Probiotics in premature infants: focus on necrotising enterocolitis

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Abstract

The premature infant may be exposed to an environment that is associated with the development of gastrointestinal complications. In preventing the latter, it is crucial that, if probiotics is chosen as a preventive measure, the selection of a safe product with documented probiotic properties together with close monitoring of patients is mandatory before offering this therapy for routine use in this high-risk deserving population. It is important to note that the effect of a probiotic bacterium is strain-specific. When considering the evidence from randomized control trials, researchers believe that probiotics should be offered as routine therapy for preterm infants, and that additional placebo-controlled trials are not necessary. The available guidelines may be a helpful tool in optimizing the use of probiotics in research settings.

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Introduction

Necrotising enterocolitis (NEC) is predominantly seen in premature infants and is the leading cause of mortality and morbidity in neonatal intensive care units (NICU).[1-3] NEC is rare in term infants, whereas in the preterm infant it begins at 10-15 days after birth.[1] It is characterized by bowel wall necrosis of various length and depth. NEC has an overall incidence of 2-5% in all premature infants and up to >10% in babies weighing less than 1 500 g at birth.[4,5]

Pathogenesis of necrotising enterocolitis

Although research has been conducted, the pathogenesis of NEC has not yet been fully elucidated but it is considered to be a multi-factorial disease.[6,7] The most common known risk factors are prematurity, enteral feeding, ischaemia, infective agents and bacterial colonization.[4,5,7,8] Epidemiological studies have reported a strong association between prematurity and NEC because of the structural and functional gastrointestinal incompetence of prematurity. Premature babies also present with lower gastric acid and pepsin production and lower levels of protective mucus.[4,9]

The fetal gut is exposed to amniotic fluid containing hormones and peptides that may have a role in intestinal maturation and preparation for postnatal feeding. Preterm infants may not have completed this maturation process when they are initially fed. Preterm infants are unable to digest carbohydrates and proteins completely, leading to the production of organic acids, which may be harmful to the developing gut.[9] Several studies have shown that formula-fed infants have a higher incidence of NEC compared to breast fed infants. Breast milk contains multiple factors that improve intestinal maturation. In addition, human milk provides passive immunity factors such as polymeric immunoglobulin A (IgA) and macrophages that have immune protective properties.[4,9]

The premature infant may also be exposed to antibiotic treatment during this early life stage, which may alter the intestinal micro flora, facilitate colonisation of the gut by more pathogenic organisms, and activate the inflammatory cascade, leading to high expressions of pro-inflammatory mediators. The combination of these events is currently thought to lead to the manifestation of NEC.[5]

Diagnostic criteria of NEC

NEC is diagnosed on clinical grounds and roentgenographic findings. The initial symptoms may be subtle and non-specific and include apnoea, irregular temperature and lethargy. The most common sign of NEC is abdominal distension, which may be accompanied by bilious vomiting and feeding intolerance with high gastric aspirates. Gross blood appears in the stool in 25-63% of cases whereas occult blood is present in 22-59%.[1,4,6] Severe NEC presents with respiratory failure, rapid cardiovascular and haemodynamic collapse, and shock.[4] An abdominal X-ray is the current investigation of choice to confirm the clinical diagnosis of NEC. The radiological signs in early NEC include dilated and tubular in appearance bowel loops. The pattern of pneumatosis intestinalis and portal venous gas is diagnostic of NEC.[10] Bell et al described three Stages of NEC, with Stage 1 being suggestive, Stage 2 being definitive, and Stage 3 being severe. Stage 1 is extremely non-specific and may reflect feeding intolerance, sepsis or gastrointestinal haemorrhage. These

signs may also simply be manifestations of severe prematurity. Stage 1 should not be considered as definitive NEC but is useful, primarily to alert the clinician to early signs that may predict the development of NEC. Stage 2 represents early definitive NEC, is usually diagnosed radiologically by the presence of pneumatosis intestinalis and/or portal venous gas. Stage 3 is indicative of more advanced disease and it is usually associated with major systemic signs such as shock, and bowel perforation. Stage 3 usually requires surgical intervention.[1,3,11]

The role of probiotics in premature infant nutrition

The intestinal microbial community is obtained from the birth canal and from close parental contact after birth.[12] In contrast, the preterm infants acquire colonizing bacteria from the intensive care environment rather than their mother's vaginal canal and skin surface.[13] These infants often also receive antibiotic treatment perinatally to prevent acute sepsis which may further alter the composition of intestinal bacteria. Moreover, preterm infants have delayed colonization with healthy bacteria, such as *Lactobacillus* and *Bifidobacterium* species, which may lead to decreased function of the gut microbial community and immune functions.[13-19]

The administration of probiotic to this vulnerable population may, at least on theoretical grounds, be an effective way to change the gut colonization with the so called healthy bacteria. It has been suggested that introducing probiotics to preterm infants might be beneficial to avoid overgrowth of pathogenic organisms. Probiotic supplementation has also been proposed to increase feeding tolerance, decrease the amount of days until full feeds are reached and prevent nosocomial infections in preterm infants. Probiotics administration potentially competes with other organisms for binding sites and substrate in the bowel, which increases the production of anti-inflammatory cytokines, decreases the production of pro-inflammatory cytokines, reduces intestinal permeability, and enhances enteral nutrition.[20]

A recent meta-analysis of 11 randomized clinical trials that involved 2 176 premature infants treated with oral probiotics concluded that there are significant benefits with regards to the use of probiotic supplements in reducing all-cause mortality and NEC in preterm neonates. Overall evidence indicates that additional placebo controlled trials are unnecessary, if a suitable probiotic product is available.[21] The data from a recently updated systematic review was used to develop basic guidelines on the use of probiotics in preterm infants. These guidelines give some clarity on specific strain selection, probiotic dose and the duration of supplementation.[22]

Strain selection

Bifidobacteria and lactobacilli have been found to be the most promising probiotic cultures in preterm neonates.[12,23,24] It is important to bear in mind that there are different mechanisms underlying the clinical benefits of probiotics and that such benefits are also strain-specific. Bifidobacteria are the dominant strains in infancy, and the combination of lactobacilli and bifidobacteria is known to enhance the bifidogenic effect.[12,25,26] *Lactobacillus* and *Bifidobacterium* produce acidic end products during their metabolism and in so doing they lower the pH of the intestinal environment and create a locally unfavourable setting for pathogens. The literature indicates that *Lactobacillus* binds to mucins and intestinal epithelial cells, and may be able to reverse the permeability of the immature gut.[27]

It would also appear that the functionality of a multistrain or multispecies probiotic preparation could be more effective and more reliable than that of a monostrain probiotic.[28-30] A high number of different probiotic strains is not, in itself, indicative of greater efficacy when compared to that containing a lower number of strains.[31] The guidelines indicate that it would be sensible to use probiotic products that have been shown to be effective in randomized clinical trials.

Recommended dose

An optimal dosage is vital for any probiotic strain to survive and optimally colonize the intestinal tract. The concept of viability refers to the ability of the probiotic strain to survive and proliferate in 'adequate' numbers to benefit the host. Evidence indicates that to be functional, probiotics have to be viable and in adequate dosage levels, typically 10^6 to 10^7 colony-forming units (CFU)/g of product.[28,32,33]

Based on the median dose used in clinical trials in preterm neonates, it is suggested that a daily dose of 3×10^9 CFU/day may be appropriate for neonates with a gestational age of less than 32 weeks. Currently, there are no data available regarding a dose beyond which the risk of probiotic complications will be high in extremely low birth weight (ELBW) neonates. Until such research is available it is recommended that the starting dose should be 1.5×10^9 CFU/day for ELBW neonates until they reach enteral feeds of 50-60 ml/kg/day. Because neonates are often intolerant to large enteral volumes, the probiotic dose may be decreased by half. [34] The reduced dose is still expected to be beneficial.[22]

When to start administration

The importance of early bacterial colonization in preterm neonates has been well established.[21] With this in mind, it is recommended that probiotic supplementation should be started as early as possible before pathogens colonize the gut or antibiotics destroy the existing beneficial organisms.[12,23,35] The majority of the clinical trials started probiotic supplementation when enteral feeds were initiated. The earliest reported age at which supplementation was initiated was four hours of life.[22] It is desirable that premature neonates should be clinically stable (no signs of sepsis or ileus) to ensure that gut function is optimal with minimal risk of intolerance or translocation. The optimal protocol for probiotic administration in ELBW neonates with intrauterine growth restriction needs to be confirmed.[36]

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