Enteric parasitic infections: From environmental enteric dysfunction to gut microbiota and childhood malnutrition

Hanan M Abou-Seri[1], Mohammad Abdalgaber[2], Fatima Zahran[3]

Medical Parasitology Departments, Faculty of Medicine, Ain-Shams University[1,3], Cairo, and Gastroenterology Department, Police Authority Hospital, Giza[2], Egypt

ABSTRACT

Malnutrition accounts for high morbidity and mortality in children. Specifically, linear growth failure (stunting) has long-term consequences. It affects approximately 25% of children under the age of five worldwide and has been linked to increased mortality, cognitive dysfunction, and productivity loss. Understanding that a significant proportion of stunting is not caused solely by lack of nutrition, diarrhea, and repeated exposure to intestinal infections implies that other factors must be analyzed to clarify continued growth faltering. Enteric parasitic infections are prevalent in many tropical environments and are linked to poor nutritional status and growth stunting. Environmental enteric dysfunction (EED) is an undefined syndrome characterized by inflammation, decreased absorptive capacity, and impaired barrier function in the small intestine. The dysfunction has been allied to malnutrition, as well as oral vaccine failure causing delayed development in children from poor resource settings. This syndrome might be triggered by unhygienic environmental conditions that cause frequent exposure to fecal pathogens and decreased nutrient absorption. Additionally, childhood malnutrition was strongly linked to changes in the gut microbiome. Motivation for the present review was the relatively obscure cumulative effect of repeated enteric parasitosis on nutritional status of children in developing countries from various perspectives. Accordingly, intestinal parasites infections, EED, and microbiota alteration are all likely issues that must be concurrently addressed. Addressing all these conditions would resolve the grave public health issues of malnutrition and infection susceptibility, and consequently, lead to application of behavioral and therapeutic policies among vulnerable pediatric populations.

INTRODUCTION

Child health is a prerequisite for the development of nations' futures. Therefore, maintaining optimal child health and growth is necessary for the economic development of countries[1]. Child malnutrition is a major public health issue, particularly in many low and middle income countries. In approximately 45% of all deaths reported for children under the age of five, undernutrition is the underlying cause[2]. Malnutrition is induced by a child's shortage of essential nutrients, and accounts for underweight, stunting, and even wasting[3].

Many factors contribute to malnutrition. In particular, EED, is considered one of the leading causes of malnutrition. The pathway from EED to malnutrition and stunting is hypothesized to be through malabsorption and chronic inflammation, which arise from microbial and parasitic infections associated with an impaired gut barrier[4,5]. Later, gut helminths, protozoa, and more recently, microbiota have all been linked to the multifaceted web of elements involved in undernutrition[6].

Enteric parasitic infections are a significant public health issue, particularly in developing countries. Worldwide, more than three billion people (mostly children) are believed to be infected[7]. Soil-transmitted helminths (STH); namely, hookworms, *A. lumbricoides*, *T. trichiura*, and *S. stercoralis* are responsible for the majority of these infections[8]. These STHs are ranked as the most crucial human parasitic infections in terms of disability adjusted life years (DALYs) lost; outranking other infections such as African trypanosomiasis, Chagas disease, and leprosy[9]. *T. trichiura*, alone, infects an estimated 477 million individuals, with children recording the highest infection prevalence and intensity[8]. Additionally, children under the age of five were found to be frequently infected with *Cryptosporidium* spp., *E. histolytica*, and *G. duodenalis* in Sub-Saharan Africa[10].

Substantial evidence links between parasitic infection and poor nutritional status, in geographical areas where both are prevalent[11,12]. Malnutrition renders the populace more vulnerable to parasitic diseases and *vice-versa*. Some nutrient deficiencies can impair the host's immune function, potentially increasing susceptibility to infections[13]. Enteric parasitic infections, in particular, can impair the nutritional status by causing intestinal bleeding

and nutrient competition, resulting in nutrient malabsorption[14]. These parasites may also lessen the benefits of food intake by causing anorexia, reducing fat absorption and protein utilization; as well as increased nutrient waste through vomiting and diarrhoea. Protein energy malnutrition (PEM), anemia, and other nutrient deficiencies are the result of these conditions[14]. Moreover, chronic infections with intestinal parasites can interact with microbiota, also leading to malnutrition[6].

Hence, the aim of the present review was to highlight a set of interacting pathways that might aid in elucidating the link between enteric parasitosis and malnutrition (stunting in particular) due to micronutrient deficiency, EED, and parasite-micobiota interplay.

Stunting

This impediment of development is a landmark of malnutrition resulting in reduced productivity in adulthood. The role of intestinal parasitic infections in stunting and even wasting were significantly observed among children with helminthic infections[15]. In fact, *A. lumbricoides* is one of the most prevalent enteric geohelminths globally[16], strictly linked to stunting among children[17], with subsequent lagging of their linear growth and deterioration of their cognitive functions[18]. Simultaneously, the etiology of malnutrition has been related to diarrhea-causing intestinal protozoan infections, where repeated diarrhoeal attacks were considered as a risk factor for stunting[19,20]. In Bangladesh, stunted infants were at a higher risk of developing severe diarrhoea, particularly that linked to infection with *E. histolytica* and *Cryptosporidium* spp.[21]. Children with asymptomatic and symptomatic cryptosporidiosis were found to gain less weight in the first month of infection, and once infected they are not liable to "catch up growth" and are predisposed to growth stunting[12]. Nevertheless, the mechanisms underlying growth impairments after infection are complex, and most likely linked to EED[21].

Micronutrient deficiencies

Vitamins A, C, D, E, B6, B12, folate, zinc (Zn), selenium, copper (Cu), and iron all have immunomodulatory properties that affect the course of an infection[22]. Iron, Cu, Zn, and magnesium are essential for growth and development. They are implicated in multiple metabolic functions and are responsible for the integrity of the natural human defense mechanism. Their deficiency causes impaired immunity that exacerbates the nutritional status[23]. Iron, in particular, is the most common deficient micronutrient and the leading cause of anemia worldwide, especially among infants[24]. An intense correlation between iron deficiency anemia in children and parasitic infections was established owing to multiple risk factors, mainly fecal iron leakage caused by parasitic infections such as hookworms, schistosomiasis, and trichuriasis[24]. Trichuriasis was

also linked to low intakes of macronutrients and micronutrients such as protein, energy, iron, thiamine, and riboflavin[25].

Vitamin A deficiency and exposure to STH infections overlap vastly among children, especially in poor resource settings. They are implicated in major health and economic disabilities and have been addressed by public health measures for years[26,27]. To overcome this deficiency, supplementation of deworming drugs with vitamin A might show potential synergistic health benefits[28,29]. Analysis of various micronutrient supplements on intestinal parasitic reinfections showed that while Zn supplementation is ineffective, iron supplementation had a positive effect[30]. In order to augment hemoglobin level and nutritional status in STH endemic areas, the World Health Organization (WHO) recommends regular-interval deworming of school children with anti-helminthic medications[31]. Accordingly, academic performance improvement, child mortality decline, and raised economic productivity should occur[31].

Environmental enteric dysfunction
1. Role of enteric parasitic infections in enteropathy:

A variety of environmental and host factors are thought to contribute to EED[32]. The scarcity of specific disease knowledge regarding this pathological condition requires further research into its pathogenesis, complications, and possible treatments. This enteropathy shares common features with other gut chronic inflammatory conditions, including celiac disease and inflammatory bowel disease (IBD)[33].

Repeated enteric infections in the first two years of a child's life can result in impaired intestinal absorptive function[34]. It is thought that even an infection load that is inadequate to trigger diarrhea can cause EED[35]. Human protozoal infections, such as cryptosporidiosis, microsporidiosis, cyclosporiasis, isosporiasis, and *Giardia*sis, in addition to STH can directly disrupt the intestinal barrier by binding to cell surface molecules, causing cell damage and apoptosis, or by disrupting tight junctions and cell cytoskeleton[36]. Besides, the parasites elicit a strong innate mucosal immune response, including neutrophil activation and other cells that contribute to the intestinal lesions[37]. The inflammatory response in the intestine is affected by the invasive ability of the parasite and host's immune status, which in turn will have an impact on parasite load, and duration of infection[38].

Infection with *Cryptosporidium* spp. has been linked to increased gut inflammation and villus architecture loss; and murine models suggest that immune signalling in the gut may be interrupted, resulting in enteropathy and poor growth[12]. *Blastocystis* spp. are opportunistic parasites with a negative impact on gut health in the presence of other pathogens. However, evidence of its pathogenicity in humans remains speculative and

inconclusive[39]. *Blastocystis* spp. was found prevalent in patients with impaired intestinal barrier function and altered gut permeability. But the relation between *Blastocystis* spp. and EED remains inconclusive[40]. It is unknown whether the presence of this parasite is an association due to decreased immunity or if it causes harm through EED. However, EED is believed to occur as a result of repeated exposure to fecal pathogens like *Blastocystis* spp.[40].

The definitive diagnosis of EED is through gastrointestinal tract endoscopic and histopathological examination. Changes in the intestinal structure recorded in EED include blunt villi, increased crypt depth, reduced compartmental features, and increased shedding of epithelial cells[41]. Moreover, increased cellular infiltrates with the predominance of lymphocytes and plasma cells also occur. Hence, the intestinal functions are affected by abnormalities of cell adhesion and tight junctions[41]. Many non-invasive biomarkers were developed for EED, such as alpha-1 anti-trypsin, calprotectin, myeloperoxidase, and lactulose:mannitol (L:M) ratio. However, lack of validation hampered research, raising difficulties in assessing EED[42]. It worth mentioning that L:M ratio was used as a biomarker for young children due to the practical and ethical concerns entailed by endoscopic biopsies. An association was also revealed between parasitic infection and higher L:M ratios, indicating increased intestinal permeability[43]. Novel biomarkers are constantly sought, but finding a 'gold standard' test for assessment has not been achieved yet[42].

Nutritionists are collaborating with experts in the fields of water, sanitation, and hygiene (WASH) in countries with high stunting rates, and their combined efforts are assisting the regional hygiene programmes[32]. Essentially, improvement of WASH is a critical component of achieving global stunting elimination. Its development can disrupt the fecal-oral transmission pathway[44]. However, there are few studies that specifically investigate baby WASH, which is designed to target maternal and newborn health during the first 1,000 days . They revealed its effectiveness in reducing stunting in children under 2 years[44-46].

2. Role of extensive use of antibiotic in enteropathy:
Antibiotic treatment could counteract chronic exposure to environmental microbes and pathogens that cause enteropathy, thereby improving child growth in developing countries[47,48]. However, antibiotic overuse may affect the gut microbiota, which plays an important role in pathogen regulation, resulting in a change in their diversity and increased susceptibility to harmful pathogens, and thus enteropathy[47,48]. It was shown that patients who had previously received antibiotics were more susceptible to *Escherchia coli, Salmonella, Shigella,* and *Campylobacter* infections; as well as recurrent *Clostridioides difficile* infections[48].

Overuse can also result in antibiotic resistance to many pathogens, including bacteria and parasites. Parasites may develop novel mechanisms to achieve drug resistance, which necessitates substantial efforts for combat[48,49].

3. Role of food additives in enteropathy:
As indicated by Marion-Letellier *et al.*[50], the increased consumption of ultra-processed food in developed countries, may be a significant cause of chronic diseases; although it is still unknown whether this association is due to the poor nutritional composition or the presence of food additives. The various additives reported to keep foods fresh or enhance their color, flavor, or texture include glucose, salt, emulsifiers, organic solvents, gluten, microbial transglutaminase. Additionally the authors indicated that also nanoparticles are increasingly used by the food industry to improve the quality of food, and warned that most of these additives can trigger gut inflammation causing tight junction dysfunction and increased intestinal permeability. For example, processed food was found to include high levels of sodium chloride, which can exacerbate colitis resulting in enteropathy or worsening of inflammatory bowel disease. Another element incorporated in processed food is aluminum, added from wrapping foils or cooking vessels. A high level of aluminum was found to worsen colitis. All of these factors indicate the role of food additives in causing gut inflammation, which can increase susceptibility to infection and enteropathy[50]. Former studies had indicated that the opened tight junction could result in foreign immunogenic antigens entering and activating an autoimmune cascade causing autoimmune disease[51,52]. Another statement implicated artificial emulsifiers and sweeteners in inducing dysbiosis associated with alteration of the intestinal barrier, activation of chronic inflammation, and abnormal immune response accelerating the onset of IBD[53].

Parasite-micobiota interplay
Gut microbiota are a diverse and stable microbial community that is established at birth. This ecosystem performs a wide range of anti-infectious, anti-inflammatory, and immune-modulating functions, essential for intestinal homeostasis[54]. Microbiota interact with the host on a molecular level by producing and responding to a variety of neurotransmitters and endocrine molecules that affect appetite, intestinal transit time, lipid and glucose metabolism[55]. In a study conducted by Kane *et al.*[56], malnutrition was linked to delayed normal development of the gut microbiota in early childhood, coupled with the disruption of the microbiota composition that can lead to a lack in vital roles for healthy growth, and/or an elevated risk of intestinal inflammation[56].

Chronically malnourished children were observed to exhibit an immature microbiome, which was linked

to linear growth failure[57]. Besides, since microbiota are required for the development of the mucosal immune system of the intestine, "dysbiosis," or altered microbiota composition, is thought to be involved in the development of EED and, as a result, malnutrition. This was conveyed by researchers who transplanted the feces of malnourished Malawian children to gnotobiotic mice, resulting in malnourishment among the murines[58,59].

Studies documenting the interaction between parasites and gut microbiota showed that the direct or indirect modifications in the microbiota might be positive, neutral, or negative[60,61]. Parasites can affect microbiota populations by stimulating an anti-inflammatory immune response caused by their attachment and secretion of molecules. These molecules improve barrier function by stimulating goblet cell hyperplasia and increasing mucus volume, thus reducing bacteria adherence to the epithelium[6]. Several trematodes including *Schistosoma, Fasciola, Opisthorcis, Clonorchis*, and *Paragonimus* spp. secrete peptides known as helminth defence molecules (HDMs), which are similar to human antimicrobial peptides and might have both direct bactericidal and immunomodulatory effects[62].

In this context, *G. lamblia* was found to interact directly with the intestinal microbiota, altering the immunopathology and infection outcomes[63]. It is able to cause microbial dysbiosis with shifting towards virulent microbiota. The same was reported with *Blastocystis* spp. infection that was associated with a huge bacterial popupation in malnourished adults[40]. On the other hand, it was suggested that the different microbiota inhibit parasitic infections by stimulating immune response through bacterial toll-like receptors[6].

Attempts to comprehend the role of the human gut microbiome in childhood malnutrition, did not employ intestinal biopsy to characterize the microbiome[64]. The mucosa-associated microbiome is widely thought to be more informative than fecal microbiota analysis, and future research will undoubtedly address this particular question[64]. Three methods are suggested for manipulating microbiota: the use of antibiotics, probiotics (and related pre- and pro-synbiotics), and fecal transplantation[56]. Apart from the role of gut commensal microbiota in the mechanisms that influence the survival and outcome of many parasitic infections, probiotics might be beneficial in lowering the pathogenicity of many parasites[65]. Probiotics, according to WHO, are "live organisms that, when administered in adequate amounts, grant a health benefit to the host"[66]. Probiotics have been shown to be effective in treating respiratory infections, allergic symptoms, and gastrointestinal disorders. They could also kill or inhibit pathogens via strain-specific mechanisms that involve competition, molecule

secretion, and/or immune induction[66]. Accordingly, probiotics may be a factor in preventing the spread of several parasites, including some helminths like *A. lumbricoides* and *Trichuris* spp., and protozoans such as *Cryptosporidium* spp., and *G. lamblia*[65].

Several lactobacilli species were found to have cytostatic and/or cytotoxic effects on *Giardia* trophozoites, both *in vitro* and *in vivo*. Other probiotic strains, demonstrated potent anti-*Giardia* properties both *ex-vivo* and *in vivo*, including *Weissella paramesenteroides*, *Bifidobacterium* spp., *Saccharomyces boulardii, Enterococcus faecium,* multi-strain probiotic, mixed bacteria, and yeast cultures as Slab51 and kefir grains[67]. Furthermore, dietary prebiotics could be used to treat parasitic infections by promoting the growth of specific gut microbes that constrain or mitigate parasite virulence. Notably, simple dietary modifications might also be an effective anti-parasitic intervention[6]. Hence it was suggested that new and innovative areas of research, such as the parasitome and metabolome of gut microbiota during chronic parasite infection, in addition to their relationship with host immunoregulatory mechanisms, should now be confronted in an integrated approach[66].

CONCLUDING REMARKS

1. Malnutrition constructs a major public health issue in low resource settings. Underlying determinants are insufficient food intake, poor food hygiene, and recurring infectious diseases. Recurrent infections combined with poor nutrition creates a vicious cycle of increasing susceptibility to infection and worsening nutritional status, which in turn impacts child development in such a devastating way that might be irreversible.

2. Enteric parasitosis, in particular, is frequent in resource constrained regions known for high prevalence of different forms of malnutrition particularly, stunting. The means by which parasites can impact nutritional status include impairing of appetite, hindering intestinal absorption, increasing catabolism, and conveying nutrients away from growth. Some nutrient deficiencies also can hamper the host's immune response potentially lowering resistance to infections and rendering the host more vulnerable to infections. Additionally are the associated disruptions in intestinal absorptive and/ or barrier function, with or without overt diarrhoea.

3. The EED is becoming a rising concern because of its impact on long-term public health issues. However, flaws in our understanding of its pathophysiology and its relationship to stunting limit ability to diagnose, prevent, and treat this condition effeciently. Furthermore, poor WASH conditions are increasingly regarded as a major contributor and are increasingly becoming the focus of targeted interventions aimed at improving nutritional status of children. Owing to the importance of intestinal microbiome in the development and maintenance of gut homeostasis,

its alteration might also contribute to both the onset and advancement of intestinal diseases. Accordingly, intestinal parasite carriage, micronutrient deficiency, EED, and alteration of gut microbiota interact through various pathways, that should be addressed concurrently to fight malnutrition among vulnerable pediatrics population in poor resource settings (Figure 1).

4. Hence, paving the way for implementing behavioural and therapeutic approaches are important factors for curing children with enteric parasitic infection and improving their nutritional status.

5. Suggested strategies should include routine screening for parasitic infections in the stool, anemia, and growth follow-up among children in primary health care units and schools; and administration of deworming medications. Vitamin A supplementation on regular basis would be valuable for both asymptomatic carriers and those with hidden nutritional issues. Water (advancements in both quantity and quality), sanitation (proper disposal of feces in particular),

and hygiene (education/promotion) interventions are also regarded as both helpful and beneficial tools in reducing undernutrition. Prescription of appropriate antibiotic therapy could overcome the chronic exposure to environmental microbes and pathogens that induce enteropathy. Furthermore, if malnourishment caused by helminthic infection triggers dysbiosis, supplements in the form of probiotics (and related pre- and pro-synbiotics) might be a beneficial therapeutic tool for the complementation of standard helminth treatment) (Figure 2).
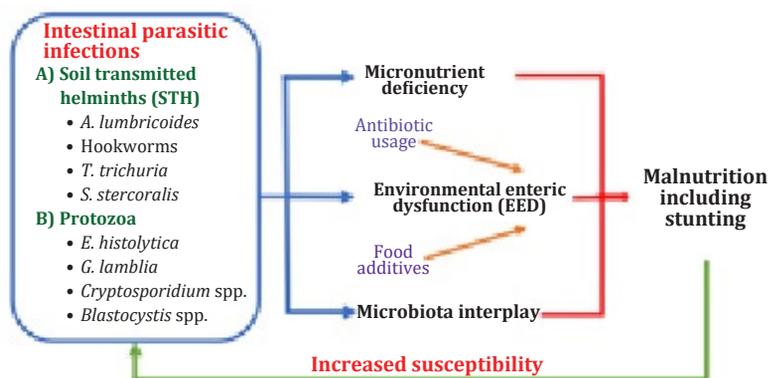
Fig. 1. Cumulative effect of repeated intestinal parasitic infections on children's nutritional status from different aspects. Illustrated by Zahran F.
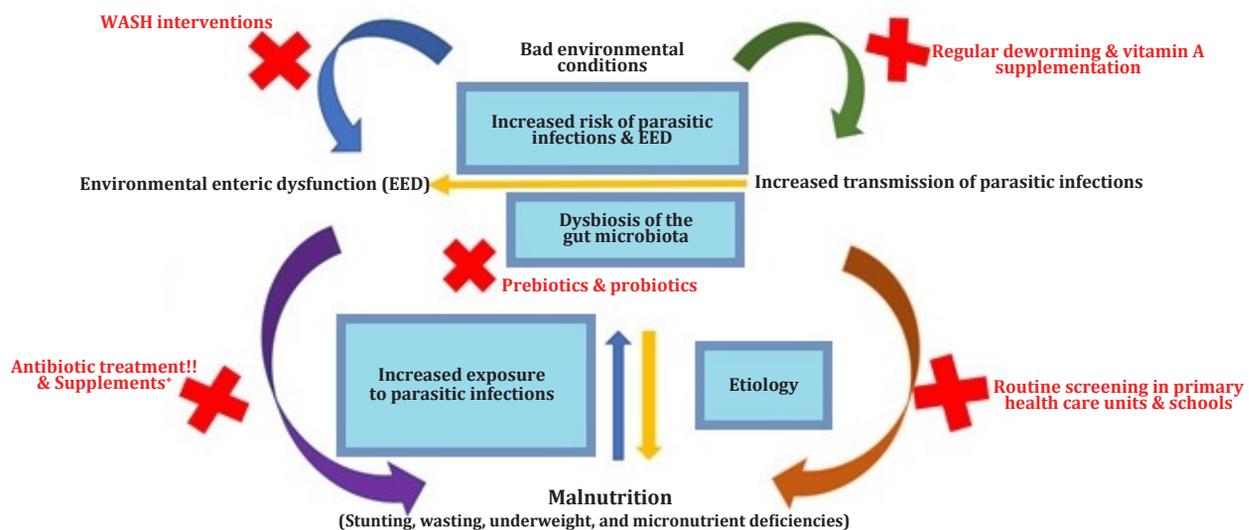

Fig. 2. Suggested interventions to overcome the cumulative effect of repeated intestinal parasitic infections on children's nutritional status. **WASH:** Water, sanitation, and hygiene; ✗: How to interrupt the cycle?; *: Probiotics and related pre- and pro-synbiotics. Illustrated by Zahran F.

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