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[We will be on a brief hiatus while we seek funding to continue to provide you with relevant and compelling topics every month.]



Neonatal Nosocomial Infection

In this Issue...

In this issue, we provide an overview of the perennial problem of neonatal nosocomial infection (NNI) addressing the significant burden of illness imposed by NNI (with a particular focus on the impact of NNI on neurodevelopment), and exploring the epidemiology of NNI. We will also evaluate the current statistical methodology used to define and measure NNI. Although this issue is primarily concerned with the current advances in quantifying and potentially modulating the premature immune system, we also revisit the proven efficacy of hand hygiene and details of care that remain the mainstay of prevention. In addition, we review recent speculation about "deintensifying" the neonatal intensive care unit (NICU) environment, a concept that may ultimately prove to be one of the most efficacious approaches to infection control.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Describe the potential morbidity associated with nosocomial infections in neonates
- Evaluate multifactorial and interdisciplinary responses to nosocomial infections in neonates
- Explain the need for appropriate epidemiologic handling of nosocomial infections in neonates

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1.0 hour Physicians
1 contact hour Nurses

Release Date

January 14, 2010

Expiration Date

January 13, 2012

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Guest Faculty Disclosure

Drs. Gill and Strunk do not have any relevant financial relationships to disclose.

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Commentary & Reviews

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COMMENTARY

Neonatal nosocomial infection (NNI) remains a significant factor in both mortality and morbidity within our NICUs. The rapid and often unexpected decline of an infant from acute septicemia has a devastating effect on both parents and staff. Although NNI mortality is relatively low, it has become increasingly evident that nonfatal, late-onset septicemia contributes significantly to the incidence and severity of common adverse neonatal outcomes. A review of outcomes of >6000 extremely low birth weight (ELBW) infants with respect to NNI, published by the National Institute of Child Health and Human Development (NICHD) network, found NNI was statistically associated with adverse cognitive and motor development after correcting for the known confounders.¹ Shah and coworkers (see Review 1) have recently taken this a step further by demonstrating an

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association between NNI, cerebral white matter damage, and later neurodevelopmental delay. Their work builds on the concept of remote effects of inflammation on the brain associated with chorioamnionitis.² Perhaps of greatest concern is that both studies demonstrated a clear propensity for coagulase-negative *Staphylococcus* (CoNS) infection to induce brain injury, and adverse neurologic development. Despite its relatively low mortality rates, CoNS infection must be considered a serious illness with long-term complications.

To address any issue, one must first accurately quantify the problem. In order to compare NNI rates from nursery to nursery, collected data must be comparable. When assessing NNI appropriately, it is vital to use robust definitions for the numerator, while the denominator must reflect exposure and account for the fact that an individual infant may have multiple NNIs. The adoption of infant “days” rather than a simple count of infants has been a major advance in quantifying data, and is now an accepted standard. The evolution of a robust epidemiologic methodology for describing NNI is discussed in Review 2. It is only through the continuous application of such methodologies that we can accurately delineate true rates of NNI and determine the effects of interventions in an individual unit or the variations in practices between units.

The high prevalence of NNI is not surprising when one considers the etiologic factors. The newborn is relatively immunodeficient, and poorly equipped to deal with the challenging and microbial-rich extrauterine environment. The neonatal immune system is an area of intense study, and we are slowly unveiling its secrets. Although neonatal vaccination and immune modulation are promising approaches to boost responses to nosocomial pathogens, much remains to be learned before they enter the clinical stage, as discussed in Review 3.

In addition to the immature neonatal immune system, we must also consider the environment into which the infant is delivered. The average NICU is a warm, moist, and cramped environment ideal for the propagation of microorganisms. The liberal use of disinfectants and antibiotics may ensure their rapid destruction but also allows for more virulent and resistant species to emerge. The natural barrier defenses of the respiratory tract, gut, and skin are continually breached during many routine neonatal care practices. The remainder of this issue explores the ways in which we can collectively shift the balance to favor the “blossoming of the babies and not the bugs.”

In tackling NNI, there is no magic bullet. Attention to detail in all facets of neonatal care and harnessing a collective will to change is necessary. Edwards was the first to describe the effects of unit “culture” on responses to NNI (see Review 4) and the author supports the need for a collective mind shift away from an “entitlement” to a “prevention” model of thinking. Rather than a fatalistic approach, the prevention model views NNIs in the neonate as preventable with appropriate and continuously evolving care practices. The introduction of a quality improvement team approach has repeatedly demonstrated both changes in culture and reduction in NNIs. An exemplary protocol for the introduction of a quality improvement initiative is discussed in Review 4, with similar work having been conducted within the Vermont Oxford Network³ and by many other neonatal units.

Practice changes in all facets of neonatal care have been associated with decreased NNI. Perhaps the most significant and fundamental is the need for appropriate hand hygiene. This concept was first introduced in 1847 by Dr. Ignaz Semmelweis, who documented that hand washing with chlorine could halt the spread of puerperal fever. A latter-day champion of adequate hand hygiene has been Dr. Didier Pittet, who has successfully introduced alcohol-based gels. One of Dr. Pittet’s original papers is addressed in Review 5. Dr. Pittet has continued to promote this work through the recognition of opportunities for hand hygiene (moments of care).⁴ The ergonomics of the work environment can also be designed to minimize the likelihood of lapses in practice. The current requirements for adequate separation of neonatal beds, and the trend toward clear and distinct boundaries between beds, are good examples of this approach.

Other notable discoveries have included the recognition of the strong association between NNI and central lines. Benchmark care now involves a more conservative use of long lines, meticulous asepsis in their insertion, and minimal breaches in lines during care. Many of these aspects are addressed in the paper by Schulman and colleagues, also discussed in Review 4.

Where are we going in the prevention of NNIs? Moving from documented evidence to informed speculation, it appears that much could be gained from the “deintensifying” of our neonatal intensive care units (NICUs). Such strategies appear not only to reduce NNIs, but to decrease the occurrence of other common morbidities as well. The move toward “gentilation” and the introduction of rapid extubation to nasal continuous positive airway pressure (nCPAP) is one example. Similarly, we will need to reduce our reliance on parenteral nutrition and improve our enteral feeding practices. The paper by Rønnestad and associates (Review 6) describes a potential reduction in NNIs through very early introduction of breast milk. In addition to decreasing the need for central lines and antibiotic use, this practice may facilitate colonization of the gut with physiologic rather than nosocomial organisms. Reduction in NNIs, and particularly necrotizing enterocolitis (NEC), has been demonstrated with supplementation of feeds with probiotics⁵ or lactoferrin.⁶ Although early introduction of breast milk would seem to be physiologic, combined approaches should be explored.

Considerations must also be given to the role of antibiotics, as they can predispose infants to NNIs. A recent NICHD publication by Cotton and collaborators addressed this issue, demonstrating a significantly increased risk for NEC in ELBW infants receiving prolonged initial courses of antibiotics despite having negative cultures. There were similar trends for an increase in NNIs.⁷ Interestingly, these effects were more pronounced in infants in whom enteral feeds were delayed (>day 5).⁷ It is tempting to speculate that a reduction in the antibiotic load prescribed for such infants may actually reduce NNIs. Future clinical studies should use our increasingly sophisticated immunologic knowledge and technology to allow for early and accurate identification of true infections to minimize unnecessary antibiotic exposure. In addition, emerging understanding of the intricacies of early immune development may facilitate prediction of those infants at highest risk for NNI and allow for targeted preventive intervention.

The future of NNI prevention in NICUs is at a crossroads. We can continue to pursue a nihilistic “entitlement” model, whereby we continue to treat ever more resistant bugs with increasingly more powerful antibiotics. Alternatively, we might adopt a physiologic model and collaborate to identify and institute best practices for “deintensifying” nurseries, thereby reducing our reliance on antibiotics, and improving the outcomes for our infants.

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Shah DK, Doyle LW, Anderson PJ, et al. **Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term.** *J Pediatr.* 2008;153(2):170-175,175.e1.

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Shah and coworkers tested the hypothesis that the adverse late neurodevelopmental consequences of infection are mediated through cerebral white matter damage that can be quantified by magnetic resonance imaging (MRI) of the neonatal brain at term. Subjects included 204 of a series of 208 infants of <30 weeks' gestation consecutively admitted to the Royal Women's Hospital, Melbourne, Australia, from 2001 through 2003. These infants underwent routine MRI imaging of the brain at term and formal neurodevelopmental assessment at 2 years corrected age. The MRI images were blindly scored for white matter and gray matter abnormalities, and the results correlated with the number of proven septic episodes the infant acquired during his/her neonatal stay, together with the results of neurodevelopmental assessment. Sepsis was defined as a positive blood culture associated with a raised immature to total white cell count on blood smear, or a rise in C-reactive protein >8 mg/dL. Infants with definite NEC were also considered to be septic.

A total of 192 infants from the original cohort were included in the final analysis; the remaining 12 were excluded because of death or incomplete data. A total of 68 infants experienced at least 1 septic event, with CoNS being the most common causative pathogen, although other organisms were also represented. In all, 9 infants developed NEC, 4 were managed medically, and 5 required surgery. No infant had culture-proven cerebrospinal fluid (CSF) infection, but 3 demonstrated culture-negative meningitis. When compared against aseptic controls, statistically significant increases in white matter abnormality were demonstrated on MRI for all septic infants (excluding those with NEC), and when isolated CoNS sepsis was considered. After correcting for possible confounders, septic infants exhibited trends for decreased physical and mental development scores at 2 years, although these scores did not achieve statistical significance. Analysis of interactions suggested that the white matter abnormality score was a significant determinant of neurodevelopment.

This study is important in unraveling the links between NNI and neurodevelopmental abnormalities. In 1998, Dammann and Leviton¹ described the association between chorioamnionitis and cystic periventricular leukomalacia, and the concept of remote effects of inflammation has since been proven in animal models. Shah's study demonstrates that the effects of infection are not limited to the prenatal period but also extend to postnatal NNI. Very importantly, this study also demonstrates the impact of CoNS sepsis on neurodevelopment. In the past, there has been a perception that CoNS is a relatively benign organism with a low risk for mortality. However, this work clearly demonstrates the influence that CoNS can have on later morbidity.

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1. Dammann O, Leviton A. [Infection remote from the brain, neonatal white matter damage, and cerebral palsy in the preterm infant.](#) *Semin Pediatr Neurol.* 1998;5(3):190-201.

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Gill AW; Australian and New Zealand Neonatal Network. **Analysis of neonatal nosocomial infection rates across the Australian and New Zealand Neonatal Network.** *J Hosp Infect.* 2009;72(2):155-162.

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In this paper, Gill applied the current statistical principles for handling NNIs to data across the Australian and New Zealand Neonatal Network. The study cohort comprised >3000 ELBW infants admitted from 2002 through 2004, spread across 26 neonatal units. Infection rates were calculated and adjusted for gestational age and gender, and data were censored to the first 35 days of life. The observed and standardized expected rates were presented as a funnel plot to depict those units with statistically higher or lower NNIs. The population NNI rate was 14 per 1000 patient days — a figure consistent with other published results. Three units were identified as having statistically reduced NNIs.

One of the paramount principles in the epidemiologic handling of NNIs is to define a robust numerator. The most robust definitions are those that hone in on “definite” neonatal sepsis, and revolve around a positive sterile-site isolate (blood or CSF) in association with a clinical picture of sepsis and supportive biochemical and/or hematologic data. Similarly, an appropriate denominator must be used to define exposure. “Episodes per 1000 patient days” has become an accepted standard. The risk for exposure has been further refined in the current study by including data from only the first 35 days (5 weeks) of life. This censor point was chosen because the early admission period accounts for 85% of all NNIs. Discounting the “tail” of a neonatal admission reduces the “signal-to-noise” ratio and negates the effect of variations in “step-down” transfer practices on NNI rates.

Next, we must consider what confounding factors need to be evaluated. If the aim is to compare NICUs, then it is important that factors of care remain in the model and that only those factors describing the preadmission status of an infant are considered as confounders. The most important factor to be considered is gestational age. In this study, a 7-fold increase in NNI rates was observed between infants born at 28 weeks’ gestation and those born at 23 weeks’. It would be more logical to define cohorts by gestation than by birth weight. The effect of gender is small but statistically consistent and should therefore be retained. Lastly, we need to consider appropriate statistical distributions for data modeling. NNI is a nonbinary rare event and a reasonable fit to a Poisson distribution. This methodology can therefore be used to derive probabilities and confidence intervals for NNI rates.

The current models are still evolving and being continually refined. To date, the statistical analysis used assumes a model of random effects, however, this may not hold true because there is increasing evidence that a primary infection may predispose an infant to a second infection. The current model also fails to discount the days following one infection during which a second infection cannot be recorded. We are now collectively evolving epidemiologic standards for the handling of NNIs, and future publications should either comply with or enhance these standards.

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THE NEONATAL INNATE IMMUNE SYSTEM

Levy O. **Innate immunity of the newborn: basic mechanisms and clinical correlates.** *Nat Rev Immunol.* 2007;7(5):379-390.

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Strunk T, Richmond P, Simmer K, Currie A, Levy O, Burgner D. **Neonatal immune responses to coagulase-negative staphylococci.** *Curr Opin Infect Dis.* 2007;20(4):370-375.

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These 2 papers provide a comprehensive overview of the recent understanding of the neonatal innate immune system. Dr Levy's review outlines the complex set of immunologic demands faced by the human fetus and newborn. These include the intricate balance of providing protection against infection, avoidance of harmful inflammatory immune responses that can lead to preterm delivery, and balancing the rapid transition from a sterile intra-uterine environment to a world that is rich in potentially detrimental microorganisms. These demands shape a distinct neonatal innate immune system that is biased against the production of pro-inflammatory cytokines rendering the newborn at risk for infection; responses to many vaccines administered during the neonatal period are also impaired. The review by Strunk and associates focuses on the innate immune responses of preterm and term infants to CoNS, which has emerged as the most common nosocomial pathogen in NICUs worldwide.

Very limited data are available on innate immune responses to CoNS in neonates. In their article, Strunk and colleagues collate the available evidence and elaborate on the factors that lead to virulence of these ubiquitous and primarily harmless commensals. The authors then examine the available data on essential neonatal host factors that contribute to susceptibility to CoNS infection. Levels of serum proteins, including transplacental anti-CoNS immunoglobulin and complement, correlate with gestational age. Their relative deficiency in preterm infants contributes to their suboptimal opsonization, affecting both phagocytosis and intracellular killing of CoNS. Furthermore, the production of essential immune mediators (cytokines) after uptake of CoNS, serving as an amplification signal for the immune response, is significantly impaired in a gestational age-dependent fashion. The authors identify the need for new innovative therapeutic strategies, given the largely disappointing results of previous interventional trials, including intravenous immunoglobulin and specific antistaphylococcal antibodies.

They conclude that the susceptibility of human preterm infants to CoNS relates, at least in part, to the immaturity of the neonatal innate immune response. Strategies to reduce the burden of CoNS infections require a thorough understanding of complex host-pathogen interactions, particularly the recognition, engagement, and elimination of CoNS by the innate neonatal immune system.

The current understanding of innate immunity in newborns, with particular reference to CoNS, is reviewed and the authors discuss potential new strategies for preventing and treating invasive NNIs in this exquisitely vulnerable population. Several immunologic strategies are currently being examined in animal models and early human trials: (1) substitution of deficient soluble innate immune factors, such as recombinant bactericidal/permeability increasing protein (rBPI); (2) stimulation of the innate immune response by selective Toll-like receptor (TLR) agonists; and (3) novel vaccines that use TLR agonists to enhance vaccine efficacy in neonates.

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THE CULTURE OF CONTINUOUS IMPROVEMENT FOR REDUCING NNI RATES

Schulman J, Stricof R, Stevens TP, et al; New York State Regional Perinatal Centers; New York State Department of Health. **Development of a statewide collaborative to decrease NICU central line-associated bloodstream infections.** *J Perinatol.* 2009;29(9):591-599.

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Edwards WH. **Preventing nosocomial bloodstream infection in very low birth weight infants.** *Semin Neonatol.* 2002;7(4):325-333.

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Schulman and colleagues describe an iterative process of quality improvement undertaken by a consortium of perinatal centers in New York State to reduce central line-associated NNIs. An appropriate statistical tool was devised along the principles discussed previously to describe and compare central line-associated NNIs between the centers. The baseline results indicated a variation of 2.6 to 15.1 NNIs per 1000 central line days. Practices across centers were reviewed with the intention of identifying the “good” practices in the better performing centers. The consortium then developed benchmark care “bundles” for the use and management of central lines. These care bundles included the facilitation of adequate hand hygiene, adequate staffing for line placement, clear policies for line changes, daily considerations of line removal, and the creation of a unit culture that values a team approach to reducing NNIs.

The review article by Edwards introduces the concept that a unit’s approach to NNI — that is, the “culture” of the unit — may significantly influence NNI rates. Edwards refers to work within the Vermont Oxford Network, published by Horbar and associates,¹ in which a quality improvement program was instituted between the best performing units and their less favorably performing counterparts. The author describes 2 opposing collective responses to NNI. In an “entitlement” model there is a belief that NNI is inevitable, arising from innate immune deficiency and the invasive necessities of intensive care. Because NNI is therefore viewed as unavoidable, the primary intervention strategy is early recognition and antibiotic therapy. In the contrasting “prevention” model, NNI is believed to be a consequence of a breakdown in the systems of care — each NNI leads to investigation and review of care practices. Edwards argues that this second viewpoint provides motivation for continued iterative improvement.

The author describes units practicing an “entitlement” model as performing a larger number of septic screens, greater antibiotic use, and having higher NNI rates. The vicious cycle of breaking skin integrity and subsequent risk of colonization with resistant pathogens are also explored further.

It is increasingly clear that the prevention of NNIs is a multifactorial task that relies on the active contribution of all members of the clinical care team. The introduction of a culture of prevention is a prerequisite for focusing the energies of team members on the continuous quality improvement cycles required to reduce NNI rates.

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1. Horbar JD, Rogowski J, Plsek PE, et al. [Collaborative Quality Improvement for Neonatal Intensive Care.](#) *Pediatrics.* 2001;107(1):14-22.

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THE IMPORTANCE OF HAND HYGIENE

Pittet D, Hugonnet S, Harbarth S, et al. **Effectiveness of a hospital-wide programme to improve compliance with hand hygiene.** *Infection Control Programme. Lancet.* 2000;356(9238): 1307-1312.

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This is one of several published articles by Professor Didier Pittet and collaborators evaluating alcohol-based hand hygiene gels in clinical practice. Compliance with traditional hand washing was poor during pre-intervention assessments at the study

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hospital in Geneva, Switzerland, as in many observational studies at other centers. The authors hypothesized that the introduction of readily available alcohol gel at points of patient contact would considerably increase compliance with hand hygiene. Gel usage was reinforced with a poster campaign, with the posters themselves being created by the staff of the hospital of study (thus forming part of a positive feed-forward loop). In addition to compliance, other outcome measures included total gel use, nosocomial infection rates, and rates of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates. Observations occurred over a 4-year period from 1994 through 1998.

The study interventions produced an overall increase in hand hygiene compliance from 48% to 66%. This rise was attributable to an increase in the use of alcohol gel. Overall, gel usage increased from 3.5 to 15.4 L/1000 patient days. The physicians were the worst offenders, with compliance rising from 31% to 40%, but the prevalence of hospital nosocomial infections decreased from 17% to 10%, and MRSA isolates decreased from 2.1 to 0.9 episodes per 10,000 patient days with use of the gel.

This simple but very effective intervention paved the way for the introduction of alcohol-based gel as the preferred method of hand hygiene in hospitals. The main advantages of a gel are that the process of hand hygiene is rapid and that it can be conveniently supplied at points of patient contact, thus encouraging use. Furthermore, gels have been shown to be less damaging to health care workers' hands aiding compliance and reducing the risk of hand colonization through dermatitis and abrasions. Another further advantage is that the antiseptic barrier exists for some time after application, further reducing the risk from inevitable lapses in compliance. Additional studies have demonstrated the effectiveness of gels in clinical practice, including use as an operating room scrub.

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ARE FEEDING PRACTICES IMPORTANT?

Rønnestad A, Abrahamsen TG, Medbø S, et al. **Late-onset septicemia in a Norwegian national cohort of extremely premature infants receiving very early full human milk feeding.** *Pediatrics*. 2005;115(3):e269-e276.

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Rønnestad and coworkers describe a prospectively collected cohort of Norwegian infants born at <28 weeks' gestation or <1000 grams birth weight, from 1999 through 2000. The interrelationship between feeding and NNIs was evaluated with appropriate handling of potential confounders using a Cox regression analysis model.

A total of 464 infants (3.87/1000) within bounds were delivered, 405 of which survived until day 7 and were included in the analysis. Overall NNI rates were remarkably low, with 97 infections in 80 infants. The feeding practices consisted of uniform early introduction of either mother's or donor breast milk within a few hours of birth. The regression analysis concluded that days when full enteral feeding (FEF) were not reached were the dominant predictor of NNI.

Perhaps the most remarkable facet of this paper is the very low NNI rates described. Sepsis was recorded in 22% of infants, which is about half the rate described in other published data. The authors provide sufficient information to estimate a sepsis rate per 1000 days of 2.8 uncensored and 6.9 censored to day 35. In comparison, the respective rates for the Australian cohort (Review 2) were 5.0 and 13.88. It is tempting to attribute this low NNI rate to a socioeconomically advantaged delivering population, however, the low base rate of NNIs has been shown to be further reduced in those infants in whom FEF was more rapidly achieved. This suggests that even from an advantageous starting point, feeding practices may still be important. The rates of NEC (2.2%) were approximately half of those previously reported.

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The authors also compared their data for some neonatal care practices against those described in a similar NICHD cohort of infants.¹ This comparison highlights the early feeding and rapid advancing of enteral nutrition, as well as the reduced utilization of central lines in the Norwegian population. Although not conclusive, this analysis suggests that the Norwegian feeding practices of giving newborns breast milk almost exclusively, the very early introduction of enteral feeds, and the fairly rapid increase to FEF might serve as a benchmark for best practice that bears further attention.

There are many potential biological advantages to early feeding practices. The markedly reduced need for central lines significantly decreases one of the main causative factors of bloodstream infections. The many advantages of breast milk feeding are also dominated by the immune competence provided by fresh mothers' milk, however, advantages are also being demonstrated for using pasteurized donor milk. Lastly, one could speculate on the possibility that very early feeding practices promote colonization of the gut with healthy commensal organisms.

References

1. Stoll BJ, Hansen N, Fanaroff AA, et al. [Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network](#). *Pediatrics*. 2002;110(2 pt 1):285-291.

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