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# Building better barriers: how nutrition and undernutrition impact pediatric intestinal health

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Chronic undernutrition is a major cause of death for children under five, leaving survivors at risk for adverse long-term consequences. This review focuses on the role of nutrients in normal intestinal development and function, from the intestinal epithelium, to the closely-associated mucosal immune system and intestinal microbiota. We examine what is known about the impacts of undernutrition on intestinal physiology, with focus again on the same systems. We provide a discussion of existing animal models of undernutrition, and review the evidence demonstrating that correcting undernutrition alone does not fully ameliorate effects on intestinal function, the microbiome, or growth. We review efforts to treat undernutrition that incorporate data indicating that improved recovery is possible with interventions focused not only on delivery of sufficient energy, macronutrients, and micronutrients, but also on efforts to correct the abnormal intestinal microbiome that is a consequence of undernutrition. Understanding of the role of the intestinal microbiome in the undernourished state and correction of the phenotype is both complex and a subject that holds great potential to improve recovery. We conclude with critical unanswered questions in the field, including the need for greater mechanistic research, improved models for the impacts of undernourishment, and new interventions that incorporate recent research gains. This review highlights the importance of understanding the mechanistic effects of undernutrition on the intestinal ecosystem to better treat and improve long-term outcomes for survivors.

## KEYWORDS

human milk, undernutrition, immune system development, intestinal epithelium, digestion

## Introduction

Malnutrition encompasses conditions of both undernutrition and overnutrition in terms of energy intake and includes disorders of inadequate vitamins and minerals (1). This review will focus on malnutrition in the form of undernutrition.

Nearly half (45%) of all deaths in children under 5 are linked to undernutrition (1). Severe acute malnutrition (SAM) consists of both nutritional edema (Kwashiorkor) and Marasmus (severe wasting) (2). Malnutrition significantly alters the structure and function

of the intestine and is a major contributor to illness and death in children worldwide (1). Stunting is one long-term effect of malnutrition that is not significantly reduced by providing supplemental food (3). This demonstrates that simply restoring balance to the diet is insufficient to correct long-term pathological changes and points to underlying changes in the intestinal physiology, which impact nutrient digestion and absorption that must be remedied before increased nutrient intake can functionally impact growth. There are several groups, such as Bandsma et al. (2, 4–7) looking at the physiological impact of undernutrition on the intestine, however, more studies are urgently needed to mitigate and potentially reverse the damage caused by this deadly condition. This review discusses normal intestinal development and digestive function, including the closely associated immune and microbiome compartments under normal nutrient conditions and what is known about the effects of undernutrition on GI tract function (Figure 1). We then aim to highlight areas that require further study and critical unanswered questions in the field with the ultimate goal of improving the survival and lives of millions of children worldwide.

## Intestinal development

The intestinal epithelium refers to the single layer of intestinal epithelial cells (IEC) that lines the luminal surface of the intestine. These cells form the most significant barrier within the human body and exist at the interface between ingested nutrients and the body cavity. The IEC barrier coordinates nutrient digestion and absorption, bacterial interactions, immune cell modulation, cell proliferation, and cell death (8). Regulation of these processes and maintenance of the barrier is critical to intestinal and organismal health.

The human intestine develops from the hindgut endoderm during weeks 3–7 of human embryonic development. The hollow tube that will become the intestinal tract elongates, and the luminal surface area increases through the eventual folding and evagination of the epithelial cell layer to form crypt evaginations that house the intestinal stem cells (ISC) and finger-like projections called villi. Villi increase the absorptive surface of the intestine by 6.5-fold when compared to a surface without villi to achieve a surface area of ~30m<sup>2</sup> in an adult human (9). Much is still unknown about how the intestine forms and the gene expression programs that govern epithelial remodeling. For a more detailed discussion, we refer readers to this detailed review (10). The fully developed intestinal epithelium is composed of multiple specialized cell types that work

in concert to perform the digestive, absorptive, secretory, and barrier functions of the intestinal epithelium (11).

The human intestinal epithelium is the most dynamic tissue in the human body, turning over every 3–5 days (12). IEC renewal is driven by a small pool of ISCs (13, 14), which continuously divide to replenish the stem cell pool and generate transit-amplifying progenitor cells to maintain the entire intestinal epithelium. Absorptive enterocytes comprise >80% of IECs and arise from highly proliferative transit-amplifying progenitor cells (13, 15), while the secretory cell types arise from a common secretory progenitor (11). Goblet cells migrate onto the villi where they secrete mucus, which serves as an additional barrier and protects the IEC from bacteria (16). Enteroendocrine cells are also largely present on the villi, where they respond to nutrients within the lumen and secrete hormones and growth factors that contribute to intestine growth (17–19). Tuft cells are rare cells comprising <1% of all IECs. These sensory cells coordinate signaling from luminal microbes, the host immune system, the enteric nervous system, and the intestinal barrier itself (20). Paneth cells migrate down to the base of the crypt; intercalated between the ISC, Paneth cells secrete ISC niche factors and antimicrobial peptides to regulate the intestinal microbiota (21, 22). Lastly, M cells are an epithelial component of Peyer's patches that sample luminal bacteria and antigens and transport these factors to tissue macrophages and lymphocytes below (11). Peyer's patch development and function will be discussed in more detail in the intestinal and systemic immunity section.

These epithelial cell types are joined together by tight junctions to form a selectively permeable barrier between the body and the complex luminal environment of digestive contents, chemicals, and bacteria. Maintaining an intact epithelial barrier is key to proper intestinal function, appropriate nutrient absorption, regulation of bacterial diversity, and balanced immune cell activation.

At birth, the intestinal barrier is somewhat permeable (23–26) allowing for immune system priming with select intestinal bacteria, as well as transport of large intact proteins, such as immunoglobulins from human milk into the body (27). Within days the barrier rapidly closes, typically as a result of human milk feeding and interactions with the developing microbiota (26), to prevent unwanted immune activation, bacterial translocation, or transit of undigested nutrients (23–25, 27). This barrier consists of epithelial cells joined together by tight junctions, adherens junctions, and desmosomes, which form a strong seal between adjacent cells (28). Tight junctions are composed of lipid and protein components in which variations can alter barrier permeability (29). They allow for the selective restriction of intestinal bacteria but the regulated flux of ions and molecules through the epithelial layer. Tight junctions are stabilized by adherens junctions and desmosomes (30, 31). Selective movement of nutrients and ions is mediated through the paracellular pore (32–34) and leak (35, 36) pathways, which mediate the passage of molecules based on their size and or charge as in the pore pathway. Inflammation, infection, or damage are examples of barrier breach, opening the unrestricted pathway and allowing for the passage of ions, nutrients, and bacteria across the barrier (37, 38). Rapid sealing of the barrier and restitution of the lost epithelium

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**Abbreviations:** AHR, aryl hydrocarbon receptor; EEC, enteroendocrine cell; GALT, gut-associated lymphoid tissue; HMO, human milk oligosaccharide; IEC, intestinal epithelial cell; ILF, isolated lymphoid follicles; ISC, intestinal stem cell; miRNA, microRNA; mTORC1, mammalian target of rapamycin complex 1; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PPAR, peroxisome proliferator-activated receptor; RUSF, ready-to-use supplementary food; SAM, severe acute malnutrition; SCFA, short chain fatty acids; sIgA, secretory immunoglobulin A; SIRT1, sirtuin 1; TLR, toll-like receptor.

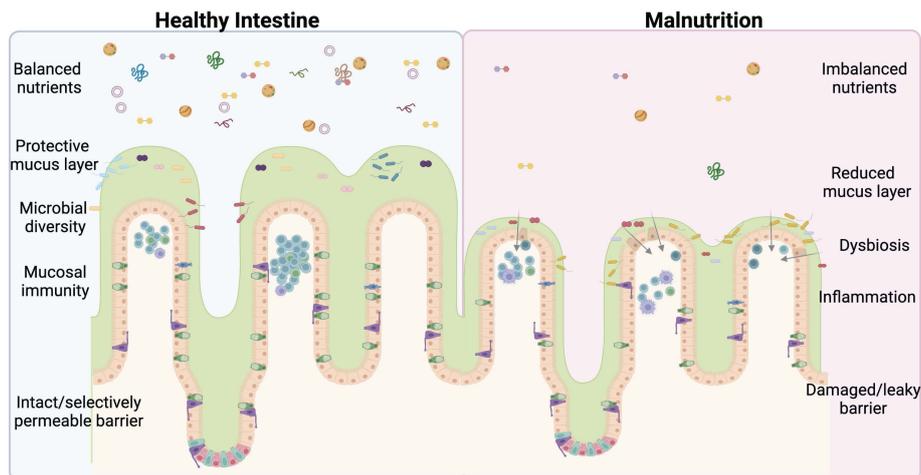


FIGURE 1

Undernutrition negatively impacts every facet of intestinal health. An imbalance of lumen nutrients is detrimental to the mammalian intestine. The villi atrophy in the absence of balanced nutrients, including Goblet cell loss and reductions in the protective mucus layer. Less mucus and varied nutrients allow for bacterial retention, dysbiosis, and infection, exacerbated by deficiencies in the mucosal immune system and ultimately culminating in barrier damage and leakage of lumen contents into the submucosal space. This perpetuates a vicious cycle further promoting inflammation and permitting bacterial invasion. The ideal treatment and cure for undernutrition will address each of these facets of intestinal health. Figure composed using BioRender.

requires cellular proliferation and expansion. For a more detailed discussion on intestinal barrier function, we refer readers to this review (28).

## The effect of nutrition on the intestinal epithelium

Intestinal barrier maintenance is a highly energetic process closely coupled to the presence or absence of nutrients. This is exemplified by snakes whose intestine rapidly rebuilds upon feeding and atrophies after digestion is complete to conserve energy that would be consumed by continuous epithelial upkeep (39). Similar less dramatic adaptations occur within the mammalian gut in response to dietary changes (40–44), primarily driven by nutrient responsive ISC.

Modulation of calorie intake expands and contracts ISC populations. In instances of calorie restriction, where calorie consumption is reduced but dietary balance is maintained, ISC and other niche cell types expand and differentiation is decreased (40–43). This process is driven through mTORC1 and SIRT1 activation, both of which are core regulators of cellular metabolism (40, 42) and PPAR-gamma downstream of fatty acid oxidation (43). ISCs expand in response to fasting ketone bodies and rely on oxidative phosphorylation and lactate produced by glycolytic Paneth cells for their metabolism (45, 46). This may be a protective mechanism to ensure the continued survival of ISC when nutrients are scarce. Similar to a fasting snake, this pool of ISCs sits ready to differentiate into functional daughter cells in response to nutrient intake (40). Differentiation into secretory cell types is driven by Notch gene expression and stimulated by dietary fat and glucose consumption (46). ISC differentiation is also linked to nutrient metabolism as reactive oxygen species generated by ISCs contribute to the differentiation of daughter progenitors (45). These

changes are in contrast to stem expansion and uncoupling from Paneth cell niche signals that occurs with high fat diet feeding (44, 47, 48) and can lead to cancer (44, 49).

ISC and the epithelium at large are also responsive to specific dietary nutrients. For example, the human and murine intestines respond to dietary vitamin D by enhancing stem cell proliferation and strengthening the intestinal barrier (50, 51). Interestingly, dietary activation of the aryl hydrocarbon receptor (AHR) via feeding of compounds present in green, leafy vegetables can limit proliferative signals and promote functional differentiation within the intestinal epithelium (52). In animal models, loss of AHR results in stem cell expansion, reduced differentiation, and compromised barrier function (52).

In animal studies of calorie restriction, reduced calorie consumption expanded the stem cell pool and increased the regenerative capacity of the intestine in response to discrete insults (40, 43, 46), suggesting that reduced calorie consumption may be beneficial to promote intestinal health with aging or in preparation of targeted damage, such as radiation treatment. However, these benefits of priming the intestine for regeneration in the face of injury are not seen in the malnourished state; in fact, undernutrition increases risk of disease and intestinal barrier breach in the face of infection or insult. One could speculate that imbalances in nutrient-coupled proliferation/differentiation signaling pathways (such as AHR) contribute to barrier disruption and inflammation in malnutrition, either directly through IEC or indirectly through the immune system (53–57).

## Early infant nutrition

Human milk is the ideal nutrition for infants, with numerous benefits, including reducing all-cause mortality in the first year of

life and, compared to bovine-based formula, improved neurodevelopment (58–61). Data suggests the benefits of human milk are dose-dependent (58). Thus, the provision of optimal amounts and composition of human milk as nutrition during early infant life is critical to the current and lifelong health of the developing child. Undernutrition beginning early in the infant years would be expected to decrease the benefits conferred by milk. Surprisingly, maternal milk production volume is protected in the setting of maternal undernutrition; only in severe malnourishment is milk volume or macronutrient content impaired (62–64). Although the lactating mother will scavenge energy and macronutrients from body stores to preserve milk production, micronutrient content can be impacted (65). Despite the preservation of milk volume production, impaired infant growth has been observed in infants who breastfed from mothers with malnourishment (66). While some of this may be due to maternal micronutrient deficiencies transmitted to the infant, there may be a contribution from increased infant inflammation (64).

Human milk is a complex fluid with thousands of proteins, lipids, oligosaccharides, microRNAs (miRNAs), maternal cells, and metabolites, which have been selected for millennia to provide optimal infant nutrition and development (67). In addition to the provision of energy and nutrients, milk is a system of bioactive proteins, lipids, sugars, miRNAs, and metabolites that assist in infant development, with examples being intestinal, immune, and central nervous system development (67, 68) and development of the intestinal microbiome (69–72). It remains to be defined if severe maternal undernourishment impacts the bioactive components of milk in a manner that might adversely affect early infant development and growth.

## Early infant digestion and milk

There are several ways that undernutrition may alter human milk digestion, particularly with regard to human milk proteins. Human milk proteins are often divided into two classes, caseins and wheys. Wheys are highly proteolyzed during digestion and caseins are less degraded. Caseins include proteins with bioactivities in their intact forms, such as lactoferrin, immunoglobulins, and growth factors (73). It is unknown whether the human milk proteome is affected by maternal undernutrition or malnutrition. The proportion of bioactives in human milk may differ in abundance or ability to survive digestion in undernutrition than in the well-nourished state. There is evidence that human milk proteins may encode cryptic bioactive peptides with activities important for infant health (67). These include enterocyte and monocyte immune modulation (74, 75) and modulation of bacterial growth and survival (76). How undernutrition may alter the production of these milk protein digestion products is unknown. Moreover, how undernutrition could alter milk's digestion or survival of other bioactive or cryptically bioactive components (e.g., HMOs, lipids, metabolites, extracellular vesicles) remains to be defined.

Given the role of human milk in health (77), defining the impacts of undernutrition and malnutrition on the production, consumption, and digestion of milk is of high importance.

## Development of intestinal immunity

The intestine is considered the largest immune organ in the body (78, 79), containing concentrated regions of lymphoid tissue called gut-associated lymphoid tissue (GALT), as well as myriad innate and adaptive immune cells present throughout the epithelial, submucosal, lamina propria, and muscle layers (79, 80). These cells are tasked with maintaining intestinal homeostasis, preventing inappropriate immune reactions to harmless antigens or microbes (tolerance), while also mounting swift immune reactions to pathogens (activation).

Intestinal macrophages and dendritic cells (DCs) exist in different compartments throughout the small intestine and colon where they perform distinct functions, recently reviewed here (80). Within the lamina propria macrophages participate in barrier maintenance, removal of dying cells, and tolerance of the microbiota (80). Subpopulations of macrophages are also present within Peyer's Patches where they present antigen or clear apoptotic immune cells (81–83). Muscularis macrophages are found in the myenteric plexus where they mediate crosstalk with the crosstalk with the enteric nervous system during infection (84). DCs are also present throughout the intestinal lamina propria, including Peyer's patches and lymphoid follicles. Here they sample luminal antigens and migrate to mesenteric lymph nodes (85) where they facilitate oral tolerance (86). Notably, draining lymph nodes from each intestinal region harbor DCs with differing levels of tolerance and sensitivity to inflammatory cytokines, for example duodenal DCs are more tolerogenic, while ileal DCs possess more inflammatory cytokine receptors (87). DCs are shaped by their microenvironment, including stromal cell interaction, dietary ligands, and the microbiota. Interestingly, certain subclasses of DCs can affect nutrient uptake, as recently demonstrated for CD11c<sup>+</sup> cells, which stimulate expression of epithelial lipid transporters (88).

The intestine is also home to a large adaptive immune population. B and T cells are found within small intestinal GALT, which develops alongside the IEC cells *in utero*, with B and T cell clusters visible as early as 14–16 weeks' gestation (89, 90). These clusters exist as large multi-follicular lymphoid aggregates known as Peyer's Patches or isolated lymphoid follicles (ILF) of varying sizes throughout the small intestine (SI) (79). ILF are also present within the colon but develop later than small intestinal GALT (90). Both SI and colonic GALT development are influenced by stromal-immune cell crosstalk (90) and house primarily B and T cells (adaptive immunity) as well as dendritic cells to facilitate immune cell priming, mast cells, and granulocytes (91, 92). The intestine is also home to numerous innate immune cells, including the largest population of macrophages in the body, innate lymphoid cells, dendritic cells, and eosinophils. Eosinophils begin to populate the intestine before birth and participate in parasitic and allergic responses (93).

This large and diverse collection of intestinal immune cells, which composes the mucosal immune system, is responsible for surveying the epithelial barrier, protecting against pathogen breach, and maintaining a healthy balance of intestinal microbes. M cells and the follicle-associated epithelium (FAE) (94) which overlay Peyer's Patches, selectively take up antigens, to facilitate adaptive immunity via DC-mediated antigen presentation (95, 96). For a more detailed discussion of B cells in mucosal immunology, we

refer readers to this recent review (97). After antigen exposure, either from luminal contents or deliberately via an oral vaccination, primed B cells clonally expand and migrate between germinal centers. Upon repeat antigen exposure, high-affinity B cell clones are selected. These will be distributed within Peyer's patches and the lamina propria along the length of the intestine where they produce high affinity secretory immunoglobulin A (sIgA) antibodies against the target antigen as part of the mucosal barrier (92, 98). IgA is one of the primary mediators of the mucosal immune response. sIgA promotes either bacterial clearance through mucus shedding or retention when mucus flow is low (99). sIgA selectivity and specificity shape and regulate the intestinal microbiota (99–101). sIgA also neutralizes pathogen toxins while preventing bacterial proliferation and antigen absorption (102).

## Shaping the intestinal microbiome

Intestinal barrier function, mucosal immunity, and nutrition are intimately connected to the intestinal microbiota. The intestinal tract contains the body's most abundant and diverse microbial community. The term gut microbiome refers to the community of microbes, their DNA, and byproducts, including the associated metabolome and proteome, which is shaped by host genetics, as well as environmental factors, including mode of birth, diet, antibiotic use, geography, and the host immune system as discussed above (103). Many intestinal microbes coexist within their human host in a mutualistic and beneficial fashion, digesting insoluble fiber (104), modulating host gene expression (105–107), shaping the host immune system (108–111), and providing natural competition for pathogenic organisms within the gut environment (69, 71, 112).

### *In utero* colonization

Whether or not bacteria colonize infants *in utero* remains controversial. A collection of studies detected microbial components in the placenta (113), amniotic fluid (114), umbilical cord blood (115), and meconium (116). However, these studies lack information about the mother's health, leaving open the argument that the detection of bacteria and bacterial components in the fetal environment could be due to maternal infection or other inflammatory conditions during pregnancy. Although *in utero* microbial colonization is debated, a recent study showed that embryonic IECs can sense short chain fatty acids (SCFAs) produced by the maternal microbiota through G-protein coupled receptors (117), a process that is essential to facilitate the development of fetal IECs. This finding demonstrates that maternal microbial byproducts such as SCFAs can communicate directly with the fetal environment to shape intestinal development, eliminating the need for *in utero* bacteria.

### Postnatal colonization: delivery mode

Bacterial colonization begins at birth and is profoundly influenced by delivery mode (118–120). Vaginally-delivered term

infants are introduced to the vaginal microbiota. These first colonizers of the neonatal gut are usually aerobic or facultative bacteria, including *Enterococcus*, *Streptococcus*, *Prevotella*, *Lactobacillus*, *Bacteroides*, and *Escherichia* (119). Classic culture-based studies between the 1970s and 1980s revealed that the infantile gut microbiota is less complex and has a higher proportion of facultative bacteria than the adult microbiota (121–124). As these bacteria grow, they consume oxygen, making the intestinal environment more hospitable for the proliferation of facultative and anaerobic bacteria, including *Bifidobacterium*, *Clostridium* and *Bacteroides* (122). Once these oxygen-sensitive species establish, the population of aerobic and facultative bacteria decline, and the complexity of the microbiota increases, resulting in a more diverse microbiota (125), closer to that of their adult parents by age five (126, 127).

The microbial communities of infants born by c-section and those born vaginally will eventually converge; however, differences can persist for the first 1–2 years of life (119, 128). In comparison, newborns delivered by cesarean section are deprived of contact with their mother's gut and vaginal microbiota. They are usually colonized by bacteria associated with the maternal skin and mouth, found on hospital staff, or in the surgical environment (118, 119), delaying the acquisition of *Bacteroides*, *Bifidobacteria* and *E. coli* (129).

### Feeding mode

Infant nutrition is a significant driver of intestinal microbial colonization and diversity. Human milk contains all the essential nutrients infants need to thrive, including all three primary macronutrients (fats, carbohydrates, proteins), bioactive factors (130) (cytokines, cells, immunoglobulins), immunological factors, prebiotics (e.g., human milk oligosaccharides), and even bacteria, which all contribute to shaping the infant microbiome.

Human milk is a rich source of commensal and mutualistic bacteria (131–136). It is estimated that breastfed infants consume  $8 \times 10^4$  -  $8 \times 10^6$  bacteria per 800 mL milk per day, with human milk being the second source of microbes to infants after vaginal birth (131). Human milk contains immunological factors such as maternal IgG and IgA antibodies, which shape the early gut microbiome by dampening mucosal CD4<sup>+</sup> T helper cell responses and protecting against enteric pathogens (137, 138). Prebiotics in the form of human milk oligosaccharides (HMOs) are another highly abundant and important component of human milk that are indigestible by humans (72, 139) and therefore not present for infant nutrition (140). Rather, HMOs are a rich nutrient source for bacteria, such as *Bifidobacterium longum* ssp *infantis* (141), that shapes the infant microbiome. Early infant gut microbiome is enriched in genes that facilitate lactose utilization found in *Lactobacilli* (142). High levels of *Bifidobacterium* species and bacteria capable of metabolizing HMOs are also found in term infants' gut (143) and in human milk (119). HMOs are the primary nutrient source in the colon that supports the healthy growth and colonization of these saccharolytic microbiotas, helping to prevent or reduce colonization with specific pathogens (71, 144). In turn, metabolites produced by these bacteria, such as SCFAs,

are an important source of energy for enterocytes and key signaling molecules for gut health maintenance (145, 146). There is growing interest in events that shape the milk microbiome, inspired by findings that delivery mode and lactation stage alter the milk microbiota composition (147), suggesting an impact of the physiological labor process, stress, and hormonal signals on the infant microbiota composition (70, 147–151).

## Antibiotic treatment

The use of broad-spectrum antibiotics in infants drastically alters the microbiota. In neonatal intensive care units (NICUs) where antibiotic treatment is common, infants usually acquire a very sparse microbiota almost absent of anaerobes (152, 153). Yeasts, *Enterococcus*, and *Enterobacteriaceae* dominate the microbiota (152, 153). This dysbiosis or imbalance in the gut microbiota places these infants at increased risk of diseases, such as necrotizing enterocolitis (NEC) (154).

## Beneficial roles of the intestinal microbiome on intestinal function

The intestinal microbiome plays an integral role in gut barrier function, including roles in early immune development and immune system priming, as well as direct effects on the IECs, all aimed at restricting bacteria to the luminal compartment of the intestine (155). Commensal microbes compete for space and resources with pathogenic colonizers, which helps reduce disease and can alter the host metabolism (156). The earliest colonizers (*Bifidobacterium*, *Clostridium*, and *Bacteroides* spp.) (125) interact with the mucosa to shape immune system development and intestinal function (157–162). *Lactobacillus* spp. and *Akkermansia muciniphila* proteins stimulate mucus production and strengthen the epithelial barrier (38, 163–167). IEC detect bacterial byproducts or the bacteria themselves through pattern recognition receptors, such as toll-like receptors (TLRs). These signals regulate numerous aspects of the IEC barrier, including mucus and antimicrobial peptide production, tight junctions, and IEC proliferation and differentiation (38, 164, 165, 168, 169).

Bacteria facilitate nutrient digestion by providing the enzymes infants lack for the breakdown of milk glycans (170, 171). The genomes of these bacteria encode a large number of carbohydrate-metabolizing enzymes that are involved in HMO consumption (170, 171), allowing infants to obtain more usable calories from their food. For example, term infants with a diverse community dominant in *Bifidobacterium* and *Bacteroides* have a higher concentration of SCFAs, the end products of fermentation of dietary fibers, than low-birth-weight infants (142). These observations indicate that the microbiota contributes to the digestion of more than 200 different oligosaccharide structures in human milk (172). Moreover, intestinal bacteria possess genes for vitamin synthesis, including vitamin B12 and folate (142).

## Impact of undernutrition on intestinal development and function

The physiology of the intestine in the undernourished state mirrors that of other chronic intestinal diseases, such as Celiac or Crohn's disease. The villi are sparse and stunted, reducing both the absorptive surface area and the presence of digestive enzymes to mediate nutrient breakdown. This reduced digestive and absorptive surface area likely contributes to failed nutrient absorption and secretory diarrhea following therapeutic feeds. Lactose and glucose malabsorption are highly prevalent among malnourished children (4, 5) and constitute a significant barrier to success with therapeutic feeds. Circumventing these deficiencies through feeding reduced carbohydrate and lactose-free formulations does not improve outcomes (6), indicating that more work is needed to understand the molecular pathophysiology as it impacts nutrient digestion and absorption in malnourished children. There is limited information about the effect of severe undernutrition on the intestinal epithelium.

The effects of undernutrition on the ISC compartment are varied depending on the model. In wasting marmosets, there is no change in ISC or Paneth cell number, but the progenitor pool expanded (173). Several mouse models of undernutrition (1–2% protein) exhibited reduced expression of ISC marker mRNAs (7, 174). These are in sharp contrast to caloric restriction studies in which marked ISC and progenitor expansion occurs (40, 42, 175). In a 28-week, 60% calorie restriction model, Paneth cells also expanded (40); however, this has not been seen in other studies. These expanded progenitor cells are poised for differentiation once nutrient signals direct their specification, but in the case of undernutrition, these signals may be drastically reduced or absent, leading to dysfunction (42, 43, 175, 176). For example, chronic loss of fatty acid oxidation (3 months) in response to undernutrition compromises ISC and progenitor cell function and abolishes the pro-regenerative effects of reduced nutrient consumption (43). How undernutrition alters the ISC niche of human patients remains an open question.

There is also relatively little known about the effects of undernutrition on specific differentiated cells of the intestinal epithelium. Villus atrophy is universally seen across caloric restriction and undernutrition models (7, 40, 42, 173, 175–178), accompanied by a decrease in absorptive enterocytes (40, 42, 173). Goblet cell numbers are reduced in the intestines of mice, rats, and piglet models of undernutrition, as well as mouse models of caloric restriction (40, 42, 173, 179–183). Goblet cell loss leads to reduced mucus (2) leaving the epithelial barrier more susceptible to insults from pathogens or toxins (184). Goblet cell atrophy could result from limited differentiation, dysbiosis (185, 186), or both. Enteroendocrine cells (EEC) produce hormones that regulate growth, hunger, and satiety and are reported as unchanged in wasting marmosets and calorie-restricted mice, although Igarashi et al. found a reduction in EECs in their mouse model of modest (30%) calorie restriction (42). A subset of EECs exhibit reserve stem cell potential (187), which can enhance regeneration after damage (175). The effects of undernutrition on human EECs require further

investigation. EECs regulate intestinal growth (17, 18); therefore, dietary modifications influencing EEC form or function could be important for developing targeted dietary therapies for undernutrition. The effect of undernutrition on human tuft cells is unknown, although these cells are drastically expanded in wasting marmosets (173). Given the chemosensory role of tuft cells (20), this expansion may protect the intestinal barrier through immune surveillance and nutrient monitoring.

Undernutrition is characterized by leakiness of the intestinal barrier, which is often measured by urine sugar excretion in human studies (188). Barrier breakdown results from a reduction in tight junction proteins (178) and elevated apoptosis leading to cell loss (177, 178). Reductions in vitamin D signaling may contribute to the disrupted barrier, as seen in inflammatory bowel disease patients (189). Breaches in the barrier allow for luminal bacteria to translocate into the circulation, loss of unabsorbed nutrients through the unrestricted pathway (37, 38), and a loss of absorptive surface area. These effects are exacerbated by decreased bacterial diversity, presumably resulting from the reduction in nutrient intake coupled with changes in the luminal environment (190, 191). The intestinal microbiome is integral to intestinal maturation (190, 192, 193) and its role will be discussed below.

While we do not completely understand the underlying intestinal pathophysiology of undernutrition, several dietary modulations show promise in preclinical models of undernutrition. One study used a mouse model of undernutrition (1% protein diet) to show that bovine milk extracellular vesicles could restore intestinal barrier function after only 4 days of feeding. Although the study did not see differences in growth, the short four-day time point was likely not long enough to appreciate the benefits of a strengthened intestinal barrier (7). Interventions such as bovine milk extracellular vesicles hold promise for reducing the devastating toll of undernutrition on children in the developing world. Another study used germ-free mice colonized with bacteria from a stunted infant to demonstrate that sialylated bovine milk oligosaccharides expand intestinal tuft cells, among other physiological changes. This indicates the importance of understanding the bacteria-substrate interactions and how they may be altered in the presence of dysbiosis to impact growth (192). These studies underscore the importance of the intestine-microbiome relationship on systemic physiology, especially in the context of undernutrition, and how much remains to be discovered in this research realm.

## Adequate nutrition is intimately linked to intestinal immune function

The innate and adaptive immune systems are modulated by nutrient status and key dietary components. Intestinal macrophages and DCs respond to dietary nutrients, indicating the potential for altered functionality in undernutrition. Macrophages are influenced by retinoic acid (194), short chain fatty acids, amino acids (195), and aryl hydrocarbon receptor ligands (196). For example, activation of the aryl hydrocarbon receptor promotes intestinal barrier function and limits inflammation-induced damage (197, 198). DC activity and

homing can be shaped by retinoic acid (199), vitamin D (200, 201), and glucose (202) levels.

The presence of enteral nutrients is key to GALT maintenance and function through the maintenance of blood flow through the tissue and continual antigen exposure. Intestinal macrophages are also highly responsive to nutrients and dietary components. In rats, administration of parenteral nutrition, whereby nutrients bypass the digestive system and are administered into the circulation, attenuates immune function in response to a bacterial insult (203, 204) and reduces macrophage regeneration (195). In mice, a 12-hour fast is sufficient to induce GALT atrophy (205) and autopsies of undernourished children reveal a loss of GALT tissue (206). Adequately enterally-nourished hospitalized patients with preserved mucosal immunity exhibit reduced infections and faster discharge times compared to patients experiencing undernutrition or fed parenterally (207–209), emphasizing the importance of enteral nutrition in critically ill patients.

In addition to GALT tissue loss, undernourished children secrete less sIgA (206, 210, 211) or secrete IgA that binds and retains pathogenic bacteria capable of disrupting the intestinal barrier and causing weight loss when transplanted into mice (210). sIgA function is intimately linked to nutrition (101, 210). sIgA selectivity and specificity are shaped by interactions between the IgA molecule and bacterial surface glycans. These bacterial glycans are influenced by the host's diet and mediate differential bacterial retention or shedding based on binding specificity (101). Retention of beneficial bacteria has health benefits, such as enhanced barrier function (212) and shaping the overall microbiome ecosystem (71), while retaining pathogenic bacteria can lead to disease (210). Imbalances in the microbial community increase the risk of bacterial infections, which are exceedingly common in malnourished children (213). sIgA is therefore a critical mediator of intestinal microbial balance and, when disrupted, magnifies the adverse effects of under or malnutrition by promoting pathogenic colonization, reducing commensal colonization, and exacerbating weight loss and barrier defects concomitant with low nutrient states (101, 210).

Collectively, this suggests that nutrient status is linked to immune tolerance and the ability to mount appropriate immune responses indicating that undernutrition likely hampers immune function.

## Impact of undernutrition on the intestinal microbiome and host

The symbiotic relationship between IEC, barrier function, and the associated microbiome is intimately impacted by nutrition (214–218). Numerous studies over the last decade illustrate that undernutrition is linked to reduced microbial diversity and microbiome immaturity (111, 190, 210, 219–221) and that this “malnourished microbiome” is a major contributor to undernutrition phenotypes as these can be transferred to animal models with resulting impaired growth despite the provision of adequate calories (111, 210, 221). Undernutrition is also associated

with alterations in bacterial retention due to changes in bacteria glycans and IgA affinity, which can affect the intestinal barrier (101). In a 2014 study, microbiota maturity indices were used to measure postnatal microbiota development in humans from birth up to 24 months, giving rise to a means to classify malnutritional states (190). They used machine-learning approaches to identify a set of “age-discriminatory” taxa that defines “microbiota age.” The model was then verified in a second cohort of Bangladeshi children and a cohort of healthy children in Malawi, suggesting that it may be used universally as a reference for normal intestinal microbial ecology, and for comparison with a malnourished microbiome.

The microbiota of undernourished children is less efficient at energy extraction from dietary nutrients, resulting in changes in microbial metabolite production (222). Microbial metabolites are critical regulators of intestinal barrier function (223), therefore dysbiosis can exacerbate barrier leakiness and inflammation. Additionally, microbial metabolites alter the host epigenome, which can have long-term impacts on host health and physiology, suggesting a potential mechanism for the sustained adverse effects of undernutrition even after proper nutrients are provided (111, 222).

Loss of various dietary components, including protein and antioxidants, can severely impact microbiota composition and in turn barrier function. A meta-analysis across malnourished children at five geographic sites suggests that loss of dietary antioxidants, such as vitamins C and E and carotenoids, can alter the redox potential of the gut, causing dysbiosis (224). They observed a loss of specific anaerobic bacterial species, such as those from the Bacteroidetes or Eubacteriaceae families, and increases in aerotolerant bacteria like *Escherichia coli*, *Enterococcus faecalis*, and *Staphylococcus aureus*, which are considered common pathogens (224), indicating the importance of dietary antioxidants in maintaining intestinal bacterial diversity and reducing risk of enteric infection.

The ability to induce a sustained shift from an immature, malnourished microbiome to a healthier, more diverse set of bacteria is a major focus of current research (193, 225, 226). Simply increasing nutrient intake is insufficient to permanently shift the microbiome away from a malnourished state to a more healthy and diverse population that maximizes energy extraction and beneficial metabolite production. Recent work indicates that microbiota-directed food interventions for undernourished children may improve long-term health outcomes in undernutrition (225, 226). These interventions provide foods that not only offer adequate energy but also support a shift in bacterial taxa away from the malnourished microbiome. In an interventional study, Chen et al. (193) administered microbiota-directed complementary food prototype (MDCF-2) or the standard ready-to-use supplementary food (RUSF) to Bangladeshi children with moderate acute undernutrition for three months and monitored growth, plasma protein biomarkers, and fecal bacteria one month following the intervention. The results indicated that the MDCF-2 diet promoted growth and was linked to circulating proteins associated with bone growth and neurodevelopment, as well as a more substantial restoration of the intestinal microbiota, indicating

the importance of nutrients that mediate healthy shifts in the microbiome and not simply those that add calories (193). Although these findings need to be validated in more sites and at a later time post-treatment, they show promise for improved therapeutic diets for undernutrition. Maintaining this sustained shift to a mature and diverse gut microbiome is critical to preventing long-term negative consequences of undernutrition, such as neurodevelopmental delays and the development of obesity and metabolic disease later in life (218, 227).

Modulating the intestinal microbiome in undernutrition has the potential to improve intestinal barrier and immune function, as well as host energy extraction to improve long-term outcomes.

## Limitations of current models and future directions

To combat malnutrition successfully, particularly undernutrition, we need a more detailed understanding of the associated underlying intestinal pathophysiology and intestinal microbiome derangements. Presently, most non-interventional undernutrition studies are conducted in mice or rats using reduced or very low protein diets in isolation (7, 174, 176, 177, 228) or in combination with a germ-free background (229). While these models exhibit some similarities to human undernutrition, especially reduced growth, intestinal epithelial villus stunting, and reduced IEC proliferation, they do not always mimic the physiologic or morphologic changes (27). Additionally, the intestines of mice and rats are immature and permeable at birth (27, 230), whereas the human neonatal intestine is relatively mature and only selectively permeable, more similar to the intestines of young pigs (183, 231) or guinea pigs (232–235). Notably, most studies of GALT took place in murine models where development and composition are distinct from humans in several important ways. Murine ILF develop early in prenatal development (236) and consist almost entirely of B cells, whereas human ILF develop shortly before and after birth and contain proportionally more T cells (237–239). Therefore, modeling undernutrition in animal models should account for these intestinal differences, recognizing the caveats of using less mainstream species. Non-human primate models of undernutrition could address the shortcomings of more distantly-related models, with a potential for more relevant and detailed understanding of the impacts of the effects on the intestinal epithelium and microbiome, but cost is a factor in such research.

Human enteroid culture could circumvent many of these challenges and allow for testing therapies and delineating pathophysiological mechanisms within malnourished human tissue. Enteroids are a rapidly emerging model system for studying complex intestinal diseases and interactions (240), including necrotizing enterocolitis (241, 242), bacterial or viral infection (243–249) and fundamental IEC dynamics (250, 251). The ability to model undernutrition *ex vivo* using human tissue could accelerate progress in reducing and eliminating the devastating consequences of undernutrition.

Important unanswered questions include (1) how specific nutrients or dietary components such as vitamin D, substrates for the aryl hydrocarbon receptor, protein, carbohydrates, or even food-derived extracellular vesicles impact intestinal cell populations in the malnourished intestine; (2) how nutrients alter barrier function in the malnourished intestine; (3) the timing of physiological changes to the intestine in response to undernutrition; (4) what constitutes the composition of a healthy gut microbiota in well-fed individuals; and (5) which core gut microbes will lead to the most favorable health outcomes. To tackle these questions and more, we need improved models to study undernutrition, including those that incorporate the microbiome (252). Furthermore, we need to understand how maternal health and the microbiome prior to and during pregnancy shape the foundations of infant gut development and health, and how the dynamic interactions of the mother-child dyad influence the same through long-term longitudinal studies.

## Author contributions

The corresponding author had the responsibility for the decision to submit the manuscript. All authors assisted in manuscript preparation and all authors read and approved the final version of the manuscript.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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