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NECROTIZING ENTEROCOLITIS ASSOCIATED WITH DYSBIOSIS OF PRETERM GUT MICROBIOME: A REVIEW

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ABSTRACT
Preterm birth is defined as any birth before 37 weeks of completed weeks of gestation. Preterm infants are said to have an imbalanced intestinal and immune system. Alteration of the gut microbiota in preterm infants has been associated with the development of short term diseases such as sepsis or Necrotizing enterocolitis. Necrotizing enterocolitis is a catastrophic disease affecting the preterm infants. Although its pathogenesis is poorly known, risk factors like gestational age, birth weight, formula feeding and bacterial colonization of the gut are found to be associated with its emergence. This review was aimed at describing the latest literature related to Necrotizing enterocolitis and its association with dysbiosis of preterm gut microbiome. Moreover several studies have shown the use of fecal samples in detecting the presence of Necrotizing enterocolitis. Microbial dysbiosis preceding Necrotizing enterocolitis in preterm infants is characterized by increase relative abundances of Firmicutes and Bacteriodetes .Immune responses like Toll-Like Receptors also trigger the severity of Necrotizing enterocolitis. Necrotizing enterocolitis can be reduced through administration of probiotics, thus, reducing the rate of morbidity and mortality of preterm infants.
Keywords: Dysbiosis, Microbiota, Necrotizing enterocolitis, Preterm infant, Probiotics.

INTRODUCTION

Necrotizing enterocolitis is a devastating inflammatory disorder found mostly in preterm neonates associated with high morbidity and mortality rates (Neu and Mohan, 2018). It occurs when intestinal tissue becomes damage and starts to die (Maheswari *et al*., 2014). Necrotizing enterocolitis usually affects the premature babies within two weeks of delivery. In a serious case, a hole appears in the intestinal wall thus enabling the bacteria to pass into the abdomen and spread the infection (Abdulkadir *et al.,* 2016). The early stages of necrotizing enterocolitis are inversely proportional to the gestational age of the infants at birth. Necrotizing enterocolitis has been associated with severe neurodevelopment delay, poor growth, intestinal obstruction due to scarring, short bowel syndrome and potential liver failure due to prolonged hyper alimentation *(*Embleton *et al*., 2008). The common symptoms of necrotizing enterocolitis include swelling in the abdomen, bloody stool, diarrhea, inflammation, presence of intestinal fluid and intestinal perforation (Abdulkadir *et al.,* 2016). Necrotizing enterocolitis affects approximately 6-10% of very low birth weight babies with fatality rate as high as 20-40%. Risk factors of necrotizing enterocolitis include gestation age, birth weight, formula feeding and bacterial colonization (Itani *et al.,* 2017). Infants who are very premature are at greater risk of necrotizing enterocolitis than those born closer to term (Wiedmeier *et al*., 2011).

Preterm birth

A term birth has been defined as birth between 37 and 42 weeks of gestation and use to describe the optimal timing for a good outcome for the mother and baby *(*Divanovic *et al*., 2017).

Preterm birth has been defined as any birth before 37 weeks of completed weeks of gestation (Abdulkadir *et al.,* 2016). Preterm birth is among the single conditions with highest mortality and considerable risk of lifelong impairment. Preterm births occur in high income countries and contribute substantially to neonatal morbidity and mortality (Tarrant *et al*., 2017). Prematurity is a risk factor for infant morbidity and mortality and is associated with high risk of bacterial and inflammatory diseases such as sepsis and Necrotizing enterocolitis (Korpela *et al*., 2018).

Preterm gut microbiome

The microbiome is defined as microbial flora inhabiting the human body (Henneke, 2017). The composition of the microbiome is complex and distinct between individuals and subject to environmental changes and adaptation to host factors. Each body site contains a unique microbial community (Henneke, 2017).

The fetal gut contains no bacteria and bacterial DNA sequences have been identified in freshly produced meconium (Michel *et al.*, 2017). However the initial colonization of the fetal gut is affected by several factors including mode of delivery(Gregory *et al.*, 2015).

Neonates born vaginally typically are colonized with vaginal microbiota including *Lactobacillus* and *Prevotella* spp. while neonates born by caesarean section delivery are colonized by bacteria of the skin microbiota including *Staphylococcus* and *Corynebacterium* (Miche *et al.*, 2017).

Moreover, after birth the neonates gut bacterial population rapidly expands especially during the first week of life. The first bacteria that colonize normal infants are mainly aerobes and facultative anaerobes such as *Enterococcus* spp*, Staphylococcus* spp*,* Enterobacteriaceae and Lactobacilli (Pearl and Allan, 2016).

The gut microbiome plays an important role during the physiological development of humans. Compared to term infants, the intestinal microbiota of preterm infants has fewer bacterial species, less diversity and increased proportion of potential pathogens (Itani *et al.*, 2017).

Microbial colonization of the gut is altered in preterm infants. This abdominal colonization can affect their intestinal development and maturation and is therefore associated with short term and long term health consequences (Hosny *et al.*, 2017).

Many common practices such as caesarean section, antibiotic use and formula feeding may disrupt normal microbiota development. Deviation from the normal flora gives rise to opportunistic and potentially pathogenic bacteria such as *Enterobacter, Enterococcus* and *Staphylococcus* (Angelakis and Raoult, 2018).

The preterm gut microbiome has important influences in both disease and health of neonates. Premature infants have an immature gastrointestinal tract with a gut epithelium that has diminished barrier function and increased permeability (Moles *et al.*, 2015). This allows the movement of bacteria from the gut to the bloodstream thus leading to systemic inflammation or sepsis (Michel *et al.*, 2017).

Dysbiosis of preterm gut microbiome

Disruption of the gut microbiota development and homeostasis is termed as gut dysbiosis and has been associated with development of multiple intestinal disorders including Necrotizing enterocolitis (Michel *et al*, 2017). Associations between bacterial diversity and the presence of microorganisms like *Clostridia, Klebsiella pneumoniae* and *Escherichia coli* have been related to subsequent increase of Necrotizing enterocolitis development (Brower-Sinning *et al.*, 2014).This pathological process is characterized by lack of beneficial commensal microbes, a low diversity of bacteria allowing the overgrowth of pathogenic bacteria inducing an excessive inflammatory response (Berrington *et al.*, 2014).

The intestinal mucosa recognizes bacterial products via pattern recognition receptors and the best studied are the Toll-Like Receptors (TLRs). The TLRs recognize microbial associated molecular patterns (MAMPs) (Michael *et al.,* 2015). Patterns of intestinal colonization help to regulate TLR expression. As a result of abnormal colonization patterns, it trigger inappropriate responses. MAMPs activate specific TLRs which lead to activation of nuclear factor kappa-beta and its inflammatory pathway and caspases. Commensal and pathogenic bacteria contain MAMPs and can be pro-inflammatory if host conditions are abnormal. However, TLRs must maintain a delicate balance between appropriate inflammatory response to pathogenic bacteria and homeostasis by supporting important intestinal functions including cell growth and proliferation (Naomi, 2018).

Toll-Like Receptor 4 (TLR4) plays a critical role in the development of NEC. Its activation leads to mucosal damage and reduced epithelial repair. TLR4 is up regulated in preterm gut than term gut and plays an important role in the regulation of normal gut development in-utero (Neu and Mohan, 2018). When the gut is subsequently colonized with numerous Gram-negative bacteria, there are deleterious consequences of exaggerated TLR4 signaling including increased release of pro inflammatory cytokines and impaired mucosal healing. In addition to increased signaling, there are other factors that predispose the premature gut to the development of NEC such as decreased digestion and nutrient absorption (Michel *et al.*, 2017).

Management of necrotizing enterocolitis

Necrotizing enterocolitis can be reduced through administration of breast milk (Hackam and Sodhi, 2018). Human breast milk is said to be the best source of nutrition for new born infants including preterm infants (Abdulkadir *et al.,* 2016). Breast milk contains important development and immune promoting factors such as oligosaccharides, immunoglobulins that are thought to protect the new born both dynamically and reflexively against excessive intestinal inflammation (Abdulkadir *et al.,* 2016). The ingestion of maternal breast milk from mothers delivering prematurely particularly when given as soon as possible after birth is considered a preventative measure for the development of necrotizing enterocolitis (Katherine *et al.*, 2016). The use of probiotics is also said to reduce the effect of Necrotizing enterocolitis. Probiotics are defined as live microbial supplements that provide benefit to the host when administered (Abdulkadir *et al.*, 2018). Potential benefits from probiotic feeding for preterm infants include a reduction in the bowel reservoir of more pathogenic species, improved enteral nutrition, and reduced dependence on intravenous nutrition, an increased gut mucosal barrier to bacteria and bacterial products and upregulation in protective immunity. Potentially, use of probiotics could lead to improvements in nutrition, a reduction in the incidence of sepsis and use of antibiotics (Millar *et al.*, 2003).

CONCLUSION

The gut microbiome plays an important role in physiological development of infants. However, Necrotizing enterocolitis is a severe disease affecting the preterm infants as a result of dysbiosis of their gut microbiome and it is associated with many risk factors. This gives rise to increase in morbidity and mortality of preterm infants.

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