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REVIEW

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Gut Microbiota Modulation and Prevention of Dysbiosis as an Alternative Approach to Antimicrobial Resistance: A Narrative Review

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Background: The importance of gut microbiota in human health is being increasingly studied. Imbalances in gut microbiota have been associated with infection, inflammation, and obesity. Antibiotic use is the most common and significant cause of major alterations in the composition and function of the gut microbiota and can result in colonization with multidrug-resistant bacteria. **Methods**: The purpose of this review is to present existing evidence on how microbiota modulation and prevention of gut dysbiosis can serve as tools to combat antimicrobial resistance. **Results**: While the spread of antibiotic-resistant pathogens requires antibiotics with novel mechanisms of action, the number of newly discovered antimicrobial classes remains very low. For this reason, the application of alternative modalities to combat antimicrobial resistance is necessary. Diet, probiotics/prebiotics, selective oropharyngeal or digestive decontamination, and especially fecal microbiota transplantation (FMT) are under investigation with FMT being the most studied. But, as prevention is better than cure, the implementation of antimicrobial stewardship programs and strict infection control measures along with newly developed chelating agents could also play a crucial role in decreasing colonization with multidrug resistant organisms. **Conclusion**: New alternative tools to fight antimicrobial resistance via gut microbiota modulation, seem to be effective and should remain the focus of further research and development.

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Abbreviations: FMT, Fecal Microbiota Transplantation; MDRO, Multidrug-Resistant Organism; GIT, Gastrointestinal Tract; ICU, Intensive Care Unit; IL-17, Interleukin-17; INF-γ, Interferon-γ; AAD, Antibiotic-Associated Diarrhea; CDI, *Clostridium difficile* Infection; ESBL, Extended-Spectrum Beta-Lactamase; CRE, Carbapenem-Resistant Enterobacteriaceae; VRE, Vancomycin-Resistant Enterococci; MRSA, Methicillin-Resistant *Staphylococcus aureus*; HMO, Human Milk Oligosaccharide; RCDI, Recurrent *Clostridium difficile* Infection; SCFAs, Short-Chain Fatty Acids; AR, Antibiotic Resistance; RCT, Randomized Clinical Trial; HSCT, Hematopoietic Stem Cell Transplantation; SDD, Selective Digestive Decontamination; SOD, Selective Oropharyngeal Decontamination; IAP, Intestinal Alkaline Phosphatase; ASP, Antimicrobial Stewardship Program; eLBP, engineered Live Biotherapeutic Product.

Keywords: Microbiome, resistome, gut microbiota, antimicrobial resistance, fecal bacteriotherapy, fecal microbiota transplantation, antimicrobial stewardship, dysbiosis, multidrug-resistant organisms, prebiotics, probiotics, beta-lactamases, charcoal agent

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INTRODUCTION

Humans are colonized with a very large number of microorganisms (bacteria, archaea, viruses, and unicellular eukaryotes) immediately after birth. These commensal and symbiotic microorganisms, which were formerly believed to outnumber human cells 10-fold, but now their ratio is estimated closer to 1:1, comprise the host microbiota. [1,2]. The term microbiota was first described by Joshua Lederberg referring to the community of all microorganisms residing in the human body and their collective genome [3]. The majority of colonizing bacteria are found in the gastrointestinal tract (GIT), with approximately two-thirds of all microorganisms, residing in the colon [4]. The gut microbiota includes several hundred to more than 1,000 species [5]. The predominant organisms are anaerobes, followed by facultative anaerobes and aerobic bacteria and predominant phyla are Firmicutes and Bacteroidetes, followed by Proteobacteria, Fusobacteria, Cyanobacteria, Verrucomicrobia, and Actinobacteria [6].

It is known that the microbial populations residing in the GIT change throughout life in terms of both content and function [7,8]. Each individual has a unique GIT microbiota at genus and species level, influenced by host genetics, ethnicity, diet, early microbial exposure, environmental conditions, lifestyle, and immune and overall health status. However, the composition of the human microbiota is fairly stable at the phylum level. The major phyla that dominate the human intestine are conserved between all individuals, although the proportions of these groups can vary [9]. Other factors that likely physiologically contribute to microbiota variations between individuals include type of delivery, feeding pattern, diet and age-related changes in the GIT, namely low-grade inflammation [10]. Although the microbiota composition differs between individuals, certain functions encoded in the gut microbiota (core microbiota) are shared between individuals [11]. Some of these functions that are most important to the host are digestion of polysaccharides, vitamin production, lipid metabolism, regulation of the host immune response, and protection against pathogenic organisms [12].

Alterations in the composition of gut microbiota, known as dysbiosis, can be induced by several exogenous factors, with antimicrobial use probably being the most important one. Dysbiosis can promote disease, impair immune responses, but also facilitate colonization resistance imbalance and a shift to predominance of resistant pathogens [13]. The problem of increasing antimicrobial resistance worldwide is an imminent public health threat. The discovery pace of new antimicrobials cannot catch up with the development and spread of novel resistance mechanisms. Hence, there is need for novel effective preventive or therapeutic approaches, at individual or population level, against these difficult to eradicate resistant pathogens.

The purpose of this review is to describe how antimicrobial use affects the human microbiota towards the development of antimicrobial resistance and to present existing evidence on the role microbiota modulation strategies in reducing antimicrobial resistance potential.

METHODS/DATA SEARCH

Literature search included articles published in English, until April 2022, belonging to journals indexed in PubMed. We also searched the reference lists of the initial papers for further relevant articles.

THE IMPORTANCE OF MICROBIOTA IN HEALTH AND DISEASE

The importance of microbiota in human health is being increasingly recognized. The role of gut microbiota in several diseases has been well studied (inflammatory bowel disease, obesity, diabetes mellitus, irritable bowel syndrome, colorectal cancer) and its association with many others is currently being investigated [6,14]. Gut microbiota plays a fundamental role in the development of both local and systemic immunity. Specifically, it provides its host with a physical barrier to invading pathogens by competitive exclusion, and production of antimicrobial products and it also stimulates the host to produce various antimicrobial compounds [12,15-17]. Some of its other beneficial functions include digestion of plant polysaccharides and host glycans in the colon, production of essential vitamins, functional and structural maturation of the GIT and development of the intestinal surface area and microvasculature [18]. Moreover, a healthy gut microbiota influences the gut-brain axis and shapes stress related symptoms such as anxiety and pain [19] and is also implicated in appetite control [20].

Gastrointestinal microbiota contribute in the regulation of gut homeostasis by maintaining epithelial barrier integrity, stimulating angiogenesis, inducing T regulatory cells, and by their anti-inflammatory and immunostimulatory properties [21]. Gut barrier function is also regulated by the brush border enzyme, intestinal alkaline phosphatase (IAP), whose absence has been associated in the pathophysiology of certain diseases such as inflammatory bowel disease, necrotizing enterocolitis, metabolic syndrome, and type 2 diabetes mellitus [22,23].

A quantitative, qualitative, metabolic, or locational imbalance of gut commensals, called dysbiosis [24], may be associated with diseases like dental plaque, bacterial vaginosis, psoriasis, atopic dermatitis, asthma, inflammatory bowel disease, diabetes, obesity, colon cancer, and recurrent *Clostridium difficile* infection (RCDI) [25].

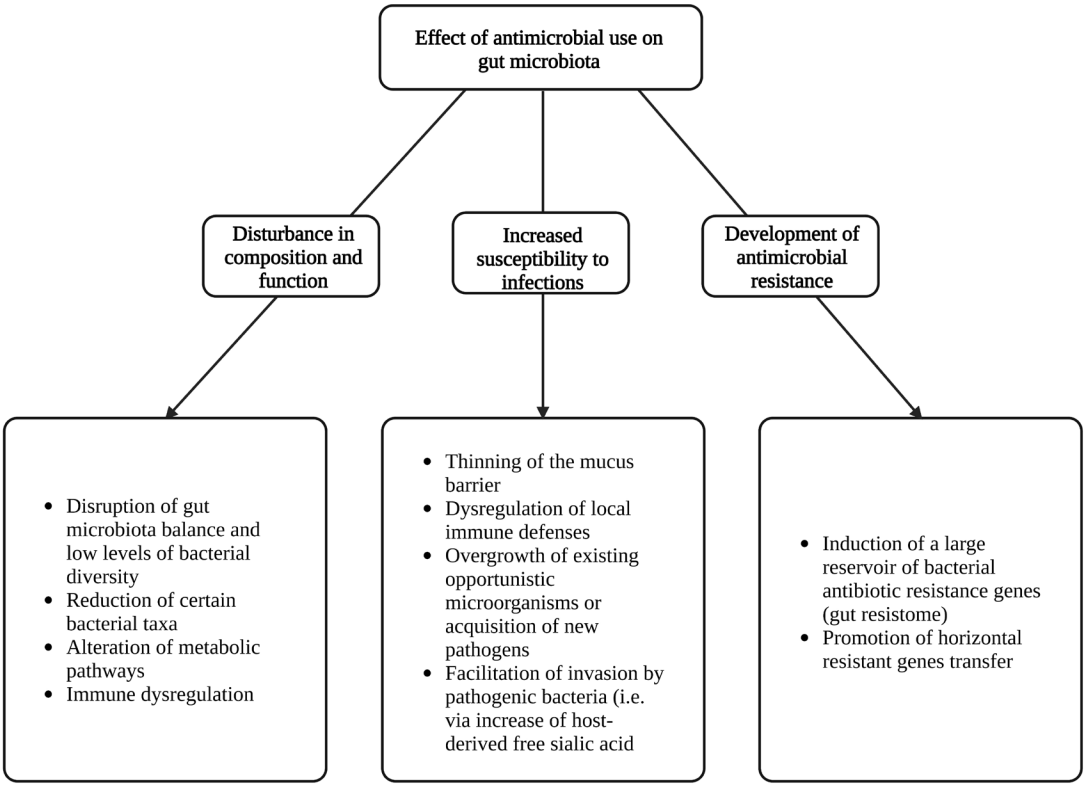

Figure 1. **Effect of antimicrobial use on gut microbiota**.

Critical illness has also been associated with the loss of normal, "health promoting" bacteria [26].

EFFECT OF ANTIMICROBIAL USE ON THE MICROBIOTA AND RESISTOME

Disturbance in Composition and Function

Many factors can harm the beneficial GIT microbiota, including antibiotic use, psychological and physical stress, radiation, altered GIT peristalsis, gastrointestinal infections, and dietary changes [27]. Antibiotic use is the most common and significant cause of major alterations in the composition and function of the normal gut microbiota [28] (Figure 1). Antibiotics cause serious alterations in gut microbiota which result in low levels of bacterial diversity, and expansions of the presence of certain taxa [29]. The potential for an antimicrobial agent to influence gut microbiota is related to its spectrum of activity, mode of action, potency, pharmacokinetics, dosage and length of administration [30], but is also associated with the existing microbiota of the host and the presence of antimicrobial resistance genes in this community [31].

Altered diversity of gut bacteria can lead to irritable bowel syndrome or infections by gut pathogens such as *C. difficile*, inherently resistant to many antimicrobials [32]. Additional unintended consequences of antibiotic use on gut microbiota include the selection for a reservoir of bacterial antibiotic resistance (AR) genes, promotion of horizontal gene transfer between bacterial strains, increased populations of enteric bacteria through altered carbohydrate composition, depletion of vitamin-producing bacteria, changes in metabolic activities that contribute to nutrition and immune dysregulation [29].

Increased Susceptibility to Infections

Besides alteration of microbiota composition, antibiotics also interfere with local gut immune defenses [33]. For example, decreased IL-17 and INF-γ production, was observed in the small intestine and decreased numbers of Treg cells in the colon post antimicrobials [34]. Hence, dysbiosis is likely an effect not only of the bactericidal properties of antibiotics, but also of the altered host-microbiota interactions [35]. Additionally, the gut microbiota induces mucin production, while antibiotics result in thinning of the mucus barrier thereby increasing susceptibility to bacterial invasion [36]. Alterations of the bacterial populations, which normally colonize the gut lumen, may result in intestinal infections either from

newly acquired pathogens or from the overgrowth and pathogenic potential of opportunistic microorganisms.

It is of interest that antibiotic exposure, by altering the gut microbiota and by changing the balance between species, as well as their interactions, can lead to an increase in host-derived free sialic acid, which may result in easier invasion by pathogens such as *Salmonella typhymorium* [9,37]. Several studies have been performed in infants treated with antibiotics, especially preterm ones. Treatment with various antibiotics such as cephalexin, gentamicin, vancomycin, and erythromycin altered the normal bacterial microbiota of infants increasing the percentage of potentially pathogenic Enterobacteriaceae and lowering the amount of bacteria like Bifidobacteriaceae, Bacilli, and Lactobacillus which are part of the healthy microbiota [38].

Development of Antimicrobial Resistance

Abuse of antibiotics has led to the development of multidrug resistant organisms (MDROs). Infections with MDROs are a major cause of morbidity and mortality worldwide [39].

Microbes can develop defensive mechanisms and employ resistance mechanisms against the agents used for their elimination. The human gut microbiota harbors a large reservoir of resistance genes, named as the gut resistome. Using metagenomic sequencing, Forslund et al. were able to detect resistance genes for 50 of 68 classes of antibiotics in 252 fecal metagenomes from individuals from different continents with an average of 21 AR genes per sample [40]. Additionally, Hu et al., again in an international cohort of 162 persons, identified a total of 1093 AR genes [41].

The gut resistance reservoir encompasses naturally occurring bacteria, bacteria with acquired resistance genes and acquired bacteria, harboring resistance genes, which do not normally colonize the gut [42,43]. The latter may survive and dominate in the gut microbiota for a long period of time. Transfer of resistance genes or virulence traits between non-pathogenic and pathogenic isolates is possible although not common. One example is the vanB-type vancomycin resistance transposon, which is commonly carried by anaerobic gut commensals of the phylum Firmicutes [44], and can be transferred to *Enterococcus faecium,* rendering it resistant to vancomycin [45]. As it has been shown from experimental studies but also in human cohorts, decreased gut microbiota variability can decrease colonization resistance and facilitate colonization of pathogenic and MDROs [33,46].

Gut Microbiota Modulation as a Tool Against Antimicrobial Resistance

While the spread of antibiotic-resistant pathogens requires antibiotics with novel mechanisms of action, the number of new antimicrobials approved for therapy remains very low [39]. For this reason, an intriguing alternative modality to combat antimicrobial resistance could be the modulation of the gut microbiota. We describe the most important interventions that have been employed for targeted as well as non-specific microbiota modulation (Table 1).

Diet and Dietary Supplements

Dietary composition affects the makeup and genetic diversity of gut microbiota. The role of individual dietary components, predominantly the ratio and type of protein, carbohydrates, and fat intake in gut microbiota variation is increasingly being studied [47]. It was shown that the feces of omnivores contained more species of the Clostridial clusters IV and XIVa, bacteria which are able to convert fiber to short chain fatty acids (SCFAs), compared with those of vegetarians and lactovegetarians [48,49]. SCFAs can regulate the expression of virulence genes of *Salmonella* spp. or *E. coli in vitro* [50]. Moreover, in a study where mice were fed a "Western" high-fat/simple carbohydrate or a low-fat/complex plant polysaccharide diet, the former had less bacterial diversity, a lower proportion of Bacteroidetes and an increased proportion of Firmicutes compared to the group which received a low-fat diet [51].

We know that limited bacterial diversity is considered an "unhealthy" microbiota [52], which is a risk factor for decreased colonization resistance. Elderly individuals who resided in long-term facilities and had limited variety in their diet, also had decreased gut bacterial diversity, compared to their counterparts that resided in the community; this was associated with worse health status [53]. In another experimental model, a high-protein diet disrupted gut microbiota, suggesting that avoiding a high-protein diet could help preserve colonization resistance [54]. On the other hand, a diet high in fibers was associated with a quicker restoration of the gut microbiota after antibiotic exposure when compared to a high-protein diet [55]. There are also reports of specific substances such as konjac glucomannan (glucomannan derived from *Amorphophallus konjac*, a plant with edible tubers) with protective effects on the gut microbiota [56], and reports of Chinese dietary remedies that have a beneficial result on the gut restoration [57,58]. Other studies found that chemically created human milk oligosaccharides (HMOs), if given as a dietary supplement, could restore human gut microbiota by promoting the development of beneficial commensal bacteria (bifidobacteria) [59,60]. In addition, oral supplementation of IAP has been linked with the maintenance or even restoration of normal gut microbiota after its disruption [61]. In two experimental

Table 1. Gut Microbiota Modulation as a Tool Against Antimicrobial Resistance

Intervention	Mechanism of action	Advantages	Disadvantages	References
Diet and dietary supplements	-Wide variety, low fat and plant polysaccharide diet, low protein or high in fiber diets preserve the bacterial diversity of the gut microbiome and the colonization resistance. -Addition to the diet of substances such as konjac glucomannan, HMOs or some Chinese remedies protect the gut microbiome and promote its restoration. -Oral administration of IAP which maintains or even restores gut microbiota.	-Simple to apply. -Accessible to everyone. -Naturally derived components so fewer side effects.	-Lack of evidence in humans.	[53-57,59-61]
Prebiotics and probiotics	-Prebiotics stimulate, while probiotics serve as, lactobacilli or bifidobacterial that reduce the growth or interfere with the survival of pathogenic microorganisms in the gut. -Targeted eradication of pathogens by newly developed engineered probiotics.	-Easily accessible and administered.	-Difficult to find the most suitable probiotic for each dysbiosis condition. -Data mainly on ICU patients. -Conflicting results in protecting gut microbiota from MDROs, especially gram(-) pathogens. -Reports of bacteremias in ICU patients.	[65,66,71,73]
Fecal Microbiota Transplantation (FMT)	-Infusion of donor feces into patient's gut (administered mainly orally) in order to repopulate it with a healthy and balanced microbiota as a weapon against *C. difficile* infections (especially recurrent), as a "barrier" to colonization by multi-drug resistant bacteria, and as a method of reducing the load of antibiotic resistance genes. -Enhancing host responses.	-Successful against difficult-to-treat situations. -High rates of effectiveness.	-Lack of large randomized clinical trials. -Incidents of serious adverse events.	[9,88-90,92,93,95-97,103,108,111-113]
Antimicrobial compounds	-Use of bacteriocins to inhibit the growth of pathogenic bacteria and preservation of gut microbiota.	-Targeted therapy. -Avoidance of using broad-spectrum antibiotics.	-Lack of scientific data. -No available clinical trials.	[119]
Selective Digestive Decontamination (SDD) and Selective Oropharyngeal Decontamination (SOD)	-Prophylactic use of antibiotics to reduce the gut colonization with MDROs.	-Successful into wards with low rates of resistant bacteria.	-Lack of data in centers with high rates of resistance. -Need for rigorous surveillance of patients.	[122-124,124,126,127]

HMOs: human milk oligosaccharides, IAP: intestinal alkaline phosphatase, ICU: intensive care unit, MDRO: multi-drug resistant organism

mouse models, oral supplementation of IAP was effective in preventing infections from *Salmonella enterica* (serovar Typhimurium), *C. difficile*, and possibly other pathogens, by restoring commensal gut microbiota [62]. An ongoing cross-sectional study, named the Wisconsin microbiota study, will provide us with fruitful information about the relation between diet, gut microbiota, and MDROs [63]. Although, relevant studies in humans are still lacking, modulation of diet in order to increase bacterial diversity could serve as an adjuvant strategy in order to decrease antimicrobial resistance.

Prebiotics and Probiotics

Prebiotics are defined as "selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the GI microbiota that confer benefits upon host well-being and health" [64]. Prebiotics are considered to stimulate lactobacilli or bifidobacteria growth and have been associated with beneficial effects in human metabolism through modulation of the gut microbiota [65,66]. In a murine study, diet supplementation with SCFAs or fructooligosaccharides caused a shift in microbiota composition [67]. Similarly, fructooligosaccharides were found to result in a reinstitution of the gut microbiota [68], while other inulin-type probiotics were found to inhibit the disruption of gut microbiota by preserving the commensal bacteria [69].

Probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host" as defined by the World Health Organization [70]. The most commonly used probiotics are strains from the genera Lactobacillus and Bifidobacterium. According to Rijkers et al., probiotics exert their beneficial role in three ways, namely by interfering with the growth or survival of pathogenic microorganisms in the gut lumen, by improving mucosal barrier function or mucosal immune system and by having an effect on the systemic immune system and other organs [71]. *Lactobacillus plantarum* and *L. acidophilus* were shown to reduce enteric counts of multidrug resistant enteroaggregative *E. coli* in an experimental murine study [72]. However, because of the great interindividual variability of gut microbiota, and the different mechanisms with which dysbiosis promotes disease, more research is needed to determine the most suitable probiotic for each dysbiosis-related condition.

More recently, engineered probiotics have been employed for targeted *P. aeruginosa* eradication in two studies. These probiotics are programmed to detect quorum sensing molecules and upon detection of the pathogen, they express antimicrobial compounds or activate other previously engineered mechanisms in order to eradicate their target [73]. Apart from probiotics, phages have also been the focus of genetic engineering to enable targeted killing of bacteria with AR or specific virulence traits [74]. Although there are many systematic reviews with a recent umbrella review focusing on the role of probiotics on reducing infections among critically ill patients, there are no large studies examining the effect of probiotics on colonization resistance [75]. There are many studies showing their effectiveness on gram-positive bacteria, such as MRSA or VRE [76-78], while the outcome in gram-negative pathogens is disappointing [79,80].

The current need for the development of future probiotics is to determine which bacteria could enhance colonization resistance, as well as to design a more customized probiotic administration [81]. Finally, as there are reports of clinically significant bacteremias with bacterial strains contained in probiotic supplements in ICU patients, it is advisable to use them with caution in this population [82,83], and always in the context of a clinical trial.

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT), the transplantation of stool from a healthy donor into the GIT of a patient, was first used 1,700 years ago, in China, to treat food poisoning and severe persistent diarrhea [84]. The first case of application of this method in the treatment of pseudomembranous colitis was described by Eiseman in 1958 [85]. In recent years, and most importantly after the epidemic of the hypervirulent BI/NAP1/027 strain in North America, donor feces infusion is used for the treatment of RCDI, showing excellent results with high cure rate, up to 90%, and minimal adverse effects [86,87].

FMT has shown important clinical success in eliminating *C. difficile*, in decreasing *C. difficile* relapses and in resolving *C. difficile* infection (CDI) associated symptoms. Patients suffering from RCDI have decreased diversity of bacterial species and reduced number of Bacteroidetes and Firmicutes phyla in their feces compared with patients experiencing the first episode of CDI or antibiotic-associated diarrhea (AAD) [88]. The rationale of using FMT is to repopulate the colon with a healthy and balanced microbiota, characterized by wide diversity and to displace harmful bacteria, which colonize the gut [89].

It is believed that the transplanted microbiota may hinder colonization by pathogenic bacteria through changes in the luminal microenvironment and antagonism for nutrients and binding sites. Also, pathogenic bacteria can detect microbiota derived signals or host derived signals that have been modified by the microbiota, which alter their virulence or colonization potential [9]. Such mechanisms may also come into play for the inhibition of colonization by multi-drug resistant pathogens, although strong data to support such an argument is still lacking.

Also, there is evidence that changes in gut microbial metabolites may enhance host responses. Enrichment in secondary bile acids after FMT is associated with al-

terations in regulatory T cells [90]. FMT has also been associated with restoration of IgA mediated interactions, and T cell populations, even reversing a CDI-related immunosenescent phenotype [91]. Murine models also suggest a beneficial immune response associated with FMT [92,93]. In one study, ceftriaxone-induced dysbiosis leading to intestinal membrane compromise and increased inflammatory cytokine release, was restored and cytokines decreased, three weeks post-FMT [94]. Similarly, FMT reversed intestinal lymphocyte and dendritic cell depletion induced by broad spectrum antibiotic use in an experimental model [95].

Considering the favorable outcome in *C. difficile* infection and relapse other applications of FMT were explored, especially in diseases where dysbiosis is thought to play an important role [96]. Moreover, researchers observed that persons who underwent FMT for RCDI also had more favorable outcome regarding gut decolonization from resistant pathogens [96]. In a case report by Crum-Cianflone et al., a critically ill patient received FMT to treat *C. difficile* colitis. After FMT the investigators observed that except for the resolution of symptoms related to CDI, the patient was also decolonized from MDROs and had reduced episodes of sepsis, health care associated infections. and antibiotic use [97]. The rationale for using FMT to eradicate MDROs is that especially for gram-negative pathogens, the gut is their main reservoir and thus elimination from the GIT may lessen the risk for systemic infection due to bacterial translocation and may eradicate them from other body sites [97]. Evidence on the role of FMT for MDRO decolonization or treatment is increasing [98-106]. However, findings are often contradictory and due to the lack of large randomized trials (RCTs), assessment of long-term effectiveness is limited.

Recent studies have revealed that the normalization of gut microbiota following successful FMT resulted in reduction of the load of AR genes and this favorable outcome was maintained during the follow up period [91,105]. Furthermore, in a single center prospective study, FMT was associated with a decrease in the number as well as downregulation of the expression of antibiotic resistant genes (*Van A*, bla_{KPC}, bla_{NDM}, bla_{OXA}). Data from metagenomic sequencing showed that after FMT, there was depletion of 95 resistance genes, including important quinolone, β-lactamase, ESBL, and vancomycin resistance genes [107]. There is also evidence from a murine study, suggesting that transplantation of a healthy microbiota displaced both VRE and *Klebsiella pneumoniae* from the intestinal lumen despite an increased colonization burden [108]. In a small study by Wei et al., FMT resulted in cure of MRSA enteritis in five patients and in eradication of gut MRSA colonization [109].

However, RCTs have yet to prove such beneficial effect for FMT. The only RCT directly addressing MDRO decolonization found only a small, non-significant reduction in ESBL and CRE colonization after the combination of antibiotics and FMT [110]. FMT appears to be a safe and potentially effective intervention in eradicating *Carbapenem-resistant Enterobacteriaceae* (CRE) colonization. In a recent systematic review, which included ten studies (one RCT) CRE decolonization rate was estimated 61.1% and 78.7% at 1 month and 6-12 months after FMT, respectively [99].

FMT appears to have few, often mild to moderate and self-limiting side effects including nausea, fever, abdominal tenderness, constipation or diarrhea, cramping, and abdominal distension [111]. However, there have been reports of serious adverse events such as death, aspiration pneumonia, viral and bacterial infections, transient relapse of irritable bowel disease, and adverse effects related to the procedure such as sore throat and bowel perforation [112]. Furthermore, a possible transmission of *Van B* resistance gene after FMT has been described [113]. Last, concerns about long-term outcomes of FMT are not negligible. Remarkably, FMT was safe even when used in severely immunocompromised patients, such as those with hematological malignancies receiving intensive chemotherapy and immunosuppressive drugs and in patients with allogeneic HSCT; bacteremia due to pre-FMT colonizing bacteria was potentially prevented [114-116]. In summary, FMT may protect against intestinal translocation of MDROs preventing bloodstream infections [100] independently of gut decolonization, as several studies showed a reduction in the incidence of clinical infection post-FMT in MDRO-colonized patients [109,114,116,117]. Currently, there are several ongoing studies designed to evaluate the role of FMT in decolonization from MDROs (NCT03479710, NCT04181112, NCT04759001, NCT04431934, NCT04593368, NCT02922816, NCT04583098, NCT04759001, NCT02543866, NCT04146337, NCT04746222, NCT0418874, www.clinicaltrials.gov).

Antimicrobial Compounds for Targeted Therapy

Several gut microbial strains produce bacteriocins, which are antimicrobial compounds of high-potency and low toxicity [118]. The role of a gut derived bacteriocin, namely thiuricin CD, has been used in a CDI mouse model and showed that it was able to inhibit the growth of *C. difficile*, without a major shift in the gut microbiota [119]. Such molecules could represent future targeted therapeutic interventions in order to minimize unnecessary use of broad-spectrum antimicrobials [52].

Selective Digestive Decontamination (SDD) and Selective Oropharyngeal Decontamination (SOD)

SOD was introduced as a theoretical concept of preventing bacterial pneumonia by altering the pharyngeal flora and averting the aspiration of these pathogens [120] while the idea of SDD was first introduced as a means to reduce the load of resistant pathogens colonizing the digestive tract of ICU patients [121]. The first study which showed a reduction of MDRO gut colonization was a single-center study [122] followed by two larger randomized cross-over studies supporting that SOD/SDD resulted in a significant decrease of resistant pathogens on the gut [123,124]. However, a more recent randomized multicenter study revealed that the use of SOD/SDD did not lead to a change in the gut resistant pathogens [125]. An explanation of the different outcomes between the first three and the last study could lie in the rates of antimicrobial resistance in the participating ICUs. Therefore, SOD/SDD could be used in patients hospitalized in ICUs with low rates of resistant bacteria while more research should be done in centers with high prevalence of antimicrobial resistance [126]. However, a substantial concern raised from the use of SDD was the emergence of colistin-resistant *Enterobacteriaceae* in the gut of SDD-treated patients [127].

PREVENTION OF DYSBIOSIS

We describe here the main approaches of preventing gut dysbiosis which are also presented briefly in Table 2.

Control Measures

A first step to prevent gut colonization with MDROs in hospitalized patients is the application of effective infection control measures [103,128,129]. Measures to prevent in-hospital transmission of MDROs include primarily hand hygiene followed by environmental cleaning, contact precautions, or even topical decolonization processes for some pathogens (ie, MRSA) [130].

Antimicrobial Stewardship and the Gut Antimicrobial Resistome

A significant approach in order to avoid major disruptions in gut microbiota is rationalizing antimicrobial use by implementing effective antimicrobial stewardship strategies [102,103,129,131].

Several large meta-analyses have supported that antimicrobial stewardship programs (ASPs) lead to a decrease in infections with MDROs [129,132,133] while others found the correlation inconclusive [134]. One large meta-analysis concluded that ASPs are successful in reducing MDRO colonization, independently from infection, and this success was higher when ASPs were combined with good infection control protocols (ie, hand hygiene) [129].

Choice of antibiotics: The type and spectrum of the antimicrobial used, is crucial for the development of resistance. For example, the unnecessary and prolonged use of anti-anaerobic antimicrobials has been related to a higher possibility of colonization with MDROs [135]. Avoiding anti-anaerobic antimicrobials and using narrow-spectrum agents whenever possible is beneficial to the human's gut microbiota as fewer commensals will be affected [131,136].

Duration of antimicrobial therapy: Duration of antimicrobial therapy has been linked to greater alterations of gut microbiota. Shorter courses of antibiotics result in fewer microbiota disruptions and easier restoration of gut microbiota, which is supported by many studies in neonates [131]. Also, the use of ceftriaxone for more than 14 days was correlated with higher number of resistance genes in gut microbiota [137]. However, the duration of treatment with fluoroquinolones was not associated with the emergence of resistant *E. coli* strains in another study [138]. Similarly, in patients receiving antibiotic therapy for gram-negative bacteremia, shorter antibiotic treatment (7 days) was not associated with reduced resistant genes in the gut microbiota or with better preservation or restoration of the gut microbiota when compared with longer treatment courses (14 days) [139].

Dose: Lower doses of antibiotics have been associated with a lower or slower risk of acquiring resistant genes [140]. However, appropriate dosing is very important since antimicrobial underdosing can also lead to resistance.

Route of administration: Several animal studies showed that oral antibiotics disturb the gut microbiota more prominently than parenterally administered ones (IV or IM) [140,141]. However, recently published evidence had contradictory findings, showing that oral or parenteral route of administration has the same disrupting effect on gut microbiota [142]. Besides, the key components contributing to the preservation of gut microbiota after antibiotic exposure relies on the latter's properties, like bile excretion, intestinal absorption, and presence in the feces [143,144]. Antibiotics that are not or only partially fecally and/or biliary excreted, may have fewer repercussions on the gut microbiota and therefore prevent the augmentation of gut resistome [131,136]. Furthermore, alternative modes of administration, like local application of antimicrobial agents, nebulized agents, or even transdermal administration lack strong data from clinical trials to support their non-inferior efficacy and beneficial profile for the gut microbiota [131,136]. Another interesting approach is to limit the use of oral antibiotics on discharge, granted there is clinical amelioration, after the completion of an inpatient intravenous antibiotic treatment course [136].

Table 2. Prevention of Dysbiosis

Intervention	Mechanism of action/Application	Advantages	Disadvantages	References
Control measures	-Screening via nasal or rectal swabs for multidrug-resistant organisms. -Good hygiene, environmental cleaning, contact precautions etc.	-Easy to apply.	-Difficult to measure its direct effectiveness.	[103,128-130]
Antimicrobial stewardship programs	-Wise choice of antibiotics (e.g. avoidance of anti-anaerobic antimicrobials) and use of narrow-spectrum agents help to preserve gut microbiota. -Shorter courses of antibiotics lead to fewer microbiota disruptions and easier restoration. -Lower doses of antibiotics result in a lower risk of resistant genes. -Use of antibiotics that are not faecally and/or biliary excreted prevents the development of gut resistance.	-Good rates of preventing infections with multidrug-resistant organisms. -Applicable in every healthcare facility. -No need for adjuvant equipment/substances.	-No many directly focused studies on the colonization of the gut microbiota. -In some cases, it is inevitable to avoid some antibiotics. -Needs coordinated action between many specialties.	[102,103,129,131,136, 137,139,140,143,144]
Chelating/degradating agents	-Use of substances such as beta-lactamase enzymes and charcoal-based substances that absorb the remaining amount of antibiotic before reaching the colon protecting this way the gut microbiota without affecting the serum levels of the antibiotic.	-Promising preliminary results. -No serious adverse events.	-Need for more clinical trials. -Difficult to measure their long-term clinical benefit.	[102,145,147,150-153, 156,158,159,161,163]

Chelating/degradating Agents

Another interesting approach for maintaining gut microbiota, is the use of newly developed substances such as beta-lactamase enzymes and charcoal-based substances, that absorb the remaining amount of a fecally or biliary excreted antibiotic before reaching the colon, thus protecting the gut microbiota without affecting antibiotic serum levels [102,145].

Beta-lactamase enzymes: The idea of using a beta-lactamase was derived by the observation that the simultaneous existence of cephalosporins and b-lactamase-producing pathogens resulted in less bacterial colonization [146]. P1A was the first beta-lactamase used to degrade the residual penicillin, aminopenicillins, and ureidopenicillins in the gut [147]. Except for its effectiveness in animal models [148,149], P1A was found to prevent the disruption of gut microbiota and the emergence of antibiotic resistant genes in colonizing bacteria [147,150].

A new agent was further developed to include the class of cephalosporins. Ribaxamase is an oral b-lactamase, and when administered concurrently with an IV b-lactam antibiotic, like ceftriaxone, or a β-lactam/β-lactamase inhibitor combination, can hydrolyze the excess of antibiotic at the small intestine, potentially enhancing colonization resistance [151-153]. This agent was well-tolerated and effective in both animal models [149,154] and humans [151-153]. Another ribaxamase-based agent, SYN-007, was evaluated in animal models to expand the use of oral ribaxamase. SYN-007 resulted in the protection of the microbiota and prevention of emergence and proliferation of resistant genes (ie, encoding ESBLs) while simultaneously preserving the concentration of antibiotics in serum [155,156]. However, ribaxamase is not effective against all b-lactam antibiotics and especially against carbapenems, which are associated with a greater risk of gut dysbiosis and antimicrobial resistance [157]. Therefore, a novel carbapenemase, SYN-006, was developed and tested in a rigorous animal model to expand the protection of gut microbiota from the detrimental effects of all beta-lactam classes [158,159]. Clinical trials in humans are needed to investigate the safety and efficacy of such complementary therapeutic strategies. A more recent discovery is the development of a beta-lactamase containing engineered live biotherapeutic product (eLBP), which introduces a more effective delivery of the active enzyme, also combining easier and cheaper manufacturing [160].

Charcoal-based agents: DaV-132 is a novel, orally administered, absorbent charcoal targeted-agent aiming to degrade the remaining antibiotic from the GIT by acting on the late ileum or proximal colon [161,162]. Although in clinical trials it was only administered with fluoroquinolones [161-166], the agent showed effectiveness in protecting gut microbiota and preventing colonization of resistant strains, without compromising therapeutic efficacy and safety [161,163].

CONCLUSION

Modulating the gut microbiota through diet, probiotics, prebiotics, antimicrobial molecules, phage therapy, or FMT could be a promising intervention in the fight against antimicrobial resistance. Strategies that will selectively inhibit pathogens without causing major shifts in the gut microbiota are most desirable. As our knowledge of the host-microbiota interactions, microbial quorum sensing and the drivers of colonization resistance will expand, a more targeted modulation of the microbial communities may be possible, allowing for a selective elimination of pathogenic bacteria and a less disruptive approach to gut microbiota homeostasis.

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