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REVIEW

Gut Microbiota Modulation: Implications for Infection Control and Antimicrobial Stewardship

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ABSTRACT

The human microbiome comprises a complex ecosystem of microbial communities that exist within the human body, the largest and most diverse of which are found within the human intestine. It has been increasingly implicated in human health and diseases, demonstrably playing a critical role in influencing host immune response, protection against pathogen overgrowth, biosynthesis, and metabolism. As our understanding of the links between the gut microbiota with host immunity and infectious diseases deepens, there is a greater need to incorporate methods of modulating it as a means of therapy or infection prevention in daily clinical practice. Traditional antimicrobial stewardship principles have been evaluated to assess their impact on the gut microbiota diversity and the consequent repercussions, taking into consideration antibiotic pharmacokinetic and pharmacodynamic properties. Novel strategies of selective digestive decontamination and fecal microbiota transplantation to regulate the gut microbiota have also been tested in different conditions with variable results. This review seeks to provide an overview of the available literature on the modulation of the gut microbiota and its implications for infection control and antimicrobial stewardship. With increased understanding, gut microbiota profiling through metataxonomic analysis may provide further insight into modulating microbial communities in the context of infection prevention and control.

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Key Summary Points

Strategies to limit the negative effects of antibiotics on the gut microbiota include restricting the duration and spectrum of antibiotic use.

Different routes of antibiotic administration have varying effects on the gut microbiota due to pharmacokinetic parameters, and these effects should be considered.

There is insufficient evidence to recommend the routine use of selective oral decontamination and selective digestive decontamination to reduce the risks of nosocomial pneumonia in critically ill patients.

The use of fecal microbiota transplants and probiotics have some role in restoring the gut microbiota diversity in the setting of dysbiosis, but require further study.

Gut microbiota profiling through metataxonomic analysis may provide further insight into modulating microbial communities in the context of infection prevention and control.

INTRODUCTION

Our knowledge of the human microbiome has increased over the past decade. It comprises a complex ecosystem of microbial communities that exist within the human body. The largest and most diverse of these exists within the human intestine. Collectively known as the gut microbiota, they have increasingly been found to play a significant role in the maintenance of human health and the development of diseases [1]. The human microbiome was first characterized by The Human Microbiome Project sponsored by the National Institutes of Health [2]. Using high-throughput sequencing, the human lower intestinal microbiota has been estimated to contain at least $10^{11–12}$ microorganisms per gram of content, comprising mainly anaerobes, more than 90% of which belong to the phyla *Firmicutes* and *Bacteroidetes* [3, 4]. Its composition is highly variable, changing with age, diet, and geographic distribution [5].

In recent years, increased understanding and analysis of the gut microbiota have shed light on the impact of alterations in it on human health. It plays a critical role in influencing host immune response, protection against pathogen overgrowth, biosynthesis, and metabolism [1]. There are implications for health and diseases even from birth [6]. Additionally, the gut microbiota serves as an important reservoir of antibiotic resistant genes, also known as the "resistome", which can become an amplifier of antimicrobial resistance [7].

As our understanding of the link between the gut microbiota with host immunity and infectious diseases increases, there is a greater need to incorporate methods of modulating it as a means of therapy or infection prevention in daily clinical practice. However, much of the available data are in the realm of in vitro data or animal studies. This review seeks to provide an overview of the available literature on the modulation of the gut microbiota, and its implications for infection control and antimicrobial stewardship. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

GUT MICROBIOTA AND ANTIMICROBIAL STEWARDSHIP

In this section, we review antimicrobial stewardship strategies and evaluate their impact on the gut microbiota and the development of antibiotic resistance.

Narrowing Antibiotic Spectra and Limiting Duration Of Use

Antibiotic use reduces the diversity of the gut microbiota through the elimination of

susceptible strains that make up normal flora. This can subsequently lead to the overgrowth of resistant or potentially pathogenic bacteria, increasing the risk of infection, especially with multidrug-resistant organisms (MDRO) [8, 9]. The degree to which the microbiota is affected varies with the type and duration of the antibiotic used [10]. Anti-anaerobic antibiotics have a great impact on the gut microbiota as anaerobes form a significant proportion of it [8, 11]. It has been shown that just 4–8 days of piperacillin-tazobactam for intra-abdominal infections resulted in a substantial decrease in anaerobic commensals [11]. A study by Hecker et al. reported that anaerobic cover accounted for about 35% of the 576 unnecessary antimicrobial days of therapy [12]. Inappropriate use of anti-anaerobic antibiotics can increase the likelihood of colonization by resistant organisms [13]. In a randomized clinical study comparing the use of piperacillin-tazobactam versus ertapenem, the resistance of *Enterobacterales* to piperacillin-tazobactam developed at a significantly higher rate compared with ertapenem [14]. Several studies have demonstrated that newer fluoroquinolones such as levofloxacin and moxifloxacin had greater ecological effects on Gram-positive organisms than ciprofloxacin [15–17].

Logically, advocating the prescription of narrower spectrum antibiotics whenever appropriate should reduce disruption of the microbiota and resultant opportunistic infections, such as *Clostridiodes difficile* infection (CDI) and fungal infections. Benefits were demonstrated in the comparison of vancomycin and fidaxomicin in the management of *C. difficile* diarrhea. Fidaxomicin exposure had a smaller impact on microbiota composition in mice and conferred higher colonization resistance to *C. difficile* spores compared with vancomycin [18]. Consequently, this was associated with a lower recurrence rate in patients treated with fidaxomicin compared with vancomycin [19]. A study by Lew et al. suggested that classical antimicrobial stewardship strategies, specifically switching to narrower spectrum antibiotics, antibiotic cessation once treatment is completed, or when there is no bacterial infection, can reduce rates of antibiotic resistance and CDI [20]. This concurred with Tay et al. who reported the usage of carbapenem as a risk factor for severe CDI [21].

Excessively prolonged antibiotic use is a global concern [12, 22, 23], and can lead to significant alteration in the gut microbiota, restoration of which can take months to years [24, 25]. Conversely, shorter antibiotic duration results in less collateral damage to the gut microbiota, and allows for earlier restoration. Late-preterm infants who received longer courses of antibiotics had more prolonged alterations in their gut microbiota compared with those who received a shorter duration [26]. There is increasing evidence that a shorter duration of antibiotics of less than 8 days for commonly encountered infections, such as skin and soft tissue infection [27] and male urinary tract infections [28], are not associated with increased treatment failures. Antibiotic stewardship principles of making an accurate diagnosis of infection, appropriate antibiotics, and a shorter duration of antibiotic treatment or prophylaxis, would reduce unnecessary antibiotic exposure to the gut microbiota without compromising patient outcomes [29].

Exploiting Antibiotic Pharmacokinetics

The route, dose, and excretion of antibiotics affect the gut microbiota differently. Zhang et al. compared oral versus intravenous tetracycline and ampicillin using murine models, and recovered higher copies of resistant genes in mice fed with oral antibiotics compared with those which received intravenous antibiotics [30]. Lower tetracycline doses were associated with slower resistance development with fewer copies of resistant genes being isolated [30]. When clindamycin was administered via the oral route, a higher concentration of clindamycin were found in feces compared to when administered via an intravenous route. This resulted in a greater reduction of anaerobic colonic flora, leading to an overgrowth of clindamycin-resistant bacteria, such as *enterococci* and *C. difficile* [8].

However, compared with oral agents that are highly absorbed and excreted minimally

through the bile or feces, intravenous antibiotics that undergo enterohepatic re-circulation or are excreted through bile, feces, or secreted into the intestinal tract may have a greater impact on the gut microbiota [31]. Various studies have found that imipenem and meropenem are excreted minimally in fecal samples after administration, and minor changes to the gut microbiota when administered for a limited duration (6–11 days) have been observed [32, 33]. Oral penicillin was also reported to have a low fecal concentration, with almost no change in microflora [8]. In contrast, ceftriaxone, a broad-spectrum cephalosporin with high biliary excretion, effectively suppressed *Enterobacterales* [34]. Among macrolides, erythromycin has lower absorption from intestines compared with clarithromycin. About 95% of erythromycin versus 60–70% of clarithromycin is metabolized in the liver and excreted in bile as its active form [35]. This explains the higher impact of erythromycin on intestinal microflora [36].

In light of the above, antibiotic prescribers should firstly, only start antibiotics in the presence of a clear indication. Secondly, prescribers should choose the narrowest spectrum antibiotic available for treatment to reduce the impact on the gut microbiota (e.g., the omission of anaerobic cover if not indicated). Thirdly, antibiotics should be prescribed for the shortest duration to allow the recovery of the gut microbiota as soon as possible, and finally, oral antibiotics should be used if possible to reduce line-related infections and reduce hospitalization days. Oral agents that are highly absorbed and excreted minimally through the bile or intestinal tract are preferred. Prescribers will also need to consider the resistance potential of antibiotics. Although carbapenems are excreted minimally through the gut with a smaller impact on the gut microbiota, antibiotic prescribers should be aware of the association between carbapenem use and the increase in carbapenem resistance, which should limit its use [37, 38]. Additionally, other factors, such as side effects, allergies, and penetration to the site of infection, will also need to be considered during prescribing, in addition to the impact of antibiotics on the gut microbiota.

Targeted Local Antibiotic Delivery

The use of non-systemic antibiotics for localized infections may help to minimize the impact on the gut microbiota and the development of antibiotic resistance. Getting the drug to only where it is needed in high concentrations is a concept that has been used in some infections. Inhaled antibiotics have been used for respiratory infections in patients with cystic fibrosis [39]. Studies have been conducted for other respiratory infections, such as pneumonia, infective exacerbation of chronic obstructive pulmonary disease, and non-cystic fibrosis bronchiectasis, but there has been a paucity of good quality studies and the outcomes have been modest [39]. Palmer et al. reported a reduced need for systemic antibiotics in the treatment of ventilator-associated tracheobronchitis with the use of inhaled antibiotics [40]. However, another study by Rattanaumpawan et al. did not observe additional benefit when using inhaled colistin as adjunctive therapy in ventilator-associated pneumonia [41]. In the clinical practice guidelines published by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society in 2016, the expert panel concluded that there is a need for better quality studies to look for optimal dosing as well as aerosol delivery [42]. Local administration of antibiotics in the form of antibiotic-impregnated cement and antibiotic powder have been explored over the years for the treatment or prevention of bone and joint infections [43]. Further research is needed in the area of localized administration of antibiotics in the treatment of infections to reduce the impact on the gut microbiota while achieving optimal patient outcomes.

GUT MICROBIOTA MODULATION FOR INFECTION PREVENTION

Colonization resistance is the ability of the healthy microbiota to prevent expansion of potential pathogenic bacteria [44]. Maintaining or re-establishing colonization resistance by

modulating the gut microbiota to prevent infection have been evaluated. The next section discusses how this can be achieved.

Fecal Microbiota Transplant (FMT)

The intestine is a reservoir for MDRO that can be opportunistic pathogens selected for by antibiotic pressure, especially in critically ill and hospitalized patients [45]. Studies have shown that patients colonized with MDRO are at risk of developing infections that arise endogenously, or may transmit them to other individuals [46, 47]. These pathogens may translocate across a damaged intestinal barrier, or result in contamination to cause infections at other sites, such as central line infections or catheter-related urinary tract infections. The gut microbiome thus serves as a prime target for infection prevention strategies, giving rise to increased interest for use of fecal microbiota transplant (FMT) and selective digestive decontamination as infection control strategies to reduce carriage of MDRO.

FMT has been found to be one of the most effective ways to regulate the gut microbiota. It was first described in 1958 [48] and has since gained increased acceptance as a medical intervention in recent decades. Eiseman et al. observed that the administration of fecal enemas resulted in dramatic responses in critically ill patients with pseudomembranous colitis [48]. It usually involves the transfer of processed stool from a healthy donor into the colon of a recipient, and is delivered enterally either endoscopically or via oral capsule preparations. This presumably allows the donor's microbiome to repopulate the gut with a healthy microbiome to restore gut dysbiosis.

At present, recurrent CDI is the only indication for which FMT has been proven to be efficacious, and it is recommended when appropriate antibiotic therapies have failed [49]. Cure rates in this group of patients were up to 90% with repeated FMT in randomized controlled trials [50–52]. Engraftment of specific bacteria and viruses with physiologic effects within the gut was thought to play a significant role in reversing dysbiosis [53]. Cheng et al. demonstrated in a piglet model that FMT had several effects on metabolic pathways that occurred within the gut to improve gut mucosal barrier integrity [54].

A number of case reports and case series have described successful decolonization of MDRO as a primary outcome among patients treated with FMT [55]. These reports included both immunocompetent and immunocompromised patients colonized with carbapenemase-producing Enterobacterales [56, 57], vancomycin-resistant enterococci (VRE) [58] and extended spectrum ß-lactamase-producing Enterobacterales [59]. Unfortunately, these studies were often uncontrolled with high levels of heterogeneity and short follow-up periods, resulting in no conclusive evidence to support the safety and efficacy of FMT in this regard.

In addition to the clinical implications on patient outcome, the successful decolonization of MDRO via FMT may have several infection control implications. It reduces the burden on healthcare facilities to provide isolation rooms for such patients who require contact precautions and allows re-entry into long-term care facilities that would otherwise not have the adequate infection control resources to care for these patients [60] (see Table 1).

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

Selective oropharyngeal decontamination (SOD) has gained interest as an infection prevention strategy in critically ill patients in the intensive care unit (ICU). In the 1960s, Johanson et al. observed that the prevalence of Gram-negative bacteria in the pharyngeal flora increased markedly within a few days of hospitalization [70]. It was postulated that, since the pathogenesis of bacterial pneumonia began with the aspiration of the oropharyngeal contents into the lung, altering the pharyngeal flora in ill patients may be important to prevent pneumonia secondary to Gram-negative bacilli.

In the 1980s, Stoutenbeek et al. introduced the concept of selective digestive decontamination (SDD) in the ICU population [71]. Given

Table 1 Summary of key concepts in modulation of the gut microbiota in infection prevention and control and antimicrobial stewardship

Domain	Key concepts	Key references
Antimicrobial Stewardship	Broad-spectrum antibiotics can cause significant alteration to the gut microbiota diversity, in particular those with anti-anaerobic activity	[8, 11]
	Alterations to the gut microbiota by antibiotics take months to years to restore	[24, 25]
	Shorter duration of antibiotic is equally effective than prolonged use and can reduce alterations to the gut microbiota	[26–28]
	Oral antibiotics and intravenously administered antibiotics that undergo enterohepatic re-circulation and excretion into bile have a greater impact on the gut microbiota compared to intravenous antibiotics alone	[30–33]
Infection Prevention and Control	Fecal microbiota transplant has been found to be one of the most effective ways to regulate the gut microbiota dysbiosis in the setting of CDI	[49]
	Fecal microbiota transplant has been studied in gut decolonization of MDRO, but has not conclusively been found to be effective	[55, 56, 58]
	Selective oral decontamination and selective digestive decontamination with oral antibiotics has been evaluated as a means of reducing infections caused by endogenous MDRO, but has not been found to be efficacious	[61–63]
	Restoration of the gut microbiota diversity through probiotics and prebiotics have some role in restoring gut diversity in specific diseases, such as necrotizing enterocolitis, acute infectious diarrhea and antibiotic-associated diarrhea	[64–69]

that most infections in the ICU are primary endogenous infections, reducing bacterial load within the gastrointestinal tract, in particular potentially pathogenic microorganisms, would theoretically reduce infection risks. In SDD, enteral antibiotics are selected for their inability to be absorbed into the systemic circulation, and are active against the most common nosocomial pathogens within the gut (e.g., *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*).

Unfortunately, a randomized trial conducted in 13 European ICUs among patients receiving mechanical ventilation found that SOD and SDD were not associated with reductions in ICU-acquired bloodstream infections caused by multidrug-resistant Gram-negative organisms compared with standard care [61]. In addition, a study conducted in ICUs in the Netherlands demonstrated the "rebound phenomenon" that SOD and SDD had on the gut microbiota, with increased rates of ceftazidime resistance in the intestinal tract after discontinuation of SDD.

A combination of both interventions has been considered. A randomized trial reported no significant reduction in extended-spectrum β-lactamase or carbapenemase-producing *Enterobacterales* intestinal carriage between patients who received a 5-day course of oral antibiotics followed by frozen FMT obtained from unrelated healthy donors and controls [62]. In view of the lack of conclusive evidence of the efficacy of FMT and SDD, the European clinical guidelines do not recommend routine decolonization of third-generation cephalosporin-resistant and carbapenem-resistant Enterobacterales carriers [63].

Pre-Operative Oral Antibiotic Preparation (OAP)

Extrapolating the principles of SDD, the role of the gut microbiota in the development of surgical site infections (SSI) has been considered in colorectal surgery where surgeons operate in a clean-contaminated field. Oral antibiotic preparation (OAP) with variable combinations of aminoglycoside, macrolide, and metronidazole have been used to evaluate if they reduced rates of SSI, surgical complications of anastomotic leak, and length of hospital stay [72]. A network meta-analysis of randomized controlled trials revealed that OAP alone was not associated with a statistically significant reduction in SSI [73]. Koskenvuo et al. similarly reported no reduction in SSI or overall morbidity in colon surgery when mechanical and oral antibiotic bowel preparations were used compared with no bowel preparation [74]. There is no strong evidence to suggest that OAP as pre-operative prophylaxis is effective in reducing SSI.

Probiotics and Prebiotics

Probiotics are "living microorganisms which when administered in adequate amounts confer a health benefit on the host" [75]. Prebiotics are non-viable substrates that are selectively utilized as nutrients by beneficial microorganisms, both indigenous and exogenously administered strains, thereby conferring a health benefit [76].

Current literature shows effective reduction of colonization by Gram-positive organisms through the use of probiotics. Manley et al. and Szachta et al. both reported that VRE in the gut can be significantly reduced even to the point of eradication through oral consumption of *Lactobacillus rhamnosus* GG [77, 78]. Gut colonization of *S. aureus* including methicillin-resistant *S. aureus* was reduced after 4 weeks of oral *Lactobacillus rhamnosus* HN001 in a recent clinical trial [79]. However, this beneficial effect of probiotics was not in Gram-negative MDRO in hospitalized patients and residents in long-term healthcare facilities [80, 81].

Randomized controlled trials have shown positive effects on gut health by probiotics in a myriad of conditions, such as infectious and antibiotic-associated diarrhea (AAD), irritable bowel syndrome, and enterocolitis [64]. Lactic-acid bacteria, such as *Lactobacillus* and yeast-based *Saccharomyces boulardii* (*cerevisiae*) probiotics, are the commonest choices for treatment of gastrointestinal conditions [79–81].

Our knowledge of the effects of prebiotics are evolving. Human studies which used-high throughput sequencing demonstrated stimulation of *Bifidobacteria* in response to prebiotic use [82, 83]. In these studies, there were variations in other microorganisms, with increased *Faecalibacterium prausnitzii* [83] and *Anaerostipes* spp, whereas *Bilophila* spp. decreased [82]. Although proof of causality is difficult to determine, the beneficial effects of prebiotics have been evidenced through numerous randomized controlled trials, albeit variable as a result of both environmental and host factors [76].

Probiotics in Necrotizing Enterocolitis (NEC)

Necrotizing enterocolitis (NEC) is a debilitating gastrointestinal disorder in neonates characterized by transmural inflammation and bowel necrosis. Bacterial invasion of the bowel walls can occur, and empirical treatment with broad-spectrum antibiotics forms part of the backbone of management [84]. Morbidity and mortality are high [85]. NEC most frequently occurs in neonates who are preterm or have very low birth weight [65, 66]. They are inherently at a higher likelihood of receiving antibiotics due to their susceptibility to infections, and prolonged antibiotic use is a known risk factor for NEC [86]. The growth of gut-friendly commensal *Bifidobacteria* is greatly compromised [86, 87]. Consistent benefits of probiotics in the prevention of NEC have been extensively described in systematic reviews and meta-analyses [65–67]. Sawh et al. reported that, when compared with placebo, probiotics reduced the incidence of severe NEC in 38 trials (10,520 patients) [RR 0.53, 95% CI (0.42–0.66)] [66]. The incidence of all-cause mortality was significantly reduced with probiotics in 29 trials (9507 patients) [RR 0.79, 95% CI (0.68–0.93)] [86]. As such, probiotics may have a role in reducing the occurrence

of NEC, and thus antibiotic usage and potential negative outcomes caused by NEC.

Probiotics in acute infectious diarrhea and antibiotic-associated diarrhea

Acute infectious diarrhea is one of the leading reasons for antibiotic prescription. Reduction in diarrheal incidence, severity, and duration through probiotic use may reinforce antimicrobial stewardship principles of reducing antibiotic prescriptions. Probiotics have been heavily studied in patients with acute infectious diarrhea and evidence of its benefits is well described [88, 89]. A Cochrane review of 63 studies, mainly in infants and young children, reported an average reduction of 1 day in the duration of diarrhea, reduction in the likelihood of diarrheal episodes lasting more than 3 days, and stool frequency on day 2 of illness [89].

AAD affects approximately 30% of patients and is frequently associated with broad-spectrum antibiotic use [90, 91]. AAD can outlast the period of antibiotic use and makes the patient more vulnerable to infections and other diseases [25, 92]. Positive associations between probiotics and a decrease in AAD have been reported [68, 93, 94]. However, studies were consistently limited as they were underpowered and used varying probiotic strains, formulations, and doses. The studied population had differences such as age, health conditions, and genetic factors. These factors resulted in the heterogeneity of the studies. Therefore, the extent of purported benefits remains unknown [93].

Probiotics for C. difficile*-associated diarrhea*

Up to 30% of AAD are secondary to CDI. It is the commonest cause of infectious diarrhea in healthcare settings [95, 96]. The care of such patients requires intensive infection control measures of isolation, contact precautions, and terminal cleaning to limit nosocomial transmission. The clinical practice guidelines for CDI in adults and children by the Society for Healthcare Epidemiology of America and the IDSA make no recommendation with regard to the administration of probiotics for the treatment and prevention of primary or recurrent CDI [49]. Meta-analyses have shown that probiotics may be effective at preventing CDI with up to 70% risk reduction [68, 69]. However, in post hoc analysis, it was demonstrated that this large risk reduction was significant only in patients who had a higher baseline CDI risk of $> 5\%$ (3.1% in the robiotic group vs. 11.6% in the control group).

Risk of CDI recurrence is approximately 25%, and attempts have been made to lower the recurrence rate. A randomized placebo-controlled trial showed that patients with CDI treated with *S. boulardii* plus standard antibiotics had a significantly lower relative risk of CDI recurrence than placebo plus standard antibiotics [97]. While there was a trend that *S. boulardii* could reduce CDI recurrence in patients with initial CDI and recurrent CDI, significance was demonstrated only in the latter [97]. In a double-blind, placebo-controlled trial, among patients who received high-dose enteral vancomycin (2 g/day), Surawiez et al. demonstrated a significant reduction (16.7% vs. 50.0%) in CDI recurrence when *S. boulardii* was administered [98]. However, the high-dose vancomycin arm only had 32 subjects, and most were severely ill with CDI complications such as pseudomembranous colitis. In the low dose (1 g/day) vancomycin and metronidazole arms ($n = 85$ and 53, respectively), co-administration of *S. boulardii* was not associated with reductions in CDI recurrence. The efficacy of probiotics in preventing CDI recurrence is promising, but studies are still limited by small sample sizes and the lack of consistently reproducible data [49, 69].

Safety Considerations

Few clinical trials have addressed the safety profile of probiotics because of the lack of safety documentation. Often, they are underpowered for this purpose [99]. However, rare events such as bacteremia and fungemia have been reported, especially in vulnerable populations such as immunocompromised patients [100]. Lastly, there have been reports where commercial probiotic strains carried antibiotic resistance genes [101]. This is a threat, especially when lateral transfer of these undesirable genes to pathogens and commensal the gut microbiota is possible.

CONCLUSIONS

The maintenance of a healthy and diverse gut microbiota plays an important role in the prevention and acquisition of MDRO, and strategies that modulate its composition have great potential in impacting human health. This serves to reinforce antibiotic stewardship principles that limit the negative effects of antibiotics on the gut microbiota. Specific strategies include developing models for assessing the impact of various antimicrobial combinations on the gut microbiota, and promoting the development and use of such therapies with demonstrable reduced impact. Novel interventions, such as microbiota auto-banking and transplantation to perform studies for reducing colonization by MDRO, as well as developing more advanced probiotics that are reflective of the complexity of the native gut microbiota, can serve to restore gut microbiota diversity in the face of dysbiosis. As we discover more about the host protective mechanism afforded by an intact microbiota, further research should be invested in promoting the development of molecular therapeutics to mimic normal host–microbiota interactions.

The VITORA (NCT03944369) and EFFECT-CPE (NCT03802461) trials are ongoing clinical trials that have been publicly registered to assess the effectiveness of the manipulation of the gut microbiota for the eradication of MDRO carriage. A trial conducted by the Memorial Sloan Kettering Cancer Center to see how different antibiotics affect the commensal bacteria existing in the intestinal tract is currently underway. With increased understanding, gut microbiota profiling through metataxonomic analysis may provide further insight into modulating microbial communities in the context of infection prevention and control.

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