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Impact of childhood malnutrition and intestinal microbiota on MDR infections

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The global burden of infection from MDR organisms (MDROs) disproportionately affects children residing in low- and middle-income countries and those with increased healthcare exposure. These populations have high rates of malnutrition making them increasingly vulnerable to infection with intestinal-derived pathogens. Malnourished children experience increased incidence of intestinal carriage and invasive infection with intestinal-derived MDROs including ESBL- and carbapenemase-producing Enterobacterales. However, the relationship between malnutrition and MDRO infection remains to be clearly defined. Impairment in intestinal barrier function and innate and adaptive immunity in malnutrition increases the risk for infection with intestinal-derived pathogens, and there is an increasing appreciation of the role of the intestinal microbiota in this process. Current evidence from human studies and animal models suggests that diet and the intestinal microbiota influence each other to determine nutritional status, with important implications for infectious outcomes. These insights are crucial to developing microbiota-targeted strategies aimed at reversing the growing burden of MDRO infections in malnourished populations worldwide.

Introduction

Bacterial antimicrobial resistance represents a pressing global concern, with an estimated 4.95 million deaths associated with antimicrobial-resistant bacteria annually.[1] The greatest burden of mortality exists in low- and middle-income countries (LMICs) in sub-Saharan Africa and South Asia, where intestinal-derived bacteria of the order Enterobacterales, including *Escherichia coli*, *Klebsiella pneumoniae* and *Salmonella* species, are among the most frequently reported antimicrobial-resistant organisms in children.[1–3] A large proportion of Enterobacterales infections are due to MDR organisms (MDROs), defined by the CDC as bacteria resistant to one or more drug classes, including ESBL-producing and carbapenem-resistant (CR) bacteria.[1,4] Although the trend in prevalence of MDRO infections in children in LMICs is not known, there is evidence of a growing burden in EU nations, with a 2.5-fold increase in attributable infection from MDROs in the prior decade.[5,6] In these EU nations, infections caused by ESBL *E. coli* are associated with the highest incidence of mortality, and ESBL and CR *K. pneumoniae* are also among the most frequently reported MDROs.[5]

Intestinal-derived MDROs including ESBL and CR Enterobacterales (ESBL-E and CRE) can colonize the intestinal tract as non-pathogenic members of the intestinal microbial community.[7] However, intestinal carriage risks invasive infections and is associated with transmission and spread.[8,9] Risk factors for MDRO carriage and infection include living in high endemicity areas, healthcare exposure and antibiotic administration.[10–12] Antibiotics promote MDRO carriage and infection through induction of de novo resistance and also through disruption of the colonization resistance provided by resident intestinal microbiota.[13] Nutritional status has an established influence on microbiota composition, and malnutrition is common in children in LMICs where MDRO infection rates are high.[14–16] Here, we summarize the available data on the impact of malnutrition in children on rates of MDRO infection and carriage. We will emphasize the role of the intestinal microbiota in the interaction between nutrition and the pathogenesis of intestinal-derived ESBL-E and CRE (Figure 1).

Global burden of malnutrition

The WHO defines malnutrition as a state of either deficiency or excess of nutrients, an imbalance in essential nutrients or an impaired ability to utilize nutrients. Malnutrition can be further divided into categories including micronutrient deficiency, referring to inadequate intake and/or absorption of critical vitamins and minerals; overnutrition, defined as a BMI that is elevated above the normal range; and undernutrition, encompassing the categories underweight, stunting and wasting (see Table 1).[17–19] The preponderance of literature devoted to infection and nutritional status in children is dedicated to undernutrition; thus this

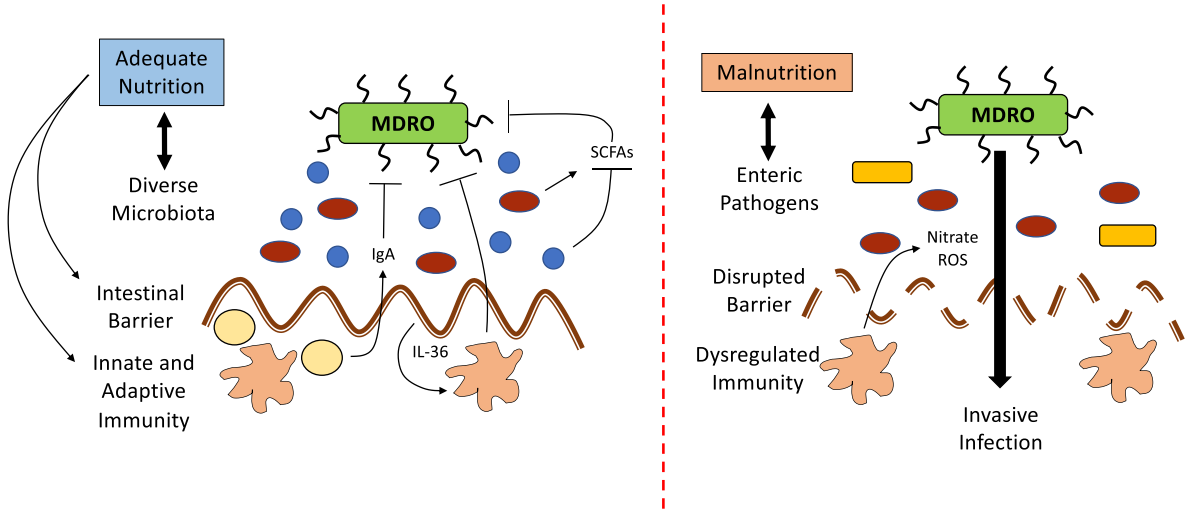

Figure 1. Nutrition and microbiota composition are co-dependent, with influences on intestinal barrier function and immunity. Adequate nutrition is associated with a strong intestinal barrier and IgA production as well as a diverse microbiota able to inhibit multidrug-resistant organism (MDRO) colonization through production of short-chain fatty acids (SCFAs) and through host defences such as IL-36-mediated macrophage stimulation. Malnutrition may coexist with enteric pathogen colonization and is associated with increased inflammation and nitrate and reactive oxygen species (ROS) production that promote MDRO carriage along with barrier dysfunction allowing for invasive infection.

review will focus on undernourished children, and the term malnutrition will be used synonymously with undernutrition, except where otherwise indicated.

The WHO-defined categories of undernutrition are based on anthropometric measurements and stratified by severity based on standard reference values.[17] Underweight is defined as low weight-for-age and may occur alongside wasting and/or stunting.[20,21] Stunting is defined as low height-for-age and is associated with chronic or recurrent nutritional deficiency. Wasting is defined as low weight-for-height and may be associated with either acute or chronic nutritional deficiency.[17] Severe acute malnutrition (SAM) is a clinically important condition referring to a state of severe wasting with a height-to-weight ratio 3 SDs from the reference. Children with SAM can further be defined as oedematous (previously called kwashiorkor) and non-oedematous (previously called marasmus).[22] Despite reductions in the prevalence of stunting in recent decades, 149 million children representing approximately 22% of the world population still meet this definition. In addition, 45 million children are afflicted with wasting. South Asia and sub-Saharan Africa account for the most undernourished children, including 54.3 million and 55.2 million of all stunted children, and 25 million and 10.2 million of all wasted children, respectively.[23]

Malnutrition and MDR infection

Malnutrition in immunity and childhood infection

Malnutrition is strongly associated with increased mortality, with a large proportion of deaths in malnourished children associated with or directly attributable to infection.[24,25] Children with malnutrition experience an increased incidence of a broad array of infectious syndromes including infectious diarrhoea, viral and bacterial pneumonia, tuberculosis, malaria and intestinal helminth infections.[26–29] This susceptibility to infection has traditionally been attributed to widespread dysregulation in host immune defences, a topic covered in several recent reviews.[30–32] Numerous studies have examined the impact of malnutrition on intestinal barrier function, with notable findings of reduced intestinal IgA production and increased permeability of the epithelium.[33,34] This is related in part to increased systemic inflammation during acute malnutrition as demonstrated by increased acute-phase reactants and dysregulated intestinal CD4 T-cell activity.[31,35]

Dysregulation of mucosal defences in the intestine during malnutrition can promote an environment permissive to diarrhoeagenic pathogens.[36] Prior studies of children in sub-Saharan Africa and South Asia have demonstrated an association between malnutrition and infectious diarrhoea with enteric pathogens including, but not limited to, enterotoxigenic *E. coli* (ETEC), *Shigella*, *Cryptosporidium* and *Entamoeba histolytica*.[37,38] Chronic T-cell-mediated inflammation and high enteric pathogen burden can drive environmental enteric dysfunction (EED), a condition characterized by intestinal epithelial dysfunction and malabsorption.[39] In EED, a vicious cycle is postulated in which malnutrition increases susceptibility to enteric pathogens resulting in chronic intestinal inflammation and exacerbated malnutrition. This process is thought to underlie the development of stunting, highlighting the bidirectional relationship between malnutrition and infection in resource-poor settings.[38–40] Whether similar processes also increase risk of MDRO carriage and intestinal-derived infection is poorly understood.

Several retrospective studies in malnourished children in Africa have revealed the high prevalence of bloodstream infections (BSIs) from bacteria associated with the intestinal tract and other mucosal sites. In two studies of hospitalized children in Kenya there was a two- to four-fold increased rate of bacterial BSI in individuals with severe malnutrition, with *Streptococcus*

Table 1. Definitions and epidemiology for important malnutrition terms and diagnoses[17–21,23]

Term	Description	Criteria	Epidemiology
Micronutrient deficiency	Deficiency in intake or absorption in one or more vitamins or minerals necessary for normal growth and development	Based on laboratory testing with individual levels below the normal range of various reference standards	Varies by specific micronutrient
Overnutrition	Excessive intake of calories relative to calories expended	Based on BMI: overweight >25 kg/m^2, obesity >30 kg/m^2	1.9 billion overweight or obese adults worldwide 379 million children overweight or obese worldwide
Undernutrition	Chronic or acute deficiency in intake or absorption of calories and/or protein or other macronutrients	**Underweight:** Weight-for-age below median: 76%–90% mild, 61%–75% moderate, ≤60% severe	663 million
		Stunting: Weight-for-age *z*-score below median: −1 to −2 mild, −2 to −3 moderate, <−3 severe	144 million children worldwide 2.6% in North America, 9% in Latin America and the Caribbean, 21.8% in Asia, 29.1% in Africa
		Wasting: Weight-for-height *z*-score below median: −1 to −2 mild, −2 to −3 moderate	38.3 million children worldwide 0.4% in North America, 1.3% in Latin America and the Caribbean, 6.4% in Africa, 9.1% in Asia
		Severe acute malnutrition (SAM): Acute wasting above with height-for-age *z*-score < −3 May be further classified with oedema (kwashiorkor) or without oedema (marasmus)	14.3 million children worldwide 10.5 million in Asia, 3.5 million in Africa

pneumoniae, non-typhoidal *Salmonella* species (NTS) and *E. coli* most enriched in these populations.[41,42] A study of hospitalized children from Ghana also found a two-fold increase in bacterial BSI in underweight and wasted (but not stunted) children, with NTS, *Staphylococcus aureus* and *S. pneumoniae* the most frequent isolates.[43] Studies looking at children presenting with malnutrition to hospitals in several African nations found that 17%–27% had positive blood cultures, with NTS, *S. aureus*, *S. pneumoniae*, *E. coli* and *K. pneumoniae* most frequently isolated.[44–46]

Antibiotic use and MDR infections in malnourished children

The high risk of intestinal-derived bacterial infection in malnourished children coupled with the concern for infection-related exacerbation of malnutrition form the basis of WHO guidelines recommending antibiotic treatment for SAM in childhood.[22] These guidelines were supported by two randomized controlled trials (RCTs), the first conducted in Malawi showing improved nutritional recovery in children treated with antibiotics versus placebo, with mortality reduced from 7.4% in the placebo arm to 5% in children treated with amoxicillin.[47] A subsequent RCT conducted in Niger found no improvement in nutritional status in children with SAM treated with 7 days of amoxicillin; however, there was a reduced need for inpatient care with treatment (7.5%) versus placebo (10.8%).[48]

Widespread antibiotic administration in malnourished children increases the risk for MDRO infection in this population. A follow-up to the Niger study regarding amoxicillin treatment for SAM found a two-fold increased rate of faecal carriage with ESBL-E following amoxicillin treatment compared with placebo, and an increased rate of ESBL-E in household contacts following amoxicillin treatment.[49] A separate study of 55 hospitalized children in Niger who received antibiotics as part of their treatment for SAM found an increase in ESBL-E carriage from 31% at time of admission to 94% at discharge.[50] These findings are particularly troubling in the setting of increasing rates of resistance to amoxicillin and other β-lactams among conventional intestinal pathogens such as *Salmonella* and diarrhoeagenic *E. coli* that are frequent contributors to malnutrition in these populations.[51,52]

There is growing evidence that malnourished children are at increased risk of MDRO infection independent of initiation of antimicrobial treatment, as demonstrated in a separate study from Niger in which 9.1% of children hospitalized for SAM had BSI on admission, the majority of these due to Enterobacterales, of which 61.5% of non-NTS isolates were ESBL.[53] Additional evidence of increased MDRO infection in malnourished children was seen in a case-control study of children admitted to a Senegal hospital in which two-fold increased odds of ESBL-E BSI was observed in patients with malnutrition, although the criteria for nutritional diagnosis were undefined.[54] Another study of children admitted for SAM in Tanzania found that 20% had Enterobacterales bacteriuria, of whom 37% had ESBL species.[55] Despite these findings concerning for significant rates of MDR bacterial carriage and infection in malnourished children, other studies have mixed findings, with high rates of co-trimoxazole

Table 2. Publications examining antimicrobial-resistant infections in malnourished children

Citation	Country	Population	Specimen site	Findings
Bachou *et al.* 2006[45]	Uganda	450 children admitted to acute hospital for SAM	Blood	BSI in 17.1%. Of Enterobacterales isolates, 90% resistant to ampicillin, 78% to co-trimoxazole, 7.3% to ceftriaxone
Okomo *et al.* 2011[44]	Gambia	140 children admitted for malnutrition	Blood	BSI in 10.7% on admission. 100% amoxicillin resistant, no ESBL-E detected
Nielsen *et al.* 2012[43]	Ghana	1196 children under 5 admitted to acute hospital for all causes	Blood	BSI in 19.9% with 2.0 increased odds in wasted versus non-wasted. 53.3% of isolates NTS, 15.5% other Enterobacterales. Of NTS isolates, 85% resistant to amoxicillin, 78% to co-trimoxazole
Page *et al.* 2013[46]	Niger	311 children admitted to ICU for SAM	Blood	BSI in 17%. Of *E. coli* and *K. pneumoniae* isolates 100% resistant to amoxicillin, 89% to co-trimoxazole, 6% to ceftriaxone
Ndir *et al.* 2016[54]	Senegal	1800 blood cultures drawn from children admitted for all causes	Blood	BSI in 9.1%, including 49% of isolates ESBL-E. Malnutrition present in 38.1% of patients with ESBL-E BSI versus 4.1% of patients with no BSI
Andersen *et al.* 2022[53]	Niger	2187 children admitted for SAM	Blood	BSI in 9.1% on admission and 1.2% with nosocomial BSI. Of 26 non-NTS Enterobacterales isolates, 61.5% ESBL-E
Woerther *et al.* 2011[50]	Niger	55 children admitted for SAM, all treated with antibiotics	Rectal swab	ESBL-E carriage 31% at admission. Non-carriers sampled at discharge had 94% conversion to ESBL-E carriage
Maataoui *et al.* 2020[49]	Niger	472 children admitted for SAM treated with amoxicillin versus placebo. 209 family members of ESBL-E carrying children	Rectal swab	ESBL-E carriage 57.2% in amoxicillin group versus 32.2% in placebo group. Family member carriage of matching ESBL-E strain 11.5% in amoxicillin group versus 3.8% in placebo group
Ahmed *et al.* 2015[55]	Tanzania	402 children under 5 years admitted for malnutrition	Urine	Enterobacterales bacteriuria in 20.9% including 37% of isolates ESBL-E

BSI, bloodstream infection; ESBL-E, extended-spectrum β-lactamase-producing Enterobacterales; NTS, non-typhoidal *Salmonella*; SAM, severe acute malnutrition.

and amoxicillin resistance ranging from 78% to 100% in Enterobacterales bloodstream isolates from malnourished African children but ESBL-E frequency below 10%.[43–46]

There is a paucity of studies examining the burden of MDR infections in malnourished children, and nearly all such studies have been conducted in sub-Saharan Africa (see Table 2). A recent study of mass administration of biannual azithromycin showed a mortality benefit in children under 5 years in several nations in sub-Saharan Africa at the expense of significantly increased rates of colonization with bacteria resistant to both macrolide and non-macrolide antibiotics in treated populations.[56,57] The results of this study suggest a future where a greater proportion of the world's malnourished children are likely to be exposed to antibiotics with some possible short-term benefits but unknown long-term consequences regarding the likely escalation in MDR infection prevalence.

Impact of nutrition on the microbiota

Composition and activity of microbiota during healthy and malnourished states

Diet has an important impact on the non-pathogenic members of the intestinal microbial community, as discussed in several reviews.[14,58,59] During adequate nutritional intake, the intestinal microbiota is dominated by several major phyla, with Firmicutes (including species of *Clostridium* and *Lactobacillus*) and Bacteroidetes (including species of *Bacteroides* and *Prevotella*) most abundant along with a smaller proportion of Actinobacteria (including species of *Bifidobacterium*) and Proteobacteria (including species of Enterobacterales).[60] Within these major groupings, certain bacterial taxa have a defined beneficial impact on the host, and these play an important role in nurturing the intestinal epithelium for optimal digestion, absorption of dietary nutrients and resilient barrier integrity. Other important functions of the intestinal microbiota include production of micronutrients including B vitamins, vitamin K and folate, assistance with metabolism of amino acids, and digestion of complex carbohydrates (typically from plant sources) into short-chain fatty acids (SCFAs) including butyrate, acetate and propionate. These SCFAs provide energy for colonic enterocytes and act as signalling molecules for various host cellular processes.[60]

Through regulation of nutrient absorption and metabolism, the intestinal microbiota influences the nutritional status of the host. Conversely, the composition of the microbiota itself is greatly affected by host nutrition and dietary intake. Studies have demonstrated that long-term dietary habits determine host microbiota composition, with high-fat and high-protein diets common in high-resource countries associated with an increased proportion of *Bacteroides* species in comparison with carbohydrate-rich diets, which are associated with a greater proportion of *Prevotella* species.[61,62] Whereas the intestinal

microbiota associated with an individual's dietary intake is generally stable, major dietary interventions such as alteration of macronutrient composition (for example, changing dietary fibre/fat ratio) or source (animal- versus plant-based) can greatly alter the host microbiota within days.[61,63] For instance, animal and human studies have shown that dietary fibre from plant sources can promote growth of *Bifidobacterium* and *Lactobacillus* species capable of producing SCFAs that promote healthy metabolism.[59,64] In contrast, mice on a high-fat diet demonstrate a reduction in SCFA-producing bacteria resulting in a chronic inflammatory state related to excess LPS from resident Gram-negative bacteria.[65]

Mouse studies have demonstrated that a protein-deficient diet leads to enrichment of Actinobacteria, Firmicutes and Proteobacteria, whereas fibre deficiency promotes bacteria that break down the mucus layer of the intestinal epithelium for carbohydrate utilization.[66,67] The Proteobacteria species *Biophila wadsworthia* was enriched in germ-free (GF) mice after faecal microbiota transfer (FMT) from a cohort of Bangladeshi children with oedematous SAM (kwashiorkor), and these mice exhibited a malnourished phenotype that improved with dietary supplementation.[68] Similarly, a consortium of duodenal bacterial taxa isolated from Bangladeshi children with biopsy-proven EED was introduced into GF mice leading to development of EED with evidence of enteric bacteria translocation to the bloodstream.[69] A separate study collecting IgA(+) bacteria from malnourished Malawian children identified a consortium enriched for Enterobacterales that recapitulated enteropathy and a septic phenotype in recipient GF mice.[70] These studies demonstrate that childhood malnutrition and EED are associated with changes in the microbiota with critical implications for clinical disease of the host.

The impact of nutrient intake on composition of the microbiota begins in utero, with breast milk providing oligosaccharides after birth that support early intestinal colonization with *Bifidobacterium longum* ssp. *infantis*.[71] *Bifidobacterium infantis* is known to reduce inflammation and promote healthy digestion and growth, and was found to be depleted in children with SAM as well as children who have been formula fed, in whom *Bacteroides* species instead predominate.[72,73] Childhood malnutrition often presents after weaning from breast milk and is associated with changes in the microbiota. Separate studies of children with SAM from rural Gambia and of malnourished children from Bangladesh found that there was a significant reduction in the interindividual diversity in the faecal microbiota in comparison with nourished children. In particular, Enterobacterales were enriched in both these populations in the setting of undernutrition.[74,75] Another study of stunted children from Madagascar and the Central African Republic found an enrichment of oral taxa including *Streptococcus* species and pathogenic Enterobacterales including *E. coli*, and a reduction in butyrate-producing *Clostridium* species.[76] Similarly, a study of a small cohort of Indian children found that *Streptococcus* and genera of Proteobacteria including *Escherichia*, *Shigella* and *Enterobacter* were enriched in malnourished children. In comparison, nourished children in this cohort had a greater proportion of Firmicutes genera beneficial for digestion and metabolism including *Roseburia* and *Butyrivibrio*.[77]

Interaction between microbiota and intestinal pathogens

The intestinal microbiota is known to play an important role in a wide variety of non-communicable diseases through regulation of metabolism, immune development and neural signalling; however, its role in infection is arguably underappreciated. Colonization resistance is a property of the intestinal microbial community that restricts growth of enteric pathogens including Enterobacterales, *Clostridioides difficile* and *Enterococcus*.[78] It is accomplished through numerous mechanisms including nutrient and niche competition, stimulation of host innate and adaptive immune responses, and direct killing via antimicrobial peptides or type VI secretion systems, as described in prior reviews.[79,80] Colonization resistance was initially demonstrated over decades of research in GF and antibiotic-treated rodent models demonstrating increased susceptibility to infection with Enterobacterales species including *Salmonella*, *Shigella* and *E. coli*.[81–83] The clinical importance of colonization resistance is suggested by the rapid expansion of intestinal MDRO populations after antibiotic administration.[9,84] Although these MDROs may exist as benign intestinal colonizers at low levels, increased intestinal burden has been observed to precede BSI with colonizing strains of ESBL and CR *K. pneumoniae* in haematopoietic stem cell recipients and patients in ICUs.[8,9]

The role of SCFAs in Enterobacterales colonization resistance

The mechanistic basis of colonization resistance against Enterobacterales has been investigated in mice infected with experimental invasive pathogens such as *Citrobacter rodentium*, which models enteropathogenic *E. coli* infection in humans. *C. rodentium* was found to induce inflammation and consequential alteration of the intestinal microbiota composition with enrichment of Enterobacterales species in infected mice.[85] A separate study found that the indigenous microbiota member *Bacteroides thetaiotamicron* was particularly important in resisting *C. rodentium* via competition for plant fibre-derived monosaccharides.[86] Interestingly, infected mice on a low-fibre, high-fat diet had reduced intestinal burden of *C. rodentium* but greater persistence over the time.[87] In contrast, mice on a low-fibre diet infected with *C. rodentium* experienced reduced SCFA production along with microbiota-mediated breakdown of the mucosa for carbohydrate acquisition resulting in increased infection burden and lethal colitis.[66,88]

The role of SCFAs in opposing Enterobacterales infection was confirmed in a study showing that acetate produced by *Bifidobacterium* species was able to restrict intestinal growth of the model ETEC strain O157:H7 in mice via enhanced epithelial defences.[89,90] Under homeostatic conditions the microbiota-produced SCFA butyrate was also found to restrict the pathogenesis of *Salmonella enterica* serovar Typhimurium and *E. coli* in mice through down-regulation of nitrate production.[91] In contrast, separate studies showed that under inflammatory conditions *E. coli* and *S.* Typhimurium were able to utilize excess nitrate and reactive oxygen species, respectively, for respiration in order to outcompete other members of the microbiota.[92,93] Collectively these studies suggest that an inflammatory environment supports the

growth of pathogenic Enterobacterales, and this is opposed by microbiota through production of SCFAs.

A recent study confirmed the significance of SCFAs in mediating colonization resistance to MDR-E, demonstrating that butyrate production by Clostridiales in cooperation with *Lactobacillus* restricted MDR-E including *K. pneumoniae* in mice and in patients with acute leukaemia.[94] A separate study found that SCFAs mediated intestinal clearance of MDR *K. pneumoniae*, *E. coli* and *Proteus mirabilis* through intracellular acidification and neutralization of respiration utilizing reactive oxygen species and nitrate.[95] In contrast, a separate study found that unchecked inflammation in the setting of experimental colitis supported higher intestinal burdens of *K. pneumoniae* in mice treated with dextran sodium sulphate.[96] Another study found that intestinal Bacteroidetes inhibit intestinal colonization and transmission of *K. pneumoniae* in mice via stimulation of IL-36 production and macrophage stimulation.[97] Thus, the microbiota is critical in determining if there is an appropriate immune response able to clear intestinal pathogens or an aberrant inflammatory response that promotes MDR-E carriage and infection (see Figure 1).

Dietary and microbiota-targeted interventions for MDRO colonization

The importance of colonization resistance in preventing serious infection and disease in humans is best illustrated by the successful use of FMT for treatment of patients with *C. difficile*.[98] Besides *C. difficile* there are no widely agreed indications for FMT as treatment for infection; however, there have been several studies investigating use of FMT in intestinal decolonization of MDROs. A number of single-centre prospective and retrospective studies have been performed describing FMT for decolonization of MDROs including CRE and ESBL-E in adult patients, with wide variability of efficacy ranging from 53% to 80%.[99–101] However, there is just one published RCT utilizing FMT for ESBL-E and CRE decolonization, which reported 41% decolonization of patients in the treatment arm (5 days of antibiotics followed by FMT), which was not significantly greater than patients treated with placebo (29%).[102] Of note, two subsequent single-arm cohort studies found that increased microbiota diversity both before and after FMT was associated with improved rate of decolonization of CRE and vancomycin-resistant *Enterococcus*, suggesting that antibiotic treatment during the prior RCT may have hindered efficacy.[103,104] Collectively, these studies demonstrate that microbiota-targeted interventions may have promise in MDRO decolonization. However, future interventions should incorporate the precise role of specific microbiota members in eliminating these potential pathogens.

Animal studies have demonstrated some success in using probiotic therapies consisting of one or several strains of indigenous intestinal bacteria for treatment of enteric infection. But no commercial probiotic therapy has been approved for use in human infection, and recent studies even suggest commercial probiotics may negatively impact the recovery of a healthy microbiota after antibiotic administration.[105,106] However, a recent RCT demonstrated strong efficacy of an oral therapy consisting of a select consortium of indigenous intestinal bacteria for treatment of *C. difficile* infection in adults, raising the hope for microbiota-based therapeutics that could be more easily administered than FMT for elimination of MDRO carriage in children.[107] In the short term, the availability of such treatments is unlikely to match the increasing global burden of MDR infection, particularly in under-resourced settings.

In consideration of the frequent concurrence of malnutrition and MDR infection in children, dietary therapies may be a low-cost alternative for generation of a microbiota with optimal colonization resistance. Dietary interventions have proven effective in altering the microbiota of malnourished children and healthy adults in clinical trials.[108,109] The impact of diet on antimicrobial resistance in intestinal microbiota was revealed in a study of healthy US adults in which individuals with higher protein and reduced fibre intake had a greater density of microbiome antimicrobial resistance genes (ARGs) corresponding with reduced diversity and a greater proportion of Enterobacterales and *Streptococcus*. In contrast a higher fibre diet was associated with a reduced density of ARGs and a greater proportion of obligate anaerobes, particularly species of the family Clostridiaceae.[110] The potential for diet to shape the antimicrobial resistance profile of the intestinal microbial community was supported by a trial of a dietary intervention in obese Chinese children aimed at shifting the microbiota from protein to carbohydrate metabolism. This diet, enriched in whole grains with high fibre content, resulted in improved metabolic activity and weight loss in these children, but additionally was found to impact the microbiome with significant reduction in ARGs associated with Enterobacterales taxa including *Escherichia*, *Klebsiella* and *Enterobacter*.[111,112] Although the significance of ARG density alteration on MDRO carriage and/or infection is unknown, this study provides proof of concept that dietary intervention may be a viable strategy for addressing MDR infections in malnourished children.

Conclusions

Infection with intestinal-derived MDROs is associated with millions of deaths annually and disproportionately affects malnourished children in LMICs.[1,3] The deleterious impact of malnutrition on immunity and intestinal barrier function has been well described, and the important role of the intestinal microbiota in this context is beginning to be unravelled. More studies are needed to better understand the relationship between malnutrition and MDR infection given the frequent concurrence of these conditions. Additional prospective studies are needed to evaluate community and hospital prevalence of MDR infections in malnourished children in both LMICs and developed nations. The studies should also evaluate how interventions such as dietary change and antibiotic use impact MDR infection rates in malnourished children. Additional animal studies will also be useful in defining which dietary components have the greatest impact on MDRO carriage and infection and how the microbiota is implicated in this process. Future studies will ultimately inform the next generation of therapeutics including dietary supplements and defined consortia of microbiota aimed at reducing MDR infections. Such novel approaches will be needed to combat the ever-growing burden of antimicrobial resistance in the most vulnerable global populations.

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