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Review Article

Probiotics in Neonatal Infection :A Review

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Definition of probiotics:
The term probiotics, a greek word means literally "for life." This term was first introduced in 1953 by Werner Kollath[1]. In contrast to antibiotics, probiotics were defined as microbial derived factors that stimulate the growth of other microorganisms. An expert panel commissioned by FAO and WHO defined probiotics as "Live microorganisms which when administered in adequate amounts confer a health benefit on the host" [2].

To be defined as a probiotic, a microorganism must be of human origin, exert a beneficial effect on the host organism, be neither pathogenic nor toxic, must not have transferable resistance to antibiotics, be capable of surviving gastrointestinal transit and having the ability to colonize the intestines, needs to have a pleasant taste, possess clinical evidence of safety, have a favorable cost/efficacy ratio, must remain alive during storage and use [3].

Prebiotics and Symbiotics:
These are two other related terms mentionable in this regard. **"Prebiotics"** are 'non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thus having the potential to improve host health[4]. Thus prebiotics enhance the survival of endogenous probiotic organisms[5,6]. The food ingredients most likely to meet these criteria at present are oligosaccharides (including inulin) and their derivatives, the fructo-oligosaccharides[7,8]. A **"symbiotic"** combines both a probiotic and a prebiotic in a single product [9].

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History of probiotic:
The origin of probiotics predates recorded history. Probiotics in fermented milk have been ingested by humans for thousands of years. Russian scientist and Nobel laureate Élie Metchnikoff, in 1908 made observations that human health and longevity are associated with the ingestion of lactic acid-producing bacteria and he concluded that it would be possible to modify the gut flora by replacing harmful microbes with useful microbes[10,11]. In 1907, Russian Nobel laureate, Dr. Elie Metchnikoff published The Prolongation of Life in which he noted that exceptionally long-lived Bulgarian peasants, consumed large quantities of sour milk containing *Lactobacillus bulgaricus*. He wrote, "The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes" [11].

The idea of reducing risk and managing infections by probiotics was first demonstrated by Nissle In 1916; he showed that transferring members of the human gut microbiota to healthy typhoid carriers resulted in *Salmonella* being cleansed from their intestines[12]. The potential impact that probiotics may have at the level of gut microbiota, on gut epithelium and its associated mucosal immune system, as well as systemically provides a rationale of why probiotics are promising food components for the reduction of risk or management of infectious diseases[13].

Strains used as Probiotics:
Bifidobacteria and *Lactobacilli* are the species of choice in probiotics, given the evolution of the gut flora in preterm neonates[14]. *Bifidobacteria* are the dominant strains in infancy, and the combination of *Lactobacilli* and *Bifidobacteria* is known to promote the growth of indigenous lactic-acid bacteria (bifidogenic effect) by formation of short-chain fatty acids as a product of the fermentation process[15].

Table- I. Probiotic micro-organisms used for oral bacteriotherapy in humans

Bacteria
Lactobacillus (acidophilus, plantarum, casei, rhamnosus, delbrueckii subsp. bulgaricus, reuteri, fermentum, brevis, lactis, cellobiosus)
Bifidobacterium (bifidum, infantis, longum, thermophilum, adolescentis, animalis)
Streptococcus (lactis, cremoris, thermophilus, intermedius)
Leuconostoc
Pediococcus
Propionibacterium
Bacillus
Enterococcus (faecium)
Yeast and moulds
Aspergillus saccharomycies
Candida pintolopesii
A. niger
A. oryzae

Monostrain or multistrain probiotics:

Evidence indicates that the functionality of a multistrain or multispecies probiotic could be more effective and more consistent than that of a monostrain probiotic[16,17]. Colonization of an ecosystem providing a niche for more than 400 species in combination with individually determined host factors is anticipated to be more successful with multistrain rather than monostrain probiotic preparations[18].

An optimal dose is essential for any probiotic strain to survive and colonise the gut. Evidence indicates that to be functional, probiotics have to be viable and in sufficient dosage levels, typically 10^6 to 10^7 colony- forming units (CFU)/g of product [19,20]. Based on the median dose used in the randomized controlled trial (RCTs) in preterm neonates , a daily dose of 3×10^9cfu/day may be appropriate for neonates of less than 32 weeks gestation [21,22].

Probiotic supplementation should be started as early as possible before pathogens colonize or antibiotics destroy the prevailing commensals. Most of the trials started supplementation when newborns are ready for oral feed and clinical stability is desirable to ensure that the gut function has recovered after the initial illness, with minimal risk of intolerance or translocation. It seems appropriate to stop supplementation after reaching the corrected gestational age of 36 to 37 weeks, when the risk of Necrotizing enterocolitis (NEC) is minimal[23].

Postulated mechanism of probiotics action:

Probiotics regulate intestinal microbial homeostasis, interfere with the ability of pathogens to colonize and infect the mucosa, modulate local and systemic immune responses, the stabilization or maintenance of the gastrointestinal barrier function, the inhibition of procarcinogenic enzymatic activity and the induction of enzymatic activity that favours good nutrition[24].

There are several mechanisms by which probiotic administration may be expected to reduce the incidence of infection in preterm infants: (a) an increased mucosal barrier to translocation of bacteria and bacterial products[25] (b) a reduction in the incidence of suspected or proven neonatal NEC[26] (c) improved enteral nutrition[26], leading to a reduction in the use of intravenous feeding, which is a major risk factor for bacterial infection in hospital patients; (d) changes in the pattern of gastrointestinal tract colonisation, leading to a reduction in the extent to which preterm infants are colonised with potential pathogens such as enterococci[26] and possibly increased colonisation with desirable microflora such as *Streptococcus salivarius*[27] and upregulation of immune responses[28].

Sepsis and it's magnitude in newborns:

Neonatal sepsis is a clinical syndrome of systemic illness accompanied by bacteremia occurring in the first month of life[29]. It can be very early onset (within 24 hours), early onset (EOS) in between 24 hours to six days, and late onset (LOS) beyond six days[30]. Approximately 20% of very-low-birth-weight (VLBW, <1500 g) infants suffer from culture-proven sepsis, and 10-20% die from sepsis in spite of antimicrobial therapy[31]. NEC is the most common acquired abdominal emergency in preterm infants receiving intensive care[32]. In addition to the known risk factors include enteral feeding and prematurity, bacteria also contribute to the pathogenesis of NEC[33].

Due to improvements in obstetric and neonatal care, large number of low birth weight newborns are surviving and it is a great challenge for the neonatologist to control and prevent sepsis, NEC in this population.

Abnormal colonization of gastrointestinal tract in preterm low birth weight babies contributes to increased susceptibility to sepsis and NEC. Preterm infants acquire colonizing bacteria from the intensive care environment rather than their mother's vaginal canal, skin surface and milk[34]. Their gut harbour potential pathogenic bacteria like *Klebsiella, Enterobacter* and *Citrobacter* species rather than *Bifidobacterium* and

Lactobacillus which are the predominant strains in healthy breast fed neonates[35]; these enteric pathogenic bacteria are responsible for up to 60% of nosocomial infections in neonatal intensive care units [36].

Risk reduction and management of infections by probiotics:
Based on the finding demonstrated by Nissle in 1916, probiotics are considered as promising food components for the reduction of risk or management of infectious diseases. Use of probiotic has been targeted in a number of infective conditions like infectious diarrhea in infants and children including acute infectious diarrhea and antibiotic associated diarrhea (AAD), Traveler's diarrhea (TD), NEC in infants, Helicobacter pylori infection, respiratory tract infections in adults and children, ear, nose, and throat (ENT) infections, infectious complications in surgical and critically ill patients[37].

In preterm neonates, use of probiotics results in reduced mucosal colonisation by potential pathogens, increased barrier to translocation of bacteria and bacterial products across mucosa competitive exclusion of potential pathogens, modification of host response to microbial products, improved enteral nutrition and reduced dependence on intravenous nutrition. Thus probiotics potentially leads to reduction in the incidence of sepsis and use of antibiotics, and prevention of neonatal NEC.

Studies on use of probiotics in preterm infants:
Beneficial effect of probiotic supplementation has been tested by different clinical trials. Early comparative studies concentrated on the safety and colonisation potential of probiotics in this population and the impact of feeding probiotic bacteria on the enteric microflora of infants[38]. Supplementation with *Bifidobacterium breve* caused colonization of immature bowel and resulted in fewer abdominal signs[39].

Other trials conducted later on concentrated on protective role of probiotic supplementation on NEC, a life threatening, devastating morbidities of preterm infants. The result is promising in most of the trials as reflected in two systematic reviews. concentrating the effect of probiotic supplementation in preterm newborns. The first one, reported in 2007, identified 7 RCTs included 1393 infants[40]. This systematic review found that most of the investigated probiotics might reduce the risk of NEC in preterm neonates with, 33 wk gestation. Similarly, the Cochrane Review, published in 2008, found that supplementation of certain probiotics reduced the risk of severe NEC and mortality in preterm infants born with less than 1500 g[41].

However, recently published result of multi-centre, double-blinded randomized placebo-controlled trial conducted in 9 NICUs in Columbia showed probiotic supplementation did not reduce rate of NEC significantly[42]. Some other earlier reports also demonstrated lesser decline of incidence of NEC after probiotic supplementation. Significant decline might be associated with use of multistrain product[26,27]. Avoidance of use of single strain alone without further evidence has been suggested on the basis of some other reports[43,44].

Probiotic supplementation did not significantly reduce risk of blood born infection as found in meta analyses. Meta-analysis of data from 10 trials estimated no significant difference in the risk for sepsis between the probiotics and control group neonates; however, there was significant heterogenecity. Only one trial reported significantly lower risk for sepsis in the probiotic group[45], and another reported higher risk for sepsis in the probiotic group, which was not significant after adjustment for gestation and birth weight[46]. Statistically significant difference in incidence of blood culture positive sepsis has been demonstrated in some other studies[47,22]. There are two ongoing large trials (PIPS and Propem) evaluating effects of probiotics on sepsis.

Safety of probiotics
The most important area of concern with probiotic use is the risk of sepsis. Probiotics have been widely used in food processing for many years, and overall have an excellent safety record, as supported by reviews[48,49]. Many small studies also support the safety of particular probiotic strains in particular high risk populations[50-52]. But several reports have directly linked cases of *Lactobacillus* and other bacterial sepsis to the ingestion of probiotic supplements[53].

Probiotic supplement related sepsis in the form of liver abscess and endocarditis has been reported in adult population[54,55].

Bacterial sepsis related to probiotic use in children and infants has also been reported. Two premature infants with short gut syndrome who were fed via gastrostomy or jejunostomy and developed *Lactobacillus* bacteremia while taking LGG supplement[56,57]. Probiotic supplementation in early infancy is also associated with LGG endocarditis[58].

All the reported cases of probiotic sepsis was related to Lactobacillus strain. In contrast to this, Bifidobacteria sepsis related to probiotic use is not documented possibly due to its low pathogenecity[28] and dominance of Lactobacilli genera along with Bifidobacteria in currently available probiotic

preparation[59]. Most cases of probiotic sepsis have resolved with appropriate antimicrobial therapy[60]. Few fatalities as reported were usually related to underlying disease rather than directly to probiotic sepsis[61-63].

Conclusion:

Safety issue for use of probiotic in neonates cannot be under-estimated. Despite overall excellent safety records they should be used with caution in certain patient groups-particularly neonates born prematurely or with immune deficiency. They should be supplied as biological/ pharmaceutical product with approval by regulatory authority not merely as dietary supplement.

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