Published in final edited form as:

MCN Am J Matern Child Nurs. 2017 ; 42(6): 332–337. doi:10.1097/NMC.0000000000000375.

The Neonatal Microbiome: Implications for Neonatal Intensive Care Unit Nurses

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Abstract

Nursing care of the neonate in the neonatal intensive care unit (NICU) is complex, due in large part to various physiological challenges. A newer and less well-known physiological consideration is the neonatal microbiome, the community of microorganisms, both helpful and harmful, that inhabit the human body. The neonatal microbiome is influenced by the maternal microbiome, mode of infant birth, and various aspects of NICU care such as feeding choice and use of antibiotics. The composition and diversity of the microbiome is thought to influence key health outcomes including development of necrotizing enterocolitis, late-onset sepsis, altered physical growth, and poor neurodevelopment. Nurses in the NICU play a key role in managing care that can positively influence the microbiome to promote more optimal health outcomes in this vulnerable population of newborns.

Keywords

NICU; Microbiome; Preterm; Neonate

Nursing care of the neonate in the neonatal intensive care unit (NICU) is complex. Care is often dictated by the neonate's vulnerable state and that care, in turn, can greatly influence the neonate's functional status. A factor that has only recently been considered is the microbiome.

The microbiome is the community of microorganisms that reside in and on the human body (NIH HMP Working Group et al., 2009). Microbial colonization of the neonate can be affected by numerous factors including the maternal microbiome, mode of infant birth, and various care choices implemented in the NICU (Hartz, Bradshaw, & Brandon, 2015). An

imbalance of microbes at any one body site, commonly referred to as dysbiosis (Proctor, Thiennimitr, Chattipakorn, & Chattipakorn, 2017), has been linked to short- and long-term health outcomes. The relationships between various care choices implemented in the NICU, the neonatal microbiome, and health outcomes of the NICU neonate are presented.

An Overview of the Neonatal Microbiome

The fetal microbiome was initially assumed to be relatively sterile; however, researchers noted that microbial colonization begins in utero largely influenced by the maternal microbiome (Groer et al., 2014). Additional colonization occurs during the birthing process, with differing microbial compositions noted in and on various neonatal body sites based on the method of delivery (Groer et al., 2014). After birth, various factors have an impact on the proliferation of microbes including feeding and antibiotic usage to name a few (Groer et al., 2014).

The neonatal microbiome has a symbiotic relationship with its human host (NIH HMP Working Group et al., 2009). While various host factors foster the growth and diversity of the microbiome, the microbiome is responsible for roles such as vitamin synthesis and promotion of absorption of nutrients (Kane, Dinh, & Ward, 2015). During the first two years of life the microbiome plays a critical role in the development of the immune system and metabolic pathways (Koleva, Bridgman, & Kozyrskyj, 2015).

Neonatal Microbiome Development in the NICU

The microbiome of neonates requiring a NICU admission differs from that of full term, healthy neonates in composition and diversity (Groer et al., 2014). The NICU infant microbiome is less diverse and lower in the number of anaerobes, which contributes to increased rates of infection and inflammatory processes in this population (Groer et al., 2014). These differences in microbial composition are likely due in part to required modifications in care practices in the NICU such as feeding choices, skin-to-skin care (SSC), antibiotics, and mechanical ventilation.

Feeding Choice

Maternal breast milk has many compounds that provide the infant with nutrition and aids in establishing an advantageous microbiome (Hartz et al., 2015; Unger, Stintzi, Shah, Mack, & O'Connor, 2015). In cases where mother's own milk may not be available, donor milk or formula may be used. Researchers have noted, however, that when donor milk was compared to mother's milk, the amount and composition of oligosaccharides differed significantly (Marx et al., 2014). Given that oligosaccharides are a primary contributor to the continued development of the gut microbiome, the promotion of beneficial gut microbiota through donor milk may be questionable (Sherman, Zaghoulani, & Niklas, 2015).

Human milk manipulation in the NICU may also result in alterations of the gut microbiome. Human milk, regardless of the source, is routinely frozen and thawed, and altered through the addition of human milk fortifiers to increase caloric density and nutritional value. Freezing reduces the immunologic protective components and bacterial composition of

human milk (Sherman et al., 2015). Fortification can influence the gut microbiome by changing the nutritional composition of human milk (Sherman et al., 2015). The nutritional composition of food heavily influences the growth of bacteria in the gut making the integrity of neonatal nutrition a crucial component of care (Gritz & Bhandari, 2015; Yatsunenko et al., 2012).

Human milk and formula are often delivered via an orogastric or nasogastric tube to infants in the NICU. These tubes are not sterile and could contribute pathogenic bacteria to the gut microbiome (Hurrell et al., 2009). Further investigation is needed to determine if routine tube changes have an influence on tube contamination, the gut microbiome, and clinical outcomes.

Use of Prebiotics and Probiotics

Alternative therapies, such as prebiotics and probiotics, may restore balance in under-developed gut microbiomes, such as those in preterm infants. Prebiotics, are non-digestible food ingredients that promote the growth and activity of anaerobic/microaerophilic flora in the colon (Panigrahi, 2014). In a meta-analysis of prebiotic supplementation in neonatal and preterm infants, there were no obvious benefits of prebiotics to infant health, but significant increases in beneficial microbiota were noted (Srinivasjois et al., 2013).

A key prebiotic component of breast milk, oligosaccharides, are found in human milk and are thought to aid in the development of bifidus-predominant flora, a beneficial gut microbe (Stiverson et al., 2014). Prebiotics such as inulin, lactulose, short chain fructooligosaccharides and galacto-oligosaccharides are not well studied in the neonatal population with respect to their use, efficacy, or safety (Panigrahi, 2014). Formula companies, however, are routinely supplementing their products with these prebiotics to potentially mimic the benefits of human breast milk.

Probiotics contain live microorganisms of a few bacterial species intended to alter and complement the gut microbiome by promoting healthy change in the microbial environment (Grady, Petrof, & Claud, 2016). Use of probiotic supplements in neonates and preterm infants remains highly debated among the scientific community despite systematic reviews and meta-analyses reporting a significant reduction in necrotizing enterocolitis (NEC) with the use of preventative probiotics in preterm infants (Aceti et al., 2015; AlFaleh & Anabrees, 2014; Olsen, Greisen, Schroder, & Brok, 2016). However, most of the studies in these reviews were observational or had significant methodological flaws. In a recent randomized-controlled trial, the incidence of NEC and LOS did not differ between preterm infants prescribed a probiotic and the placebo group (Costeloe, Hardy, Juszczak, Wilks, & Millar, 2016). Given the inconsistent findings, many researchers reason insufficient datum exist to recommend routine probiotic use (Costeloe et al., 2016).

Use of Antibiotics

Use of antibiotics is common in the NICU and the practice of empirical use is widespread (Cantey, Wozniak, & Sanchez, 2015). Antibiotics, especially those that are broad spectrum, have the potential to perturb the growth of beneficial bacteria in the gut and elsewhere, limit bacterial seeding of the microbiome, encourage growth and overgrowth of pathogenic

bacteria, and negatively affect the functional capability of the existing microbiome community (Vangay, Ward, Gerber, & Knights, 2015). These alterations may contribute to problems seen in the NICU, such as NEC and LOS (Vangay et al., 2015).

Few investigators have focused on the association between use of antibiotics and the gut microbiome in preterm infants. Researchers have noted, however, that maternal intrapartum antibiotic use and direct use in preterm infants results in an overall decrease in gut microbial diversity, with a prolonged course of antibiotics producing a more dramatic decrease than a shorter course (Arbolea et al., 2015; Dardas et al., 2014; Greenwood et al., 2014). Use of breast milk seemed to positively modify some of the effects on gut microbial diversity due to antibiotic usage (Azad et al., 2016).

Use of Skin-to-Skin Care

When providing SSC of newborns, the infant is clothed only in a diaper and held upright against the chest of the caregiver (Baley & AAP Committee On Fetus and Newborn, 2015). Benefits of SSC care about the establishment of the infant microbiome are now being studied (Hendricks-Munoz et al., 2015; Rautava, Luoto, Salminen, & Isolauri, 2012).

During gestation, labor, and birth, infants are exposed to various microbial systems including the maternal vaginal or skin microbiome and/or those of hospital surfaces and staff skin (Dunlop et al., 2015). Skin-to-skin care serves to further inoculate the neonate with microbes from the caregiver that will serve as the colonizing microflora in various sites, including skin and gut (Hendricks-Munoz et al., 2015). This colonization also helps build resistance against potential pathogens, aids in the development of the immune system, stimulates the maturation of the infant intestinal system, and aids in neurocognitive development (Olszak et al., 2012; Sekirov & Finlay, 2009; Yang et al., 2016).

It is believed that neonates in the NICU benefit not only from SSC due to the transfer of microbes, but also because it has been associated with a decreased stress response (Hendricks-Munoz et al., 2015; Johnston et al., 2014). In the NICU, excessive stress can result from the pain of invasive procedures, ambient noise, and other excessive stimulation (Gorzilio, Garrido, Gaspardo, Martinez, & Linhares, 2015). Stress responses are thought to perturb the developing infant microbiome through gut-brain communication channels (Yang et al., 2016).

Use of Mechanical Ventilation

Approximately one-third of all infants admitted to the NICU in the United States will undergo mechanical ventilation to treat pulmonary insufficiency and related respiratory disorders (Bellu, de Waal, & Zanini, 2010). Despite this, studies of its influence on the infant microbiome remain scant (Bellu et al., 2010; Neu, 2015). In preterm infants, increased number of days of mechanical ventilation has been linked to the development of LOS (Shaw et al., 2015). A potential mechanism for this relationship is a change in the microbial growth pattern of the gut microbiome due, in part, to exposure to oxygen-rich mechanical ventilation (Moles et al., 2013; Shaw et al., 2015). Typically, the microbiome of the gastrointestinal tract develops a microflora dominated by anaerobic organisms as oxygen is reduced to this system during development (Arbolea et al., 2015; Sim et al., 2015). A

change in the microbial growth pattern due to oxygen-rich mechanical ventilation can alter the immune supportive properties of the gut microbiome that help thwart infection. Further evidence of this connection is seen with preterm infants requiring continuous positive airway pressure with supplemental oxygen use. These infants demonstrate increased risk for NEC and changes in their gut microbiome profiles (Sim et al., 2015).

Short- and Long-Term Neonatal Health Outcomes

Many short- and long-term outcomes of the neonate admitted to the NICU are of concern to the NICU nurse. Care choices in the NICU directly and indirectly contribute to the development of NEC, LOS, altered physical growth, and poor neurodevelopmental outcomes through the microbiome.

Short-Term Outcomes: NEC and LOS

Prevention of NEC was one of the primary outcomes researchers were interested in as investigations of the gut microbiome began. Comparison of infants with NEC and a control group revealed a clear deviation in microbiota composition weeks before diagnosis (Torrazza et al., 2013). In a study involving twins, researchers noted a similarity in bacterial composition between siblings compared to unrelated individuals, yet a different profile emerged when one twin developed NEC and the other did not (Sherman et al., 2015).

There also appears to be a connection between the neonatal gut microbiome and LOS. Similar to NEC, gut dysbiosis has been noted in infants with LOS weeks prior to diagnosis (Mai et al., 2013). Following a septic event, changes have also been observed in the gut microbiome. These infants demonstrate a reduced microbial diversity without specific enrichment of potentially pathologic organisms (Madan et al., 2012; Mai et al., 2013). Some have found LOS in preterm infants induces inflammation in the gut mucosa and changes in the gut microbiota, possibly extending inflammation-associated damage to other sensitive organs (Cernada et al., 2016).

Long-Term Outcomes: Physical Growth and Neurodevelopment

The early gut microbiome also has an influence over long-term health outcomes such as physical growth and neurodevelopment. A lack of gut microbial diversity during early life results in (1) increased extraction, absorption, and storage of macronutrients, (2) deactivation or a lack of activation of key enzymes and molecules associated with energy storage, and (3) an increase in microbiota associated with obesity (Backhed et al., 2004; Luoto et al, 2013; Samuel et al., 2008). Researchers have reported high rates of overweight and obesity during adolescence and early adulthood in individuals born preterm (Ford, Doyle, Davis, & Callanan, 2000). The gut and brain communicate (Cong et al., 2015). Dysbiosis of the gut microbiome is thought to affect social and emotional behaviors and contribute to altered brain development and function (Yang et al., 2016). However, much of the research on long-term outcomes has been on animal models, so it is difficult to draw definitive conclusions.

Implications for Nurses in the Neonatal Intensive Care Unit

It is important that from the time of NICU admission that the NICU nurse begin considering factors that influence microbiome development and the role that the microbiome may have in the development of disease. There are several key nursing interventions that can be performed during the NICU stay to ensure optimal microbiome development and potential disease prevention. These include encouraging mothers to provide their own fresh breast milk for infant feedings and enabling SSC involving both parents. Other practices may require collaboration with the healthcare team, such as supplementation with pre- and/or probiotics when ordered and monitoring for side effects including bloating, diarrhea, and flatulence. During care team meetings, nurses can advocate for shorter, more targeted antibiotic therapy by monitoring pertinent laboratory results, including organism sensitivity. They can also highly encourage the use of mother's own fresh breast milk during antibiotic therapy. Nurses can be attuned to clinical improvement, which may warrant non-invasive respiratory support and advocate for its use. Nurses can maintain SpO₂ within set parameters and titrate oxygen to meet those needs. It is vital that nurses provide education to the entire team about the impact care may have on the microbiome while advocating for the patient and family.

Conclusion

The infant microbiome is influenced by care delivered in the NICU. Nurses can play a key role in implementing nursing care and health care team practices that foster the development of a healthier microbiome. A healthier, more diverse microbiome will foster improved health outcomes for a vulnerable population.

Acknowledgments

The authors also acknowledge that the concept of this article stems from work being done under funding from the National Institute of Nursing Research NIH (R01-NR14800) Elizabeth J. Corwin PhD, RN, FAAN, Professor, Associate Dean for Research, Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA

Funding for Dr. Rodriguez is from the National Institutes of Health for the following grants: Centers for Children's Health, the Environment, the Microbiome, and Metabolomics (C-CHEM2), National Institute of Environmental Health Sciences (P50ES026071), National Institute on Minority Health and Health Disparities (R01 MD009746).

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Callouts

- The nutritional composition of food heavily influences the growth of bacteria in the gut making the integrity of neonatal nutrition a crucial component of care.
- Given the inconsistent findings, many researchers reason insufficient data exist to recommend routine probiotic use.
- Maternal intrapartum antibiotic use and direct use in preterm infants results in an overall decrease in gut microbial diversity.
- Skin-to-skin care serves to further inoculate the neonate with microbes from the caregiver that will serve as the colonizing microflora in various microbiomes across the neonate, including skin and gut.
- Comparison of infants with necrotizing enterocolitis and a control group revealed a clear deviation in microbiota composition weeks before diagnosis.

Clinical Nursing Implications for NICU Nurses

- The microbiome has an impact on health outcomes in preterm infants.
- Facilitate the use of mother's own, fresh breast milk for feedings, especially for infants exposed to antibiotics in utero or after birth.
- Encourage and facilitate SSC as early as medically possible.
- Discuss with the healthcare team the possibility of supplementing with pre- and/or probiotics.
- Monitor laboratory results, particularly cultures and microbial sensitivities and advocate for shorter durations and/or more targeted antibiotic therapy with the health care team.
- Monitor for respiratory improvement that may warrant use of non-invasive respiratory support measures and maintain SpO₂, titrating oxygen as indicated.