Chapter 8
Nutrition and Diarrheal Disease and Enteric Pathogens

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Abbreviations

AhR	Aryl Hydrocarbon Receptor
APP	Acute phase protein
C	Complement
CD2	Cluster of Differentiation 2
CD69	Cluster of Differentiation 69
CRP	C-reactive protein
DALY	Disability Adjusted Life Year
DC	Dendritic cell
DNA	Deoxyribonucleic acid
EED	Environment Enteric Dysfunction
EPEC	Enteropathogenic *Escherichia coli*
ETEC	Enterotoxigenic *Escherichia coli*
GALT	Gut Associated Lymphoid Tissue
IFN-γ	Interferon gamma
IgA	Immunoglobulin A
IL	Interleukin
ILC	Innate Lymphoid Cell
IMCI	Integrated management of childhood illnesses
LPS	Lipopolysaccharide
MAM	Moderate acute malnutrition

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MHC	Major histocompatibility complex molecules
NK	Natural Killer cell
NO	Nitric oxide
PEM	Protein-energy malnutrition
PGE2	Prostaglandin E2
RUTF	Ready to use therapeutic food
SAM	Severe acute malnutrition
SDG	Sustainable development goal
SDI	Sociodemographic Index
SIgA	Serum Immunoglobulin A
Th1	Helper T cell (Type 1)
WHO	World Health Organization

Key Points

- Malnutrition, as protein calorie and micronutrient deficiency, still remains a formidable challenge for public health experts.
- Malnutrition increases the exposure to diarrhea causing pathogens, adversely affects the components of gut barrier including the gut microbiome and gut mucosa.
- Malnutrition generally reduces the ability of the immune system to mount adequate responses against pathogens although some components of the immune system remain unaffected or are enhanced in response to infection.
- Disease progresses faster, leads to more severe symptoms, takes longer to resolve, and has worse outcomes in malnourished individuals.
- Antibiotics, though lifesaving, have detrimental effects on the gut microbiome, a key defense mechanism against gut pathogens.
- Infection by some pathogens (e.g., *Entamoeba histolytica*) becomes less likely in malnourished individuals.
- More research will help identify newer intervention targets.

Introduction

Definitions

Diarrhea is defined by the World Health Organization (WHO) as "the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual) [1]. It is one of the most common symptoms of gut infection, frequently caused by bacteria, viruses, and parasites (see Chaps. 4–7) [2–5]. Diarrhea is classified clinically into various types, which are not necessarily mutually exclusive: acute watery diarrhea which lasts several hours or days, and includes cholera; acute bloody diarrhea, also called dysentery; prolonged acute diarrhea which lasts for 7–13 days; and persistent diarrhea which lasts 14 days or longer. Enteric infections refer to a group of disorders that affect gut function but may or may not cause diarrhea [6]. The term "diarrheal diseases" is used for the collection of diseases that frequently result in diarrhea caused by infectious agents [7].

Epidemiology

Diarrhea ranked fifth among the most common causes of death in 2017 globally and is the third leading cause of death and disability in countries with a low social development index (SDI) [8]. Out of 2.3 billion diarrheal episodes estimated for the year 2015 globally, 957 million occurred in children younger than 5 years (yrs) and caused nearly half a million deaths in this age group. Diarrhea also resulted in loss of over 71 million disability adjusted life years (DALYs), 63% of which were among children younger than 5 yrs. [9]. These children are more likely to develop malnutrition [10].

The burden of enteric infections estimated by the Global Burden of Disease project provides the following figures for 2017: globally there were over 6.3 billion diarrheal episodes resulting in 1.7 million deaths; children younger than 5 yrs. experienced 1.1 billion episodes that resulted in 589,000 deaths. Almost all of these deaths occurred in low- and low-middle and middle-SDI countries [11]. While there has been significant reduction in diarrhea mortality and morbidity in the last decade owing to various interventions, such mortality and morbidity are still a major public health problem [9].

Etiology

Thirteen organisms have been identified as causing diarrheal episodes [11]. If all age groups are considered, rotavirus, *Shigella* and *Salmonella* spp. are the top three leading causes of death. However, the etiology of diarrheal disease is slightly different for children younger than 5 yrs., where rotavirus caused 29.3% of deaths, *Cryptosporidium* spp. caused 1.1% and *Shigella* spp. 5.5%. Table 8.1 provides a list of the microbial agents that are the most important contributors to enteric infection-related deaths [9, 11]. Use of advanced diagnostic techniques for identifying causes of diarrhea implicated six pathogens in 75% of the diarrhea burden in seven countries, including *Shigella* spp., rotavirus, adenovirus 40/41, enterotoxigenic *Escherichia coli* (ETEC), *Cryptosporidium* spp., and *Campylobacter* spp. [12].

Risk Factors and Determinants of Diarrhea

During the first decade of the twenty-first century, large reductions in child mortality have been observed. Yet the burden of child mortality is still high, with diarrhea and pneumonia as the leading causes [13]. Reduction rates are slower than that required to meet the relevant Sustainable Development Goals (SDGs) [14, 15]. Increasing the reduction rates in order to achieve the SDGs requires a better

Table 8.1 Commonly implicated microbial agents in enteric infections

Bacteria	Viruses	Protozoan Parasites
Campylobacter spp	Adenoviruses	*Entamoeba histolytica*
Vibrio cholerae	Rotavirus	*Cryptosporidium*
Enterotoxigenic *Escherichia coli* (ETEC)	Norovirus	*Giardia*
Enteropathogenic *Escherichia coli* (EPEC)		
Shigella spp.		
Salmonella spp.		
Aeromonas spp.		
Clostridium difficile		

understanding of the risk factors and determinants of the major killers of children under 5 yrs. The most common, but non-modifiable, factors are age and gender. Over 80% of the mortality associated with diarrhea in children under 5 yrs. occurs in children under 2 yrs. [13]. There is some evidence indicating a higher risk of diarrhea in boys compared to girls of the same age [13]. The pathogens involved in the diarrheal burden also differ with age [13].

Modifiable risk factors for both morbidity and mortality include absence of breastfeeding, being underweight, stunted, or wasted and being vitamin A deficient [13]. Intensity of exposure is also directly associated with outcomes [13]. A systematic review from India identified several other risk factors [16], including low socioeconomic status, low mother's education, unsafe drinking water, and anemia. This combination of factors suggests sociodemographic improvements as an important avenue for further reduction of morbidity and mortality due to diarrheal diseases.

Ways in Which Malnutrition Contributes to Enteric Infection

The importance of malnutrition as an underlying cause of childhood deaths has been long established [17]. Undernutrition plays a significant role in enteric infections and diarrheal diseases through a variety of pathways, and the relationship is bidirectional. In order to appreciate the phenomenon, we have chosen to begin with malnutrition, then to explore the impact of nutritional status on diarrheal diseases and enteric infections, and finally to circle back to the impact of diarrheal diseases on nutritional status.

While significant steps are being taken to address malnutrition globally, undernutrition still underlies 45% of childhood deaths, and 20 million babies are born underweight each year. Simultaneously, overweight and obesity among children are growing and have reached record high levels among adults [18]. This double burden of malnutrition can coexist in the same country, community, household, and even in the same person—all at the same time [18].

Undernutrition is particularly problematic for low- and middle-income countries where the socioeconomic environment restricts access to resources needed to meet basic nutritional requirements. In this context, malnourished mothers give birth to malnourished children with compromised immunity (see Chap. 3) [19] and diminished developmental potential, outcomes that have lifelong consequences for the child and intergenerational consequences for society.

The impact of socioeconomic context can be clearly seen in the disease burden disparities that exist and persist between countries. While noncommunicable diseases have become the leading cause of early death in the most socioeconomically developed countries, communicable diseases, like diarrheal diseases, remain the biggest problems where development indicators are lowest [20]. Notably, undernutrition is a primary underlying risk factor for deaths caused by communicable diseases and also the most important risk factor for diarrheal disease-related mortality, accounting for nearly 3 in 4 deaths [20, 21]. Hidden hunger, referring to invisible micronutrient deficiencies (see Chap. 2) [22], also plays a role. Children with micronutrient deficiencies have increased rates and severity of diarrheal episodes, and studies investigating the effects of micronutrient supplementation (specifically, iron, zinc, and vitamin A) have consistently demonstrated significant benefits [23–27].

Malnutrition has wide-ranging deleterious impacts on the immune system (see Chap. 3) [19]. The complex mechanisms involved have yet to be fully elucidated although a few explanations have been put forth as no theory completely explains all immune system events observed during malnutrition. Following are the salient features of current explanations. Rytter et al. can be referred for finer details [28].

Lack of energy and building blocks: Due to lack of energy and nutrients, immune system-related proteins cannot be produced leading to a subnormal immune response. However, this fails to explain

why all parameters of the immune system are not equally affected. Rather, some immune response pathways appear to become more pronounced in malnutrition.

Mixed hormonal profile: Changes in hormones that activate or suppress immune system components lead to elevated positive acute phase proteins (APP) among malnourished children, signaling subclinical inflammation resulting in catabolism which exacerbates malnutrition. However, numbers of activated T cells and dendritic cells (DCs) do not correspond to the acute phase reaction, and their numbers remain either unaffected or lower than expected.

Tolerance: This mechanism hypothesizes that, to avoid an autoimmune reaction against self-antigens released due to ongoing catabolism, the body downregulates the immune response. A counter argument to this theory is that one would expect to see some breakthrough of autoimmune reactions among malnourished children. However, research to explore this has not yet been conducted.

Hormonal interplay: This mechanism suggests that thymus-stimulating hormones such as leptin, prolactin, and growth hormones are deficient with malnutrition, and thymus-suppressing hormones such as adrenaline and cortisol are high in malnourished children. This is consistent with other observed immune system events in malnourished children like elevated APP and depressed negative APP. However, why growth hormone is low when needed by the body needs is unexplained.

In this chapter, we will consider how undernutrition increases the risk of exposure and susceptibility to enteric infections, contributes to suboptimal immune responses, and can lead to more rapid disease progression, increased severity of disease, and slower or delayed responses to treatment, all of which result in the high morbidity and mortality associated with what remains a leading cause of death in children under 5 yrs. Figure 8.1 provides an overview of the complex relationship between malnutrition and diarrhea. The vicious cycle frequently begins with inadequate nutrition, either in utero or after birth, initiating a cascade of events all augmented by a worsening of malnutrition throughout the cycle. At other times, repeated infections push a well-nourished child into this cycle. In the following sections, we will describe mechanisms whereby malnutrition as a trigger.

Increased Risk of Exposure

Malnutrition, once established, increases a child's risk of exposure to enteric pathogens through several potential mechanisms. Malnutrition-related hospitalizations for severe acute malnutrition increase a child's exposure to hospital-acquired enteric infections [29, 30]. Another sequence of events that leads to increased risk of exposure starts with the difficulty of feeding malnourished children, as they are often irritable, anorexic, and intolerant of larger amounts of food. As a result, caregivers make more frequent feeding attempts, increasing the number of opportunities of exposure to pathogens if personal and environmental hygiene is sub-optimal—which is frequently the case. There are also significant challenges associated with food storage, as protecting food from microbes is a formidable task in resource-constrained environments. Access to clean water is yet another challenge that can lead to contamination of many of the foods recommended for malnourished children, whether cattle milk, homemade meals, or ready-to-use therapeutic foods (RUTF) [31]. The WHO identifies all the above as avoidable risks that can prevent microbial contamination of foods, especially during complementary feeding, and thus reduce a major cause of gastrointestinal illnesses in childhood [32].

Cultural beliefs and practices related to malnutrition have been reported to influence risk of exposure as well. These reports are mostly anecdotal. However, one study from Talensi district in the Upper East Region of Ghana documented a traditional treatment of malnourishment using water in which avian feces had been soaked, a practice that can obviously increase risk of exposure to bird pathogens that also infect humans [33]. There are likely to be other common but undocumented beliefs and practices related to malnutrition in different communities which, when practiced, can put malnourished children at higher risk of exposure to enteric pathogens.

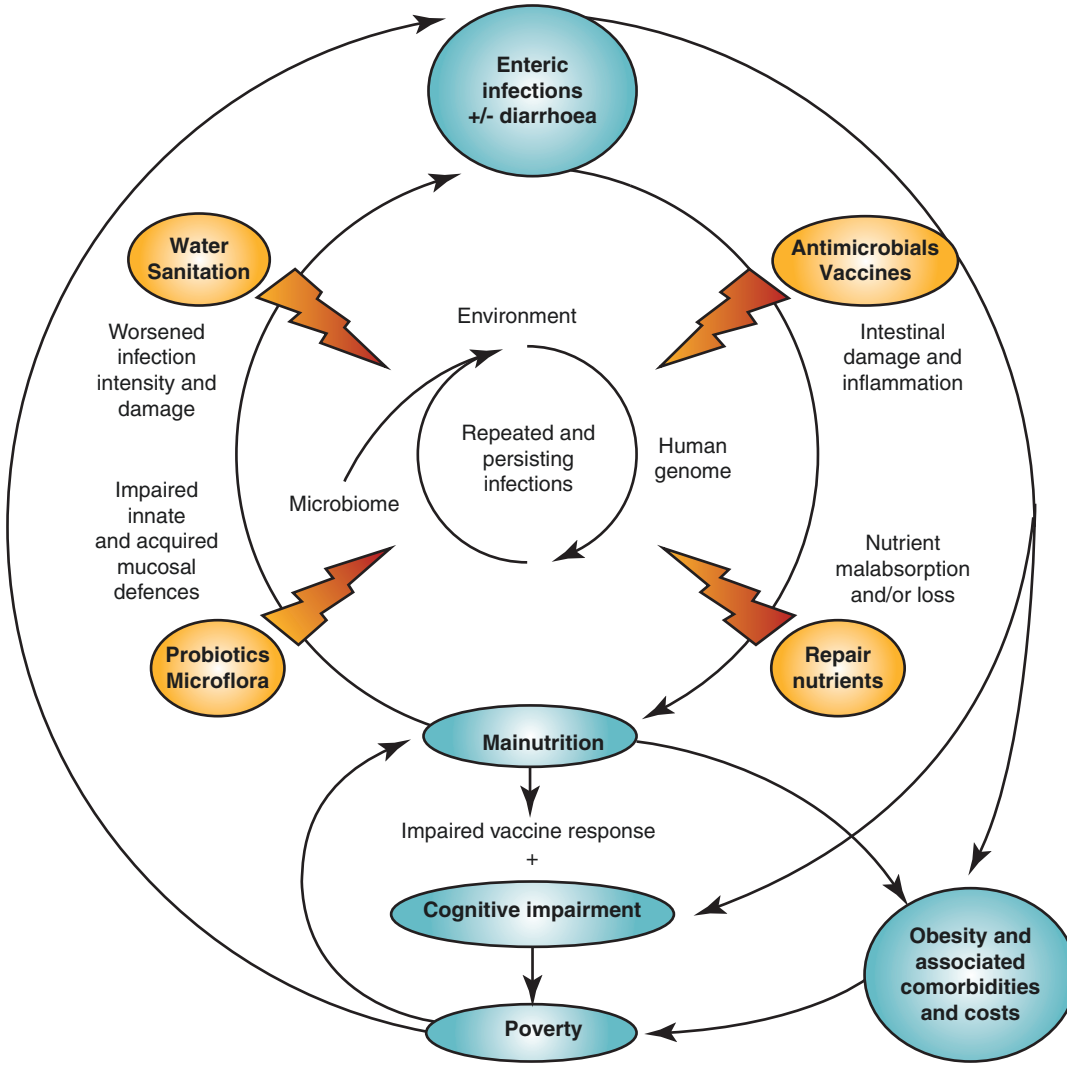

Fig. 8.1 The complex interconnections among factors that perpetuate the malnutrition-infection cycle. Enteric infections, especially in the first 2–3 years of life, with or without overt diarrhea, can predispose an individual to malnutrition and stunted growth through multiple mechanisms. Stunting by 2 years of age, in turn, is associated with impaired cognitive development that extends into later childhood and even adulthood and adult productivity. In addition, malnourished children experience both greater frequency and duration of diarrheal illnesses, and, documented in animal models, heavier infections. The latter is documented with *Cryptosporidium* and with enteroaggregative *Escherichia coli*. Finally, enteric infections or stunting can predispose to obesity and its comorbidities of diabetes, hypertension, cardiovascular disease, metabolic syndrome, and burgeoning health-care expenditures, contributing to individual and societal poverty in vicious cycles. Reprinted from Guerrant et al. [162] with permission from Springer Nature

On the other hand, there is evidence of an association between decreased risk of certain gut infections and malnutrition. This is particularly observed for rotavirus and *Giardia* [34, 35]. Although the mechanisms have not been fully elucidated, malnourished hosts may not be able to provide the energy and nutrients needed by pathogens (see Chap. 14) [36]. Similarly, iron deficiency affords protection against *Entamoeba histolytica* infection, as both adherence and cytotoxicity of this protozoan pathogen have been found to be lower in children with iron deficiency [37, 38]. No such effect was observed with other mineral deficiencies that were tested [38]. Further research is needed to learn the exact mechanisms.

Reduced Immune Response Increases Susceptibility to Pathogens

Malnutrition adversely affects immune functioning, preventing the maintenance of core functions critical for survival. Reduced functionality has wide-ranging effects on both innate and adaptive immunity (see Chap. 3) [19]. Effects are particularly pronounced in the first 1000 days of life when development of the immune system is most sensitive to nutritional status [39]. If the immune system has been weakened by malnutrition either in utero or postnatally, susceptibility to infections can be increased through a number of pathways. These include weakening or alteration of the gastrointestinal mucosal barrier, defects in immune function in both the innate and humoral arms, impaired inflammatory response, and changes in the microbiome. All are discussed in detail below. Figure 8.2 shows the interlinks between malnutrition, immune function, and susceptibility to infections [39].

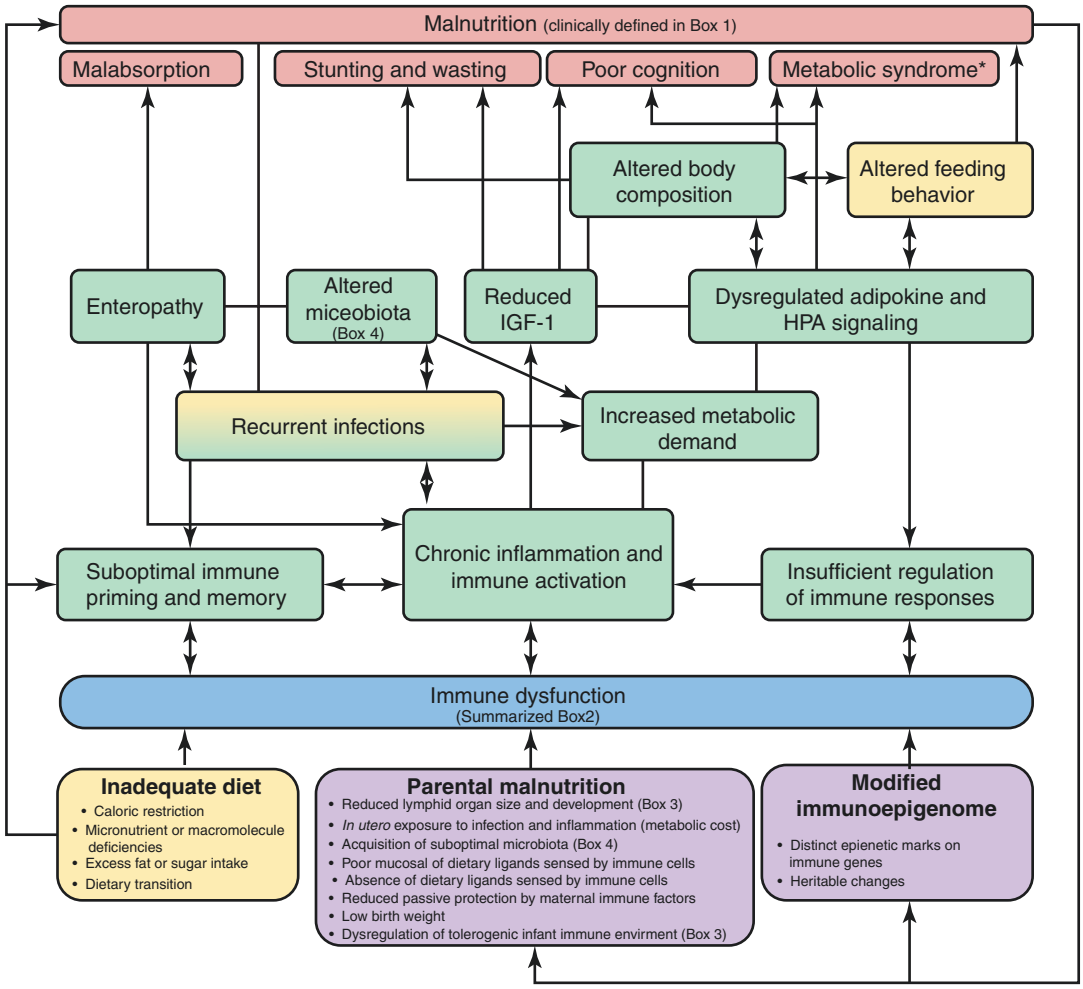

Fig. 8.2 Conceptual framework for immune dysfunction as a cause and consequence of malnutrition. Immune dysfunction can arise before birth via developmental pathways (purple), compounded by environmental and behavioral factors (yellow), particularly those experienced during early life. Immune dysfunction (blue) can contribute both directly and indirectly to a range of causal pathways (green) that lead to clinical malnutrition (red). HPA, hypothalamus–pituitary–adrenal axis; IGF-1, insulin-like growth factor 1; *, refers to predisposition to metabolic syndrome in adulthood following exposure to undernutrition in infancy. Reprinted from Bourke et al. [39]; Creative Commons CC-BY license

Alterations of the Gastrointestinal Mucosal Barrier

The gastrointestinal tract houses the largest mucosal surface in the human body. With a single epithelial layer, the intestinal lining protects the interior of the body from the large and diverse population of bacteria that inhabit the gut [40, 41]. The same epithelial layer is also responsible for nutrient absorption and waste secretion, and, as such, a healthy gastrointestinal mucosal barrier is selectively permeable. Permeability is primarily mediated by tight junctions that seal the paracellular spaces and thus maintain the barrier's integrity (see Chap. 6) [4, 40]. The epithelial layer is made up of a variety of cells. Goblet cells produce a mucus layer that covers the surface of the epithelium and functions to protect the epithelium from harmful substances and to bind and flush away pathogenic bacteria. Other epithelial cells secrete salts, hormones, cytokines, proteins, and antibodies to maintain a neutral pH at the epithelium despite acidic surroundings, regulate cell proliferation and differentiation, protect against toxins, bind bacteria, and repair lesions [42].

Structural changes to the mucosa of malnourished children include decreased height of villi and microvilli, lymphocytic infiltration, and increased vascularity [28]. The thinned mucus layer, sometimes referred to as a "tissue paper intestine," increases opportunities for pathogens to adhere and invade epithelial cells. Animal models have shown that the intestinal barrier loses its functional robustness in malnutrition. In vitro research conducted in the early 1990s found that when incubated with *Salmonella typhimurium* epithelial cell destruction and lysis were markedly higher in malnourished mice, while cells from well-nourished mice remained unaffected [43]. Another consequence of a thinned mucosa is decreased production of mucus, likely through interruption of cyclooxygenase 2 enzyme activity [44], which interrupts the barrier function of mucus in the intestine [45]. Detection of elevated titers of antibodies against bacterial endotoxins in the stools of malnourished children as compared to their healthier counterparts indicates that malnourished children are either making more antibodies against bacterial endotoxins or have a greater burden of bacterial endotoxins than their well-nourished peers [46, 47]. More recent studies confirm these findings as well. Mechanisms include protein energy malnutrition (PEM) that alters B-cell development in the bone marrow and increases the frequency of IgA-secreting B cells, as well as IgA secretion by long-lived plasma cells in the small intestinal lamina propria [48].

Likewise, deficiencies in specific nutrients can also lead to alterations of the gastrointestinal mucosal barrier and thus affect a child's susceptibility to enteric infection. For example, the epithelial cells of the mucosal barrier are constantly being shed and replaced by new cells that proliferate and differentiate from stem cells in the colonic crypts [49]. Vitamin A (via retinoic acid) is critical to the proper differentiation of these cells, and deficiency induces the loss of various cell types including mucus-producing goblet cells, which leads to a degradation of the mucus layer [50–52]. Vitamin A deficiency also leads to reductions in the population of innate lymphoid cells (ILC3s), which result in less production of interleukin (IL)17 and IL22 and, in turn, less antimicrobial functionality in the mucus layer [51]. Such impacts have been observed in children with high rates of subclinical vitamin A deficiency, where serum retinol concentrations were inversely correlated with intestinal permeability [53]. Zinc also promotes a healthy mucosal barrier, and its deficiency leads to defective Paneth cells, with less antimicrobial activity, as well as atrophy of villi and lymphoid tissues, thereby impairing the epithelial barrier's ability to prevent invasion of pathogens [51, 54–57]. Deficiencies of particular amino acids also appear to play a role, as supplementation of L-arginine and alanyl-glutamine hass been shown to improve intestinal barrier function in an animal model and in infants [58, 59]. In contrast, iron supplementation is associated with increased permeability of the small intestine and increased susceptibility to diarrheal disease and enteric infection [25].

Environmental Enteric Dysfunction

Environmental enteric dysfunction (EED) is a subclinical chronic intestinal disorder that, once established, erodes the mucosal barrier function that is important for immunity. It, however, has been demonstrated that dysbiosis of the normal microflora precedes the actual invasion of gut mucosa by microbes, leading to EED, which can in turn lead to subclinical harmful effects even without manifesting as diarrhea [60]. EED was first named as an entity in 2014 by Keusch and colleagues who cited functional deficits as prominent features of the condition [61]. While the definition of EED is still being crafted, the hallmark morphological features (villous flattening, crypt hyperplasia, local and systemic inflammatory biomarkers, lymphocytic infiltration of the lamina propria) all indicate pathophysiological changes and morphological injury to the gut mucosa [62, 63]. Shortening of villi reduces the surface available for nutrient absorption, contributing to malnutrition. This has been supported by indirect evidence, where complementary feeding interventions were less effective in children with EED [47]. Such changes can also lead to malabsorption, further enhancing malnutrition [47]. Observational studies have found associations of stunting with EED, suggesting a potential role for EED in chronic malnutrition [64, 65]. Hypercellularity of the gut mucosa in EED is a sign of chronic inflammation of the intestines, and the chronic inflammation is associated with appetite suppression [66]. The role of appetite suppression leading to reduced food intake may be an important contributor to chronic malnutrition in children [67]. Hormonal disturbances leading to adverse inflammatory events have also been proposed as a mechanism of growth failure in EED, although evidence is limited [68].

As the gut is a potential site of entry for pathogens, it is critical to have a functioning intact barrier. Components of gut barrier functions are impaired in EED. With the thinned mucous layer, capacity for trapping and blocking invasion of harmful microbes is reduced. The presence of an increased number of inflammatory cells suggests the failure of the epithelial barrier to restrict luminal contents from crossing the epithelium and activating an inflammatory response. These effects have been shown to result in linear growth retardation [69]. Finally, sub-optimal response to oral polio and rotavirus vaccines has also been associated with EED [70–73].

Defects in Immune Function

Malnutrition impacts both innate and adaptive immunity (see Chap. 3) [19]. Innate immunity is comprised of cell and complement complex-mediated immunity that is not specific to the pathogen. Leukocytes, T cells, and cytokines, together with the complement complex, are the main drivers of this arm of the immune system [74]. Adaptive immunity is largely based on T cells, B cells, plasma cells, and antibodies that are produced in response to a particular pathogenic agent and that create immunological memory with the thymus as the central coordinating organ [74]. As highlighted in Fig. 8.3, the responses of the gut epithelium to malnutrition alone and to specific deficiencies when combined with different pathogens can be quite distinctive. Other components play role in protecting the body from infections. Research to date has demonstrated that not all immune functions are adversely affected by malnutrition, although many important functions are [28]. Figure 8.4 summarizes the evidence based on a systematic review of studies on children where the underlying cause of the immune response was not considered. The following details explain how components of immune system are affected by protein calorie or micronutrient deficiencies.

Compounds in saliva and acid production in the stomach are some of the innate mechanisms that protect the body from infection (see Chap. 3) [19]. In malnutrition, primarily due to lack of energy and protein, the quantity and quality of these secretions deteriorate, allowing increased invasion of enteric

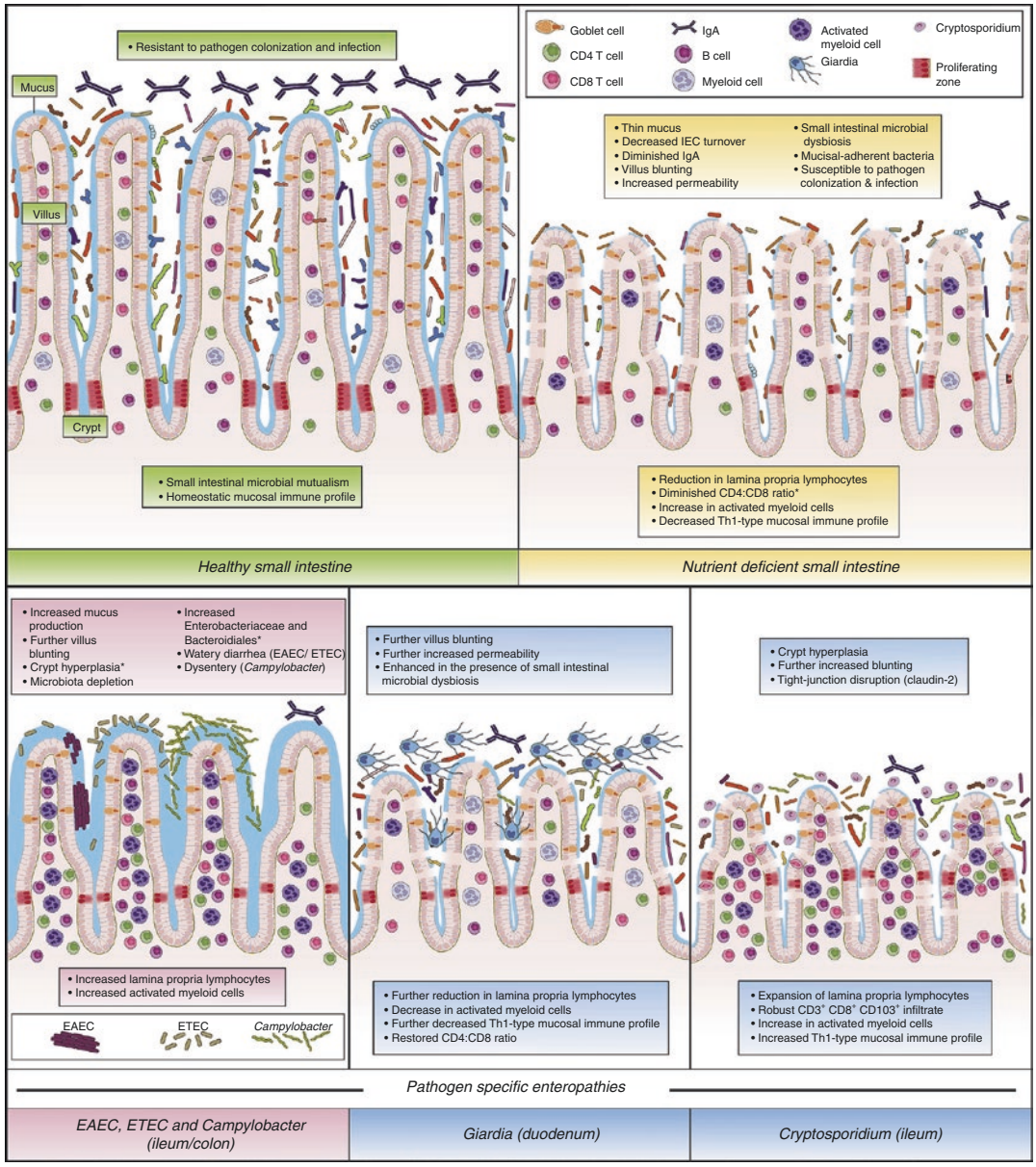

Fig. 8.3 Schematic diagram contrasting the pathology and immune responses in the intestinal epithelium during a healthy state (green boxes) to that of malnourished individuals (yellow boxes) to the combination of zinc deficiency and bacterial infections (pink boxes) to that of protein deficiency and *Giardia* or *Cryptosporidium* infection. Reprinted from Bartelt et al. [62]; Creative Commons CC-BY License

microbes. Salivary IgA (SIgA) has been found to be reduced in severely malnourished children [75]. Other studies have identified lower gastric secretions in malnourished children with higher (less acidic) pH contributing to reduced protection against infections [76–79].

The total number of immune cells has generally been found to be higher in malnourished children, although some functions were adversely affected, including adherence and ingestion of foreign material [28]. More of the leukocytes show signs of damage to DNA [28]. Levels of APPs such as C-reactive protein (CRP) and haptoglobin were found to be higher in malnourished children with clinical infec-

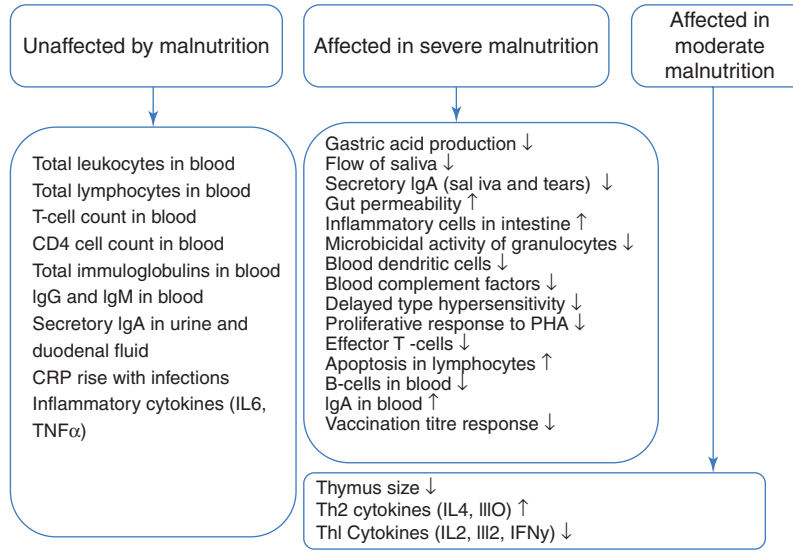

Fig. 8.4 Impact of malnutrition in children on components of immune system, without consideration of underlying factors generating an immune response. Reprinted from Rytter et al. [28]; Creative Commons CC-BY License

tions, and results were mixed in children without apparent infections. Proteins of the complement system were largely found to be lower in malnourished children, particularly serum levels of complement (C)3. Insufficiency of C3, the central pillar of this system, significantly reduces microbicidal capacity of leukocytes, especially against gram-negative bacteria, early in the infection [61, 80]. The reduction in complement proteins has mainly been attributed to reduced production although increased utilization due to infections also plays a role [81, 82]. While malnutrition has been found to be associated with reduced production of interferon (IFN)γ, above average IFNγ production has been found to have protective effect against *E. histolytica* [83]. IL10 similarly has a protective effect against *E. histolytica* in mice, but malnourished mice had less IL10 and hence were more susceptible to this infection [84].

Thymus size was found to be reduced in even mild malnutrition and partially reversed after treatment for malnutrition [28]. Extreme malnutrition may cause "nutritional thymectomy" as has been seen upon autopsy of malnourished children [85]. Other defects in adaptive immune function include reduced levels of soluble IgA in saliva and tears, elevated levels of soluble IgA in blood, largely no effect on IgG or IgM antibodies, reduced delayed-type hypersensitivity responses, fewer circulating B cells, a shift from T helper (Th)1-associated to Th2-associated cytokines, and lymphocyte hyporesponsiveness to phytohemagglutinin, with preserved lymphocyte and immunoglobulin levels in peripheral blood [28, 39]. In children with severe malnutrition, seroconversion rates have been found to be either reduced or delayed for typhoid and measles [86–94]. In children that achieved seroconversion following vaccination, titers remained lower than normal among severely malnourished children [28, 86–91, 95–97]. While the evidence strongly suggests sub-optimal development of acquired immunity after vaccination, the results are not consistent as some studies have reported normal antibody titers among severely malnourished children (see Fig. 8.4) [28].

Impaired Inflammatory Response

The inflammatory response is a reaction of the body that occurs when tissues are injured due to any harmful exposure. The response can lead to a number of signs or symptoms, including pain, localized warmth, redness, swelling, and loss of function-mediated through various cytokines including histamine, bradykinin, and prostaglandins. The cytokines cause blood vessels to leak fluid into the tissues, and when this happens in the gut, it results in diarrhea.

Evidence of impact of malnutrition on inflammatory response is inconsistent both across studies and across the components of cell-mediated immunity. A generalized dampening of the inflammatory response on a low protein diet has been demonstrated in rats [98]. In contrast, in malnourished pigs, local T lymphocyte expansion, enhanced intestinal major histocompatibility class (MHC) I and MHC II gene expression, and elevated tissue concentrations of prostaglandin E2 were observed after rotavirus infection [99, 100].

As above, malnutrition related to specific nutrients can also influence susceptibility to enteric infection by impairment of the inflammatory response. In rats, zinc deficiency led to reduced capacity to quench free oxidative radicals which cause cell injury and also resulted in inadequate handling of nitric oxide which is a diarrhea-triggering messenger [101]. The ileum of such mice demonstrated reduced leukocyte infiltration indicating an impaired inflammatory response [102]. Although the mechanism is not fully understood, intestinal contents of zinc-deficient mice exposed to enteroaggressive *E.coli* also had higher expression of *E. coli* virulence factors than was observed in control mice, indicating that zinc deficiency may increase disease severity [102]. In another animal study, mice deficient in vitamin D developed chronic low-grade intestinal inflammation and had a more severe inflammatory response when challenged with enteric pathogens, despite elevated levels of both pro-inflammatory and anti-inflammatory cytokines [103].

Changes in the Microbiota

The gastrointestinal tract is home to a large and heterogeneous community of bacteria that protects the gut from colonization by pathogenic bacteria while simultaneously facilitating nutrient and drug metabolism, vitamin production, and development and maintenance of the mucosal barrier [39]. Acquired or adaptive immunity is permissive to nonpathogenic bacteria in the gut, allowing the creation and maintenance of a protective microbiome [74]. We are increasingly realizing that this microbiota is an important mediator of the relationship between nutrition and host.

The microbiota is highly dynamic in composition and sensitive to dietary changes due to its intimate contact with ingested food and environmental contaminants that reach the intestinal lumen. The bacterial composition of a microbiota differs from person to person and even within the same person from day to day [49]. Studies in mice have shown that modifications in dietary protein, fat, polysaccharide, and simple sugars alter the microbiota's composition in a systematic fashion [39]. This sensitivity allows for quick return to normal composition when diets return to normal. However, sustained consumption of a high-fat diet induces proliferation of gram-negative bacteria in the gut [104], and there appears to be a tipping point at which dysbiosis ensues [105]. This is especially problematic in neonatal and pediatric populations, as the microbiota and the immune system are most sensitive to diet during those periods [106]. Dysbiosis at this critical time can have lifelong, if not intergenerational, consequences. Mouse models demonstrate that introduction of the dysbiotic microbiota from malnourished children into the gut of "germ-free" mice produced wide-ranging pathological changes [107]. In contrast, introduction of healthy microbiota helped in recovery from these effects in the mice previously inoculated with dysbiotic microbiota. Such studies demonstrate the critical nature and impact of a healthy microbiome on gut function [108].

Antimicrobial therapy, and even nonantibiotic drugs, can also produce detrimental effects on the microbiome, and yet the WHO recommends antibiotics for children with severe acute malnutrition [109–116]. It is known that antibiotics can disrupt the healthy microbiota while acting on harmful microbes [117]. Silverman and colleagues have reviewed the evidence and conclude that even short courses of antibiotics can disrupt the microbiota [118]. Though most microbial strains recover in a few weeks, depending upon the antibiotic administered, others may take up to 6 months, while still others may not recover at all. Age at the time of disruption also plays an important role, as antibiotic exposure among infants and young children results in a less diverse, less stable microbiome that

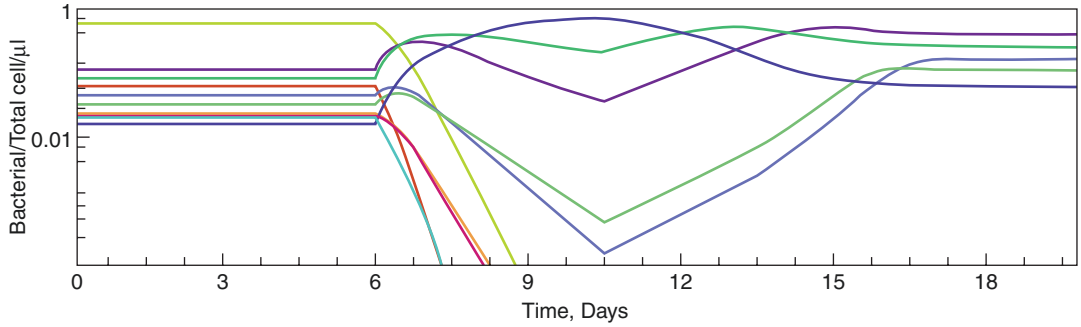

Fig. 8.5 Impact of a 4-day course of antibiotic (days 6–10) on the relative frequencies of eight of the most abundant bacteria genera (each represented by a different color) in a human gut microbiome. The five that are presumably more sensitive to the antibiotic are eliminated from the gut during antibiotic treatment. The remaining bacteria genera regrow and readapt to the new environment and are able to different but stable microbiota at around day 18. Reprinted from Nogueira et al. [119] with permission from John Wiley and Sons

matures later and shows signs of greater antibiotic resistance [118]. Therefore, disrupting the remaining healthy microbiota of malnourished children can be harmful. Figure 8.5 shows the impact of antibiotics on the microbiota. With the commencement of antibiotics at day 6, the different colonies were either eliminated or adversely affected, and, after antibiotics were stopped, some colonies regrew and readapted to the new environment while others did not [119]. Oral administration of an appropriate mix of bacteria, that have a probiotic effect, can help repair the damage done and recovery from malnourishment [120, 121].

Some pathogens are significantly more prevalent among malnourished children because of the harmful changes in the microbiota due to malnutrition. When malnutrition reduces the number of commensal bacteria, the predominant residents of the gut, it allows for increased growth of pathogenic microbes with increased epithelial adherence and mucosal uptake [122–124]. Compared to their healthy counterparts, malnourished children have microbiomes that are less mature and less diverse [39, 123, 125, 126].

While there are a variety of viruses, bacteria, and parasites associated with diarrheal diseases and enteric infections, globally, greater than 50% of all diarrheal deaths among children under 5 yrs. are attributable to rotavirus, calicivirus, enteropathogenic *Escherichia coli* (EPEC), and ETEC [125, 127, 128]. The Global Enteric Multicenter Study (GEMS), a seven-country case-control study to identify the etiology and population-based burden of pediatric diarrheal disease in sub-Saharan Africa and south Asia, found that rotavirus, *Cryptosporidium*, and ETEC were the most common diarrheal pathogens [129]. Furthermore, a study in Bangladesh found that stool samples from children with malnutrition included ETEC, *Cryptosporidium* sp., and *E. histolytica* more often than those from children without malnutrition [46]. The Malnutrition as an Enteric Disorder (MAL-ED) study, an eight-country birth cohort study investigating risk factors and interactions of enteric infections and malnutrition and the consequences for child health and development, reported that children with high enteropathogen exposure, mainly *E.coli*, and low energy and protein intake, were at higher risk of stunting [130, 131]. Disruption of the microbiota of these malnourished children may explain increased colonization and invasion of pathogenic bacteria, such as *E. coli* and pathogenic protozoan infections.

Deficiencies in specific nutrients can also cause harmful changes to the microbiome. Lv and colleagues [132] found that the gut microbiota differed significantly based on children's vitamin A status. Children with normal vitamin A levels had greater community diversity than their vitamin A-deficient counterparts, and their key phylotypes were *E. coli* and *Clostridium butyricum*, while the microbiome of children with vitamin A deficiency was dominated by *Enterococcus*, a common opportunistic pathogen [132]. Vitamin A also reduces the number of butyrate-producing bacteria, which may be a

contributing factor to increased growth of pathogenic strains as butyrate plays a role in suppressing growth of pathogenic strains [132]. Mouse models of protein, zinc, and dietary fiber deficiencies have all been shown to modulate the microbial community, with the latter leading to proliferation of mucus-degrading bacteria [133]. In contrast, both iron deficiency and iron supplementation appear to be associated with detrimental changes in the microbiome. Iron is an essential nutrient for both beneficial commensal bacteria and harmful enteropathogens. As a result, changes in the availability of iron can lead to significant shifts in the composition of the microbiome that can create favorable conditions for pathogenic strains [25]. This may explain why an iron fortification trial in Ghana resulted in increased hospitalizations and another in Pakistan resulted in an increase in diarrheal prevalence [134]. However, while studies in animal and in vitro models support this pathway, iron fortification has not consistently led to increased diarrheal disease or enteric infections across human trials [25, 134]. As such, it is possible that this pathway is only dominant where people live without improved water, sanitation, and hygiene and/or where gut microbiota already include opportunistic pathogens [25].

The microbiome also plays a significant role as an intermediary between host nutritional status and inflammatory response. For example, anaerobic fermentation of dietary fiber by commensal bacteria produces short-chain fatty acids such as butyrate and propionic acid, which, among other immunosuppressive functions, counter inflammation in the gut [133]. Moreover, catabolism of tryptophan, an essential amino acid, by commensal bacteria produces ligands that drive aryl hydrocarbon receptor activation, which also plays a role in protection against intestinal inflammation [135]. Diets deficient in these specific nutrients may result in impairment of the inflammatory response.

Impact of Malnutrition on Disease Progression, Resolution, and Recovery

We know that enteric infections generally progress in four phases: incubation, prodromal, invasion, and convalescence. Malnourished mice, when exposed to mouse rotavirus, became infected with a lower minimal dose, had a shorter incubation period, reached fecal viral shedding earlier, and experienced more severe disease [136]. Other studies also identified greater penetration of the virus into distant organs of malnourished mice [137]. In humans, no similar studies addressing intestinal infections have been found. However, length of hospital stay, measured as a proxy of disease severity, was longer in European children ages 1 month to 18 yrs. with moderate or severe malnutrition compared with well-nourished children [138]. These malnourished children were also more likely to experience diarrhea and vomiting when compared to their healthy counterparts [138]. Convalescence was also slower, and life-threatening events (LTEs) including deaths, severe pneumonia, severe diarrhea, were more frequent in Kenyan children with severe acute malnutrition (SAM) who were followed for 12 mo for LTEs after being stabilized and discharged from hospitals. Those who did not respond well to the treatment had a higher risk of post-discharge life-threatening events when compared to those who responded well in terms of anthropometric measurements [139]. Figure 8.6 shows the impact of severe acute malnutrition (SAM) following treatment among Kenyan children hospitalized for SAM even after treatment for enteric infections. While the number of children with WHZ < -3 decreases at each time point, children who continue to have low WHZ have significantly shorter survival times without LTEs even 6–12 months after hospital discharge [139]. An in-patient rehabilitation study of Bolivian children with severe malnutrition found that anthropometric indicators recovered in 4–5 weeks, although recovery from immune system damage took 8–9 weeks [140].

Deficiencies of particular nutrients can also contribute to intensified progression of diarrheal disease and delayed resolution and recovery. Studies in animals and humans have demonstrated that vitamin A deficiency is associated with decreased villous surface area and increased intestinal permeability leading to more severe intestinal injury during enteric infections [141]. This may explain why Colombian children with vitamin A deficiencies had an increased risk of diarrhea with vomiting and

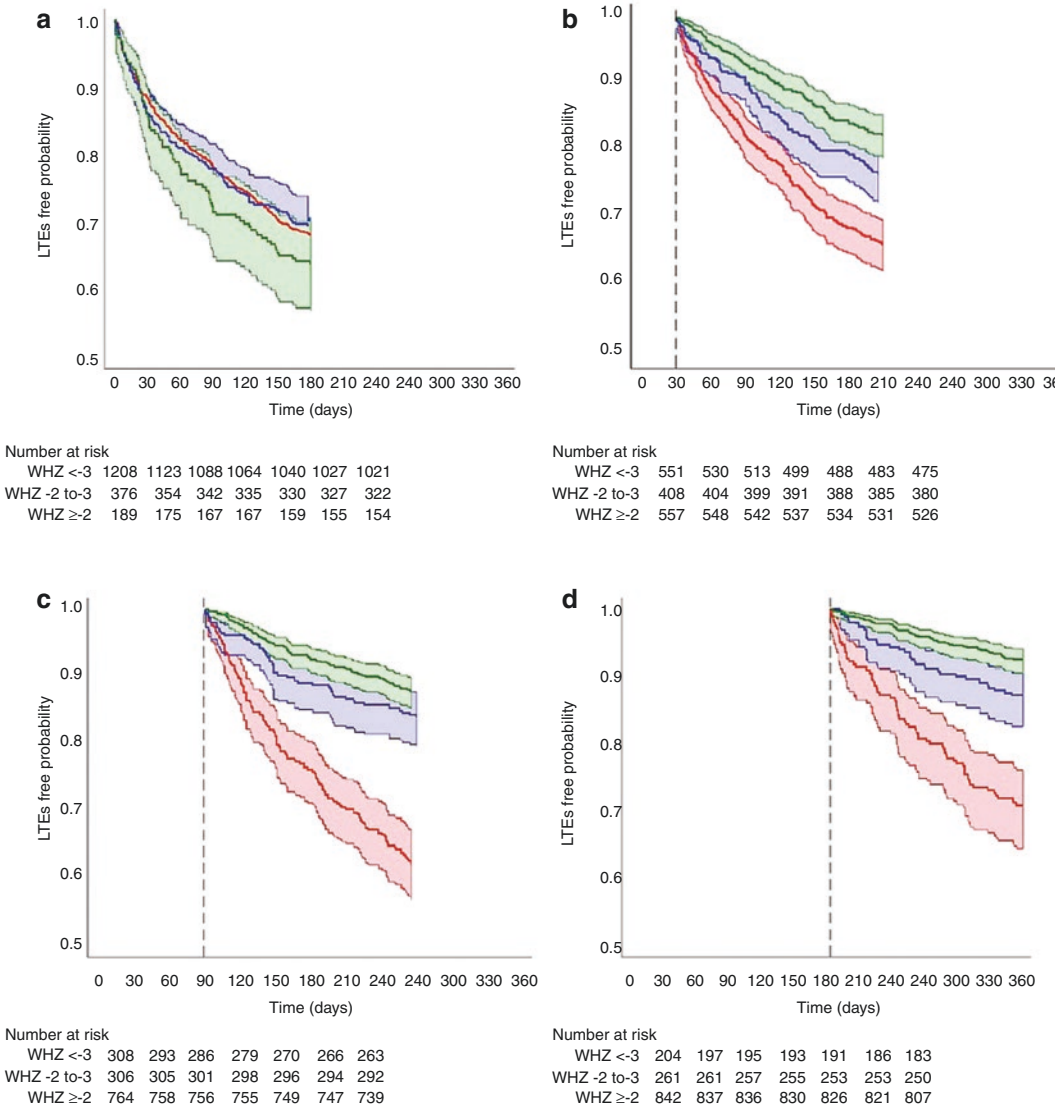

Fig. 8.6 Kaplan-Meier graphs of the impact of weight-for-height z score (WHZ) on probabilities of remaining free of life-threatening events (LTE) (death, severe pneumonia, and diarrhea) among 1778 HIV-uninfected Kenyan children ages 2–59 mos who were treated for severe acute malnutrition (SAM) at study entry. Figures show the risk of LTEs based on WHZ for 6 months following four different time points: study enrollment (0–180 days) (A), month 1 (30–210 days) (B), month 3 (90–270 days) (C), and month 6 (180–360 days) (D). WHZ with 95%: <−3 (red); −2 to −3 (blue), and ≥ −2 (green). Numbers at risk represent the number of children in the specified WHZ range at each of the indicated time points. Reprinted from Ngari et al. [139]; Creative Commons CC-BY License

why vitamin-A supplemented Ghanaian children had fewer clinic visits and hospital admissions for diarrhea even though the actual rate of diarrheal incidence had not decreased [23, 142, 143]. However, the role of vitamin A in disease progression and resolution appears to be pathogen specific. Long and colleagues found that vitamin A supplemented children had prolonged EPEC infections but faster resolution of infections by ETEC and *G. lamblia*, a difference that is likely mediated by whether the pathogen is cleared via pro- or non-inflammatory immune responses [144]. On the other hand, studies have consistently found that zinc supplementation slows disease progression and improves resolution

including reduced incidence, duration (by 12–24 hrs), fluid loss, and recurrence of diarrheal episodes, as well as reduced hospitalization and mortality rates associated with diarrheal disease by an estimated 23% [52, 145–147].

Malnutrition Increases Severity of Infection and Treatment Failure

Severity of infection or treatment failure can be assessed using a variety of indicators, including severity of symptoms and development of complications. The Integrated Management of Childhood Illness (IMCI) danger signs is one such indicator, and malnourished children exhibit IMCI danger signs more frequently than their healthy counterparts [35]. Penetration of gut microbes across the gut is another indicator, suggesting greater severity of infection or greater risk of treatment failure. Deeper penetration of infectious agents has long been reported in animal models of enteric infections. In the study of malnourished mice infected with murine rotavirus discussed previously, the malnourished mice also had a higher susceptibility to hepatitis caused by the rotavirus, more frequently reaching the liver than in the well-nourished mice [137]. Studies in a humanized pig model show that malnourished pigs with human microbiota experienced a more severe rotavirus infection when compared with the well-nourished pigs [148]. Similarly, detection of *E. coli* in blood is more likely in children with malnutrition, suggesting deeper invasion of gut pathogens [149]. As far as development of complications is concerned, intestinal perforation and enteric septicemia with *Salmonella*, *Shigella*, and *Staphylococcus aureus* are seen more frequently in malnourished children [150, 151]. Kwashiorkor increased the risk of death in hospitalized Botswanan children, another indicator of greater severity of infection although treatment failure cannot be discounted [152].

Cycling Back to Malnutrition

As mentioned earlier, the relationship between malnutrition and enteric infection is cyclical, where malnutrition and enteric infection create positive feedback loops within themselves. Malnutrition leads to morphological changes in the gastrointestinal tract, with increased permeability and reduced absorption capacity [50]. The resulting increased stool frequency increases opportunities to contaminate the environment and food which, in turn, increases risk of exposure to more enteric infection [153]. Malnutrition can drive increased exposure and susceptibility to and severity of infection, which in turn leads to higher risk of diarrheal disease and enteric infection, further perpetuating malnutrition [10]. Not only do these infections directly affect the integrity and absorptive capacity of the gastrointestinal barrier, but also diarrhea causes nutrients to transit through the gut more rapidly, reducing availability for absorption, thereby contributing to malabsorption [101].

Diarrheal disease pathogens cause malnutrition in different ways. Some, like *Vibrio* spp. or rotavirus, predominantly cause malnutrition through a net loss of nutrients from the body. Others, such as *E. histolytica* and *Giardia*, also deprive the host of nutrients because of intestinal damage that impairs absorption [154–157]. Malnutrition is also a result of the increased nutrient need for immune response and tissue repair that can ultimately lead to a negative nitrogen balance [158].

Infrequent mild to moderate episodes of enteric infection, even in an undernourished child, do not have lasting impacts as long as there is enough time for catchup growth. In contrast, the moderate or severe malnutrition caused by repeated or prolonged episodes of diarrhea that are frequently caused by enteric infections has cumulative effects that are long-lasting even for a well-nourished child [10, 159, 160]. Repeated infections are not an uncommon occurrence in lower resource settings, particu-

larly areas with limited access to safe water, sanitation, and hygiene facilities. Each infectious episode leads to a period of sub-optimal nutrition that can lead to a vicious cycle of malnutrition and infection [71].

The immune system, when triggered by enteric (and other) infections, consumes more energy and causes anorexia in ways that impact both cognition and body composition. Reduced supply and increased demand of energy contribute to inability to mount an adequate immune response against infections thereby perpetuating the cycle of malnutrition (see Fig. 8.3).

Closing Thoughts

Although we have come a long way in deciphering the interactions between malnutrition and enteric infections, much remains to be learned. Advances in our understanding of the broader malnutrition-infection interaction will undoubtedly shed light on some of what happens in the gut but may be insufficient to fully explain interactions that are driven largely by the gut microbiota, by mucosal barrier function, and by adhesion and invasion of gut pathogens.

Given the complex network of both modifiable and non-modifiable factors that influence gut health, nutritional status, and exposure and response to diarrheal pathogens, it is not surprising that inconsistencies emerge among studies. The challenge is to recognize where specific interventions can reliably be expected to reduce malnutrition and diarrheal disease and to identify the contexts under which their use is recommended. As the malnutrition-diarrhea cycle occurs more frequently in limited resource settings where low-cost interventions are needed, identification of appropriate, and possibly novel, interventions requires a more nuanced understanding of the complex interactions between various gut infections and malnutrition, so that interventions can be tailored to a given environment.

While at the individual level, malnutrition and diarrheal disease cause morbidity, mortality, and reduced productivity, at the large scale, they contribute to poverty and lack of equal access to opportunities resulting in friction between various sections of a society that can lead to political instability. In turn, political instability adversely affects nutrition. Thus malnutrition and diarrheal diseases cycle from the individual level to the local, regional, and national levels and then back to the individuals. Research on this topic is not merely an academic question but carries serious economic, political, and ethical implications [161]. Given the contribution of malnutrition and infection generally, and diarrheal disease more specifically, to the global burden of diseases, both research and interventions should be a global priority and funded commensurately.

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