



Review Article

Neonatal bacterial colonization of the intestine-Implications for the practitioner

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Abstract

Background: Neonatal intestinal bacterial colony balance has correlations with positive and negative health situations. The understanding of how neonate colonization occurs is therefore extremely important in providing life-extending and holistic care for infants. Certain medical interventions can impede optimal intestinal colonization. However, with proper screening and identification, side effects can be limited and compensated for, and complications can be minimized in an already compromised population. This study aims to identify influences on neonate microbiomes to create best practices for increased health outcomes. Develop mitigations for factors leading to intestinal microbiome conditions linked to negative neonate outcomes and increase opportunities for healthy colonization.

Methods: The research team conducted a literature review via PubMed, Cumulative Index of Nursing and Allied Health Literature, and Academic Search Ultimate to collect data regarding neonatal bacterial colonization of the intestine.

Results: Normal colonization is affected by birth age, birthing method, time spent in direct skin to skin contact with mother and feeding type. Iatrogenic influences include the use of oral and topical antibiotics, proton blockers, and practices that limit direct contact.

Conclusion: The nursing process and policy adaptations can have a positive effect on developing a protective neonate intestinal microbiome. Awareness of risks and early clinical signs can improve positive interventions that may prevent life-threatening complications in susceptible neonates.

Keywords: Neonate; infant; intestine; bacterial colonization; post-natal; bacteria; screening.

Introduction

Intestinal microbe colonization is believed to occur after birth and has a lasting impact on health. With an average of 1011–1012 microbes/ml in the intestinal lumen, including an estimated 400 species, the intestinal microbiome makes a significant contribution to the health of an individual [1]. The importance of microbial colonies has been acknowledged by the National Institutes of Health in their Human Microbiome Project, a work to identify and categorize a comprehensive data set of bacteria found in the normal flora of human tissues. Neonatal colonization has been shown to be influential through adulthood [2,3]. Initial colonization balance and composition is strongly influenced by birthing factors, feeding method, and early environment.

Background

Microbial colonization occurs within days of birth, and due to rapid replication, bacterial cells quickly outnumber human cells [1,4]. The organs most affected by microbial colonization are the intestine, skin, mouth, vagina, and bladder [2,3]. Colonization of the intestine appears to be the first epithelium colonized after birth [5]. Initial immunocompetence begins when maternal lymphocytes cross the placental barrier during the last 6 weeks of pregnancy and colonize the fetal lymph nodes [5]. The remaining fetal immune tissues maintain “niches” that appear to be colonized by maternal microbes from vaginal delivery and ingestion of breastmilk [1]. In the absence of these opportunities, neonate tissues are colonized by environmental and skin microbes [6]. Recent research indicates differences in these sources creates alternative lifelong microbiome balances in the individual [1,6]. Bacterial species, and balance of those species, have shown to persist to six months of age in infants [7].

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Initial neonate colonization influences the intestinal microbiome of children until seven years of age [2,7,8,9] and has a lasting impact on adult microbiomes [2].

The intestinal lining provides the largest surface area of a neonate, and its immunoreactive function is directly tied to the microbes living there [2]. Microbes perform local physiological functions, including fermentation of unused energy substances, production of biotin and Vitamin K, training the immune system, creating oral tolerance, and prevention of overgrowth of non-commensal bacteria such as *Clostridium difficile* [2,3]. Normal gut bacteria also stimulate angiogenesis and regulate host fat storage [1] There is evidence that intestinal microbes also establish gut associated lymphoid tissue (GALT), such as the creation of Peyer’s patches, which are not found in fetal intestines [2,5].

Each person has a specific balance of microbes, creating a distinct bacterial fingerprint, and a child’s gut microbiome balance does not correlate to their familial adults [1,10]. Differences in microbe balance exists between adults sharing domestic quarters and foods, so it is not surprising that child intestinal differences occur as well [1]. However, the

persistence in balance and components indicates that the first year is the formative period for intestinal microbes.

Methods

Study design

This study used a systematic review of peer-reviewed articles found in indexed databases. The Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines were used to ensure consistent and precise reporting of results. The initial search was conducted on January 4, 2018 and final search was completed on January 15, 2018 using PubMed (MEDLINE), the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Academic Search Ultimate. The Medical Subject Headings at the National Center for Biotechnology Information were used to discover keywords for the queries, as well as keywords discovered during searches. These discovered keywords were examined to determine the final tapered scope of the search. Understanding the most commonly revealed keywords led to the complex, seven-string Boolean search included in Figure 1. A review of articles found in the databases led to additional resources that met the inclusion criteria which were included in the final number of articles.

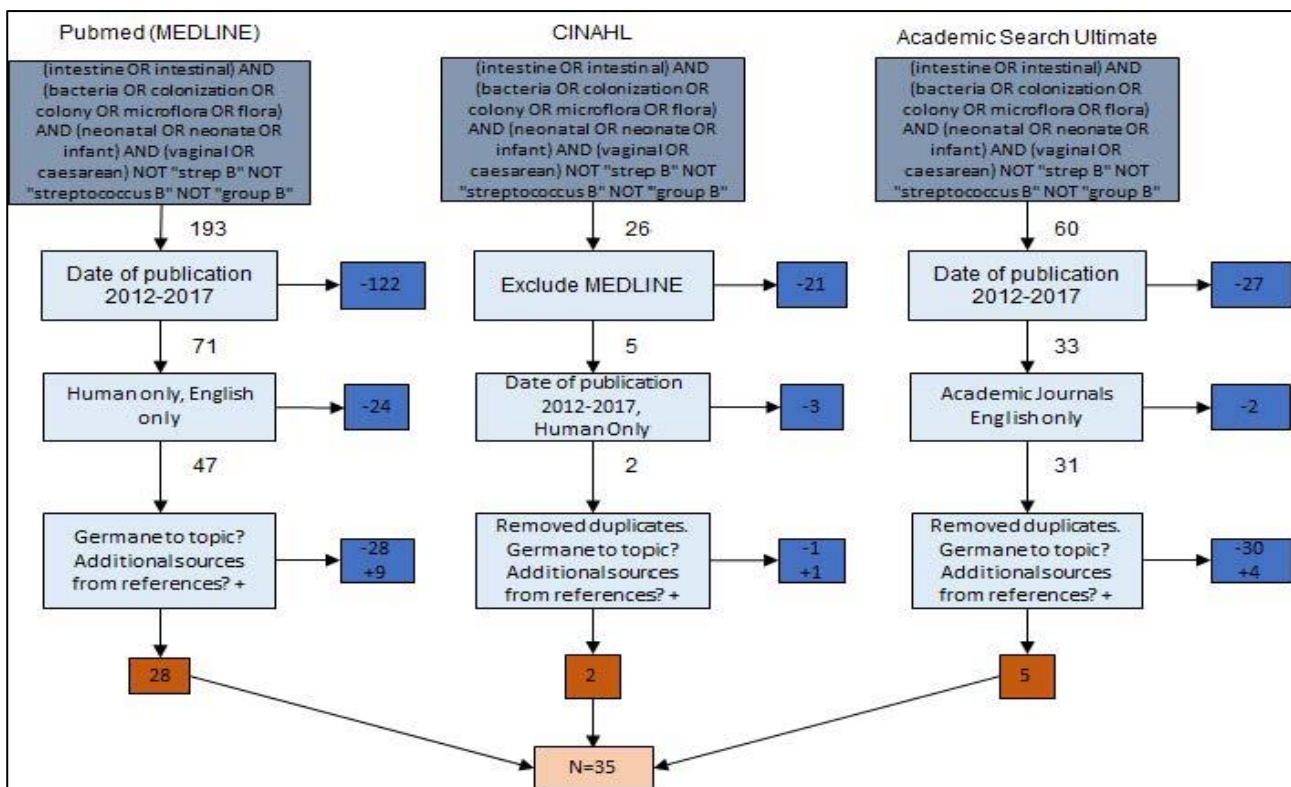


Figure 1: Preferred reporting items for systematic reviews flow diagram

Inclusion criteria

Authors individually reviewed the articles from the search, determined germane literature, and summarized pertinent findings from each of the included articles. Inclusion criteria included English-language and peer-reviewed articles published by academic journals or universities between January 1, 2012 and December 31, 2017 (a five-year period). Articles had to explore neonatal intestinal bacterial colonization and some aspect of either vaginal or Cesarean delivery.

Exclusion criteria

Articles were only incorporated if deemed germane by all authors. Trade industry reports and poster presentations without clear, scientific format, and a peer-review process were excluded. Articles which dealt with any aspect of streptococcus B infection were not included. Similar examination outcomes from the articles demonstrated that the authors had a parallel understanding of the research subject and scope. Bias was not considered when reviewing the research involved in this study.

The final sample of articles after meeting exclusion criteria was then analyzed further for consensus among all authors for final inclusion. When analyzed, this sample yielded a kappa statistic ($k=1$), showing strong reliability among researchers.

Results

Study Selection

The article selection process is outlined in the PRISMA flow diagram in Figure 1. The initial search protocol identified 279 potential articles from the databases queried. Articles were then excluded from the search for not meeting predetermined inclusion/exclusion requirements, leaving 21 articles which were germane. The references included in these articles was then assessed for further potential literature, and an additional 14 articles were found and utilized. 6 articles not meeting the five-year search requirement were included in the article upon review of references due to their importance to the topic, and the lack of significant research in the area. A total of 35 articles were used for qualitative analysis.

Discussion

Bacterial Balance Implications

The impact of different bacterial balances of the neonate intestine are significant to short and long-term outcomes. In research focusing entirely on neonate balances, fecal samples are typically collected and compared to the health of the infant [6,11]. A summary of some of the differences with the highest impact are as follows.

Clostridium coccooides and *leptum* are normal components of the healthy infant and adult intestinal microbiome. *C. coccooides* plays a known role in defense against invading bacteria and is present in term breastfed infants by 1 month of age [12]. The closely related *C. leptum* has a known correlation to healthy brain development and production of free catecholamines including norepinephrine and dopamine [12]. It is currently unknown why *C. leptum* was found in term and preterm infants, while *C. coccooides* was not found in any of the tested preterm infants [13].

Bacteroides is an anaerobic bacterium, often used as a marker of diversity and health of the intestinal microbiome [12] and has been associated with decreased sensitivity to common digestive system allergens [1]. It is encouraging that all infants born vaginally have these bacteria in their intestine but concerning that it is decreased in cesarean delivered infants [13].

Preterm infants exhibit a delay of *Bifidobacterium* presence, which warrants more investigation. This genus of bacterium is found within a day of birth in term infants, but in preterm infants, it is not measurably present until 6 months of life [13,14]. The *Bifida* genus is medically associated with direct competition of several pathogenic bacteria, including pathogenic *Clostridium* and *Staphylococcus* strains [12]. The cause of the delay is unknown, as the mode of birth and feeding source did not have any noticeable effect on either the term or preterm group [13].

Another significant difference between term and preterm infant guts is the presence of *Staphylococcus epidermidis* in preterm infants. *S. epidermidis* is a pathogen associated with nosocomial sepsis, and it is not part of the normal intestinal flora at any age [13].

Identification and source

With the type of bacteria present in neonate intestines being so important to infant health, it is imperative to find ways to identify potential deleterious balances quickly and cost effectively. Techniques used for fecal bacterial identification are commonly available in acute care settings. Most commonly, microbes are genetically identified by real-time polymerase chain reaction (PCR), and gel electrophoresis or genetic sequencing. Several studies comparing these methods of bacterial strain identification have shown both methods to be consistent in correct identification of bacteria [6,10].

Databases from familial samples has demonstrated direct linkage between maternal samples and infant intestinal colonization, correlating birth method sources [5,7]. To trace sources of infant microbes, maternal samples are typically taken from vaginal and epidermal tissues, as well as feces and breastmilk [1,5,7,15]. Sibling and paternal skin and fecal swabs are typically collected when doing longitudinal work to associate familial commonalities [1]. Profiles of vaginally born infants maintained intestinal biomes very similar to their maternal vaginal colonies, at the age of 6 months [1,7]. Infants born by cesarean had balances of more aerobic bacteria and were similar to adult familial fecal and skin samples at 6 months [1,5]. While it is commonly discussed in that children convert to a balance more similar to adult fecal bacterium independent of birth mode, the age is not consistent. Rather, it ranges from 12 months [1,15] to 24 months of age [4]. The full impact of the delay is not currently known, but with the current knowledge of intestinal colonization impact on long term health, it is worth noting that improving colony balance has the potential to positively impact infant lives.

Exposure in-utero

The recent discovery of bacterial rDNA in preterm meconium and amniotic fluid indicates the preterm infant gut may not be sterile, and bacterial components may play a role in preterm birth [2,4,11,16,17]. Several studies have focused on the origin of bacteria the infant first encounters.

The initial colonization of the infant gut is of a very high importance in determining future health. Ideally, the infant is initially exposed to the bacteria of the maternal vaginal canal [5,17,18]. Then, the bacteria of the mother's skin, in combination with breast milk and its rich levels of antibodies, complete the early exposure to desirable bacterial balances [5]. Initially, the infant gut microbiome develops aerotolerant bacteria [4,10]. By the age of 18-24 months, strict anaerobic bacteria begin to colonize the gut, through exposure to breastmilk and healthy adult skin [4]. This process is sensitive to interruption through mode of delivery, feeding types, antibiotic administration, and introduction of solid foods [4].

Birthing factors

Birthing method effects the timing and content of neonate gut colonization [1,17,19,20,21,22,23,24,25,26,27]. Vaginally delivered neonates have consistently demonstrated maternal vaginal bacteria in their fecal material and intestines directly after passing meconium [1,5,23,27]. Cesarean delivery does not allow for natural exposure to these maternal biotic elements, and the infant is generally colonized by the environment instead [7]. These findings are of specific importance with the

increasing level of maternally requested cesareans worldwide, and the decrease in vaginal births after Cesarean section (VBAC's) being performed in the United States [2]. There is correlation evidence of cesarean rates and the increase in childhood asthma, Crohn's, type I diabetes, allergy occurrence [2,10,29], stomach cancer, some lymphomas, inflammatory bowel diseases, and necrotizing enterocolitis (NEC) [1,20,21,29].

Vaginal birth exposes the infant to maternal microbe balances and establishes bacterial richness and diversity [4,14,27,28]. *Bacteroides* plays a role in immunity and complex molecular catabolism in the early infant gut [30]. There was also little difference in levels of *Bacteroides* in neonates that received antibiotics over those that did not, however, there is a significant difference in *Bacteroides* levels based on mode of birth [11]. Infants delivered vaginally, independent of gestational age, had higher levels of *Bacteroides* than those delivered by cesarean section [11]. This difference lasts at least 6 weeks post birth [15]. These colonies were still completely absent in infants delivered by cesarean section at 4 months and found at only half the rate of vaginally delivered infants by 6 months [4,7].

Gestational age at birth also appears to be significant in colony composition. Full term infants typically have intestinal microbiomes including more than 200 different microbes [10]. However, preterm infants typically have bacteria not native to a healthy gut, and far less diversity, usually closer to only 16 types of microbes [10,17,28,29].

Feeding method

Feeding method research has focused primarily on the source of the nutrition and not the equipment or process of feeding an infant. Differences in formula versus breastmilk fed infants appears to involve the types of bacteria found in the infant gut. Formula fed infants have consistently tested higher in aerobic bacteria, and lower in *Bifidobacteria* than breastfed infants [1,14]. Breastfeeding is associated with support of the vaginally acquired lactic-acid producing bacteria [5]. Combination feeding (both breastmilk and formula) has shown to create an intestinal bacterial balance that most closely resembles exclusively formula fed infants [15]. Cesarean birth alterations are often compounded by delayed lactation, and these factors appear to reinforce the difference in facultative aerobic balance in the neonate gut [7,10]. While feeding appears to influence intestinal flora, the influence is less than birth and environmental factors [2].

However, there is an additional association of skin to skin contact, which most commonly occurs during feeding.

Environmental factors

Skin is an important intermediate step of microbe colonization. Skin microbes have been found in higher concentrations in the intestines of environmentally colonized infants than those who were vaginally colonized [5,7,19,28]. Neonate skin has specific physiological and anatomical differences that influence colonization. The skin of a term infant takes 14 days to adapt to extrauterine life and become keratinized sufficiently to affect a protective layer [31]. The skin of a preterm infant requires the same 14 days, plus the number of weeks to full gestation [31]. Infant skin microbiomes were not affected by bathing practice,

indicating it is microbes that are inadvertently ingested by the neonate during and shortly after birth that establish bacterial gut colonization [31]. It is important to consider that the infant has been swallowing amniotic fluid for several months by term birth, and that this contributes significantly to their gut microbiota [7,31,32].

An example of environmental colonization impact is the commonly occurring, resistant bacteria methicillin resistant *Staphylococcus aureus* (MRSA). This bacterium is so pervasive, it is present in many healthy people's nostrils [1,33]. Yet, MRSA is highly pathogenic if found inside human tissues. In infants with colonized MRSA, normal skin bacterium colonization has been demonstrated in as little as half an hour after skin to skin contact with their mother [33]. Vaginal delivery also has some correlation to decreased infant MRSA infection rates overall [4].

Iatrogenic interference

While there is often a need for medical intervention to protect, or create neonate health, there are several interventions that compromise the normal development of neonate intestinal microbiomes. This interference begins before birth and continues throughout the life of the neonates.

The use of prophylactic ampicillin in cesarean sections has not been well studied. As ampicillin readily crosses the placental barrier, and dissolves within 1 hour from intravenous administration, it is possible that there is impact to the neonate's ability to colonize gut bacterial competently and may play a part in selection of resistant bacteria [7]. It is also possible that the maternal bacterial colonies are negatively impacted by this type of antibiotic administration [7,9]. Such as in the case of several *Staphylococcus* bacteria, that are further promoted through use of maternal and neonate antibiotics [4].

Oral antibiotics are commonly cited, in scientific literature, as disrupters of intestinal microbiome balance. Intestinal flora was unable to rebound to the original balance after repeated treatments lasting more than 4 weeks in infants who received oral antibiotics before the age of 12 months [1]. In those cases, the infant gut was rendered bereft of samples to the point of no detectable bacteria [1]. When the gut bacteria of the affected infants were reestablished, the balance was prematurely shifted toward an adult balance, rather than age appropriate colonization [1,34].

Iatrogenic actions detrimental to bacterial diversity immediately preceded all the included cases of NEC [10]. Deleterious interactions identified include the frequent use of broad-spectrum antibiotics prophylactically [10]. Other detrimental interventions included the use of opioids, proton blockers, endotracheal, and feeding or suctioning tubes [10].

Practitioner considerations

Lack of intestinal microbiome diversity is a predisposing factor for NEC, systemic inflammatory response syndrome, and neonate sepsis [4,10]. Diversity is compromised by factors including prematurity, surgical interventions, enteral and formula feeding, and other invasive procedures [15]. Biodiversity is essential for proper health and training of immune structures in the neonate intestine [5,6,10,13,35].

Medical interventions are often essential for life saving and health promoting care of infants. Yet, they are not without

impact on the infant. Use of topical antibiotics in the NICU is a common practice to control non-commensal *S. aureus* [4,5]. However, this practice can lead to drug resistant colonies, specifically MRSA and related organisms [9,33]. Many interventions are unavoidable. The role of the nurse is to identify them as predisposing factors and be aware of early signs of complications [36]. Solid nursing assessment and critical thinking skills can be implemented to protect neonates from immediate and long-term complications of compromised microbiome development [36].

Conclusion

The current state of the literature points in several potential directions for research. Interventions that promote balanced colonization in cesarean and preterm delivered infants should be developed [12]. Further research into the impacts of maternal treatment for Group B *Streptococcus* organisms is significant, as approximately 20% of United States gravid women are testing positive for Group B Strep [2]. Impact of delivery mode and feeding methods have definite influence on bacterial colonization in neonates [4,11]. It is likely that the differences in bacterial colonies impart some of the lifelong health benefits known to be associated with vaginal birth and breastfeeding [10]. However, with the continued study of these balances and influential interactions, it is likely that we will soon have some insight into how to better manage the delicate neonate gut. To achieve this level of insight, further longitudinal studies will be needed, especially those that follow infants during the first year of life.

The implication that bacterial balance may be a reliable predictor of NEC is very significant. It could be used as a screening tool to base prophylactic measures that could prevent this life-threatening disorder [9]. Since diversity appears to have a stronger correlation than bacterial type beyond the proteobacteria presence, the cost-effective screening based on colony diversity may hold promise for early intervention [9]. This could allow NICU iatrogenic interventions to increase bacterial colony diversity or implement prophylactic measures in the progression towards necrotizing enterocolitis.

A potential limitation of this study is that some of the literature reviewed had a very small sample size associated with it. Whereas this sample size does not necessarily equate to these studies being valid or invalid, it is a consideration to consider when drawing conclusions from them. These small samples show validity, and most certainly should be followed up by more comprehensive research to draw more complete conclusions. Their inclusion in this study was to show them as viable contributions to the field and that their information could be correlated to this field of study.

Abbreviations

CINAHL: Cumulative Index of Nursing and Allied Health Literature
GALT: Gut Associated Lymphoid Tissue
MRSA: Methicillin Resistant *Staphylococcus Aureus*
NEC: Necrotizing Enterocolitis
PCR: Polymerase Chain Reaction
PRISMA: Preferred Reporting Items for Systematic Reviews
VBAC's: Vaginal Birth After Cesarean section

Declarations

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All authors had equal contributions in the preparation of this manuscript.

Ethics approval and consent to participate

Systematic review of literature, no approval necessary

Consent for publication

Not applicable

Competing interest

The authors declare that they have no competing interests.

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