses of newborns against invading microorganisms [8]. According to some studies, increasing the pH of gastric secretion would result in the overgrowth of microorganisms and in predisposition to infection and NEC [18–21]. Sustained inhibition of gastric acid secretion alters the bacterial ecology favouring gastric colonisation by enteric bacteria and may facilitate microbial translocation across barrier due to decreased neutrophil activity [22, 23]. In fact, the use of ranitidine was reported to increase gastric pH within 30 min of administration [24, 25] and its effects not only restrict gastric secretion, but also activate H_2 receptors, modelling the immune response, especially in the production of inflammatory cytokines, and reducing infection control [26–28].

In this study, the presence of GERD was the main indication for the use of ranitidine, followed by prophylaxis, or therapy of stress ulcers. Our study showed that children receiving H2-blocker therapy were more likely to exhibit irritability, sleepiness, and other non-specific symptoms, leading to the false interpretation of GERD persistence and consequently leading to an increase of the drug dosage or the duration of treatment [25]. However, our findings showed that the mean dose of ranitidine administered to newborns is in agreement with other studies (range 1–5 mg/Kg/day) (16), although some studies recommend an intravenous dose of 0.5 mg/kg/day for preterm newborns presenting regular renal function [25, 29]. Furthermore, we found that the time of ranitidine use was not associated with an increase in the infection rate. In this study, the time between the first dose of ranitidine and infection outcome was only 6 days, whereas a study conducted in Croatia reported 18 days [17]. Despite these differences, there is currently no consensus with regard to the safe dose and time usage of IGAS therapy for newborns and further studies are needed.

Some studies have shown that the prolonged use of neonatal intensive care devices by neonates and infants, such as mechanical ventilation, central catheter peripherally inserted and parenteral nutrition dispositive, predispose to infections [30–34]. However, in this study, we have found that these devices were used on newborns receiving ranitidine for longer periods of

time. After controlling for confounding variables, we found that ranitidine was independently associated with a risk of infection. Indeed, similar findings were reported by Yildizdas et al. [35].

Although some studies have found an association between the use of ranitidine and an increase in NEC [7, 9], this association was not observed in this study. A possible explanation is that those researchers studied very low birth weight newborns, whereas our population was composed of neonates with a larger variation of birth weight. Therefore, it is possible that the effects of ranitidine on quantitative and qualitative changes of the intestinal microflora composition may be causing NEC in very low birth weight newborns.

In this study, we observed an increase in the hospitalisation time and mortality rate amongst newborns receiving ranitidine. This is consistent with a multi-centre study observing the relationship between ranitidine and unfavourable outcomes [7].

This was a retrospective cohort study based on medical reports and some information were not recorded, such as data on timing, volume and type of enteral feedings, rods count and blood cultures. In addition, at NSLM, the search of fungus in urine to investigate fungal infections in neonates frequently results in no clinical and laboratory improvement after antibiotic use. Despite these limitations, our results are consistent.

Conclusions

In conclusion, ranitidine use was associated with an increased risk of infections and mortality in preterm newborns, but not with NEC. The use of ranitidine in neonates must be further evaluated and used in specific situations. In addition, more studies are needed to increase the information about the use of IGAS in newborns to support the decision of the regulatory agencies authorising and adjusting its use in neonatology.

Abbreviations

CCPI: Central catheter peripherally inserted; GERD: Gastroesophageal reflux disease; IGAS: Inhibitors of gastric acid secretion; MV: Mechanical ventilation; NEC: Necrotising enterocolitis; NICU: Neonatal intensive care units; NSLM: Nossa Senhora de Lourdes Maternity; OT: Orogastric tube; PN: Parenteral nutrition; UC: Umbilical catheter; UTI: Urinary tract infection

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Availability of data and materials

Interim data is available upon request from Prof. Ricardo Q. Gurgel at ricardoqgurgel@gmail.com

Authors' contributions

VSS participated in the design of the study, performed the statistical analysis, and was involved in the writing of the manuscript. RNSS, RFRJ and MSF collected the data and were involved in the writing of the manuscript.

MASM and RC helped in interpretating the data and participated in the writing of the manuscript. RQG conceptualised and designed the study, interpreted the results, took the lead in drafting the initial and subsequent versions of the manuscript, and ensured that all authors approved the final version of the manuscript. All authors read and approved the final paper.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Federal University of Sergipe (CAAE n. 30,892,614.4.0000.5546).

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