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The Role of Probiotics, Prebiotics and Synbiotics in Combating Multidrug - Resistant Organisms

Andrew Newman[1], **Mehreen Arshad**[1,2,3]

[1]Ann & Robert H. Lurie Children's Hospital, Chicago, IL, United States

[2]Stanley Manne Children's Research Institute, Chicago, IL, United States

[3]Northwestern Feinberg School of Medicine, Chicago, IL, United States

Abstract

The prevalence of multidrug-resistant organisms is increasing worldwide, posing a unique challenge to global health care systems. Novel approaches are needed to combat the spread of infection with these organisms. The enteric microbiome, and in particular the resistome, offers a unique target in both the prevention of infection with these organisms and the acquisition and spread within the community. We highlight a novel approach to combat multidrug-resistant organisms: the use of prebiotics, probiotics, and synbiotics to manipulate the microbiome and resistome. This review summarizes the published literature and clinical trials related to these products to date, with a focus on efficacious trials. It highlights the probable mechanism of action for each product, as well as its safety profile in selective populations. Ultimately, although further research is needed before a definitive statement can be made on the efficacy of any of these 3 interventions, the literature to date offers new hope and a new tool in the arsenal in the fight against bacterial drug resistance.

Keywords

antibiotic resistance; microbiome; multidrug-resistant organisms; prebiotic; probiotic; resistome; synbiotic

INTRODUCTION

Antibiotic-resistant bacteria are a growing problem across the world. Organizations, such as the Centers for Disease Control and Prevention, the Infectious Diseases Society of America, and the World Health Organization, have all identified rising antimicrobial resistance as a top health threat. Within the United States, it is estimated that 2.8 million antibiotic-resistant infections and 35,000 deaths occur yearly.[1] Although new antimicrobial therapies continue to be investigated, the novel drug treatment pipeline is extremely limited, and the number of

Address correspondence to: Mehreen Arshad, Ann & Robert H. Lurie Children's Hospital, 225 E. Chicago Ave, Chicago, IL 60611, United States. marshad@luriechildrens.org.

CONFLICTS OF INTEREST

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therapies under investigation remains small. New strategies will be needed to combat multidrug-resistant (MDR) bacteria.

The gut commensal bacteria, termed the microbiome, is a growing field of interest within the scientific community.[2] An increasing body of literature has aimed to examine its role not only in infection but in neurologic and immune development, growth and development, and its impact on inflammatory diseases.[3] The enteric microbiome influences and affects human health, and human health can reciprocally affect the enteric microbiome. There are many external and natural influences on the enteric microbiome, including nutritional fiber, animal byproducts, and exposure to the environmental microbiology from water and soil sources.[4,5] The earliest source of inoculation is often the maternal microbiome, which can influence the neonatal microbiome and may even influence it during the prenatal period.[6] An important cause of iatrogenic influence is use of antibiotics, which can also perturb this complex system. Even short courses of antibiotics, or antibiotics within human food sources, can cause long-lasting changes to the microbial colonies in our gut.[7]

Disruption of the normal commensal flora by external stressors, such as antibiotics or dietary changes, can allow for colonization by pathogens (Figure).[2] These pathogens, as well as the existing normal commensal bacteria, bring with them their own set of antimicrobial resistance genes (ARGs). The ARGs within normal commensal flora can be present at birth as well as acquired over a lifetime of exposure to different factors, including selective antibiotic pressure.[8] The accumulation of all ARGs within a microbiome is termed the resistome; the rich complexity of the human microbiome unfortunately offers a ripe ground of genetic exchange of these ARGs, allowing transference from commensal organisms to pathogens.[5] Further exposure to other stressors can damage the intestinal mucosa, allowing translocation and infection by these acquired pathogens, a term often labeled as mucosal barrier injury–associated bloodstream infection. Previous studies have shown that colonization with pathogenic organisms is predictive of future infection, and resistance patterns within recovered pathogens from the stool correlates with the resistance pattern seen in these bloodstream infections.[9] As MDR infections become an increasing burden on global health, the enteric microbiome and resistome offer a target of modification and possible reduction in the burden of these pathogens. In particular, nutritional modification through the use of prebiotics, probiotics, and synbiotics offers a safe and affordable method of reducing the impact of MDR organisms on human health.

The present article highlights a novel approach to combat MDR organisms (MDROs): the use of prebiotics, probiotics, and synbiotics to manipulate the microbiome and resistome. This review summarizes the published literature and clinical trials related to these products to date, with a focus on efficacious trials.

PREBIOTICS

Background and Mechanism of Action

Prebiotics are nondigestible compounds that are selectively fermented by commensal microbiota in the human gut and support a favorable growth environment for commensals and increase diversity within the microbiome, thereby promoting human health.[10] Sources of

prebiotics include glucose-, fructose-, and xylo-oligosaccharide, lactulose, and inulin.[11] The digestion of prebiotics by commensal organisms produces metabolic byproducts such as the short-chain fatty acids (SCFAs) butyrate, propionate, and acetate. SCFAs serve to improve the barrier function of the gut through multiple mechanisms, including the provision of energy for enterocytes; upregulation of tight junctions between cells of the epithelial layer; promotion of mucus production; and regulation of regulatory T cells and T helper 17 cell function to decrease inflammation (Figure).[12] Through these mechanisms, prebiotics help to both expand the population of commensal organisms and decrease colonization by enteric organisms.

Side Effects

Prebiotics are not systemically absorbed and have a limited side effect profile; most notably, individuals taking prebiotics can experience increased flatulence, a change in stool consistency, and possible abdominal cramping.[13,14] Previous studies have reported that the addition of a prebiotic limited gastrointestinal symptoms after hematopoietic stem cell transplantation,[15] decreased inflammatory pouchitis in adults with ileal pouch–anal anastomoses,[16] modulated inflammation in women with type 2 diabetes,[17] increased fecal SCFAs in children with celiac disease,[18] and modified the fecal microbiome of bottle-fed neonates to resemble those of breast-fed infants.[19] In each of these studies, prebiotics were found to be safe, with limited side effects.

Summary of Published Trials

The use of prebiotics to manipulate the microbiome, and in particular the resistome, is in its infancy compared with the more widely used probiotics. In addition, randomized controlled trials are often difficult to perform, as a number of factors need to be controlled for, most importantly diet and other fiber consumption. There have been no studies published to date that have examined the impact of prebiotic supplementation on MDRO colonization and eradication. At the time of publishing this review article, 3 clinical trials are in various phases of completion to better assess the role of prebiotics. Of the registered clinical trials, 2 explore the use of inulin in patients at high risk for MDRO colonization, hematopoietic stem cell transplantation recipients, and ICU patients. The third study is exploring the use of KB109, a novel metabolic agent developed to target the microbiome (Table I).

Treatment Recommendations

Given their limited side effect profile, prebiotics seem safe to use in nearly all patient populations who are able to consume food through the enteral route. Because prebiotics are not systemically absorbed, no defined dose per body weight or age has been described. In patients who develop symptoms that interfere with daily living, reduction in the total daily dose or cessation of product all together will often reverse notable side effects.[13,14] Dosing for prebiotics is variable based on the compound used. Limited data exist on KB109 dosing. For inulin, there is a range of dosages depending on the formulation, but in general, dosages <10 g daily seem to be well tolerated in most patients.[20] If side effects do occur, including bloating, abdominal cramping, excessive flatulence, or diarrhea, the dosage can be reduced by 50%, often with cessation of side effects.

PROBIOTICS

Background and Mechanism of Action

Probiotics differ from prebiotics in that probiotics are living bacteria or fungi that are directly consumed and confer a health benefit to the host. Similar to prebiotics, probiotics exert their effect through the production of SCFAs from metabolic precursors, leading to the same downstream effects of immune modulation and increased mucosal barrier function.[12] Probiotics may have the added effect of producing their own antimicrobial compounds, as well as physically occupying the epithelial niche and limiting the ability for other pathogens to colonize the enteric microbiome (Figure).[12] Whereas prebiotics cause an indirect effect on the microbiome through metabolic pathways and growth of commensal organisms, probiotics exert a more direct effect. Other than commercialized products, probiotics are naturally occurring in fermented foods such as yogurt, cheese, kimchi, and sauerkraut.[21]

There are a variety of probiotics available commercially in many different over-the-counter preparations. Probiotics such as *Bifidobacterium*, *Lactobacillus*, and *Saccharomyces boulardii* have been used frequently to combat *Clostridioides* difficile infections, traveler's diarrhea, and irritable bowel syndrome.[22] These over-the-counter products can differ significantly in the amount of colony-forming units in each dose and also depend on the formulation. The various delivery vehicles include lyophilized tablets/powders, nonlyophilized tablets/ powders, and fermented beverages and yogurt. There are no trials comparing the efficacy of each formulation, but lyophilized versions have the longest shelf-life and therefore may be preferred.

Side Effects

Probiotics offer more risk than prebiotics. Because probiotics are the direct inoculation of live organisms into a host, there is a potential for these colonies to transform from beneficial commensal to overt pathogen.[23] For example, there are case reports of *Lactobacillus* bacteremia tied to probiotic administration, particularly in patients with central lines or active inflammatory bowel disease[24–26]; caution should be taken before administering probiotics to those with central lines or active colitis and probable enteric mucosal barrier injury, particularly those with immunocompromising conditions. In particular, although many strains of probiotics are not overtly virulent, they can cause line infections in those with permanent indwelling catheters. Unfortunately, research studies involving probiotics seem to under-report the adverse events related to infection from the administered microbe.[27] Because probiotics are often available over the counter, the US Food and Drug Administration presents regulation and standards to provide for safe consumption; however, previous studies have found that these products can be contaminated.[28] The microbial contaminants have the potential to introduce ARGs into the microbiome or cause bacteremia.

Summary of Published Trials

Probiotics are better studied in microbiome manipulation compared with prebiotics; however, studies show mixed results for a variety of reasons, with the most important consideration being the specific species of microbe used in the probiotic study. A review of

the published literature reflects these mixed results, and a strong recommendation cannot be made (Table II).

Use of Lactobacillus Species for Elimination of Vancomycin-Resistant Enterococcus—The most promising results for probiotic use are seen in elimination of vancomycin-resistant *Enterococcus* (VRE) colonization with *Lactobacillus GG* (Table III). Manley et al[32] conducted an early study examining the impact of *Lactobacillus GG* on VRE colonization in adults and found that the treatment was successful in eradication compared with placebo. Twenty-nine VRE-positive patients in one renal ward of a hospital were randomized to receive *Lactobacillus* or placebo delivered in an unlabeled yogurt vehicle. At the end of 4 weeks, all of those in the treatment group were VRE-negative, compared with only 1 of the 12 subjects in the placebo group. The study had a crossover design, with 8 of the 12 subjects in the placebo group receiving the probiotic product, and all subsequently clearing VRE colonization according to results of rectal culture in the subsequent 4 weeks.[32] Importantly, *Lactobacillus GG* had a protective effect despite the treatment group having increased rates of antibiotic usage, which may have further affected their microbiome. No follow-up was done to assess for recolonization after cessation of product, and it is unclear if the effect was sustained in this group.

Szachta et al[36] conducted a study examining the impact of *Lactobacillus GG* on VRE carriage in children, and the initial results pointed favorably to the effect of probiotic supplementation on eradication of VRE carriage. The trial used once-daily supplementation of the probiotic for a 21-day period. At the end of the 3-week period, a significant difference was observed in those who cleared VRE in the experimental group versus the control group (62.5% vs 24%). However, it should be noted that follow-up 1 week after cessation of the intervention showed no difference between the groups in VRE colonization. A significant number of patients in both groups did not complete the week 4 follow-up visit, and thus it is unclear if the effect of probiotic supplementation ends after cessation of use.

A similar study was recently completed by Buyukeren et al[49] examining the impact of *Lactobacillus GG* on VRE carriage in newborn infants. All newborns enrolled in the trial were VRE-positive according to results of rectal swab culture, and those in the treatment group received probiotic until the swab result was negative at 3 time points or until the end of the study period at 6 months. They were compared with other newborn infants known to be VRE-positive but not receiving any additional supplementation. The study found that VRE carriage was eliminated by 6 months more frequently in the treatment group compared with newborns receiving standard of care (95% vs 52%). Breastfeeding was not an associated factor in decolonization between the groups. In addition, infants who were able to stop probiotic supplementation early due to decolonization had not experienced a recolonization event at the 6-month follow-up.[49] This would suggest that the effect of probiotic supplementation in this group may last beyond the use of the product.

Probiotic Effect on Extended-Spectrum Beta-Lactamase–Producing Gram-Negative Bacteria—A study performed by Hua et al[39] in preterm infants examined the impact of probiotic supplementation in breastfed versus non-breastfed preterm infants. These infants were all admitted in the neonatal intensive care unit and received

supplementation twice daily when able to feed. The probiotic was a combination of *Bifidobacterium longum*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*. Within the non-breastfed infants, there was a notable difference in colonization with extended-spectrum beta-lactamase (ESBL)-producing gram-negative enteric species in the treatment group versus the placebo group at 14 days (71% vs 89%). There was no reported difference in terms of incidence of necrotizing enterocolitis, late-onset sepsis, or overall mortality between the 2 groups. This suggests that the probiotic was well tolerated, and there were no infections related to probiotic administration or increased feeding intolerance in the treatment group. The trial also included breastfed infants, although there was no difference in ESBL gram-negative colonization rates between the treatment groups at 14 days. This finding suggests that probiotic supplementation is most beneficial in non-breastfed infants, who do not receive the benefits of maternal microbiome supplementation from breast milk.

VSL#3, a commercial mix of multiple probiotic strains (*Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, and *Lactobacillus delbrueckii* subspecies *bulgaricus*; *Bifidobacterium longum*, *Bifidobacterium breve*, and *Bifidobacterium infantis*; and *Streptococcus salivarius* subspecies *thermophilus*), has also been used in clinical trials investigating its potential to eliminate VRE carriage, reportedly to no success.[43] The earliest trial investigating the impact of probiotics on VRE colonization used a nonresistant *Enterococcus faecium* strain in an attempt to displace VRE colonization; it unfortunately did not significantly affect the carriage rate between the placebo and intervention arms.[29] A subset of patients within a 2014 trial examining the impact of *Lactobacillus* on both methicillin-resistant *Staphylococcus aureus* (MRSA) and VRE colonization displayed a trend toward decreased colonization with VRE, although it was not powered to detect a significant difference between groups.[38]

Probiotic Effect on MRSA—For MRSA, *Lactobacillus rhamnosus* has been used in 2 separate trials, although neither reported a significant difference in intestinal or extra-intestinal carriage in the adult population.[38, 44] The largest study examining the impact of *L rhamnosus* HN001 on *Staphylococcus aureus* carriage found a trend toward reduction in *S aureus* colonization within the intestine, although unsurprisingly it did not find the same effect on extra-intestinal sites of colonization.[44]

Effects of Probiotics on Oral Flora and MDROs—Probiotic supplementation has also been studied in relation to its impact on oropharyngeal flora, including pathogens that may cause ventilator-associated pneumonia. *L casei* was used in a study with 150 patients, and a nonsignificant trend toward decreased colonization with beta-lactamase–producing pathogens was found[41]; however, this finding did not correlate with any reduction in infection in these patients. A similar and more recent study showed that concurrent probiotic use during mechanical ventilation led to a significant reduction in ventilator-associated pneumonia, days of ventilation, days in the intensive care unit, and total days in the hospital.[46] There was a nonsignificant trend toward decreased enteric colonization with MDROs in the probiotic group compared with the standard of care group, although there was no change in the colonization rate of MDROs in the airway. Taken together, these studies suggest that probiotics may play a beneficial role in critically ill patients, both in decreasing MDRO

colonization as well as in decreasing antibiotic exposure through reduced infection. Notably, neither study found any adverse events related to probiotic exposure.

Several studies are currently planned or actively recruiting patients to determine the effects of probiotics on MDRO colonization. The targets for eradication include VRE, carbapenem-resistant Enterobacteriaceae, ESBL-producing enteric organisms, and MRSA. The listed probiotics vary but most commonly include members from the *Lactobacillus*, *Bifidobacterium*, and *Bacillus* species (Table I).

Treatment Recommendations

Our review of the published literature reveals mixed results of the overall benefit of probiotics. This finding can possibly be attributed to the variety of probiotics used from study to study, as well as the lack of standardization of dose from product to product. Newer studies with more advanced methodology, including metagenomic sequencing to detect ARG, and larger sample sizes may lead to more promising results in the future. Given the variation in bacterial species used and the formulation based on the supplier, no standardized dose for probiotics can be recommended for elimination of MDR bacterial colonization. Table III lists more information regarding dosages used in successful probiotic trials. Studies published to date have shown minimal side effects of adding probiotics to typical standard of care practices, including in preterm infants and critically ill adults. These supplemental therapies may play a beneficial role for patients undergoing prolonged or extensive antimicrobial exposures, especially in areas where VRE is prevalent. Probiotics should not be routinely used in immunocompromised patients, patients with active inflammatory bowel disease, or those with central lines given the risk for line colonization and pathogenesis.

SYNBIOTICS

Background and Mechanism of Action

Synbiotics are the combination of both prebiotic and probiotic into one package.[12] As such, their mechanism of action on the microbiome combines both the indirect effect of the metabolic precursor (prebiotics) to SCFA, as well as the direct modulation of organisms (probiotics) within the enteric microbial community. Synbiotics are often available over the counter in a variety of combinations of both probiotic strains and prebiotic fibers. Probiotic strains often included in synbiotics include *Bifidobacterium* species, *Lactobacilli*, and *S boulardii*; the prebiotic it is compounded with is often an oligosaccharide such as fructose-oligosaccharide or inulin.[52]

Summary of Published Trials

There have been few published trials examining the impact of synbiotic use on colonization or eradication of MDROs. Of the 2 published trials in recent literature, Lopez et al[50] showed that the administration of a synbiotic had no impact on recovered microbial drug resistance compared with standard of care. One trial unfortunately saw an increase in *Candida* species colonization in the synbiotic group; this colonization was eliminated soon after cessation of the intervention. It is unclear why those patients became colonized, as the synbiotic preparation did not include *Candida* species, although it may have been due to overgrowth of

Candida species supported by the synbiotic preparation. The second study by Salomoa et al, [51] although larger, failed to establish a significant impact of the studied synbiotic on MDR enteric colonization compared with placebo.

Treatment Recommendations

As with prebiotics and probiotics, dosing of synbiotics is largely variable and dependent on the preparation. Synbiotics carry the same risk as probiotics and therefore should not be used in immunocompromised patients with central lines. Similar side effects, including bloating, abdominal cramping, and diarrhea, can be seen with their use, although these symptoms remain reversible with reduction in dose or cessation of product.

CONCLUSIONS

The use of microbiome manipulation with prebiotics, probiotics, and synbiotics is in its infancy compared with other measures. A review of the current scientific literature can offer no direct conclusions regarding the efficacy of these measures; however, as the field expands in both the knowledge of the microbiome and our ability to manipulate it, prebiotics, probiotics, and synbiotics are likely to play a prominent role. For now, these supplements seem safe to use and are well tolerated in most populations. Further research may better establish their role as an alternative method to combat antimicrobial resistance. These nutritionally based therapies should continue to be used in conjunction with other proven techniques, such as antibiotic stewardship and improvement in hygiene and sterilization practices, to aid in the reduction of colonization with MDROs.

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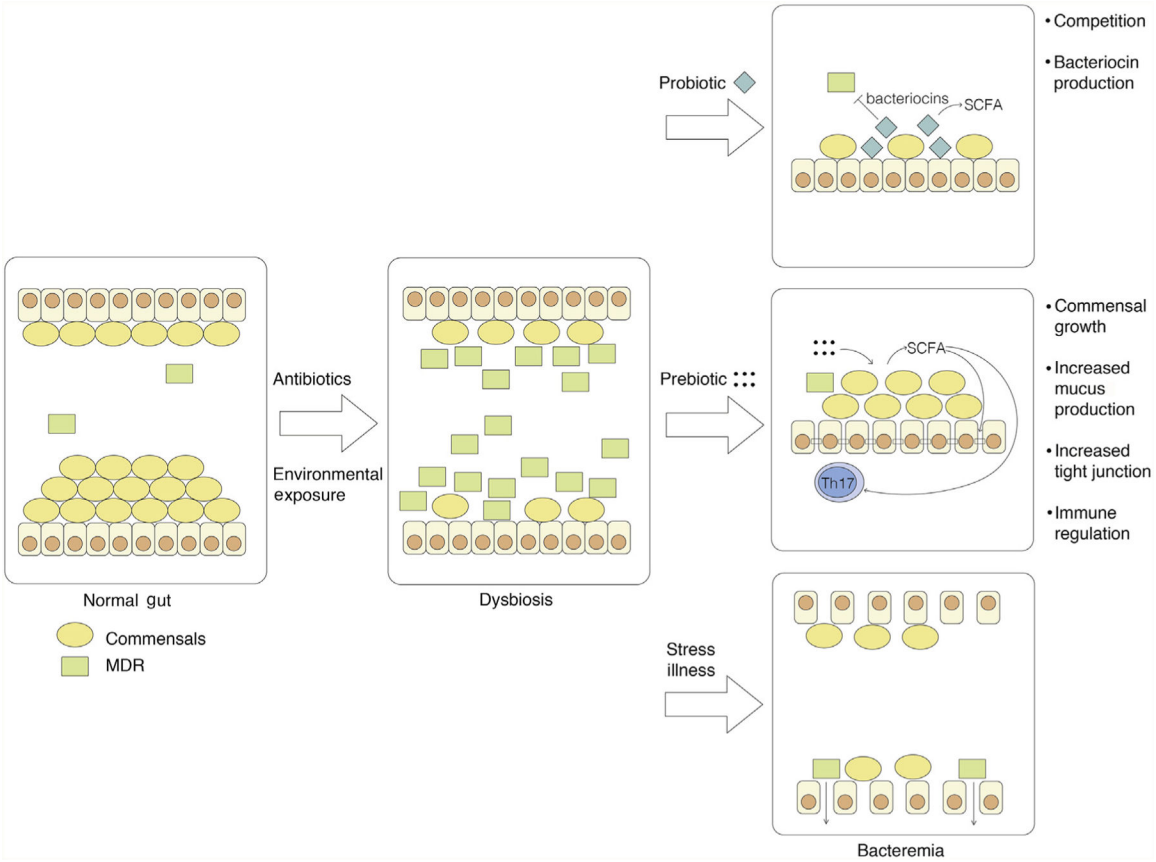

Figure.

Mechanism of action of prebiotics and probiotics on enteric multidrug-resistant organism (MDRO) colonization. The figure shows the process of developing dysbiosis and MDRO colonization, with subsequent figures on the far right detailing the action of probiotics (far right, top) and prebiotics (far right, middle). Without intervention, further stress and illness can allow translocation of MDRO pathogens into the bloodstream (far right, bottom). Th17 = T helper 17 cell.

Table I.

Trials registered at clinicaltrials.gov.

Year Posted	Study Country	Product	Control	Target	Patient	Phase	Clinical Trial
Probiotics							
–	Denmark	*Lactobacillus*	Placebo	VRE	Adult	Recruiting	NCT03560700
2018	United States	Align Probiotic	Placebo	MDR urinary pathogens	Adult	Recruiting	NCT03644966
2019	Taiwan	Not specified	Placebo	VRE	Adult	Recruiting	NCT03822819
2019	Argentina	Bioflora	Placebo	CRE	Adult	Not yet recruiting	NCT03967301
2019	Norway	Labinic probiotic	Placebo	ESBL	Newborns	Not yet recruiting	NCT04172012
2020	United States	*Bacillus subtilis*		MRSA	Adult	Recruiting	NCT04247854
Prebiotics							
2019	United States	Inulin	Placebo	MDRO	Adult	Recruiting	NCT03865706
2019	United States	KB109	SOC	VRE, CRE, ESBL-E	Adult	Recruiting	NCT03944369
2019	United States*	Inulin	Placebo	MDRO	Pediatric	Recruiting	NCT04111471

CRE = carbapenem-resistant Enterobacteriaceae; ESBL = extended-spectrum beta-lactamase; ESBL-E = extended-spectrum beta-lactamase *Escherichia coli*; MDR = multidrug resistant; MDRO = multidrug-resistant organism; MRSA = methicillin-resistant *Staphylococcus aureus*; SOC = standard of care; VRE = vancomycin-resistant *Enterococcus*.

*The authors of the present review are also the primary sponsors of this clinical trial.

Table II.

Summary of published trials evaluating probiotics and synbiotics.

Publication Year	Study Center	Product	Control	Target	Patient	Patients Enrolled	Results	Clinical Trial	Resistance Testing	Citation
Probiotics										
2000	Sweden	*Enterococcus faecium*	Placebo	VRE	Adults	40	ND		Culture based	29
2004	Sweden	*Lactobacillus paracasei*	Placebo	MDR enterics	Adults	36	ND		Culture based	30
2006	Germany	*Bifidobacterium lactis Bb12*	Placebo	MDR enterics	Preterm infants	69	ND		Culture based	31
2007	Australia	*Lactobacillus rhamnosus GG*	Placebo	VRE	Adults	27	+		Culture based	32
2010	France	*L. rhamnosus Lcr35*	Placebo	VRE	Adults	9	ND	NCT00437580	Culture based	33
2010	The Netherlands	Multiple strains	SOC	ARE, VRE	Adults	436	ND		Culture and Genotype	34
2011	New Zealand	Escherichia coli strain Nissle 1917	Placebo	MDR *E coli*	Adults	69	ND		Culture based	35
2011	Poland	*L. rhamnosus GG*	Placebo	VRE	Pediatric	61	+		Culture based	36
2014	United States	*Lactobacillus acidophilus and B lactis*	Placebo	ESBL organisms	Adults	80	ND		PCR	37
2014	United States	*L rhamnosus* HN001	Placebo	MRSA, VRE	Adults	48	ND*	NCT01112995	Culture based	38
2014	China	Multiple strains	Placebo	ESBL	Preterm infants	257	+		Culture based	39
2015	United States	*L rhamnosus GG*	Placebo	VRE	Adults	11	ND	NCT00756262	Culture based	40
2015	Thailand	*Lactobacillus casei*	SOC	MDRO Airway	Adults	150	ND*		Culture based	41
2015	United States	*L rhamnosus GG*	SOC	MDRO	Adults	70	ND		Culture based	42
2016	United States	VSL#3	Placebo	VRE	Adults	50	ND	NCT00933556	Culture based	43
2018	United States	*L rhamnosus* HN001	Placebo	MRSA, MSSA	Adults	113	ND	NCT01321606	PCR	44
2018	Norway	*L acidophilus*	SOC	MDRO	Preterm Infants	76	ND	NCT02197468	DNA extraction	45
2019	Iran	Multiple strains	SOC	MDRO	Adults	120	ND*		Culture based	46
2019	Denmark	*L rhamnosus GG*	SOC	ESBL-E, CPE	Adults	61	ND		Culture based	47
2019	Sweden	Viomixx	SOC	ESBL-E	Adults	80	ND	NCT03860415	Culture based	48
2020	Turkey	*L rhamnosus GG*	SOC	VRE	Newborn	45	+		Culture based	49
Synbiotics										

Publication Year	Study Center	Product	Control	Target	Patient	Patients Enrolled	Results	Clinical Trial	Resistance Testing	Citation
2014	Spain		SOC	MDRO	Adults	89	ND		Culture based	50
2016	Brazil		Placebo	MDR enterics		116	ND		Culture based	51

[+] = statistically significant reduction in drug-resistant organism of interest in treatment group; ARE = ampicillin-resistant *Enterococcus faecium*; CPE = carbapenemas-producing Enterobacteriaceae; ESBL = extended-spectrum beta-lactamase; ESBL-E = extended-spectrum beta-lactamase *Escherichia coli*; MDR = multidrug-resistant; MDRO = multidrug resistant organism; MRSA = methicillin-resistant *Staphylococcus aureus*; ND= no difference; PCR = polymerase chain reaction; SOC = standard of care; VRE = vancomycin-resistant *Enterococcus*.

[*] Trend toward decreased colonization with drug-resistant pathogens in treatment groups; not significantly different between groups.

Table III.

Details on effective probiotic clinical trials.

Year Published	Study Center	Product	Control	Dose of probiotic	Target	Patient Age	No. of Enrolled Patients	Detailed Results	Citation
2007	Australia	*Lactobacillus rhamnosus GG*	Placebo	1.0×10^9 CFU daily (in 100 g yogurt vehicle)	VRE	Adults	24	0/12 in treatment group remained VRE-positive vs 11/12 in control group at 3 weeks	32
2011	Poland	*L rhamnosus GG*	Placebo	3.0×10^9 CFU daily	VRE	Pediatric	61	12/32 in treatment group remained VRE-positive vs 22/29 in control group at 3 weeks	36
2014	China	Multiple strains	Placebo	*Bifidobacterium longum* (2.5×10^6 CFU) *Lactobacillus bulgaricus* (2.5×10^5 CFU), *Streptococcus thermophiles* (2.5×10^5 CFU) twice daily	ESBL enteric	Preterm infants	257	27/93 in treatment group had detectable ESBL enteric colonization by 14 days vs 40/102 in control group for non-breastfeeding infants. No difference was observed in breastfed infants	39
2020	Turkey	*L rhamnosus GG*	SOC	1×10^9 CFU daily	VRE	Newborn	45	1/22 in treatment group remained VRE + vs 11/23 in the control group at 6 months	49

CFU = colony-forming units; ESBL = extended-spectrum beta-lactamase; MDR = multidrug-resistant; SOC = standard of care; VRE = vancomycin-resistant *Enterococcus*.