The fight against malnutrition: The emerging role of probiotics

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Introduction

The first 1000 days of life present a critical window for physical and mental development of a child in the long-term. Both chronic and acute malnutrition have adverse consequences among young children, contributing to about 45% of deaths among under-5 children [(1)]. Stunting is the most predominant form of malnutrition, which is indicated by length-for-age Z less than -2 score—globally 159 million children are stunted (2). Weight-for-age Z score (WAZ) less than -2 is the WHO-recommended indicator for assessment of childhood underweight (3, 4). A pooled analysis from 62 low and middle income countries (LMICs) observed that among under 5 children stunting was 29.1% and under-weight was 13.7% (5). In addition, globally more than 18 million under 5 children are affected by severe acute malnutrition (SAM), the most extreme form of malnutrition [(6).]

Development of intestinal inflammation due to chronic exposure to a number of enteropathogens has been considered to be the attributing factors for the underlying pathophysiology of childhood malnutrition. [(7, 8)]. The human GI tract, especially the colon, represents a primary natural harbor for colonization of more than 5000 species of bacteria, making up the "gut microbiome", which is dominated by facultative and obligate anaerobes. These anaeorbes include members of the genus *Bifidobacterium, Eubacterium*, *Clostridium, Peptococcus, Peptostreptococcus, Ruminococcus, Escherichia, Enterobacter, Enterococcus, Klebsiella, Lactobacillus and Proteus* [(9)].The GI tract of neonates is colonized immediately following birth [(9)]. Mode of delivery (natural vaginal delivery or caesarian section), infant diet (exclusive breast feeding or infant formula feeding), location of the birth (developed country or low and middle income country), and the order of birth have been identified as several key factors that are extensively associated with the pattern of colonization [(10-12)].

Gut Microbiome in Human Health

The regular metabolic functions of the members of the gut microbiome provide the host system with essential nutrients and metabolite substrates that are readily absorbed while the residing gut flora are supported with energy and required nutrition that enables their continual growth and proliferation [(12, 13)]. Fermentation of endogenous mucus produced by the epithelia and that of non-digestible dietary carbohydrates have been classified as the integral metabolic role displayed by the gut microbial community. Consequently, recent works also indicates that the human gut microbiome is linked with immunomodulatory roles in the host system, whereby by the Toll-like receptors (TLR) have been identified as integral cues for signaling of these resident microorganisms [(14)]. Moreover, disturbance in the composition of the gut microbiome—a phenomenon commonly referred to as "dysbiosis"—has been attributed to a number of gastrointestinal diseases including, necrotizing enterocolitis and inflammatory bowel disease [(15)]. More recently dysbiosis has been stated to be associated with the pathophysiology of severe childhood malnutrition [(16)].

Members of the gut microbiome exhibit synergistic roles in the host system that also involves the salvage of energy in the form of short-chain fatty acids (SCFA) and production of key nutrients, such as vitamins B12 and K, tryptophan, and even some neurotransmitters [(13)]. Such beneficial roles of the gut microbiome have lead to use of certain members of the gut microbiome as "probiotics" for improvement of human health and nutrition [(17)]. Probiotics are live organisms with a GRAS (generally regarded as safe) status which when administered in appropriate levels confer health benefits to the host [(18)]. Henceforth, certain members of the gut microbiome display probiotic roles in the host system. Concurrent studies have demonstrated the beneficial roles of the use of probiotics such

as *Lactobacillus reuteri*, *Lactobacillus acidophilus, Bifidobacterium longum, Bacillus clausii, and Bifidobacterium lactis* in reducing the severity and incidences of diarrhea and other enteric diseases in pediatric population [19-21].

Childhood malnutrition and the Gut microbiome

Chronic diarrheal illnesses have been attributed to development of childhood malnutrition, with each diarrheal episode being accompanied by perturbations in the gut microbiome [22, 23]. A report from Vietnamese children aged 1-6 years with diarrhea reported consistent elevations in the populations of *Fusobacterium mortiferum, Escherichia coli,* and certain oral microorganisms in the gut microbiome [22]. Subsequent advancements in the gut microbiome have established that alterations in the gut microbiome may be a crucial contributor to childhood malnutrition [24]. A longitudinal study among Malawian twins suffering from severe malnutrition have reported poor gut microbiota diversity, which when applied to gnotobiotic (living in germ-free conditions) mice models resulted in severe reduction in weight [25]. Several subsequent studies based on malnourished children in sub-Saharan Africa, India, and Bangladesh have reported depleted diversity of beneficial members of the gut microbiome including *Bifidobacterium, Faecalibacterium, and Prevotella* with distinct increases in members of *Proteobacteria, Bacteroidetes, and anaerobic Firmicutes* [16, 26-30].

In particular, *Bifidobacterium infantis*—a distinctly beneficial gut bacterium uniquely adapted to metabolizing breast milk carbohydrates—is deficient in Bangladeshi infants with SAM (ref). These infants with SAM are often poorly breast-fed, thus the lack of breast milk carbohydrates hinders the growth of *Bifidobacterium infantis* in these infants with SAM. In breastfed infants, the gut microbiota is dominated by *Bifidobacterium infantis*, which is tailored towards the metabolism of breast milk oligosaccharides and in turn exerts beneficial effects on the health of the infant. These beneficial microorganisms are often used as food ingredients in their live form to confer health benefits to the physiology of the host and are referred to as "probiotics". Milk oligosaccharides and other similar substances that help the probiotic microorganisms to survive and thrive in the human host are often referred to as "prebiotics". Infancy is the critical period of rapid development of the gastrointestinal system. During this process, characteristic age specific changes in the intestinal microbiota develops.

Depletion of *Bifidobacterium* has been noted to be the initial step in the process of gut dysbiosis in malnutrition among infants, which is accompanied by concurrent colonization of the GI tract by potentially pathogenic microorganisms such as *Streptococcus sp, Fusobacterium mortiferum, and pathovariants of Escherichia coli,* eventually resulting in diarrhea and malabsorption of essential nutrients [31]. Subsequent depletion of age-specific beneficial microbiota such as Bacteroidaceae, Ruminococceae, Eubacteriaceae and Lachnospiroceae, along with enrichment of *Staphylococcus aureus, Escherichia coli*, *and Enterococcus faecalis* have been linked to early childhood malnutrition [32].

Severe acute malnutrition in children causes impaired gut function which can be manifested as diarrhea and malabsorption [33, 34], small bowel bacterial overgrowth [35], enteropathy [36] and suboptimal immune response [37]. Probiotics can be beneficial in ameliorating these adverse conditions which potentially affect the health of malnourished children. Diarrhoeal illness can be attributed to malnutrition and disrupted gut microbiota [38]. Data from the GEMS study (Global Enteric Multicenter Study that included Bangladesh as a study site led by icddr,b) suggests that moderate to severe diarrhoea leads to reduced bacterial diversity and altered microbiota composition among children [39]. Evidence suggests that differences in the gut microbiota of infants are associated with diarrhoea which can lead to increased risk of malnutrition (stunting and wasting) and mortality [40]. There is a clear relationship between gut microbiota and malnutrition [24]. Immature gut microbiota and their altered development is linked with malnutrition in children which should be explored for further research [24].

Use of probiotics in malnutrition

Despite the accessibility of outpatient treatment, as many as 20% of children admitted with severe acute

malnutrition (SAM) die due to improper care [41]; poor adherence to SAM therapeutic guidelines is also responsible for it [42]. Therapeutic intervention and standard commercial complementary foods also often fail to gain weight [43]. Different dietary supplementation of foodstuff is used in various studies to accelerate gut microbiota growth. An experimental study revealed that immature gut microbiota of severely malnourished children could be partially ameliorated with nutritional interventions like RUTF (Ready to use therapeutic foods) and locally made Khichuri-Halwa [16]. However, this study did not show significant improvement in weight gain of malnourished children [16]. Children with SAM have been found to suffer from gut dysbiosis, thereby impairing growth, which subsequently mediates some of their pathological conditions [25, 44]. Immaturity of the gut microbiome is also evident in less severe forms of malnutrition and affects anthropometric measurements [16]. The relationships between the type of nutritional intervention, the gut microbiota, and therapeutic responses, weight gaining, are unclear.

Early depletion of Bifidobacterium longum has been noted as the first step in gut microbiota alteration in severe acute malnutrition [45]. In poor socio-economic settings, gruels, animal milk, and complementary foods are used in the diet at an early age for economic or cultural reasons. This diet may not be optimal for B. infantis strains and gut microbial balance. Human milk contains oligosaccharides, known as human milk oligosaccharides (HMOs), which can selectively stimulate the growth of Bifidobacteria and Lactobacilli in the large intestine [46], and these probiotics produce short-chain fatty acids and lower stool pH. The prebiotic component in the mixture is hypothesized to augment the survival of the probiotic microorganism and stimulate the beneficial activities of the endogenous members of the host gut microbiota [47-50].

In a recently concluded clinical trial conducted at icddr,b in collaboration with Washington University in St. Louis known as “SYNERGIE trial”, we reported that a certain strain of Bifidobacterium infantis (B.infantis EVC001) derived from a healthy U.S donor supplemented to SAM infants with or without breast milk oligosaccharides resulted in increased weight gain and amelioration of intestinal inflammation (a characteristic feature of childhood malnutrition) [51]. A considerable correction of gut dysbiosis was also observed in these infants with SAM, through the increased colonization levels of Bifidobacterium infantis in the guts of the study infants. The SYNERGIE trial also reported that a strain of Bifidobacterium infantis (B.infantis Bg_2D9) cultured from a healthy Bangladeshi child had enhanced capability for usage of breast milk oligosaccharides. When this B.infantis Bg_2D9 was administered to mice models raised in germ free environment and colonized with fecal microbiota of SAM infants, increased weight gain was observed [51]. The researchers believe that this distinct probiotic strain of Bifidobacterium infantis (B.infantis Bg_2D9) may help to treat acutely malnourished infants, especially those who have a poor breast milk diet. However, the researchers emphasize that further clinical testing is needed to confirm whether or not B.infantis Bg_2D9 is indeed superior to B.infantis EVC001 for treatment of poorly breastfed malnourished infants.

In conclusion, it seems that there is emerging evidence from studies done in Bangladesh and elsewhere of the efficacy of probiotics (and also prebiotics) in treating malnutrition, especially in children. Even in the face of mild to moderate food insecurity in the community, probiotics can positively impact nutritional status of children.

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